Concurrent endometrial cancer in atypical endometrial hyperplasia and the role of sentinel lymph nodes: clinical insights from a multicenter experience

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ABSTRACT

Objective This study aimed to evaluate the prevalence of concurrent endometrial cancer in patients pre-operatively diagnosed with atypical endometrial hyperplasia undergoing hysterectomy. Additionally, we assessed the occurrence of high to intermediate-risk and high-risk tumors according to the ESGO-ESTRO-ESP classification. The study also compared surgical outcomes and complications between patients undergoing simple hysterectomy and those undergoing hysterectomy with sentinel lymph node biopsy.

Methods In this multicenter retrospective study, patients with a pre-operative diagnosis of atypical endometrial hyperplasia were identified and divided into two groups: Group 1, which included patients treated with total hysterectomy with or without bilateral salpingo-oophorectomy, and Group 2, where sentinel lymph node biopsy was incorporated into the standard surgical treatment.

Results Among 460 patients with atypical endometrial hyperplasia, 192 received standard surgical management (Group 1) and 268 underwent sentinel lymph node biopsy (Group 2). A total of 47.2% (95% CI 42.6% to 51.7%) of patients were upgraded to endometrial cancer on final histopathological examination. High to intermediate-risk and high-risk tumors constituted 12.3% and 9.2% in Group 2 and 7.4% and 3.7% in Group 1. Lymph node metastases were identified in 7.6% of patients with concurrent endometrial cancer who underwent nodal assessment with at least unilateral mapping. Of the 12 sentinel lymph node metastases, 75.0% were micrometastases, 16.7% macrometastases, and 8.3% isolated tumor cells. No significant differences were found in estimated blood loss, operative time, and intra-operative and post-operative complications between the two groups. The rate of patients undergoing sentinel lymph node biopsy doubled every 2 years (OR 2.010, p<0.001), reaching 79.1% in the last 2 years.

Conclusion This study found a prevalence of concurrent endometrial cancer of 47.2%, and sentinel lymph node biopsy provided prognostic and therapeutic information in 60.8% of cases. It also allowed for the adjustment of adjuvant therapy in 12.3% of high to intermediate-risk patients without increasing operative time or complication rates.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The incidence of concurrent endometrial cancer in patients diagnosed with atypical endometrial hyperplasia at hysteroscopy is approximately 50%. This raises questions about the most effective counseling and management approaches, including the need for lymph node staging. This consideration is particularly significant given the remarkable accuracy and minimal surgical risks associated with sentinel node biopsy.

WHAT THIS STUDY ADDS

⇒ Sentinel lymph node biopsy provided both prognostic and therapeutic information in 60.8% of cases without increasing operative time or complication rates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study prompts consideration as to whether sentinel lymph node biopsy should be offered to patients diagnosed with atypical endometrial hyperplasia after careful counseling, and highlights the need for further research to identify individuals at increased risk of concurrent endometrial cancer.

INTRODUCTION

Atypical endometrial hyperplasia is a pre-cancerous condition of the endometrium characterized by an elevated gland-to-stroma ratio, irregular glandular structure, and nuclear abnormalities.[1–3] Over a 5-year period there is a 25% likelihood of progression to endometrial carcinoma in patients managed conservatively.[4] However, existing literature indicates a concurrent endometrial cancer rate of 30–50% in the final pathology specimens of surgically treated patients.[5–7]

This discrepancy may arise from several factors, including the limited amount of endometrial tissue obtained during outpatient biopsies, the absence of stromal tissue for assessing invasion, and the potential risk of not targeting the cancerous lesion.[1–3]

This raises the question of what should be the most appropriate counseling and treatment for patients diagnosed with atypical endometrial hyperplasia, including the need to perform nodal staging.

The majority of endometrial cancers arising from atypical endometrial hyperplasia are low-grade endometrioid carcinoma with a low risk of lymph node metastasis; however, a non-negligible 3–9% rate of high-risk cancers has been reported.[8]

Additionally, the clinical and therapeutic use of systematic pelvic and aortic lymphadenectomy in endometrial cancer has been questioned[9] and progressively replaced by the sentinel lymph node technique, which guarantees accurate risk stratification[10] while minimizing morbidity.[11]

Regarding the rate of concurrent endometrial cancer, a role for sentinel lymph node biopsy in the surgical management of patients with atypical endometrial hyperplasia has been claimed.[12]

In this study we evaluated the overall rate of concurrent endometrial cancer in patients with a pre-operative diagnosis of atypical endometrial hyperplasia undergoing hysterectomy and assessed the prevalence of high to intermediate-risk and high-risk tumors according to the ESGO-ESTRO-ESP classification.[13]

In addition, we compared surgical adverse events and cancer histopathological and immunohistochemical features between patients undergoing simple hysterectomy and those undergoing hysterectomy plus sentinel lymph node biopsy.

METHODS

The study was conducted at the following three referral cancer centers in Italy: Fondazione Policlinico Universitario A Gemelli IRCCS in Rome, Gemelli Molise in Campobasso, and University of Parma. Data of all patients who underwent surgery for atypical endometrial hyperplasia between January 2010 and March 2022 were retrospectively retrieved.

Patients and Surgical Technique

Inclusion criteria were a pre-operative histological diagnosis of atypical endometrial hyperplasia and surgical treatment. Patients with a pre-operative diagnosis of endometrial hyperplasia without atypia or those with endometrial cancer were excluded from the analysis. Patients who underwent conservative treatment were also excluded from the study. All demographic, surgical, and post-operative variables were retrieved from our electronic database (REDCAP).

The study population was divided into two main groups based on the surgical treatment received: Group 1 which included patients treated with total hysterectomy with or without bilateral salpingo-oophorectomy; and Group 2 with patients in whom sentinel lymph node biopsy was added to the standard surgical treatment.

A standardized algorithm was not consistently applied to determine when to perform sentinel node biopsy throughout the accrual period. Instead, the decision to remove the sentinel lymph node was made by the surgeon. This decision took into account the patient's clinical characteristics (co-morbidities, performance status, body mass index, age), radiological features of the disease, and intra-operative surgical and anesthetic considerations, as well as the surgeon's confidence with the technique. Asessment of sentinel lymph nodes was conducted using a uniform procedural approach which involved the intra-cervical injection of indocyanine green. After diluting 25 mg indocyanine green with 20 mL sterile water (1.25 mg/mL indocyanine green), a superficial (1–3 mm) and deep (1–2 cm) cervical injection of indocyanine green was given (2 mL at 3 and 9 o'clock).

A sentinel lymph node is defined as the initial lymph node that captures the color along a lymphatic path or the first lymph node reached by the efferent lymphatic vessel, even in the absence of direct staining.[14] In case of failed mapping, no side-specific lymphadenectomy was performed. Bulky or suspected lymph nodes were removed according to the surgeon's intra-operative evaluation. Sentinel lymph nodes were evaluated by routine histopathological examination from 2010 to 2015, while ultrastaging analysis was introduced starting from the year 2016.

Blood loss was estimated at the end of each surgery.

Intra-operative complications were classified using the Common Terminology Criteria for Adverse Events (CTCAE),[15] while post-operative complications were described using the Clavien–Dindo classification.[16] Post-operative complications with a grade >3 according to the Clavien–Dindo classification were considered severe.

After the final histopathological evaluation, endometrial cancer was classified according to the ESGO-ESTRO-ESP classification as low-risk, intermediate-risk, high to intermediate-risk, and high-risk tumors.[13]

Statistical Analysis

The primary endpoint of this study was the incidence of concurrent endometrial cancer which was assumed to be around 50%. A sample size of 460 patients was needed to estimate this rate with a 95% CI semi-width of 5%. Absolute frequency and percentage were used for qualitative variables and median and IQR for continuous variables. The groups were compared using the Mann–Whitney U test for continuous variables and the Pearson χ^2 test for categorical variables as appropriate. A p value <0.05 was considered statistically significant (two-tailed test). Statistical analysis was performed using the SPSS version 29.0 statistical package.

RESULTS

Four hundred and sixty patients with atypical endometrial hyperplasia were identified. Of these, 192 underwent standard surgical management with total hysterectomy with or without bilateral salpingo-oophorectomy (Group 1) and 268 underwent additional sentinel lymph node biopsy (Group 2). Table 1 shows the baseline and ultrasonographic characteristics of the study population. The two groups did not differ in age, body mass index, menopausal state, symptoms, or co-morbidities. A significant difference was found in terms of ultrasound diagnosis. In Group 1, 68.8% of patients had an ultrasound diagnosis indicative of an endometrial polyp compared with 50.7% of patients in Group 2, while 31.2% of patients in Group 1 had inhomogeneous endometrial thickening compared with 49.3% in Group 2 (p<0.001).

The laparoscopic approach was the preferred one (68.3%), followed by robotic (19.3%) and open surgery (12.4%) (table 2).

A statistically significant difference was found in the distribution of surgical approaches between the two groups (p<0.001). The sentinel lymph node group (Group 2) had a higher rate of the robotic approach (28.7% vs 6.3%) and a lower rate of the open abdominal

Table 1 Baseline and ultrasonographic patient characteristics

Variable	All	Non-SLN (Group 1)	SLN (Group 2)	P value
All cases, N	460	192	268	
Age, years, median (IQR)	56	55 (29–63)	56 (50–68)	0.063
BMI, kg/m^2, median (IQR)	29	29 (24–33)	28 (24.9–33)	0.270
Menopausal state, n (%)				0.325
Pre-menopausal	163 (35.4)	63 (32.8)	100 (37.3)	
Post-menopausal	297 (64.6)	129 (67.2)	168 (62.7)	
Co-morbidities, n (%)				
Any co-morbidity	211 (45.9)	88 (45.8)	123 (45.9)	0.989
Hypertension	127 (27.6)	49 (25.5)	78 (29.1)	0.459
Diabetes	48 (10.4)	14 (7.3)	34 (12.7)	0.065
Symptoms, n (%)				
AUB	290 (63.0)	120 (62.5)	170 (63.4)	0.845
Irregular period	8 (4.9)	2 (3.2)	6 (3.7)	0.416
US diagnosis, n (%)				<0.001
Endometrial polyp	268 (58.3)	132 (68.8)	136 (50.7)	
Inhomogeneous endometrial thickening	192 (41.7)	60 (31.2)	132 (49.3)	
Endometrial thickness, n (%)				0.814
<20 mm	367 (79.8)	152 (79.2)	215 (80.2)	
≥20 mm	93 (20.2)	40 (20.8)	53 (19.8)	

*Mann–Whitney U test.
AUB, abnormal uterine bleeding; BMI, body mass index; LN, sentinel lymph node; US, ultrasound.

approach (8.2% vs 18.2%). No differences in terms of estimated blood loss, operative time, intra-operative and post-operative complications were found between the groups (Table 2).

Overall, intra-operative complications occurred in 3.5% of cases (7 in Group 1 and 9 in Group 2, 3.6% vs 3.4%, p=0.868) and were all grade 1. A statistically significant difference was not reported in 'all grade' post-operative complications (Group 1 vs Group 2: 1.6% vs 4.9%, p=0.071) nor in severe post-operative complications (Group 1 vs Group 2: 33.3% vs 15.4%, p=0.489) (Table 2).

Figure 1 shows the distribution of the final histopathological diagnosis in the overall cohort; 47.2% (95% CI 42.6% to 51.7%) of the patients were upgraded to endometrial cancer on final histopathological examination. A diagnosis of endometrial cancer was more common in the sentinel lymph node group than in the non-sentinel lymph node group (60.8% vs 28.1% respectively, p<0.001).

The histopathological and molecular features of patients diagnosed with endometrial cancer are shown in Table 3.

Among the cancer cases, 97.7% exhibited an endometrioid histotype with 92.2% falling into the G1–2 category and 85.3% with focal or negative lymphovascular space invasion. Patients who had a sentinel lymph node biopsy (Group 2) had a significantly higher rate of tumor ≥2 cm (p<0.001).

No statistically significant disparities were observed in terms of International Federation of Gynecology and Obstetrics stage and prognostic risk category between the two groups. Nevertheless, high to intermediate-risk and high-risk tumors constituted 12.3% and 9.2% of cases in Group 2 compared with 7.4% and 3.7% in Group 1 (p=0.092).

Concerning immunohistochemical assessments, 5.4% of patients had mutated p53, 16.2% showed a deficiency in mismatch repair, and 95.7% of cases exhibited positivity for both estrogen and progesterone receptor.

At univariate analysis we found that pre-operative predictors of concurrent endometrial cancer included ultrasound findings of inhomogeneous endometrial thickening and endometrial thickness ≥20 mm (OR 3.569, p<0.001 and OR 2.735, p<0.001, respectively) (data not shown).

The overall sentinel lymph node detection rate in Group 2 was 95.1% with successful bilateral mapping of 84.0% (Table 4).

Lymph node metastases were identified in 12 patients, constituting 7.6% of those with concurrent endometrial cancer who underwent nodal assessment with at least unilateral mapping and 4.7% of the entire population with pre-operative atypical hyperplasia and the identification of at least one sentinel lymph node. One patient had both a positive pelvic sentinel lymph node and a metastatic bulky para-aortic lymph node. Of the 12 sentinel lymph node metastases, nine were micrometastases (75.0%), two were macrometastases (16.7%), and one was an isolated tumor cell (8.3%) (Table 4).

Online Supplemental Figure S1 shows the percentage of patients who underwent sentinel lymph node biopsy over the years of the study period. The rate of patients undergoing sentinel lymph node

Table 2 Surgical characteristics, peri-operative outcomes, and histopathological findings of the overall cohort

Variable	All	Non-SLN (Group 1)	SLN (Group 2)	P value
All cases, N	460	192 (41.7)	268 (58.3)	
Previous uterine surgery	142 (30.9)	70 (36.5)	72 (26.9)	0.032
Previous abdominal or pelvic surgery	227 (49.3)	95 (49.5)	132 (49.3)	0.962
Previous vaginal delivery	253 (55.0)	109 (56.8)	144 (53.7)	0.569
Previous cesarean section	129 (28.0)	57 (29.7)	72 (26.9)	0.529
Surgical approach				<0.001
LPT	57 (12.4)	35 (18.2)	22 (8.2)	
LPS	314 (68.3)	145 (75.5)	169 (63.1)	
Robotic	89 (19.3)	12 (6.3)	77 (28.7)	
Surgical procedures				
BSO	413 (89.8)	168 (87.5)	245 (91.4)	0.212
Bulky pelvic lymph node removal	32 (7.0)	8 (4.2)	24 (9.0)	0.062
Bulky lumbo-aortic lymph node removal	6 (1.3)	3 (0.7)	3 (0.7)	0.697
Estimated blood loss, mL, median (IQR)	50 (50–100)	50 (50–100)	50 (50–100)	0.075
Operative time, min, median (IQR)	120 (100–120)	113 (110–120)	120 (110–120)	0.143
Intra-operative complications				
All grades	16 (3.5)	7 (3.6)	9 (3.4)	0.868
CTCAE 1	16 (100)	7 (100)	9 (100)	–
CTCAE 2–5	0 (0.0)	0 (0.0)	0 (0.0)	
Post-operative complications				
All grades	16 (3.5)	3 (1.6)	13 (4.9)	0.071
Grade 1–2	13 (81.3)	2 (66.7)	11 (84.6)	0.489
Grade 3–5	3 (18.7)	1 (33.3)	2 (15.4)	
Final histopathological diagnosis				<0.001
Atypical hyperplasia/benign condition	243 (52.8)	138 (71.9)	105 (39.2)	
Endometrial cancer	217 (47.2)	54 (28.1)	163 (60.8)	

Values shown as n (%) unless stated otherwise.
*Mann–Whitney U test.
BSO, bilateral salpingo-oophorectomy; CTCAE, Common Terminology Criteria for Adverse Events; LPS, laparoscopy; LPT, laparotomy; SLN, sentinel lymph node.

biopsy doubled every 2 years (OR 2.010, p<0.001) until reaching 79.1% during the last 2 years.

DISCUSSION

Summary of Main Results

Final histopathological examination revealed concurrent endometrial cancer in 47.2% of cases, with 18.9% classified as high to intermediate-risk/high-risk (which represented 8.9% of the whole study population). Sentinel lymph node evaluation detected lymph node metastases in 7.6% of patients with endometrial cancer and 4.7% of patients with atypical hyperplasia, primarily low volume. Sentinel lymph node mapping was properly applied to 60.8% of patients with pre-operative atypical endometrial hyperplasia and concurrent endometrial cancer at the final histopathological examination, including 21.5% high to intermediate-risk/high-risk patients, while the remaining 39.2% were 'over-treated'. The use of sentinel lymph node mapping in patients with atypical endometrial hyperplasia has steadily increased to 79.1% over the past decade, with no reported sentinel lymph node-related complications.

Results in the Context of the Published Literature

The tricky differential diagnosis between atypical endometrial hyperplasia and endometrial cancer and the high rate of concurrent endometrial cancer raises the question whether sentinel lymph node biopsy could be an option in the surgical management of atypical endometrial hyperplasia.[12]

Intra-operative evaluation of uterine risk factors at frozen section are now considered obsolete and several studies have demonstrated their poor reproducibility and concordance with definitive paraffin sections.[17 18] In addition, hysterectomy with removal of the cervix and disruption of the lymphatic channels would irreversibly impair the possibility to perform sentinel lymph node biopsy.

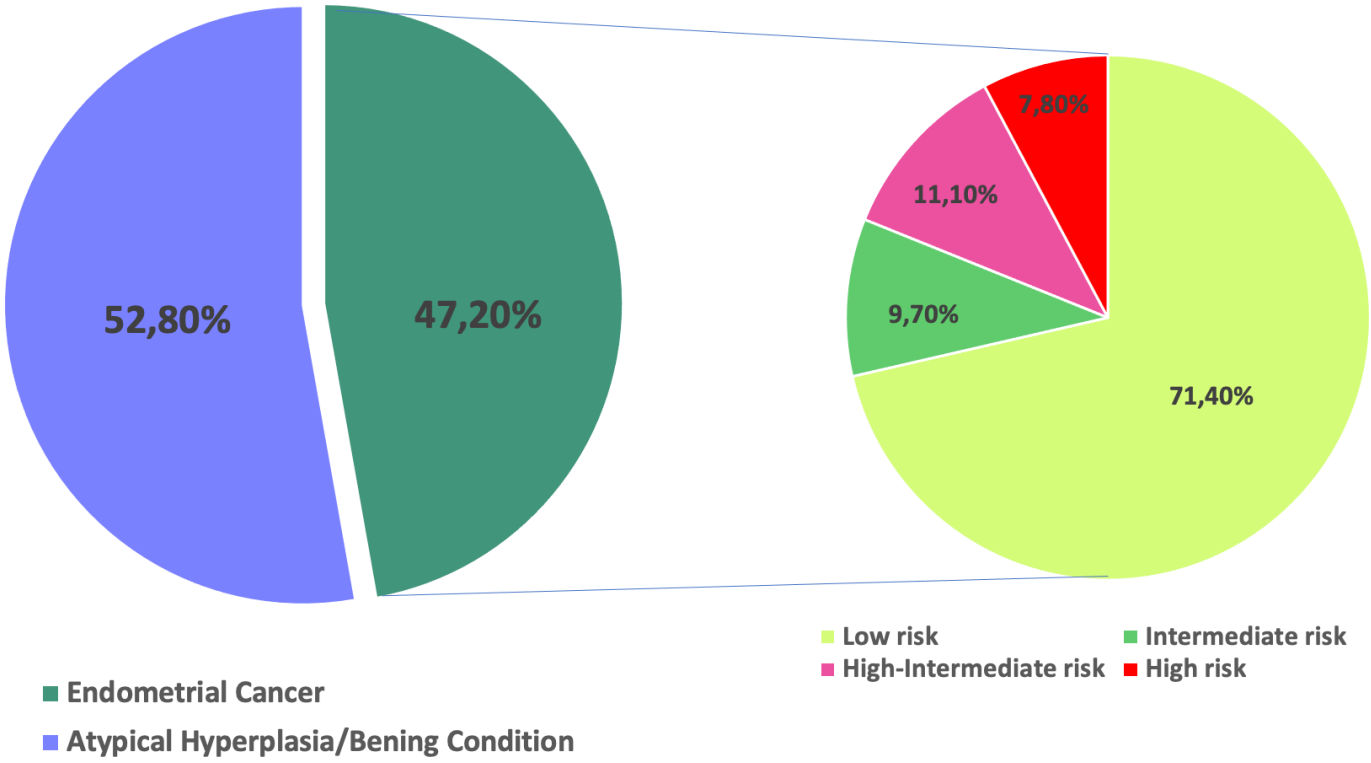

Figure 1 Atypical endometrial hyperplasia and concurrent endometrial cancer rates with distribution of prognostic risk groups.

Given the estimated threefold higher incidence of atypical endometrial hyperplasia compared with endometrial cancer[19] coupled with the approximate 50% rate of concurrent endometrial cancer,[6] the omission of lymph node staging could result in a high rate of potentially under-staged patients. Nevertheless, the vast majority of concurrent endometrial cancer are low-grade endometrioid tumors[4 6 7] and, given the low rate of lymph node involvement,[20] the role of lymph node evaluation in atypical endometrial hyperplasia is debatable. We acknowledge that, in pathologically confirmed low-risk patients, the presence of a negative sentinel node does not impact patient care. However, the analysis could enable the identification of unexpected lymph node metastases, potentially reclassifying these tumors into the high-risk category. Indeed, in a large series of low-risk patients (<50% myometrial invasion, low-grade),[21] sentinel lymph node biopsy revealed a 6% lymph node metastasis rate. This aligns with the ESGO-ESTRO-ESP guidelines which state that sentinel lymph node biopsy can be considered in low-risk and intermediate-risk disease (level of evidence II, A).[13]

Moreover, a non-negligible rate of high-risk concurrent endometrial cancer has been reported in the literature, ranging from 3% to 36.6%.[6 8 22 23] This wide range of high-risk features results from the heterogeneous criteria used to define this category by different authors.

In our series, applying the ESGO-ESTRO-ESP criteria we found 18.9% of high to intermediate-risk/high-risk patients where lymph node assessment should be performed due to the higher risk of lymph nodal metastatic spread.

Furthermore, lymph node assessment in endometrial cancer allows for better personalization of the adjuvant treatment and enables the avoidance of an escalation in treatment in patients in the high to intermediate-risk group (11.1% of our study population).[13]

We agree with other authors who have previously reported on this topic that the risks related to pelvic lymphadenectomy exceed its theoretical benefits, given the significant morbidity and the lack of a therapeutic role.[24] For these reasons, we have excluded side-specific lymphadenectomy from our surgical algorithm. Nevertheless, with a 4.9% rate of mapping failure, concurrent endometrial cancer at 47.2%, and a high to intermediate/high risk at 18.9%, very few patients would have benefited from pelvic lymphadenectomy. In view of these factors, an algorithm exclusively incorporating sentinel lymph node biopsy is deemed to be more acceptable from a risk-to-benefit perspective.

Furthermore, in our study sentinel lymph node biopsy added a non-significant 7 min increase in median operative time (113 vs 120 min). Estimated blood loss remained comparable, as did the rates of intra-operative and post-operative complications, none of which were directly associated with sentinel lymph node removal or indocyanine green injection.

Our results are in line with those reported by Mueller et al who found that sentinel lymph node biopsy was safe with similar operative times and adverse event rates to hysterectomy without sentinel lymph node biopsy.[25]

In a recently published paper by Matanes et al, 24.6% of patients had a high to intermediate/high-risk concurrent endometrial cancer according to the GOG99 classification (9.3% of the whole population) with a 3.3% rate of nodal metastasis.[12] Even in their series, no sentinel lymph node-related complications were reported, nor was there an increase in operative time or blood loss. Sentinel lymph node biopsy influenced the post-operative adjuvant treatment in 8.3% of patients. In these cases, vaginal brachytherapy was chosen over external beam radiotherapy due to negative sentinel lymph node findings, which aligns with our similar results of 12.3% in

Table 3 Histopathological features of patients diagnosed with endometrial cancer

Variable	All	Non-SLN (Group 1)	SLN (Group 2)	P value
All cases	217	54 (24.9)	163 (75.1)	
Histotype				0.193
Endometrioid	212 (97.7)	54 (100)	158 (96.9)	
Non-endometrioid	5 (2.3)	0 (0.0)	5 (3.1)	
Grading				0.059
1–2	200 (92.2)	53 (98.1)	147 (90.2)	
3	17 (7.8)	1 (1.9)	16 (9.8)	
LVSI				0.119
Negative-focal	185 (85.3)	50 (92.6)	135 (82.8)	
Substantial	32 (14.7)	4 (7.4)	28 (17.2)	
Tumor diameter				<0.001
<20 mm	292 (63.5)	142 (74.0)	150 (56.0)	
≥20 mm	168 (36.5)	50 (26.0)	118 (44.0)	
Myometrial invasion				0.692
<50%	175 (80.6)	45 (83.3)	130 (79.8)	
≥50%	42 (19.4)	9 (16.7)	33 (20.2)	
Cervical invasion				0.172
No	205 (94.5)	53 (98.1)	152 (93.3)	
Yes	12 (5.5)	1 (1.9)	11 (6.7)	
Immunohistochemical features				
p53				0.620
WT	105 (94.6)	27 (96.4)	78 (94.0)	
Mutated	6 (5.4)	1 (3.6)	5 (6.0)	
NA	106	26	80	
MMR				0.820
Proficient	93 (83.8)	23 (85.2)	70 (83.3)	
Deficient	18 (16.2)	4 (14.8)	14 (16.7)	
NA	106	27	79	
ER				0.516
Negative	4 (4.3)	1 (7.7)	3 (3.8)	
Positive	89 (95.7)	12 (92.3)	77 (96.3)	
NA	124	41	83	
PR				0.516
Negative	4 (4.3)	1 (7.7)	3 (3.8)	
Positive	89 (95.7)	12 (92.3)	77 (96.3)	
NA	124	41	83	
Staging system and risk groups				
FIGO stage				0.224
IA	164 (75.6)	43 (79.6)	121 (74.2)	
IB	28 (12.9)	8 (14.8)	20 (12.3)	
II	10 (4.6)	1 (1.9)	9 (5.5)	
III A-B-C	15 (6.9)	2 (3.7)	123 (8.0)	
Prognostic risk groups*				0.092
Low	155 (71.4)	41 (75.9)	114 (69.9)	

Continued

Table 3 Continued

Variable	All	Non-SLN (Group 1)	SLN (Group 2)	P value
Intermediate	21 (9.7)	7 (13.0)	14 (8.6)	
High to intermediate	24 (11.1)	4 (7.4)	20 (12.3)	
High	17 (7.8)	2 (3.7)	15 (9.2)	

Values shown as n (%) unless stated otherwise.
*Classified according to the ESGO-ESTRO-ESP classification.[13]
ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; MMR, mismatch repair; NA, not available; PR, progesterone receptor; SLN, sentinel lymph node; WT, wild type.

high to intermediate-risk patients who underwent sentinel lymph node evaluation.

However, while complications directly related to sentinel lymph node biopsy are low, it remains an invasive procedure. If performed in centers with low case volumes and lacking specialization in gynecological oncology, it could be complex and not free from vascular, neurological, and urological risks, particularly given the need for adequate access to the pelvic retroperitoneum.[11]

Table 4 Sentinel lymph node detection rates, histopathological findings, and anatomical localizations

Variables	N (%)
Patients who underwent SLN assessment	268
Overall detection rate*	255 (95.1)
Successful bilateral mapping	225 (84.0)
Bilateral mapping failure	13 (4.9)
Anatomical localization	
Right hemipelvis	
External iliac vessels/obturatory vessels	223 (94.5)
Common/internal iliac vessels	13 (5.5)
Left hemipelvis	
External iliac vessels/obturatory vessels	241 (98.4)
Common/internal iliac vessels	4 (1.6)
Endometrial cancer patients and SLN assessment	163
Overall detection rate*	157 (96.3)
Successful bilateral mapping	136 (83.4)
Bilateral mapping failure	6 (3.7)
Patients with lymph node metastasis†	12 (7.6)‡
SLN histological status	
Negative	145 (92.4)
Positive	12 (7.6)
Positive SLN histology	
ITC	1 (8.3)
Micrometastasis	9 (75.0)
Macrometastasis	2 (16.7)

Values shown as n (%) unless stated otherwise.
*Detection of at least one SLN.
†Rates calculated in patients with at least monolateral mapping (n=157).
‡One patient reported a positive pelvic sentinel lymph node and a metastatic bulky para-aortic lymph node. ITCs were not considered among metastatic lymph nodes.
ITC, isolated tumor cells; SLN, sentinel lymph node.

Strengths and Weaknesses

Our study has several limitations, with the primary concern being the inherent selection bias associated with performing sentinel lymph node biopsy, given the retrospective nature of the study. An additional limitation is the extended enrollment period, which resulted in a non-standardized and centralized pre-operative diagnostic work-up and an incomplete comprehensive molecular profiling of concurrent endometrial cancer. Furthermore, a centralized pathologic review by a gynecologic pathologist was not routinely performed.

However, this is the largest series available in the literature of consecutive patients in which the use of sentinel lymph node biopsy and standard surgery is compared in patients with a pre-operative diagnosis of atypical endometrial hyperplasia.

Implications for Practice and Future Research

The key question is how to effectively identify atypical endometrial hyperplasia with a high risk of concurrent endometrial cancer. First, a pre-operative diagnosis obtained through targeted biopsy using diagnostic hysteroscopy performed in referral centers could potentially reduce the rate of misdiagnosis. Moreover, some authors found that age, post-menopausal status, and endometrial thickness[6 23 26 27] are relevant risk factors for atypical endometrial hyperplasia with concurrent endometrial cancer. Others stratified the concurrent rate of endometrial cancer according to a sub-stratification of atypical endometrial hyperplasia as 'atypical endometrial hyperplasia—cannot exclude cancer versus atypical endometrial hyperplasia-only', or suspicious versus non-suspicious atypical endometrial hyperplasia or diffuse hyperplasia versus focal/polyp[27] with interesting results. However, the reproducibility of an atypical endometrial hyperplasia diagnosis has been debated for decades and sub-classifications could add further confusion. In our study we confirmed that inhomogeneous endometrial thickening and endometrial thickness ≥20 mm were predictive factors for concurrent endometrial cancer.

There are currently no standardized biomarkers to predict atypical endometrial hyperplasia with concurrent endometrial cancer. One study found that the loss of ARID1A expression in endometrial biopsy was related to a very high rate of concurrent endometrial cancer at final pathology (93.8%). On the other hand, its retention

did not preclude this possibility, although with a lower probability (13.9%).[28]

Puechl et al recently attempted to molecularly characterize endometrial intra-epithelial neoplasia using the ProMisE (proactive Molecular Risk Classifier for Endometrial cancer) classification algorithm and concluded that molecular classification of endometrial intra-epithelial neoplasia is feasible and possibly prognostic.[29]

Further studies are needed to identify reproducible pre-operative risk factors for concurrent endometrial cancer and to determine the usefulness of molecular classification and immunohistochemical biomarkers such as ARID1A in this context. This would aid in better identification of patients who should be referred to a cancer center for lymph nodal staging and allow for a more precise application of the standardized sentinel lymph node algorithm.

CONCLUSION

Sentinel lymph node biopsy is already accepted as part of the surgical staging of other pre-neoplastic diseases such as in situ breast cancer, where the rate of invasive tumors is about 50%.[30]

In our series we found an overall rate of concurrent endometrial cancer of 47.2%. Sentinel lymph node biopsy added prognostic and therapeutic information in 60.8% of patients and allowed for modulation of adjuvant therapy in 12.3% of high to intermediate-risk patients without increasing operative time and rate of complications.

Further studies are needed to identify patients with atypical endometrial hyperplasia at higher risk of endometrial cancer and to understand how clinicopathological variables or the molecular profile of atypical endometrial hyperplasia during pre-operative assessment can predict the presence of an invasive cancer.

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REFERENCES

1 Allison KH, Reed SD, Voigt LF, *et al*. Diagnosing endometrial hyperplasia: why is it so difficult to agree? *Am J Surg Pathol* 2008;32:691–8.
2 Kendall BS, Ronnett BM, Isacson C, *et al*. Reproducibility of the diagnosis of endometrial hyperplasia, atypical hyperplasia, and well-differentiated carcinoma. *Am J Surg Pathol* 1998;22:1012–9.
3 Silverberg SG. Problems in the differential diagnosis of endometrial hyperplasia and carcinoma. *Mod Pathol* 2000;13:309–27.
4 Barakat A, Ismail A, Chattopadhyay S, *et al*. Endometrial cancer incidence in patients with atypical endometrial hyperplasia according to mode of management. *Cancer Diagn Progn* 2022;2:564–8.
5 Bourdel N, Chauvet P, Tognazza E, *et al*. Sampling in atypical endometrial hyperplasia: which method results in the lowest underestimation of endometrial cancer?. *J Minim Invasive Gynecol* 2016;23:692–701.
6 Trimble CL, Kauderer J, Zaino R, *et al*. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer* 2006;106:812–9.
7 Giede KC, Yen TW, Chibbar R, *et al*. Significance of concurrent endometrial cancer in women with a preoperative diagnosis of atypical endometrial hyperplasia. *J Obstet Gynecol Canada* 2008;30:896–901.
8 Erdem B, Aşıcıoğlu O, Seyhan NA, *et al*. Can concurrent high-risk endometrial carcinoma occur with atypical endometrial hyperplasia?. *Int J Surg* 2018;53:350–3.
9 ASTEC Study Group, Kitchener H, Swart AMC, *et al*. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet* 2009;373:125–36.
10 Koh WJ, Abu-Rustum NR, Bean S, *et al*. Uterine Neoplasms, Version 1.2018 NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2018;16:170–99.
11 Capozzi VA, Riemma G, Rosati A, *et al*. Surgical complications occurring during minimally invasive sentinel lymph node detection in endometrial cancer patients. A systematic review of the literature and metanalysis. *Eur J Surg Oncol* 2021;47:2142–9.
12 Matanes E, Amajoud Z, Kogan L, *et al*. Is sentinel lymph node assessment useful in patients with a preoperative diagnosis of endometrial intraepithelial neoplasia?. *Gynecol Oncol* 2023;168:107–13.
13 Concin N, Matias-Guiu X, Vergote I, *et al*. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer* 2021;31:12–39.
14 Geppert B, Lönnerfors C, Bollino M, *et al*. A study on uterine lymphatic anatomy for standardization of pelvic sentinel lymph node detection in endometrial cancer. *Gynecol Oncol* 2017;145:256–61.
15 Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017, Available: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
16 Clavien PA, Barkun J, de Oliveira ML, *et al*. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250:187–96.
17 Frumovitz M, Slomovitz BM, Singh DK, *et al*. Frozen section analyses as predictors of lymphatic spread in patients with early-stage uterine cancer. *J Am Coll Surg* 2004;199:388–93.
18 Turan T, Oguz E, Unlubilgin E, *et al*. Accuracy of frozen-section examination for myometrial invasion and grade in endometrial cancer. *Eur J Obstet Gynecol Reprod Biol* 2013;167:90–5.
19 Reed SD, Newton KM, Clinton WL, *et al*. Incidence of endometrial hyperplasia. *Am J Obstet Gynecol* 2009;200:678.
20 Mariani A, Dowdy SC, Cliby WA, *et al*. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. *Gynecol Oncol* 2008;109:11–8.

21 Kim CH, Khoury-Collado F, Barber EL, *et al*. Sentinel lymph node mapping with pathologic ultrastaging: a valuable tool for assessing nodal metastasis in low-grade endometrial cancer with superficial myoinvasion. *Gynecol Oncol* 2013;131:714–9.
22 Costales AB, Schmeler KM, Broaddus R, *et al*. Clinically significant endometrial cancer risk following a diagnosis of complex atypical hyperplasia. *Gynecol Oncol* 2014;135:451–4.
23 Leitao MM, Han G, Lee LX, *et al*. Complex atypical hyperplasia of the uterus: characteristics and prediction of underlying carcinoma risk. *Am J Obstet Gynecol* 2010;203:349.
24 Bogani G, Dowdy SC, Cliby WA, *et al*. Role of pelvic and para-aortic lymphadenectomy in endometrial cancer: current evidence. *J Obstet Gynaecol Res* 2014;40:301–11.
25 Mueller JJ, Rios-Doria E, Park KJ, *et al*. Sentinel lymph node mapping in patients with endometrial hyperplasia: a practice to preserve or abandon. *Gynecol Oncol* 2023;168:1–7.
26 Cohen A, Tsur Y, Tako E, *et al*. Incidence of endometrial carcinoma in patients with endometrial intraepithelial neoplasia versus atypical endometrial Polyp [published online ahead of print]. *Int J Gynecol Cancer* 2023;33:35–41.
27 Rajadurai VA, Chivers P, Ayres C, *et al*. Predictors of endometrial carcinoma in patients with atypical endometrial hyperplasia at a tertiary gynaecological cancer centre in Western Australia. *Aust N Z J Obstet Gynaecol* 2021;61:275–83.
28 Yen T-T, Miyamoto T, Asaka S, *et al*. Loss of ARID1A expression in endometrial samplings is associated with the risk of endometrial carcinoma. *Gynecol Oncol* 2018;150:426–31.
29 Puechl AM, Spinosa D, Berchuck A, *et al*. Molecular classification to prognosticate response in medically managed endometrial cancers and endometrial intraepithelial neoplasia. *Cancers (Basel)* 2021;13:2847.
30 NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Version 4.2022, Available: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf