Submitted: 25 July, 2023 Accepted: 20 September, 2023 Published: 15 June, 2024 DOI:10.22514/ejgo.2024.044

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Predictive factors of concurrent endometrial carcinoma and the role of frozen section in patients with preoperative diagnosis of atypical endometrial hyperplasia

Yin-Juan Chang[1,†], Yong-Shen Fan[2,†], Reshmi Hareendra Kariyapperuma[3], Yong-An Xu[4,*]

[1]Department of Obstetrics and Gynecology, Women's Hospital School of Medicine Zhejiang University, 310006 Hangzhou, Zhejiang, China
[2]Department of General Surgery, Zhejiang Hospital, 310006 Hangzhou, Zhejiang, China
[3]School of Medicine, Zhejiang University, 310058 Hangzhou, Zhejiang, China
[4]Department of Emergency Medicine, The Second Affiliated Hospital of Medical College, Zhejiang University, 310009 Hangzhou, Zhejiang, China

***Correspondence**
xuyongan2000@zju.edu.cn
(Yong-An Xu)

† These authors contributed equally.

Abstract

Type 1 endometrial adenocarcinoma or endometrioid adenocarcinoma had developed from a precursor lesion known as atypical endometrial hyperplasia (AEH). This study aimed to evaluate the rates and risk factors of concurrent endometrial carcinoma in patients with preoperative diagnosis of AEH and assessed the role of intraoperative frozen section examination among these patients. Sixty-six patients undergone hysterectomy after the preoperative diagnosis of AEH *via* diagnostic curettage or hysteroscopy biopsy, were included in this retrospective cohort study. The major study outcomes were the rates and risk factors of co-existent endometrial cancer and the frozen section efficacy in detecting concurrent invasive disease. 31.81% AEH patients had endometrial cancer diagnosis in hysterectomy specimens. Among these endometrial cancer patients, 18 were of Stage IA, 1 of Stage IB, and 2 of Stage II. Stage III or IV was not detected in any of the patients. Patients preoperatively diagnosed as AEH *via* hysteroscopy had less probability of co-existent endometrial carcinoma than those diagnosed by endometrial curettage (17.24% *vs.* 43.24%) ($p < 0.05$). BMI (Body Mass Index) >28 kg/m^2, post-menopausal status, and endometrial thickness were the determinant factors in diagnosing endometrial carcinoma through final histopathology of AEH patients ($p < 0.05$). Regarding presence or absence of concomitant endometrial carcinoma, the frozen section diagnoses were consistent with the final histopathology in 47.06% patients. Co-existent endometrial cancer with AEH was prevalent and possessed good prognostic features. The predictive factors of harboring concomitant endometrial cancer included older age, overweight, and endometrial thickness. Intraoperative frozen section analysis of AEH might assist in the clinical decision-making during surgery.

Keywords

Atypical endometrial hyperplasia; Endometrial carcinoma; Intraoperative frozen section; Hysterectomy; Risk factors; Hysteroscopy

1. Introduction

Endometrial carcinoma is the most prevalent malignancy of female reproductive tract in developed and developing world [1, 2]. Endometrioid adenocarcinoma detected in 80–85% cases is the most common subtype evolved from precursor lesion known as atypical endometrial hyperplasia (AEH) [3]. The concurrent endometrial cancer rate is high in AEH patients. There is no tool to precisely predict concomitant endometrial malignancy, and most cases are postoperatively diagnosed in hysterectomy specimens [4]. It is thus crucial to correctly diagnose preoperative AEH and identify the risk factors ruling out concomitant carcinoma.

Surgical management is indicated in AEH patients with completed fertility, and is an absolute indication for endometrial carcinoma patients. However, extent of surgery depends on the diagnosis [5]. A preoperative diagnosis is thus pivotal. The extent of surgery in AEH and endometrial cancer patients can be determined through frozen-section examination. Nevertheless, there are diverse conclusions about its accuracy as revealed in multiple studies [6, 7].

This study estimated the rates and associated risk factors of concurrent endometrial carcinoma in patients preoperatively diagnosed with AEH and assessed the role of intraoperative frozen section.

2. Patients and methods

This retrospective cohort study included 66 patients having undergone total hysterectomy after the initial histological di-

agnosis of AEH through formal diagnostic curettage or hysteroscopy at Women's Hospital School of Medicine, Zhejiang University in Hangzhou, China from January 2016 to May 2018. The data on non-surgical management of AEH was not collected. Patients enrolled in the study underwent subsequent hysterectomy with no interval treatment.

The medical history details were reviewed. Various clinical parameters were noted including age, body mass index (BMI), gravidity, parity, menopausal status, breast cancer history, hypertension, diabetes, biopsy method, CA125 (Carbohydrateantigen 125) serum levels, and endometrial thickness measured by ultrasound. Images were taken in the longitudinal planes at Fundus Uteri by experienced sonographers.

Patients were divided into two groups based on final surgical histopathology: the endometrial carcinoma (ECa) and atypical endometrial hyperplasia (AEH) groups. Data were analyzed to explore the differences between groups and assessed coexistent cancer risk in AEH along with related risk factors. Moreover, the efficacy of intra-operative frozen section was evaluated in detecting the coexistent malignant disease.

Statistical analysis was performed on SPSS software version 17 (IBM Corporation, Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation, and categorical data as medians with a range. Statistical methods such as independent-samples *t*-test, Chi-square test, and Wilcoxon Rank-Sum test were employed as appropriate. A statistically significant difference was indicated by $p < 0.05$.

3. Results

Sixty-six women diagnosed with AEH upon endometrial sampling were enrolled in this study. Table 1 depicted the demographic and clinical characteristics of these patients. The study subjects had mean age of 48.7 years, and mean parity of 1.38 children. Among them, 10 were menopausal patients, 13 had hypertension history, and 4 had breast cancer. The final diagnosis of hysterectomy was 21 patients of ECa and 45 of AEH.

Among 66 patients initially diagnosed with AEH, 21 (31.82%) had cancer post-surgery and identified as endometrioid adenocarcinoma. Out of these 21 patients, 9 were of Stage IA Grade 1 lesions, 8 of Stage IA Grade 2 lesions, 1 of Stage IA Grade 3 lesions, 1 of Stage IB Grade 3 lesions, 1 of Stage II Grade 1 lesions, and 1 of Stage II Grade 2 lesions. None of the patients had Stage III or IV carcinoma (Table 2).

Among 66 women diagnosed with AEH, the diagnosis was performed for endometrial samples obtained by operative hysteroscopy in 29 patients (43.94%), and endometrial curettage in 37 patients (56.06%). AEH coincidence rate by operative hysteroscopy (82.76%) was higher than that by endometrial curettage (56.76%). Cancer rate after the surgery as found by hysteroscopy was 17.24% (5/29), and that by endometrial curettage was 43.24% (16/37). There was a statistical difference of $p < 0.05$ (Table 3).

The frozen section examination was intraoperatively made for 46 out of 66 patients (69.70%), ECa was detected in frozen sections of 17 patients out of 46 (36.96%). Among these 17 ECa patients, 8 were detected by intraoperative frozen section examination, and the coincidence rate was 47.06% ($p < 0.05$) (Table 4).

In univariate analysis, elevated BMI (>28 kg/m^2), postmenopausal status, and increased endometrial thickness were emerged as the predictive variables for endometrial cancer as detected in final histopathology ($p < 0.05$). Factors such as age, parity, diabetes, hypertension, and CA125 serum levels were not significantly different for AEH and ECa on the final pathology ($p > 0.05$) (Table 1).

4. Discussion

The study was mainly focused on determining the concurrent carcinoma prevalence in patients diagnosed with AEH through biopsy, which was considered as the immediate precursor lesion of endometrial endometrioid carcinoma. As early as 1995, Widra EA *et al*. [8] revealed that 50% AEH patients had ECa. Furthermore, they highlighted the atypical hyperplasia being linked to the heightened risk of concurrent invasive endometrial cancer. GOG (Gynecological Oncology Group) study [9] exhibited that the rate of concurrent carcinoma with AEH was 42.6%. Giede *et al*. [10] reported 35.7% incidence. Findings herein demonstrated that concurrent carcinoma prevalence in hysterectomy cases was 31.81%. This proportion was lower than those reported by Widra [8] and GOG [9], however results were consistent with other recent reviews [11, 12]. Endometrial cancer incidence had been on the rise in China, and might be attributed to endometrial hyperplasia of atypical type. It was thus crucial to consider that AEH was linked to an elevated risk of concurrent ECa while making clinical decisions for AEH patients.

In this study, AEH cases with coexistent ECa exhibited prognostic features of high prevalence for histologic grades 1 and 2 and infrequent myometrial invasion or cervical involvement. None of malignant cases showed serosal invasion or involvement of ovaries, fallopian tubes, or omentum, and all were classified as type I carcinoma. Tadashi Kimura *et al*. [13] demonstrated that 9 patients (27.2%) had endometrioid adenocarcinoma among 33 patients subjected to abdominal hysterectomy due to initial diagnosis of either complex or simple atypical hyperplasia. All 9 cases had well-differentiated carcinoma (Grade 1), while the superficial myometrial invasion was detected in 3. These results corroborated the previous studies [14], which depicted less advanced disease and favorable prognostic features of carcinoma diagnosed after AEH. The findings herein provided evidence of confidently managing the prognosis for these patients.

In this study, a progressive association was observed between the old age, particularly postmenopausal in AEH patients, and higher probability of coexisting endometrial cancer. The underlying physiological basis in older individuals might be attributed to immunosenescence as characterized by the declining immune function over time. Based on this study outcomes, obesity was another factor linked to concurrent ECa in AEH patients. The impact of obesity was documented as 1.6-fold heightened risk of developing endometrial cancer with each 5 kg/m^2 increase in BMI [15]. The biological mechanisms of these effects were multifaceted, particularly accentuated in postmenopausal women where adipose tissue

TABLE 1. Patient characteristics according to final histopathology.

Characteristics	All patients (n = 66)	ECa Patients (n = 21)	AEH Patients (n = 45)
Mean (SD) age (yr)	48.66 (5.78)	51.19 (6.30)	47.33 (5.32)
Mean gravidity	2.53	2.46	2.38
Mean parity	1.38	1.38	1.39
Mean (SD) BMI (kg/m^2)	24.25 (3.66)	24.41 (3.17)	24.05 (3.95)
Diabetes	4	2	2
HBP	13	9	4
Age of menarche	14.95	15.14	14.84
Mean (SD) CA125 serum levels (U/mL)	18.89 (1.34)	15.14 (1.81)	20.84 (1.40)
BMI ≥28 (kg/m^2)	8	5*	3
Mean endometrial thickness (mm)	12.50	15.45*	11.87
Menopausal women	10	5*	5
Breast cancer history	4	1	3

*AEH: atypical endometrial hyperplasia; BMI: body mass index; HBP: high blood pressure; ECa: endometrial carcinoma; SD: standard deviation; CA: Carbohydrateantigen. *: $p < 0.05$ when ECa patients compared to AEH depending on final diagnosis.*

TABLE 2. Characteristics of endometrial cancer diagnosed in final histopathology.

	No.	Percentage (%)
Endometrioid adenocarcinoma	21	
FIGO stage IA	18	85.71
No myometrial infiltration	10	
Superficial myometrial infiltration	8	
IB	1	4.76
II	2	9.53
Grade		
G1	10	47.62
G2	9	42.86
G3	2	9.52

FIGO: Federation International of Gynecology and Obstetrics.

TABLE 3. Diagnostic coincidence rate by biopsy.

	AEH	ECa	AEH Coincidence	ECa Incidence	*p*
Endometrial curettage	21	16	56.76	43.24	0.02
Hysteroscopy	24	5	82.76	17.24	

AEH: atypical endometrial hyperplasia; ECa: endometrial carcinoma.

TABLE 4. Frozen section diagnoses versus final histopathology regarding the presence or absence of endometrial cancer.

Frozen section diagnosis (n = 46)	Final pathology result (n)		Total
	No ECa	ECa	
No ECa	29	9	38
ECa	0	8	8
Total	29	17	46

ECa: endometrial carcinoma.

served as the source of circulating estrogen. Estrogen acted as growth factor for endometrial tissue, triggering gene transcription that fostered endometrial proliferation [16]. Transvaginal sonography was the major non-invasive diagnostic technique for detecting endometrial abnormalities including increased endometrial thickness. Studies revealed that measuring endometrial thickness through transvaginal gray-scale sonography distinguished the carcinoma from benign pathological lesions [17]. A thin (<4–5 mm) endometrial measurement on transvaginal sonography could rule out malignancy in most women experiencing postmenopausal vaginal bleeding. In this study, a disparity in endometrial thickness was evident between the patients diagnosed with endometrial carcinoma and endometrial hyperplasia. Therefore, endometrial thickness was an indicator to differentiate AEH and malignant endometrial disease. This study affirmed that AEH and ECa occurrence should be suspected in elderly or obese women with abnormal uterine bleeding and thick endometrium.

There was a subset of patients diagnosed with AEH through biopsy who had concurrent endometrial cancer. The challenge was how to identify these patients. The intraoperative frozen section examination of hysterectomy specimen could be adapted for the surgical management of AEH women. However, the data were scarce regarding the role of intraoperative frozen section examination in decision-making process of gynecologist [18]. In this study, frozen section examination was conducted for 48 out of 66 patients (72.73%), indicative of increased awareness among clinicians of our hospital regarding the prevalence of concurrent ECa in AEH patients and the efficacy of frozen section examination as diagnostic tool. Frozen section examination identified 35.42% of these co-existent endometrial cancers. However, Indermaur's findings [18] revealed that frozen section diagnosis for complex atypical hyperplasia (CAH) and adenocarcinoma had accuracy rates of 50% and 65%, respectively, rendering it unreliable for definitive management decisions and counseling patients and families during the postoperative period. Moreover, frozen section analysis was a limited predictor for ruling out cancer (negative predictive value of 60%) in surgeons' decisions on ovarian preservation during surgery in premenopausal CAH women. This study revealed that frozen section evaluation could not exclude the possibility of co-existent endometrial cancer. Therefore, constraints of intraoperative frozen section should be communicated to the patient before making preoperative clinical decisions.

Preoperative evaluation of abnormal uterine bleeding involved obtaining an endometrial tissue sample through either endometrial biopsy performed with Pipelle aspiration catheter, and hysteroscopy (HSC), or dilatation and curettage (D&C). The latter two procedures were often employed in China. However, D&C accuracy in diagnosing AEH and excluding concurrent carcinoma compared to hysteroscopy remained uncertain. A study [19] provided evidence that hysteroscopy might not be proficient in diagnosing hyperplasia. Similarly, a report suggested that hysteroscopy was suitable for evaluating benign endometrial lesions like endometrial polyps and submucosal myomas, however its diagnostic validity for endometrial hyperplasia was limited. Around 60% D&C specimens had sampled less than half of uterine cavity. A retrospective series from single institution revealed that using D&C for diagnosing endometrial intraepithelial neoplasia was less likely to miss cancer (observed in subsequent hysterectomy) compared to endometrial suction curette (27% *vs.* 46%, respectively). Hysteroscopy with directed biopsy had greater sensitivity than D&C in diagnosing uterine lesions [20]. Results of this study depicted significant statistical difference between the groups underwent operative hysteroscopy and endometrial curettage. This difference might be attributed to hysteroscopy providing direct visualization of entire uterine cavity and assisting in the biopsy of suspected lesions that could be overlooked in D&C. The findings from previous studies [21, 22] and this research underscored the significance of recommending hysteroscopy for suspected endometrial lesions patients.

This study had several strengths. First, the limitations of intraoperative frozen section were clarified in judging AEH patients co-existent with endometrial cancer. Second, the role of hysteroscopy was clarified in the diagnosis of suspected endometrial hyperplasia and carcinoma. The high risk factors of co-existent endometrial cancer combined with endometrial carcinoma were identified. This study had certain constraints such as the study's limited sample size and retrospective nature. Moreover, AEH was not categorized into simple and complex subtypes. Further studies should encompass these limitations.

5. Conclusions

Patients diagnosed with AEH exhibited relatively high ECa incidence accompanied by less advanced disease and conducive prognostic features. Advanced age particularly the post-menopausal status, BMI >28 kg/m^2, and endometrial thickening were sequentially linked to the elevated risks of harboring concurrent endometrial cancer. Incorporating intraoperative evaluation of hysterectomy specimen into surgical management through frozen section examination in AEH cases might be beneficial for clinical decision. Furthermore, hysteroscopy was recommended to the patients with suspected endometrial lesions.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

YJC, YSF and YAX—designed the research study. YJC—performed the research and analyzed the data. YSF and RHK—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by Zhejiang University Institutional Review Board (PRO2020-37). All patients gave their informed consent to participate in the study, and Institutional Review

Board approval was obtained.

ACKNOWLEDGMENT

We thank the Women's Hospital School of Medicine Zhejiang University for providing us with so many cases.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, *et al*. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International Journal of Cancer. 2019; 144: 1941–1953.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021; 71: 209–249.

[3] Nees LK, Heublein S, Steinmacher S, Juhasz-Böss I, Brucker S, Tempfer CB, *et al*. Endometrial hyperplasia as a risk factor of endometrial cancer. Archives of Gynecology and Obstetrics. 2022; 306: 407–421.

[4] Barakat A, Ismail A, Chattopadhyay S, Davies Q. Endometrial cancer incidence in patients with atypical endometrial hyperplasia according to mode of management. Cancer Diagnosis & Prognosis. 2022; 2: 564–568.

[5] Ring KL, Mills AM, Modesitt SC. Endometrial hyperplasia. Obstetrics & Gynecology. 2022; 140: 1061–1075.

[6] Sullivan MW, Philp L, Kanbergs AN, Safdar N, Oliva E, Bregar A, *et al*. Lymph node assessment at the time of hysterectomy has limited clinical utility for patients with pre-cancerous endometrial lesions. Gynecologic Oncology. 2021; 162: 613–618.

[7] Morotti M, Menada MV, Moioli M, Sala P, Maffeo I, Abete L, *et al*. Frozen section pathology at time of hysterectomy accurately predicts endometrial cancer in patients with preoperative diagnosis of atypical endometrial hyperplasia. Gynecologic Oncology. 2012; 125: 536–540.

[8] Widra EA, Dunton CJ, McHugh M, Palazzo JP. Endometrial hyperplasia and the risk of carcinoma. International Journal of Gynecological Cancer. 1995; 5: 233–235.

[9] Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ, *et al*. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia. Cancer. 2006; 106: 812–819.

[10] Giede KC, Yen T, Chibbar R, Pierson RA. Significance of concurrent endometrial cancer in women with a preoperative diagnosis of atypical endometrial hyperplasia. Journal of Obstetrics and Gynaecology Canada. 2008; 30: 896–901.

[11] Erdem B, Aşıcıoğlu O, Seyhan NA, Peker N, Ülker V, Akbayır Ö. Can concurrent high-risk endometrial carcinoma occur with atypical endometrial hyperplasia? International Journal of Surgery. 2018; 53: 350–353.

[12] Gao Y, Zhao M, Dai X, Tong M, Wei J, Chen Q. The prevalence of endometrial cancer in pre- and postmenopausal Chinese women. Menopause. 2016; 23: 884–887.

[13] Kimura T, Kamiura S, Komoto T, Seino H, Tenma K, Ohta Y, *et al*. Clinical over- and under-estimation in patients who underwent hysterectomy for atypical endometrial hyperplasia diagnosed by endometrial biopsy: the predictive value of clinical parameters and diagnostic imaging. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2003; 108: 213–216.

[14] Rakha E, Wong SC, Soomro I, Chaudry Z, Sharma A, Deen S, *et al*. Clinical outcome of atypical endometrial hyperplasia diagnosed on an endometrial biopsy: institutional experience and review of literature. American Journal of Surgical Pathology. 2012; 36: 1683–1690.

[15] Matsuo K, Ramzan AA, Gualtieri MR, Mhawech-Fauceglia P, Machida H, Moeini A, *et al*. Prediction of concurrent endometrial carcinoma in women with endometrial hyperplasia. Gynecologic Oncology. 2015; 139: 261–267.

[16] Pu H, Wen X, Luo D, Guo Z. Regulation of progesterone receptor expression in endometriosis, endometrial cancer, and breast cancer by estrogen, polymorphisms, transcription factors, epigenetic alterations, and ubiquitin-proteasome system. The Journal of Steroid Biochemistry and Molecular Biology. 2023; 227: 106199.

[17] Capozzi VA, Rosati A, Rumolo V, Ferrari F, Gullo G, Karaman E, *et al*. Novelties of ultrasound imaging for endometrial cancer preoperative workup. Minerva Medica. 2021; 112: 3–11.

[18] Indermaur MD, Shoup B, Tebes S, Lancaster JM. The accuracy of frozen pathology at time of hysterectomy in patients with complex atypical hyperplasia on preoperative biopsy. American Journal of Obstetrics and Gynecology. 2007; 196: e40–e42.

[19] Ben-Yehuda OM, Kim YB, Leuchter RS. Does hysteroscopy improve upon the sensitivity of dilatation and curettage in the diagnosis of endometrial hyperplasia or carcinoma? Gynecologic Oncology. 1998; 68: 4–7.

[20] Bedner R, Rzepka-Górska I. Hysteroscopy with directed biopsy versus dilatation and curettage for the diagnosis of endometrial hyperplasia and cancer in perimenopausal women. European Journal of Gynaecological Oncology. 2007; 28: 400–402.

[21] De Rocco S, Buca D, Oronzii L, Petrillo M, Fanfani F, Nappi L, *et al*. Reproductive and pregnancy outcomes of fertility-sparing treatments for early-stage endometrial cancer or atypical hyperplasia: a systematic review and meta-analysis. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2022; 273: 90–97.

[22] Vitale SG, Riemma G, Carugno J, Chiofalo B, Vilos GA, Cianci S, *et al*. Hysteroscopy in the management of endometrial hyperplasia and cancer in reproductive aged women: new developments and current perspectives. Translational Cancer Research. 2020; 9: 7767–7777.

How to cite this article: Yin-Juan Chang, Yong-Shen Fan, Reshmi Hareendra Kariyapperuma, Yong-An Xu. Predictive factors of concurrent endometrial carcinoma and the role of frozen section in patients with preoperative diagnosis of atypical endometrial hyperplasia. European Journal of Gynaecological Oncology. 2024; 45(3): 16-20. doi: 10.22514/ejgo.2024.044.