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Endometrial carcinoma in Chinese postmenopausal women with atypical endometrial hyperplasia

Ling Yin TSANG, MBBS, MRCOG. MHKCOG
Keedon WONG, MBBS, MRCOG, FHKAM (O&G)
Ares Yui Shing CHEUNG, MBBS, MRCOG, FHKAM (O&G)
Assumpta Sze Man WONG, MBBS, MRCOG, FHKAM (O&G)
Wai Hon LI, MBBS, MRCOG, FHKAM (O&G)
Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Hong Kong SAR, China

Objectives: To determine the risk factors and the rate of endometrial carcinoma (EC) among Chinese postmenopausal women with atypical endometrial hyperplasia (AEH).
Methods: We retrospectively reviewed medical records of Chinese postmenopausal women with AEH who underwent endometrial biopsy (using pipelle) or curettage between 1 January 2012 and 31 December 2023 at the Queen Elizabeth Hospital. Postmenopausal women with a final diagnosis of AEH or EC were compared to determine the risk factors for EC.
Results: In total, 45 Chinese postmenopausal women with AEH underwent hysterectomy and bilateral salpingo-oophorectomy. Of these, 15 (33.3%) underwent additional pelvic lymph node dissection with or without para-aortic lymph node dissection or subdiaphragmatic scraping, based on preoperative imaging findings (n=10) or intra-operative findings (n=5). All these 15 patients had a histopathological diagnosis of EC. Of the 45 patients, 11 and 34 had a histopathological diagnosis of AEH and EC, respectively. The final diagnosis of EC was not associated with age, body mass index, parity, hypertension, diabetes, or hyperlipidaemia in postmenopausal women with AEH.
Conclusion: Of 45 Chinese postmenopausal women with AEH, 75.6% had a final diagnosis of EC and 24.4% required lymph node dissection in addition to hysterectomy and bilateral salpingo-oophorectomy. In selected patients, preoperative imaging and referral to a gynaecological oncologist for tumour staging may be necessary for optimal treatment outcomes.

Keywords: Endometrial hyperplasia; Endometrial neoplasms; Lymph node excision; Menopause; Neoplasm staging

Background

Endometrial carcinoma (EC) is the fourth most common cancer among women in Hong Kong[1]. Its most common form is endometrioid EC, which typically develops from endometrial hyperplasia. Atypical endometrial hyperplasia (AEH) is characterised by abnormal cellular changes; the cells within the glands exhibit varying degrees of atypia including nuclear enlargement, pleomorphism, and increased mitotic activity. As the disease progresses, the cells may resist the normal hormonal regulatory mechanisms. This leads to uncontrolled cellular proliferation and differentiation and carcinoma development. In EC, the malignant cells acquire invasive properties and infiltrate the basement membrane and surrounding tissues. Lymphovascular invasion can occur, resulting in the spread of cancer cells to regional lymph nodes and distant sites.

Risk factors associated with the development of EC and AEH include age, body mass index, parity, hypertension, and diabetes, regardless of menopausal status. Nonetheless, postmenopausal status is a predictor for postoperative diagnosis of EC; 33.5 to 85% of postmenopausal women with AEH have a postoperative diagnosis of EC.[2-8]. In women with AEH, the risk of progression to malignancy is 30% and the risk of concomitant EC is 40% to 50%[3].

The Royal College of Obstetricians and Gynaecologists/British Gynaecological Cancer Society[9] and Hong Kong College of Obstetricians and Gynaecologists[10] guidelines suggest total hysterectomy as the first-line treatment for endometrial hyperplasia. In postmenopausal women, bilateral salpingo-oophorectomy is recommended. Routine lymphadenectomy is not necessary because the risk of concomitant advanced-stage cancer of the uterine corpus is extremely low. However, the risk of advanced-stage EC in postmenopausal patients with AEH was higher than expected (Table 1)[2-8]. Therefore, we aimed to determine the

Correspondence to: Dr Ling Yin TSANG
Email address: vt062@yahoo.com.hk

Table 1. Studies of women with atypical endometrial hyperplasia and the rate of endometrial carcinoma (EC)

Study	No. of patients	% of patients with EC	No. of postmenopausal women	% of postmenopausal women with EC
Non-Asian population				
Xie et al,[2] 2002	86	38.0	19	58.0
Trimble et al,[3] 2012	289	43.0	-	
Kadirogullari et al,[4] 2015	40	33.0	23	56.5
Giannella et al,[5] 2023	629	30.7	427	33.5
Asian population				
Kimura et al,[6] 2003	33	27.0	10	50.0
Yau et al,[7] 2010	62	45.0	13	85.0
Lou et al,[8] 2021	624	30.4	118	49.0

risk factors and the rate of EC in postmenopausal Chinese women with AEH.

Methods

We retrospectively reviewed medical records of Chinese postmenopausal women with AEH who underwent endometrial biopsy (using pipelle) or curettage between 1 January 2012 and 31 December 2023 at the Queen Elizabeth Hospital. Patients who were lost to follow-up or refused surgery were excluded.

Data collected included age at diagnosis, body mass index, parity, menopausal status, drinking and smoking habits, family history, hypertension, diabetes, hyperlipidaemia, history of polycystic ovarian syndrome, use of exogenous hormones, and use of tamoxifen.

Ultrasonography of the pelvis was performed through the transabdominal, transvaginal, or transrectal route. Magnetic resonance imaging of the pelvis was routinely advised. Hysterectomy with bilateral salpingo-oophorectomy was performed using the laparotomy or laparoscopic approach. Additional surgical procedures (pelvic and para-aortic lymph node dissection, peritoneal biopsy, and subdiaphragmatic scraping) were performed in selected patients, based on preoperative imaging or intra-operative findings of myometrial invasion of >50% and suspected lymph node and peritoneal involvement. Histopathological features were recorded, including the histology type, tumour grading, presence of lymphovascular space invasion, depth of myometrial invasion, cervical stromal involvement, and adnexal involvement. The International Federation of Gynecology and Obstetrics staging was used, based on imaging, intra-operative, and histopathological findings.

Data were analysed using SPSS (Windows version 22.0; IBM Corp, Armonk [NY], Unites States). The incidence of EC in postmenopausal women with AEH was calculated. Postmenopausal women with a final diagnosis of AEH or EC were compared using the Chi-squared test for categorical variables and the Fisher's exact test for continuous variables to determine the risk factors for EC.

Results

Of 112 patients diagnosed with AEH during the study period, 54 were postmenopausal. Of these, nine were excluded because of they were non-Chinese (n=2), lost to follow-up or refused surgery (n=4), or refused surgery owing to advanced age and medical comorbidities (n=3).

Among 45 patients who underwent hysterectomy and bilateral salpingo-oophorectomy, the mean duration from diagnosis to operation was 11 (range, 4-20) weeks. The diagnosis was made based on curettage (n=13) or bedside endometrial aspirate (n=32). All patients underwent an ultrasound examination; 39 (87%) of patients underwent additional magnetic resonance imaging (n=35) or computed tomography/positron emission tomography (n=4). Of these 39 patients, six had myometrial invasion of >50% and four had lymph node involvement; the remaining 29 patients had no or <50% myometrial invasion.

Of the 45 patients, 15 (33.3%) underwent additional pelvic lymph node dissection. Of these, five also underwent

para-aortic lymph node dissection and two also underwent subdiaphragmatic scraping. Indications for additional surgical procedures were based on preoperative imaging findings of myometrial invasion of >50% or suspected lymph node involvement (n=10) or intra-operative findings of myometrial invasion of >50% (n=4) or omental nodule (n=1). All these 15 patients had a histopathological diagnosis of EC. Postoperatively, 13 of these patients received adjuvant therapy. Of these, two had grade IAG1 tumour, one had lymphovascular invasion, and one had double primary of poorly differentiated Sertoli-Leydig cell tumour. No patients required a second surgery.

Of the 45 patients, 11 and 34 had a histopathological diagnosis of AEH and EC, respectively. The grades of the 34 cases of EC were IA (n=22), IB (n=6) [both were defined as <5% of non-squamous or non-morular solid growth pattern], II (n=1), IIIC1 (n=2), IIIC2 (n=1), IVB (n=1), and missing data (n=1).

The final diagnosis of EC was not associated with age, body mass index, parity, hypertension, diabetes, or hyperlipidaemia in postmenopausal women with AEH (Table 2).

Discussion

Among 45 postmenopausal women with AEH, 34 (75.6%) had a final diagnosis of EC. The tumour grade of 11 (24.4%) patients was at least grade IB, for which additional lymph node dissection was needed. Considering the higher rate of occult EC in postmenopausal women, the current guidelines on the management of AEH might not be adequate for these high-risk patients.

Postmenopausal status is a predictor for EC[5,8], because of the shift of the balance of hormones towards more oestrogen. Postmenopausal status is a hypo-oestrogenic condition. Oestrogen from the adipose tissue has greater impact after menopause, as production of oestrogen and progesterone from the ovaries stops. Hypo-oestrogenic status is a protective factor for endometrial pathology. However, in postmenopausal women with AEH, the grade

Table 2. Risk factors associated with endometrial carcinoma in postmenopausal women with atypical endometrial hyperplasia

Variable	No. (%) of patients with a final diagnosis of		95% confidence interval	p Value
	Atypical endometrial hyperplasia	Endometrial cancer		
Age, y				
≤60 (n=25)	8 (32.0)	17 (68.0)	Reference	
61-70 (n=15)	1 (6.7)	14 (93.3)	0.73-59.2	0.117
>71 (n=5)	2 (40.0)	3 (60.0)	0.1-5.1	1.0
Body mass index, kg/m^2				
<23 (n=7)	3 (42.9)	4 (57.1)	Reference	
23-25 (n=13)	1 (7.7)	12 (92.3)	0.7-113.0	0.10
>25 (n=25)	7 (28.0)	18 (72.0)	0.34-10.9	0.648
Parity				
Nulliparous (n=14)	3 (21.4)	11 (78.6)	Reference	
Multiparous (n=31)	8 (25.8)	23 (74.2)	0.17-3.5	1.0
Hypertension				
Yes (n=23)	6 (26.1)	17 (73.9)	0.2-3.3	1.0
No (n=22)	5 (22.7)	17 (77.3)	Reference	
Diabetes				
Yes (n=9)	0	9 (100.0)	0.56-0.86	0.087
No (n=36)	11 (30.6)	25 (69.4)	Reference	
Hyperlipidaemia				
Yes (n=20)	5 (25.0)	15 (75.0)	0.24-3.71	0.94
No (n=25)	6 (24.0)	19 (76.0)	Reference	

of EC was more invasive. Grade I endometrioid carcinoma in older women is more aggressive than that in younger women; old age is a predictor for shorter progression-free survival[11]. The underlying pathophysiology is unclear; confounding factors such as age, obesity, and medical comorbidities (metabolic syndrome) may be involved. In our postmenopausal women with AEH, EC was not associated with age, body mass index, parity, hypertension, diabetes, or hyperlipidaemia, probably owing to the small sample size.

According to the guidelines of The Royal College of Obstetricians and Gynaecologists/British Gynaecological Cancer Society and Hong Kong College of Obstetricians and Gynaecologists, in patients with AEH or early EC, routine pelvic and para-aortic lymphadenectomy is not recommended because only 10% of patients with AEH have myometrial invasion of >50% (ie, grade IB tumour) and no patient has grade II, III, or IV EC[3]. However, our study showed a higher rate of advanced-stage EC in postmenopausal women with AEH. Of the 45 patients, 11 (24.4%) had at least grade IB tumour. In one study, 28% of women with grade III EC and stage I outer myometrial invasion have lymph node involvement[9]. According to the International Federation of Gynecology and Obstetrics staging guidelines, patients with more than grade IA EC should undergo imaging for distant metastases and surgical staging such as lymph node dissection.

Complications associated with lymphadenectomy include lymphocoele formation, lymphoedema, and vascular, nerve, and ureteric injuries. Routine lymphadenectomy may lead to over-treatment and unnecessary surgical risks. A second surgery for tumour staging introduces additional risks associated with anaesthesia, surgery, and delay in initiating adjuvant therapy, particularly in public hospitals. Therefore, patient selection is important to minimise the need for a second surgery for tumour staging.

To reduce over-staging or under-staging of EC, preoperative imaging and intra-operative frozen section analysis are viable tools to guide surgical decision for additional lymphadenectomy and help minimise the risks associated with unnecessary surgical procedures. Re-sampling or hysteroscopically targeted biopsy should be considered in cases of preoperative imaging suspicious of invasive carcinoma.

In postmenopausal women with AEH, we recommend performing preoperative imaging to identify a suspected advanced-stage EC, for which input from gynaecological oncologists is needed. Comprehensive evaluation enables informed decision making and counselling, outcome optimisation, and reduction of the need for a second surgery for staging.

One limitation of our study was the small sample size from a single hospital. Chinese postmenopausal women with AEH are at higher risk of EC, which might be under-treated and under-staged in a primary surgery, given that the current guidelines are not specifically for Chinese postmenopausal women with AEH.

Conclusion

Of 45 Chinese postmenopausal women with AEH, 75.6% had a final diagnosis of EC and 24.4% required lymph node dissection in addition to hysterectomy and bilateral salpingo-oophorectomy. In selected patients, preoperative imaging and referral to a gynaecological oncologist for tumour staging may be necessary for optimal treatment outcomes.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. The authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have no conflicts of interest to disclose.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Kowloon Central/Kowloon East Cluster Research Ethics Committee (reference: KC/KE-23-0073/ER-2). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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