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Original Article

Progression of endometrial hyperplasia: a revisit under the 2014 WHO classifications

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Abstract: 273 patients diagnosed with endometrial hyperplasia from 1999-2001 at our institution were classified using the 1994 and 2014 WHO criteria. By 1994 criteria: 189 patients had simple hyperplasia (SH), 8 had simple hyperplasia with atypia (SHA), 23 had complex hyperplasia (CH), and 53 had complex hyperplasia with atypia (CHA). By 2014 criteria: 212 patients had benign endometrial hyperplasia (BEH) and 61 patients had atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia (AEH/EIN). The primary endpoint was development of endometrioid carcinoma. With a median follow-up of 5.2 years, progression to endometrioid carcinoma occurred in 1.6% of patients with SH, 25% with SHA, 4.3% with CH, 24.5% with CHA, 1.9% with BEH and 24.5% with AEH. In patients that did not undergo hysterectomy for at least 1-year, 20% with AEH and 2.6% with BEH progressed to carcinoma. Patients with CHA had a shorter endometrioid carcinoma free survival time (EFS) than patients with SH ($P < 0.0001$) but was not different from SHA ($P = 0.78$) or CH ($P = 0.02$) after correction for multiple comparisons. Patients with SHA had a shorter EFS than patients with SH ($P < 0.0001$) but was not different from CH ($P = 0.12$). Patients with SH did not have a shorter EFS than patients with CH ($P = 0.30$). Median EFS was shorter in patients with AEH (10.9 years) than patients with BEH (16.3 years, HR = 0.08, 95% CI: 0.008 to 0.08, $P < 0.0001$). While confirming the diagnostic validity of both schemes, our data support the emphasis on cytological atypia by the two-tiered 2014 WHO classification.

Keywords: Endometrial hyperplasia, progression, WHO classification

Introduction

Atypical endometrial hyperplasia is a pre-neoplastic condition that proceeds to the most common uterine malignancy, endometrioid adenocarcinoma (Type 1 endometrial cancer, 70-80% of endometrial cancer) [1]. While established criteria using combined evaluation of cytological and architectural abnormalities for histological classification of endometrial hyperplasia have been used since the mid 80's, recent investigations have resulted in significant discussion of the overall clinical relevance for each subcategory of endometrial hyperplasia [2, 3]. Moreover, the evolving concept of endometrial intraepithelial neoplasia or EIN has enhanced our understanding of the molecular basis for the development of endometrioid adenocarcinoma [4].

In 2014, the World Health Organization (WHO) introduced the updated classification scheme for endometrial hyperplasia that has 2 categories: benign endometrial hyperplasia (BEH), and atypical endometrial hyperplasia (AEH)/endometrioid intraepithelial neoplasia (EIN) [5]. The defining feature of the 2014 classification scheme is the presence (AEH/EIN) or absence (BEH) of cytological atypia superimposed on a background of endometrial hyperplasia. The previous 1994 WHO classification scheme, primarily based on Kurman's seminal study in 1985, uses both architectural and cytological abnormalities to classify the endometrial hyperplasia into 4 categories: simple hyperplasia (SH), simple hyperplasia with atypia (SHA), complex hyperplasia (CH), and complex hyperplasia with atypia (CHA), which assessed both cytological atypia and architectural complexity [2]. In light of the new WHO classification, it becomes necessary to compare the two schemes in a large study cohort with a long-term clinical follow-up. In this retrospective study, the prognostic values of the 1994 and

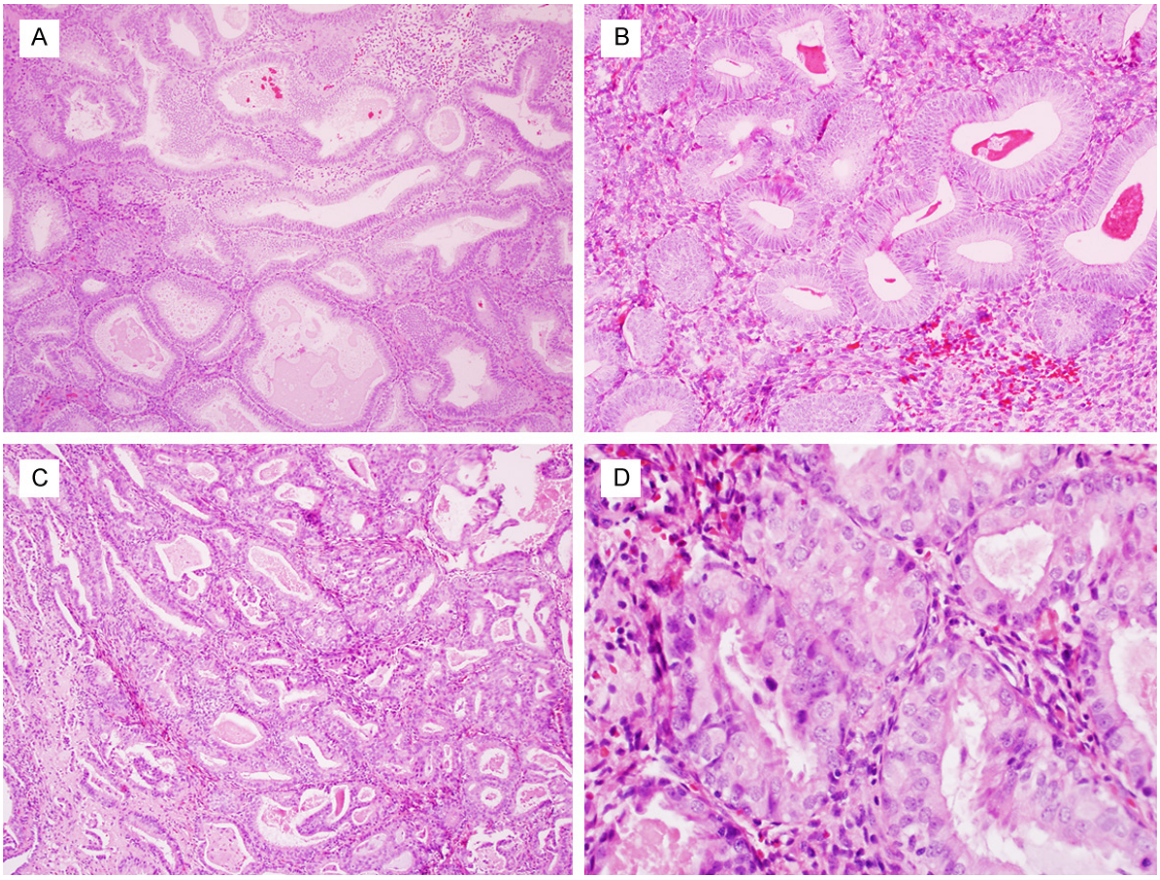

Figure 1. Representative histological presentations of endometrial lesions. A. Benign endometrial hyperplasia (BEH) by 2014 WHO classification/simple hyperplasia without atypia by 1994 WHO criteria. B. Atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia (AEH/EIN) by 2014 WHO classification/complex atypical hyperplasia by 1994 WHO criteria. C. Cytological/nuclear atypia in AEH/EIN. D. Well differentiated endometrioid adenocarcinoma, FIGO architectural grade 1.

2014 classifications of endometrial hyperplasia were compared in 273 patients consecutively diagnosed with endometrial hyperplasia at a single tertiary medical center.

Materials and methods

Study cohort

This retrospective cohort study included patients diagnosed with endometrial hyperplasia consecutively accessioned at our institution from 1999-2001 by endometrial biopsy or curettage. Eligible specimens were reviewed by three authors and categorized using the 1994 and 2014 WHO classifications for endometrial hyperplasia. All available subsequent endometrial biopsies and hysterectomy specimens were also reviewed. A total of 273 cases were eventually included in the study. The number of slides of each curettage ranged 1 to 9 with a median of 3. Follow-up endometrial sampling was available in 227 cases including curettage in 203 patients, and hysterectomy in 87 patients. Slides of the hysterectomy were reviewed in 34 cases, including all cases that had atypical endometrial hyperplasia or endometrioid carcinoma.

Study design

This retrospective study was designed to assess the differences in disease progression and endometrioid carcinoma-free survival between women with endometrial hyperplasia diagnosed using the 1994 WHO four category scheme and 2014 WHO two tiered classification.

Follow-up evaluation

All patients with at least 2 endometrial samples were assessed for regression, persistence,

Table 1. Characteristics of patients eventually diagnosed with endometrioid carcinoma (N = 19)

Initial Diagnosis of Hyperplasia	Age at Initial Diagnosis	Age at Carcinoma Diagnosis	Endometrioid Carcinoma Free Survival Time*	FIGO Architectural and Nuclear Grade	Carcinoma Diagnosed on Hysterectomy
SH/BEH	45	49	3 y 9 mo 17 d	F1N1	NO
	56	72	16 y 3 mo 24 d	F1N1	YES
	70	77	6 y 11 mo 29 d	F2N2	NO
CH/BEH	64	64	24 d	F1N2	NO
SHA/AEH	55	59	3 y 8 mo 19 d	F1N2	NO
	72	72	1 mo 2 d	F1N2	NO
CAH/AEH	48	48	8 mo 18 d	F1N1	YES
	50	50	2 mo 18 d	F1N1	YES
	51	51	1 mo 18 d	F1N2	YES
	54	54	1 mo 3 d	F1N1	YES
	54	55	4 mo 16 d	F1N2	NO
	56	56	3 mo 17 d	F1N1	NO
	56	56	2 mo 25 d	F1N1	YES
	59	61	2 y 3 mo 21 d	F1N2	NO
	60	60	1 mo 9 d	F1N2	NO
	62	62	4 mo 2 d	F1N1	NO
	69	80	10 y 11 mo 11 d	F1N2	YES
	70	74	4 y 5 mo 24 d	F1N1	NO
	78	78	1 mo 3 d	F1N1	NO

*Endometrioid carcinoma-free survival time is the duration between the initial diagnosis and the first carcinoma diagnosis by either curettage or hysterectomy. SH-simple hyperplasia; CH-complex hyperplasia; SHA-simple hyperplasia with atypia; CAH-complex hyperplasia with atypia; BEH-benign endometrial hyperplasia and AEH-atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia.

development of atypia, and progression to carcinoma. Regression in patients initially diagnosed with BEH or AEH was defined as either: 1) normal phase endometrium in premenopausal women and inactive or atrophic endometrium in postmenopausal women on the last available follow-up biopsy or hysterectomy specimen, OR 2) patients who became clinically asymptomatic and were followed for at least 1 year. Persistence in patients initially diagnosed with BEH was defined as patients that had BEH, endometrial polyps, or disordered proliferative endometrium on last follow-up biopsy or BEH on a hysterectomy specimen. The development of atypia was defined as patients who were initially diagnosed with BEH that progressed to AEH on the last available biopsy or hysterectomy specimen. Progression to carcinoma was defined as patients that were initially diagnosed with BEH or AEH that were diagnosed with endometrioid carcinoma on any subsequent biopsy or hysterectomy specimen. The time to development of endometrioid carcinoma was the time from initial diagnosis of endometrial hyperplasia to the first diagnosis of endometrioid carcinoma by either endometrial biopsy or hysterectomy. All patients with only 1 endometrial sample were considered as having no available follow-up (see above, the second criterion of regression).

Statistical analysis

Chi-square test or Fisher's exact test for categorical variables were used to compare the differences between patient groups categorized by 1994 and 2014 WHO endometrial hyperplasia criteria. Kaplan-Meier estimates were used to compute the survival functions among patient groups and were compared using log-rank tests. Endometrioid carcinoma free survival (EFS) was defined as the time from initial endometrial hyperplasia diagnosis to endometrioid carcinoma diagnosis by either curettage or hysterectomy. Only patients with follow-up endometrial sampling were included in the analysis. Patients were censored at the time of the time of their last curettage or hysterectomy. A value of $P < 0.01$ after adjustment for multi-

Table 2. Patient characteristics and endometrioid carcinoma free survival by 1994 and 2014 WHO classifications/Kaplan-Meier analysis

Index Diagnosis	No. of Patients	Median Follow-Up (years)	Develop Endometrioid Carcinoma (n)	HR [95% CI]	Mean Age (years)	TH (n)
1994 SH	189	6.86	3 (1.5%)	1	51.4±10.3	42 (22.2%)
1994 CH	23	8.21	1 (4.3%)	2.9 [0.2 to 147.4]*	54.3±13.2	10 (43.4%)
1994 SHA	8	3.79	2 (25%)	24.1 [ND]**	52.0±11.8	3 (37.5%)
1994 CHA	53	0.88	13 (24.5%)	79.4 [21.8 to 288.6]**	56.2±9.8	32 (60.3%)
2014 BEH	212	6.98	4 (1.8%)	1	51.7±10.6	52 (24.5%)
2014 AEH/EIN	61	0.88	15 (24.5%)	39.3 [12.3 to 126.2]#	55.8±9.9	35 (57.3%)

Abbreviations: TH-total hysterectomy, EFS-endometrioid carcinoma free survival. SH-simple hyperplasia; CH-complex hyperplasia; SHA-simple hyperplasia with atypia; CAH-complex hyperplasia with atypia; BEH-benign endometrial hyperplasia and AEH/EIN-atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia. *= P < 0.05 vs. CHA, **P < 0.001 vs. SH, #= P < 0.0001 vs. BEH. ND = data points had insufficient events to estimate median EFS.

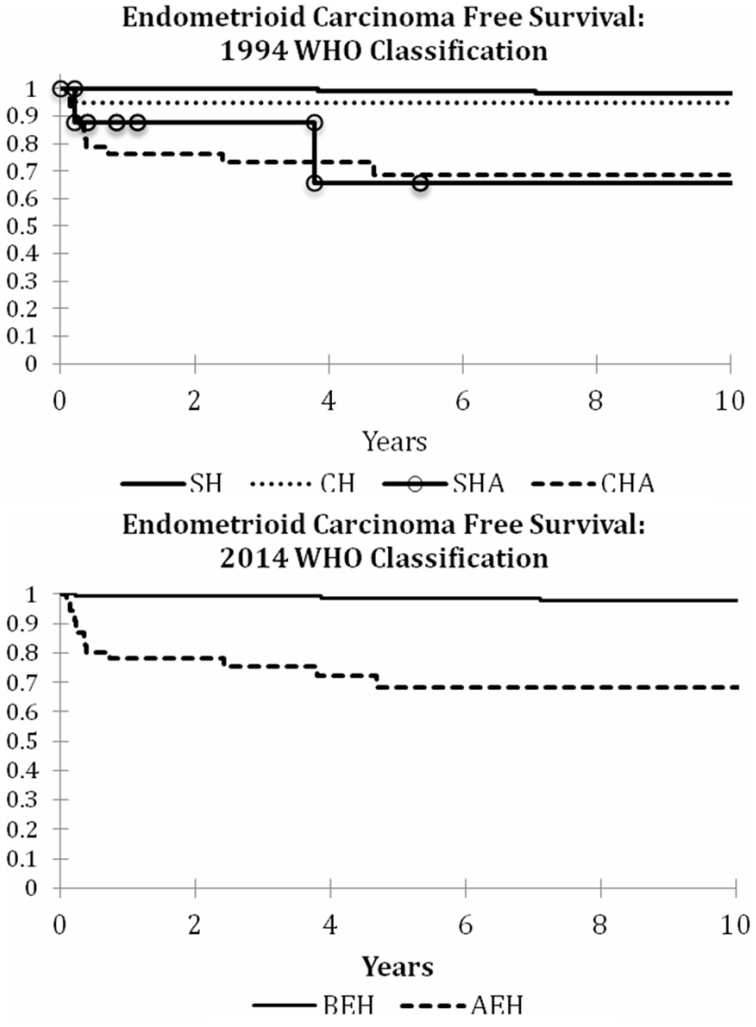

Figure 2. Endometrioid carcinoma free survival by 1994 and 2014 WHO classifications. Patients were categorized by their initial endometrial hyperplasia diagnosis using the 1994 (A) and 2014 WHO (B) criteria and endometrioid carcinoma free survival (EFS) was analyzed using Kaplan-Meier analysis. EFS is defined as the time from initial endometrial hyperplasia diagnosis to endometrioid carcinoma diagnosis by either curettage or hysterectomy. Patients were censored at the time of the time of their last curettage or hysterectomy.

ple comparisons was considered statistically significant. The Cox proportional hazards model was used to adjust for age at initial presentation. Analyses were performed using GraphPad Prism 6 for Mac OS X (GraphPad Software, Inc.) and XLSTAT for Mac OSX (Addinsoft, Inc).

Histological criteria

Simple hyperplasia is defined as diffuse abnormal glandular proliferation with balanced gland/stroma ratio without cytological atypia (**Figure 1**). The glands are abnormal in shape and size with out-pouching and branching. Complex hyperplasia shows diminished stromal component with more pronounced glandular abnormality than simple hyperplasia, and has no cytological atypia. Atypical hyperplasia (simple or complex) is defined by the presence of nuclear atypia: loss of polarity, nuclear rounding, enlargement, pleomorphism, abnormal chromatin patterns and prominent nucleoli. Benign endometrial hyperplasia is defined by the 2014 WHO classification as "an exaggerated proliferation of endometrial glands of irregular size

Table 3. Progression and persistence of endometrial hyperplasia in patients after at least 1 year of follow-up (n = 194)*

Index Diagnosis	Progress to Carcinoma (n)	Develop Atypia (n)	Persistent Hyperplasia (n)	Regression (n)	Total Cases (n)
1994 SH	3	7	40	103	153
1994 CH	0	0	3	11	14
1994 SHA	1	0	1	3	5
1994 CHA	3	0	5	14	22
2014 BEH	3	7	43	114	167
2014 AEH/EIN	4	0	6	17	27

Abbreviations: SH-simple hyperplasia; CH-complex hyperplasia; SHA-simple hyperplasia with atypia; CAH-complex hyperplasia with atypia; BEH-benign endometrial hyperplasia and AEH/EIN-atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia. *Patients were categorized by their initial endometrial hyperplasia diagnosis using the 1994 and 2014 WHO criteria and had at least 1 year of follow-up (re-biopsied at least 1 year after their initial diagnosis or patients that were clinically asymptomatic and followed by PAP smear). Patients that underwent hysterectomy less than 1 year after their initial diagnosis were excluded.

and shape, with an associated increase in the gland to stroma ratio compared with proliferative endometrium, but without significant cytological atypia". Atypical endometrial hyperplasia (AEH)/Endometrioid intraepithelial neoplasia (EIN) is defined as "cytological atypia superimposed on an endometrial hyperplasia". The separation of well-differentiated endometrioid carcinoma from AEH/EIN is based on the presence of stromal invasion characterized by one or more of the following of at least 5 mm in size: confluent glandular or cribriform pattern, complete replacement of intervening endometrial stroma by foamy macrophages; infiltrative growth with myofibroblastic or desmoplastic stromal reaction, or complex papillary architecture (villoglandular pattern).

Results

The study cohort consisted of 273 cases consecutively identified in a two-year period. According to the 1994 criteria: 189 patients were categorized as simple hyperplasia (SH), 8 as simple hyperplasia with atypia (SHA), 23 as complex hyperplasia (CH), and 53 as complex hyperplasia with atypia (CHA). According to the 2014 criteria: 212 patients were categorized as benign endometrial hyperplasia (BEH), and 61 patients as atypical endometrial hyperplasia (AEH)/endometrioid intraepithelial neoplasia (EIN). The median follow-up time was 6.9 years for patients initially diagnosed with benign endometrial hyperplasia and 325 days for patients with atypical endometrial hyperplasia. Overall, 19 patients (4 of 212 cases of BEH, 1.9% and 15 of 61 cases of AEH/EIN, 24.6%) eventually developed endometrioid adenocarcinoma and all underwent staging hysterectomy (**Tables 1** and **2**). All carcinomas except one case in the study cohort were well-differentiated FIGO architectural grade 1 endometrioid adenocarcinoma. All of the carcinomas that developed in these patients were confined to the endomyometrium and no patients had extrauterine or lymph node metastases.

Simple hyperplasia (189 patients)

The age at the time of initial diagnosis ranged from 24 to 98 years (mean = 51.4±10.3). The median number of procedures was 2 and the median follow-up time was 6.8 years (range = 0-21.6). Twenty-five patients had had at least 1 prior endometrial biopsy and 42 patients had no subsequent sampling. Forty-two patients had a hysterectomy. At the conclusion of the study: 64 patients had persistent endometrial hyperplasia, 98 patients had regressed, 7 patients had developed atypical endometrial hyperplasia, 3 patients had developed endometrioid carcinoma, and 1 patient had a hysterectomy for leiomyosarcoma.

Complex hyperplasia (23 patients)

The age at the time of initial diagnosis ranged from 25 to 77 years (mean = 54.3±13.2). The median number of procedures was 2 and the median follow-up time was 8.2 years (range = 65 days-14.4 years). Three patients had had at least 1 prior endometrial biopsy and 1 patient had no subsequent sampling. Ten patients had

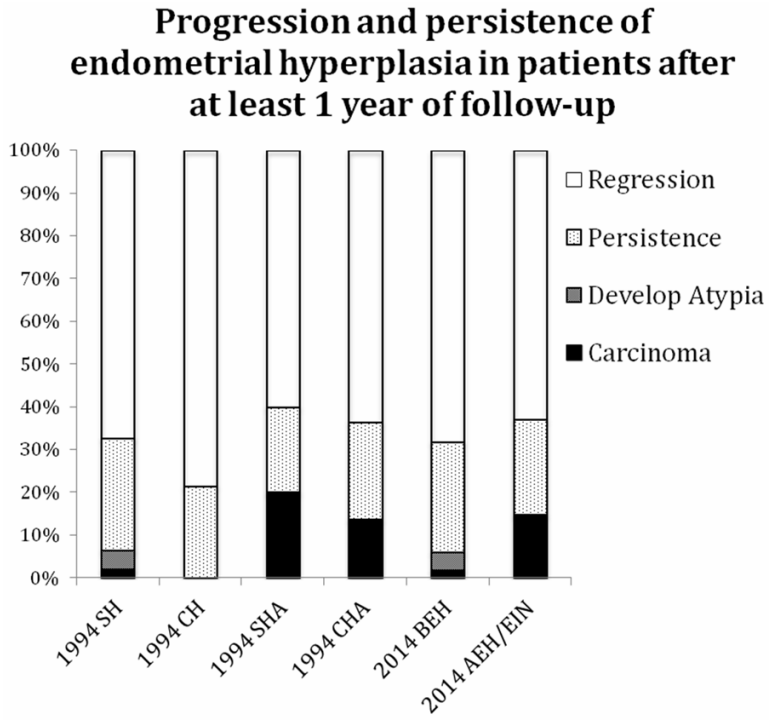

Figure 3. Progression and persistence of endometrial hyperplasia in Patients with at least 1 year of follow-up.

a hysterectomy. At the conclusion of the study: 6 patients had persistent endometrial hyperplasia, 12 patients had regressed, 2 patients had developed atypical endometrial hyperplasia, 1 patient had developed endometrioid carcinoma, and 2 patients had developed endometrial serous carcinoma.

Simple hyperplasia with atypia (8 patients)

The age at the time of initial diagnosis ranged from 34 to 68 years (mean = 52±11.8). The median number of procedures was 5 and the median follow-up time was 3.7 years (range = 77 days-16.5 years). Two patients had had at least 1 prior endometrial biopsy. Three patients had a hysterectomy. At the conclusion of the study: 2 patients had persistent atypical endometrial hyperplasia, 4 patients had regressed, and 2 patients had developed endometrioid carcinoma.

Complex hyperplasia with atypia (53 patients)

The age at the time of initial diagnosis ranged from 25 to 78 years (mean = 56.2±9.8). The median number of procedures was 2 and the median follow-up time was 321 days (range = 0-14.3 years). Eight patients had had at least 1 prior endometrial biopsy and 3 patients had no subsequent sampling. Thirty-two patients had a hysterectomy. At the conclusion of the study: 21 patients had persistent atypical endometrial hyperplasia, 15 patients had regressed, 13 patients had developed endometrioid carcinoma, and 1 patient had a hysterectomy for clear cell carcinoma. Among patients that progressed to endometrioid carcinoma, 6 of 13 were diagnosed on hysterectomy. Two of these patients had their hysterectomy less than 2 months after they were diagnosed with CHA on endometrial biopsy. One additional patient was diagnosed with endometrioid carcinoma on subsequent biopsy 33 days after the initial biopsy was diagnosed as CHA. These data suggest that 3 of 13 patients (23%) may have had concurrent endometrioid carcinoma at the time of their first CHA diagnosis.

Progression to endometrioid carcinoma using the 1994 and 2014 WHO classifications of endometrial hyperplasia

The Kaplan-Meier method and log rank test was usedto compare endometrioid carcinoma free survival (EFS) times (**Table 2** and **Figure 2**). Patients with CHA had a shorter EFS than patients with SH (Chi square = 44.2, P < 0.0001) but was not statistically different from CH (Chi square = 5.34, P = 0.02) after adjustment for multiple comparisons. The EFS in patients with CHA was not statistically different when compared to patients with SHA (Chi square = 0.07, P = 0.78). Patients with SHA had a shorter EFS than patients with SH (Chi square = 27.1, P < 0.0001) but was not statistically different from patients with CH (Chi square = 2.36, P = 0.12). The difference in EFS between SH and CH was not statistically significant (Chi square = 1.03, P = 0.30). Patients diagnosed with SH had significantly lower hysterectomy rates (22.2%) when compared with patients

diagnosed with CH (43.4%, P < 0.04), and CHA (61.3%, P < 0.0001).

Patients with AEH developed EC had a shorter EFS than patients with BEH (Chi square = 31.1, P < 0.0001). The median EFS was 5957 days in patients diagnosed with BEH and 3998 days in patients diagnosed with AEH. Patients diagnosed with AEH were 98% more likely to progress to EC (HR = 0.02; 95% CI, 0.007 to 0.08, P < 0.0001). Age at initial presentation was a significant predictor of endometrioid carcinoma free survival (HR = 1.065; 95% CI, 1.012 to 1.12, P = 0.015) and the hazard ratios were adjusted using Cox regression. In multivariate analysis, patients diagnosed with AEH were 94% more likely to progress to EC (HR = 0.06; 95% CI, 0.02 to 0.19, P < 0.0001).

Endometrial hyperplasia progression to carcinoma, regression, and development of atypia among patients with at least 1 year of follow-up

194 patients had at least 1 year of follow-up and did not undergo hysterectomy in the first year after their initial diagnosis (**Table 3** and **Figure 3**). Of the 153 patients initially diagnosed with SH: 3 developed carcinoma, 7 progressed to atypical hyperplasia, 40 had persistent endometrial hyperplasia, and 103 regressed. Of the 14 patients initially diagnosed with CH: 3 had persistent endometrial hyperplasia, and 11 regressed. Of the 5 patients with simple hyperplasia with atypia: 1 progressed to carcinoma, 1 had persistent atypical endometrial hyperplasia, and 3 regressed. Of the 22 patients with complex hyperplasia with atypia: 3 progressed to carcinoma, 5 had persistent atypical endometrial hyperplasia, and 14 regressed. A significantly higher proportion of patients initially diagnosed with AEH (4/27, 14.8%) developed endometrioid carcinoma when compared to patients diagnosed with BEH (3/167, 1.7%, P = 0.008).

Discussion

The overall findings in this study confirm the validity of both 1994 and 2014 WHO classifications in predicting the clinical outcome of endometrial hyperplasia, comparable with Kurman's original study [1]. Long-term follow-up of 273 patients diagnosed with endometrial hyperplasia shows that patients initially diagnosed with atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia (AEH/EIN) are 94% (HR = 0.06, 95% CI: 0.02 to 0.19, P < 0.0001) more likely to progress to endometrioid carcinoma than patients initially diagnosed with benign endometrial hyperplasia (BEH). The median endometrioid carcinoma-free survival time was 16.3 years among patients diagnosed with BEH and 10.9 years among patients diagnosed with AEH. Kaplan-Meier analysis for endometrioid carcinoma-free survival among the 1994 WHO classification categories reveals that patients initially diagnosed with simple hyperplasia (SH) are not more likely to progress to carcinoma than patients diagnosed with complex hyperplasia (CH, P = 0.30). Similarly, patients initially diagnosed with complex hyperplasia with atypia were not more likely to progress to carcinoma than patients diagnosed with simple hyperplasia with atypia (SHA, P = 0.78). These findings suggest that the presence of glandular architectural complexity is not an independent prognostic factor in the progression to endometrioid carcinoma. Furthermore, patients initially diagnosed with complex hyperplasia with atypia (CHA) progressed to endometrioid carcinoma more rapidly than patients initially diagnosed with SH (P < 0.0001) or CH (P = 0.02). Although the comparison between CHA and CH did not reach statistical significance when adjusted for multiple comparisons (P < 0.01), the number of patients progressing to endometrioid carcinoma was higher in the CHA group (13/53 = 24.5%) group when compared with the CH group (1/23 = 4%).

Using the 2014 WHO classification, a significant proportion of patients initially diagnosed with atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia will have concurrent endometrioid carcinoma on their hysterectomy specimen if the procedure is performed within 2 months [6-10]. Among the 15 patients initially diagnosed with AEH/EIN that progressed to endometrioid carcinoma, 3 of 15 patients were diagnosed on their hysterectomy specimen within 2 months of their initial endometrial biopsy (**Table 1**). Two additional patients were diagnosed with endometrioid carcinoma on subsequent biopsy. These data suggest that approximately 33.3% (5/15) of patients diagnosed with atypical endometrial hyperplasia by biopsy may have concurrent endometrioid carcinoma.

As previously reported in other studies, all carcinomas except one case in our cohort were well-differentiated FIGO grade 1 endometrioid adenocarcinoma [2, 11-23]. The median follow-up time was 6.9 years in patients initially diagnosed with benign endometrial hyperplasia and 325 days in patients with atypical endometrial hyperplasia. All of the carcinomas that developed in these patients were confined to the endomyometrium and no patients had lymph node metastases. When progression to endometrioid carcinoma was assessed in the subgroup of patients with at least 1 year of follow-up (**Table 3**), 4 of 27 patients initially diagnosed with atypical endometrial hyperplasia (14.8%) and 3 of 167 patients diagnosed with benign endometrial hyperplasia progressed to carcinoma (3/167 = 1.7%, P = 0.008).

The regression rates for patients that had at least 1 year of follow up was not statistically different among the 1994 categories (SH: 103/153 = 67.3%, CH: 11/14 = 78.5%, SHA: 3/5 = 60%, CHA: 14/22 = 63.6%, P = 0.78). Similarly, patients diagnosed with BEH (114/167 = 68.2%) did not have statistically different regression rates compared to AEH (17/27 = 62.9%, P = 0.66).

While our data confirm the diagnostic validity of both 1994 and 2014 WHO classifications in predicting progression of endometrial hyperplasia to endometrioid carcinoma, the simplified two-tiered 2014 WHO classification based on cytological atypia alone is sufficient in guiding clinical management of this disease. Women with benign endometrial hyperplasia (BEH) have a very low risk of progression to carcinoma and can be managed conservatively. Women with atypical endometrial hyperplasia (AEH) have a higher rate of progression to endometrioid carcinoma, which is almost always a well-differentiated one. The clinical management of patients with AEH is dependent on patient age and the desire to preserve fertility.

Disclosure of conflict of interest

None.

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