Original Article / Özgün Makale

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.758533

Anatolian Curr Med J 2020; 2(4); 129-135

Did the terminology of endometrial intraepithelial neoplasia resolve the chaos in the classification of endometrial hyperplasia? a 8-year retrospective study

Endometrial intraepitelyal neoplazi terminolojisi, endometrial hiperplazi sınıflamasındaki kaosu çözdü mü? 8 yıllık retrospektif bir çalışma

Mehmet Zengin[1], Merve Eryol[1], Merva Aydemir Akkaya[1], Tuba Devrim[1], Selim Yalçın[2], Zehra Sema Özkan[3]

[1]Kırıkkale University, Pathology Department, Kırıkkale, Turkey
[2]Kırıkkale University, Internal Medicine Department, Kırıkkale, Turkey
[3]Kırıkkale University, Obstetrics and Gynecology Department, Kırıkkale, Turkey

Cite this article as/Bu makaleye atıf için: Zengin M, Eryol M, Aydemir Akkaya M, Devrim T, Yalçın S, Özkan ZS. Did the terminology of endometrial intraepithelial neoplasia resolve the chaos in the classification of endometrial hyperplasia?a 8-year retrospective study. Anatolian Curr Med J 2020; 2(4); 129-135.

ABSTRACT

Aim: Endometrial intraepithelial neoplasia is a monoclonal glandular lesion defined in the new WHO classification (2014), which is the precursor of the development of endometrioid type endometrial adenocarcinoma. In this study, we examined the prognostic role of this new classification in patients with endometrial adenocarcinoma and its contribution to daily practice.

Material and Method: 60 cases diagnosed with endometrial adenocarcinoma between 2007 and 2015 were included in this retrospective study. The cases were reevaluated for endometrial intraepithelial neoplasia using sections stained with hematoxylin and eosin.

Results: Endometrial intraepithelial neoplasia was significantly associated with age (p=0.022), endometrial adenocarcinoma (p=0.010) and complex endometrial hyperplasia (with atypia) (p=0.038). When the univariate analysis was examined, 5-year relapse-free survival was poor (p=0.035) for endometrial intraepithelial neoplasia patients. When the multivariate analysis was examined, it was seen that endometrial intraepithelial neoplasia was an independent predictor of poor survival for relapse-free survival (HR=2.77 [1.22-4.78], p=0.046).

Conclusions: According to our study, endometrial intraepithelial neoplasia played an important role in the development of endometrial adenocarcinoma, but no significant superiority over the old classification was observed. For this reason, we recommend that the old and new classifications are noted together for a healthier decision.

Keywords: Endometrial intraepithelial neoplasia, endometrial adenocarcinoma, endometrial hyperplasia

ÖZ

Amaç: Endometrial intraepitelyal neoplazi, endometrioid tip endometrial adenokarsinomun gelişiminin öncüsü olan, yeni WHO sınıflandırmasında (2014) tanımlanan, monoklonal glandüler bir lezyondur. Bu çalışmada, bu yeni sınıflandırmanın endometrial adenokarsinomlu hastalarda prognostik rolünü ve günlük pratiğe katkısını inceledik.

Gereç ve Yöntem: Bu retrospektif çalışmaya 2007-2015 yılları arasında endometrial adenokarsinomun tanısı konan 60 olgu dahil edildi. Vakalar, hematoksilin ve eozin ile boyanmış bölümler kullanılarak endometrial intraepitelyal neoplazi açısından yeniden değerlendirildi.

Bulgular: Endometrial intraepitelyal neoplazi, yaş (p=0,022), endometrial adenokarsinom (p=0,010) ve kompleks endometrial hiperplazi (atipili) (p=0,038) ile anlamlı derecede ilişkiliydi. Tek değişkenli analiz incelendiğinde, endometrial intraepitelyal neoplazi hastaları için 5 yıllık nükssüz sağkalım daha kötüydü (p=0,035). Çok değişkenli analiz incelendiğinde, endometrial intraepitelyal neoplazi'nin nükssüz sağkalım için kötü sağkalımın bağımsız bir öngörücüsü olduğu görüldü (HR=2,77 [1,22-4,78], p=0,046).

Sonuçlar: Çalışmamıza göre endometrial intraepitelyal neoplazi, endometrial adenokarsinomun gelişiminde önemli bir rol oynamaktadır, ancak eski sınıflandırmaya göre önemli bir üstünlük gözlenmemiştir. Bu nedenle, daha sağlıklı bir karar için eski ve yeni sınıflandırmaların birlikte not edilmesini öneririz.

Anahtar Kelimeler: Endometrial intraepitelyal neoplazi, endometrial adenokarsinom, endometrioid tip, endometrial hiperplazi

Corresponding Author / Sorumlu Yazar: Mehmet Zengin, Kırıkkale Üniversitesi Tıp Fakültesi, Patoloji Anabilim Dalı, 71450, Yenişehir, Yahşihan, Kırıkkale, Türkiye
E-mail / E-posta: mz1379@hotmail.com
Received / Geliş: 26.06.2020 **Accepted / Kabul:** 13.09.2020

INTRODUCTION

Endometrial carcinoma is the most common gynaecological malignancy in the United States and its frequency is 2.5%. Most of the cases (70%-80%) are endometrioid type endometrial adenocarcinomas (EEA)(1). These tumours are generally secondary to long-term estrogen stimulation in perimenopausal women. It usually develops on the background of endometrial hyperplasia (EH)(1,2).

Endometrial hyperplasia is a term that describes premalignant and benign lesions of the endometrium in response to estrogen stimulation. The most widely used system for classifying EHs is the system of the World Health Organization (WHO, 1994)(3). This system distinguishes EHs mainly by architecture (simple and complex) and cytological atypia (with atypia and without atypia). The weaknesses of this system are low reproducibility and include four different diagnostic categories (3,4). Nevertheless, with the WHO hyperplasia system, useful information has been obtained about understanding the underlying biological processes of the EEA. True EHs are polyclonal proliferations that develop in endometrial glands and stroma in response to prolonged estrogenic stimulation (4). The morphology of these proliferations is individual, dependent on the duration and dose of the patient's exposure to estrogen (4). These polyclonal proliferations are therefore referred to as benign EH. Contrary to this assumption, in the new WHO (2014) system, the EEA is not due to the progression of the hyperplastic area, but by the genetic transformation of an individual gland that is highly localized but capable of producing premalignant lesions.This lesion, called endometrial intraepithelial neoplasia (EIN), is a monoclonal proliferation of endometrial glands with a high tendency to progress in adenocarcinoma, which differs from the surrounding glands in terms of architecture and cytology (5).

In this study, we compare EIN with the old classification and examine the prognostic power of this new classification and its use in practice.

MATERIAL AND METHOD

Ethics Committee Approval

Our study was approved by the Kırıkkale University Non-interventional Ethics Committee (permission granted: 24.06.2020/decision number: 2020.06.19). (Permission granted: 24.06.2020 / Decision number: 2020.06.19). All procedures performed during our study were carried out in accordance with national/institutional ethical standards and the 1964 Helsinki Declaration.

Design of the Study

Our study was carried out in the University Hospital in Kırıkkale. Eighty-five patients diagnosed with EEA in our hospital between 2007 and 2015 were included in the study. Exclusion criteria were determined as follows. Tumor block is missing (n=10), tissue in the block is insufficient (n=5), and multiple tumor (n=5). Cases developing secondary primary were excluded from survival analysis (n=5).As a result, the study continued with sixty EEA cases.

Data Collecting

All blocks of the cases included in our study were taken from the archives of the Pathology Department of Kırıkkale University. Clinical, pathological and survival data of the cases were taken from the database of Kırıkkale University. This information includes data such as survival, age, tumour volume, presence of complex endometrial hyperplasia (CEH) (with atypia- without atypia), and presence of simple endometrial hyperplasia (SEH) (with atypia- without atypia), and the presence of disordered proliferation. EEAs were grouped according to the following criteria. Presence of EIN, presence of CEH (with atypia-without atypia), presence of SEH (with atypia-without atypia), presence of disordered proliferation. The cases are re-examined according to the criteria of the current American Joint Committee on Cancer Classification (8^{th}).

Preparation of Tissues

All archived tumour samples embedded in paraffin were collected. All retrospective curettage of these patients were also included in the study. All blocks were reevaluated for the presence of EIN. 4 μm thick sections were taken from the required blocks (n=32) and stained with hematoxylin and eosin (H&E). Three experienced pathologists evaluated all sections.

Endometrial Intraepithelial Neoplasia (EIN)

Our work is retrospective. While creating our population, EEA cases with curettage material belonging to various stages of hyperplasia were selected. All curettage materials belonging to 60 EEA cases classified according to the old classification were evaluated again in terms of the presence of EIN. And the advantages and disadvantages of the old classification and the new classification were compared in this way. EIN was evaluated using H&E stained sections using conventional microscopy (Nikon AG Instruments, Nikon Eclipse E600, USA).EIN was defined as a gland focus larger than 1 mm, containing complexity and atypia, which looked different from surrounding glans (8). An x20 lens was used when examining the presence of EIN. It was considered positive when it was seen from any block of cases. Then EIN's relationship with survival was examined.

Reproducibility
Reproducibility was assessed by interobserver agreement. Three experienced pathologists (MZ, ME, and MAA) evaluated the EIN status, blinded by clinical and pathological information. Weighted and simple Kappa value (κ) was used for the agreement between observers.

Follow-up
In our study, survival rates were used as an outcome criterion. When calculating the time for survival, the diagnosis date of the primary tumour was taken as the starting time. The follow-up period was extended up to 120 months to make a more reliable decision about relapse and death. However, all events after sixty months were censored at sixty months. Relapse-free survival (RFS) time was defined as the time from the day the primary tumour was diagnosed to the day of death or the day of local/distant recurrence. Overall survival (OS) time was defined as the time from the day the primary tumour was diagnosed to the day of death or the last follow-up day.

Statistical Analysis
While continuous data were presented, range, mean and standard deviation were used. While categorical data were presented, percentage and frequency were used. Chi-square test, Kappa test, Log-rank test and Cox regression test were used when comparing the old and new classifications. Chi-Square test was used to analyze the relationship between EIN and clinicopathological variables. κ test was used to investigate agreement between observers. The κ value is a variance ratio and is classified as weak, moderate and perfect for the values of 0.41–0.60, 0.61–0.80 and 0.81–1 respectively. The effect of the investigated parameters on survival alone constituted the univariate survival analysis, while the combined effect constituted the survival multivariate analysis. Log-rank test was used to investigate the relationship between univariate survival groups, and Kaplan-Meier method was used when presenting survival curves. Cox-regression model was used to investigate the relationship between multivariate survival groups. The significance limit for p value was defined as 0.05. SPSS 21.0 (IBM institute, North Castle, USA) program was used for analysis.

RESULTS

Patients
Our data is not distributed normally. The median of age and volume were 63 (range: 45-87) and 4.5 (range: 1-8), respectively. 28 (46.6%) of the tumours were low/moderately differentiated and 32 (53.4%) were poorly differentiated. EIN in 32 (%53.3) cases, SEH (without atypia) in 26 (%38.2) cases, SEH (with atypia) in 31 (%51.6) cases, CEH (without atypia) in 30 (%50.0) cases, and CEH (with atypia) in 29 (%48.3) cases were detected.

Evaluation of EIN
Foci seen in EIN were heterogeneously distributed in the slides. Focal or general changes consistent with hormonal effects were noted in the cases in our study. Among hyperplasias, EIN was more common in patients with CEH (with atypia). When the relationship of EIN with prognostic factors was examined, a significant relationship was found for age (p=0.022), EEA (p=0.010) and CEH (with atypia) (p=0.038). The statistical relationship between EIN and clinicopathological features is given in **Table 1**.

Reproducibility
In general, the inter-observer agreement was in a clinically useful and ranged from moderate to significant (κ=0.38-0.70). On the other hand, we found that interobserver agreement was the lowest for EIN (κ=0.38-0.49). We found the highest agreement in CEH(with atypia)(κ=0.68-0.70).

Follow-up of Patients
In the follow-up of the cases, twenty patients died (n=13 for EIN positive cases and n=7 for EIN negative cases) and fifty-five patients recurred (n=35 for EIN positive cases and n=20 for EIN negative cases). The 5-year RFS and OS rates were 72% and 73% in EIN positive patients and 83% and 84% in EIN negative patients, respectively (**Table 2**).

Survival Analyses
In the univariate analysis for EIN, significant differences were observed for RFS between survival groups (p=0.035). CEH (with atypia) and CEH (without atypia) were other parameters associated with poor survival (**Table 2, Figure 2**). In the multivariate analysis, EIN was an independent poor survival parameter for RFS (HR=2.77 [1.22-4.78], p=0.046). CEH (with atypia)was the other independent parameter associated with poor survival (**Table 3**).

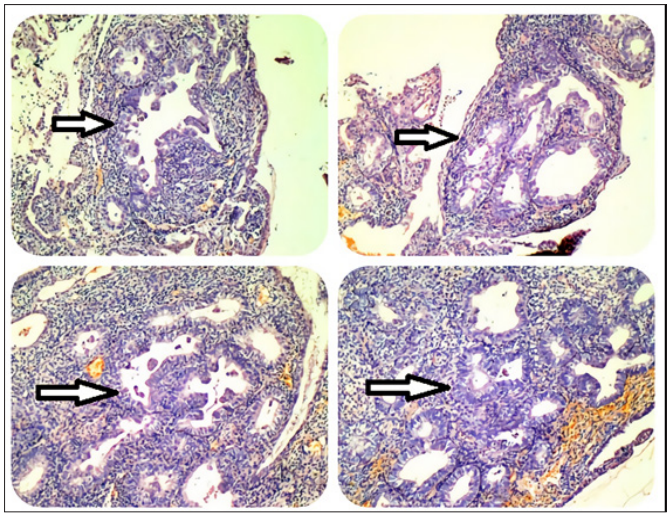

Figure 1. Examples of endometrial intraepithelial neoplasia (EIN). In the EIN examination (arrows), classical microscope, x10 - x20 objective and hematoxylin and eosin painted sections were used

Table 1. The statistical relationship between EIN and prognostic factors (n=60)

		EEA (%)			EIN(%)		
		Low/Moderate grade	**High grade**	**p-value**	**Positive**	**Negative**	**p-value**
Age	<63	9 28.1%	18 64.2%	0.004*	10 31.2%	17 60.7%	0.022*
	≥63	23 71.9%	10 35.8%		22 68.8%	11 39.3%	
Tumour volume	<4 block	11 34.3%	18 64.2%	0.020*	13 40.6%	16 57.1%	0.201
	≥4 block	21 65.7%	10 35.8%		19 59.4%	12 42.9%	
EEA	Low/Moderate grade	- -	- -	-	10 31.2%	18 64.2%	0.010*
	High grade	- -	- -		22 68.8%	10 35.8%	
SEH (with atypia)	No	14 43.7%	20 71.4%	0.030*	15 46.8%	19 67.8%	0.101
	Yes	18 56.3%	8 28.6%		17 53.2%	9 32.2%	
SEH (without atypia)	No	14 43.7%	15 53.5%	0.447	13 40.6%	16 57.1%	0.201
	Yes	18 56.3%	13 46.5%		19 59.4%	12 42.9%	
CEH (with atypia)	No	11 34.3%	19 67.8%	0.018*	12 37.5%	18 64.2%	0.038*
	Yes	21 65.7%	9 32.2%		20 62.5%	10 35.8%	
CEH (without atypia)	No	12 37.5%	19 67.8%	0.009*	14 43.7%	17 60.7%	0.189
	Yes	20 62.5%	9 32.2%		18 56.3%	11 39.3%	
Disordered proliferation	No	15 46.8%	17 60.7%	0.283	16 50.0%	16 57.1%	0.580
	Yes	17 53.2%	11 39.3%		16 50.0%	12 42.9%	

*. Chi-square test values below 0.05 are significant. Significant results are written in italics. Abbreviations: EEA: Endometrioid type endometrial adenocarcinoma, CEH: Complex endometrial hyperplasia, SEH: Simple endometrial hyperplasia, EIN: Endometrial intraepithelial neoplasia.

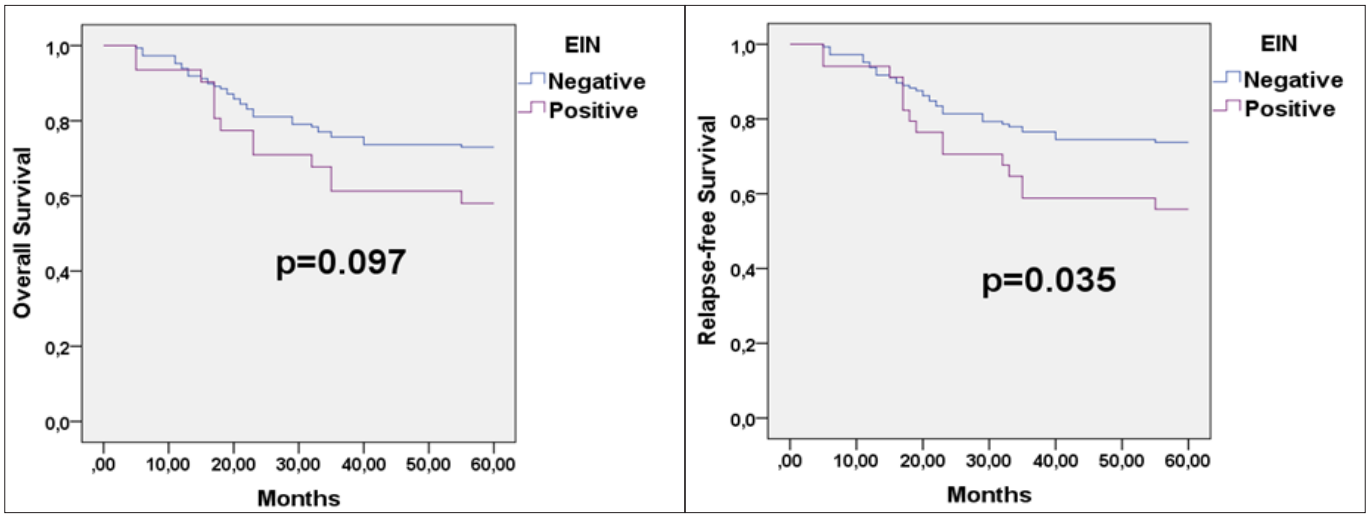

Figure 2. Survival curves of endometrial intraepithelial neoplasia. Overall survival and relapse-free survival were presented with the Kaplan-Meier survival curves. Chi-square test values below 0.05 are significant.

Table 2. Survival analysis (n=60)

	Univariate survival analysis (n=60) (%)				Multivariate survival analysis (n=60) (%)			
	OS		RFS		OS		RFS	
	5-year (%)	p-value	5-year (%)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age		0.684		0.625		NC		NC
<63	87		88		-		-	
≥63	83		84		-		-	
Tumour volume		0.266		0.546		NC		NC
<4 block	89		88		-		-	
≥4 block	81		82		-		-	
SEH(without atypia)		0.427		0.423		NC		NC
No	85		86		-		-	
Yes	80		82		-		-	
SEH(with atypia)		0.226		0.372		NC		NC
No	84		85		-		-	
Yes	78		80		-		-	
CEH(without atypia)		0.117		0.041*		0.459		0.293
No	83		85		1		1	
Yes	75		73		2.48 (0.77-7.98)		3.44 (0.58-8.22)	
CEH (with atypia)		0.030*		0.011*		0.045*		0.031*
No	83		82		1		1	
Yes	70		70		1.68 (1.17-3.25)		1.33 (1.13-3.28)	
Disordered proliferation		0.554		0.498		NC		NC
No	86		85		-		-	
Yes	80		79		-		-	
EIN		0.97		0.035*		0.209		0.046*
No	84		83		1		1	
Yes	73		72		3.48 (0.86-7.44)		2.77 (1.22-4.78)	

Here, the effects of parameters in the old and new classifications on univariate and multivariate survival are seen.Significant results are written in italics. Abbreviations: CEH: Complex endometrial hyperplasia, SEH: Simple endometrial hyperplasia, EIN: Endometrial intraepithelial neoplasia, NC: Not calculable, OS: Overall survival, RFS: Relapse-free survival, CI: Confidence interval, HR: Hazard ratio.

Table 3. Reproducibility of EIN (n=60)

	N	Weighted Kappa values
SEH (without atypia)	60	0.58 (A&B), 0.55 (B&C), 0.56 (A&C)
SEH (with atypia)	60	0.60 (A&B), 0.61 (B&C), 0.63 (A&C)
CEH (without atypia)	60	0.68 (A&B), 0.65 (B&C), 0.65 (A&C)
CEH (with atypia)	60	0.70 (A&B), 0.69 (B&C), 0.68 (A&C)
EIN	60	0.49 (A&B), 0.45 (B&C), 0.38 (A&C)

EEA: Endometrioid type endometrial adenocarcinoma, CEH: Complex endometrial hyperplasia, SEH: Simple endometrial hyperplasia, EIN: Endometrial intraepithelial neoplasia, A: First observer, B: Second observer, C: Third observer

DISCUSSION

In this retrospective study, we investigated what the new EIN classification brings to daily practice and EEA. According to our results, EIN has an important role in the development of EEA, but its superiority to the old classification is not clear. For this reason, we recommend using both classifications together in the transition to EIN.

EIN is a monoclonal proliferation of endometrial glands that show many different genetic mutations. Histopathologically, these glands display a different architecture, cytology and histopathology (6). These changes, which were initially quite focal, have the potential to develop EEA through the accumulation of genetic changes. This transition, accelerated by estrogen exposure, is balanced by progesterone exposure. In our study, these changes could be distinguished histologically. Inactivation of the PTEN gene is the most common genetic change in EEA (6,7). PTEN is a tumour suppressor gene, its mutation originates from the early stage of carcinogenesis and is found in 83% of EEAs and 63% of EINs. In terms of IHC, this mutation is detected in one-third of EIN lesions. In other words, the traditional microscopic view is very important for the diagnosis of EIN (7,8). In our study, the traditional microscope view was used to diagnose EIN. Therefore, it was not possible to comment on genetic changes. The traditional microscope view was found to be very useful in distinguishing EIN.

The risk of developing EEA (at the same time or in the future) increases in cases of EIN. 30-50% of these patients are diagnosed with concurrent EEA within a

year, and the average time to progression to EEA is four years (9,10). Also, the risk of progressing to the EEA has increased 45 times in the first two years. In our study, EEA was detected in 53.3% of EIN patients, and 68.7% of these cases were found to be high grade. On the other hand, the absence of EIN in endometrium sampling indicates that the patient does not have EEA (99%) (10,11). That is, the predictive value of EIN is higher than atypical hyperplasia because it develops from genetically defined lesions (10,11). In our study, the EEA detected in EIN patients was lower than atypical hyperplasia. This may be related to the small number of cases. However, EEA detected in EIN cases was found to be higher grade than atypical hyperplasia.

When diagnosing EIN, the following five criteria should be found. Architecturally complex gland structure, atypical cytological features, size 1 mm larger, exclusion of malignancy and similar lesions (12,13). These criteria were taken into account in our study. To meet the architectural criteria, the gland/stroma ratio should have increased (13). Therefore, attention should be paid to telescopic views, squamous morules, and artifactual displacement of the glandular epithelium while making this diagnosis. EIN typically includes more than 50% increased gland density in the centre of the lesion. Assessment of the stroma ratio within the lesion helps to distinguish it from these traps and carcinoma. Therefore, it is useful to examine the biopsy at small magnification when evaluating EIN (14,15). In our study, evaluation of EIN was performed at small magnification and it was found to be very useful. High magnification should be used when evaluating cytological atypia. Crowded glands in EIN should be different from the surrounding glands in terms of cytological atypia, nuclear size and shape, chromatin distribution (granular and coarse) and loss of polarity (15). However, not all of these features are always available. In addition, the cytological features of the background glands may vary according to the hormonal situation. Therefore, it is very important to compare EIN with surrounding glands (16). In our study, when evaluating EIN, great attention was paid to its difference from surrounding glands.

Changing a long-used classification and introducing a new classification is difficult for both the pathologist and the clinician. Overall, the transition from the old four-stage system to a 2-stage system is a success (17). In addition, treatment categories were clarified with the new system. Also, there is an ambiguity in the term atypia in the old classification, and this term is subjective for pathologists. However, studies show that clinicians easily adopt this system and pathologists find it difficult to get used to it (17-19). For example, the rate of making this diagnosis is 17% in general pathologists and 34% in gynaecological pathologists (18,19). In our study, the agreement between the observers was lower in terms of the diagnosis of EIN. This finding may be related to the innovation of this system. Further studies are needed on this subject. In addition, the appearance of neoplastic and non-neoplastic glands may differ significantly depending on the hormonal status, and there is no valid criterion for EIN in the presence of active progestational therapy (15,16). In our study, we frequently saw changes due to hormonal effects and we experienced that consultation was beneficial in this case.

After the diagnosis of EIN, the treatment that should be applied is hysterectomy. However, progestin therapy is also an option, depending on the fertility of the patient or suitability for surgery. However, following this treatment, a follow-up biopsy is required every six months until several negative biopsies are obtained (20). The aim of this treatment is to remove the lesion by progestin withdrawal. If EIN continues despite this treatment, it may show morphological differences such as mucinous changes and the pathologist should be careful about this (20,21). Therefore, the diagnosis of EIN is a very sensitive diagnosis in terms of treatment. In our study, the criteria were applied precisely when diagnosing EIN. However, it was observed that the agreement between the observers was low. This may be related to the system's scarcity of defining criteria.

There are some limitations to our study. Since our study is retrospective, there is an internal limitation. Also, cases were treated according to guidelines before 2015, so they may differ from current treatment approaches. In addition, archive records were used in our study and individual patient records were not used.

CONCLUSION

In our study, EIN was associated with poor survival, but it did not have a clear advantage over the old classification. Also, intra-observer reproducibility for EIN was quite low. Therefore, we recommend reporting the new and old classification together for accurate patient management.

Abbreviations

AJCC: American Joint Cancer Committee, CEH: Complex endometrial hyperplasia, EEA: Endometrioid type endometrial adenocarcinoma, EIN: Endometrial intraepithelial neoplasia, H&E: Hematoxylin and eosin, HPF: High power field, HR: Hazard ratio, OS: Overall survival, RFS: Relapse-free survival, SD: Standard deviation, SEH: Simple endometrial hyperplasia

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the Kırıkkale University Non-interventional Ethics Committee (permission granted: 24.06.2020/decision number: 2020.06.19).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgements: We are grateful to the pathology department staff for their help in this research.

REFERENCES

1. Jemal A, Siegel R, and Xu J. Cancer statistics. CA Cancer J Clin 2010; 60: 277-300
2. Zaino RJ. Endometrial hyperplasia: Is it time for a quantum leap to a new classification? Int J Gynecol Pathol 2000; 19: 314-21.
3. Bergeron C, Nogales FF, Masseroli M, et al. A multicentric European study testing the reproducibility of the WHO classification of endometrial hyperplasia with a proposal of a simplified working classification for biopsy and curettage specimens. Am J Surg Pathol 1999; 23: 1102-8
4. Usubutun A, Mutter GL, Saglam A, et al. Reproducibility of endometrial intraepithelial neoplasia diagnosis is good, but influenced by the diagnostic style of pathologists. Mod Pathol 2012; 25: 877–84.
5. Baak JP, Mutter GL, Robboy S, et al. The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system Cancer 2005; 103: 2304-12.
6. Mutter GL, Baak JP, Crum CP, et al. Endometrial precancer diagnosis by histopathology, clonal analysis, and computerized morphometry. J Pathol 2000; 190: 462-9.
7. Hecht JL, Mutter GL. Molecular and pathologic aspects of endometrial carcinogenesis. J Clin Oncol 2006; 24: 4783–91.
8. Zheng W, Baker HE, and Mutter GL. Involution of PTEN-null endometrial glands with progestin therapy. Gynecol Oncol 2004; 92: 1008-13.
9. Lacey JV, Mutter GL, Nucci MR, et al. Risk of subsequent endometrial carcinoma associated with endometrial intraepithelial neoplasia classification of endometrial biopsies. Cancer 2008; 113: 2073–81.
10. Gultekin, M, Diribas K, Dursan P, et al. Current management of endometrial hyperplasia and endometrial intraepithelial neoplasia (EIN). Eur J Gynaecol Oncol 2009; 30: 396–401.
11. Salman MC, Usubutun A, Boynukalin K, et al. Comparison of WHO and endometrial intraepithelial neoplasia classifications in predicting the presence of coexistent malignancy in endometrial hyperplasia. J Gynecol Oncol 2010; 21: 97–101.
12. Mutter GL. Endometrial intraepithelial neoplasia (EIN): will it bring order to chaos? Gynecol Oncol 2000; 76: 287-90.
13. Lin MC, Lomo L, Baak JP, et al. Squamous morules are functionally inert elements of premalignant endometrial neoplasia. Mod Pathol 2009; 22: 167-74.
14. Trimbel CL, Kaudener 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.
15. Wheeler DT, Bristow RE, and Kurman RJ. Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins. Am J Surg Pathol 2007; 31: 988-98.
16. Carlson JW, Mutter GL. Endometrial intraepithelial neoplasia is associated with polyps and frequently has metaplastic change. Histopathology 2008; 53: 325-32.
17. Kane SE, Hecht JL. Endometrial intraepithelial neoplasia terminology in practice: 4-year experience at a single institution. Int J Gynecol Pathol 2012; 31: 160–5.
18. 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.
19. Zaino RJ, Kauderer J, Trimble CL, et al. Reproducibility of the diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer 2006; 106: 804–11.
20. Signorelli M, Caspani G, Bonazzi C, et al. Fertility-sparing treatment in young women with endometrial cancer or atypical complex hyperplasia: a prospective single-institution experience of 21 cases. Br J Obstet Gynaecol 2009; 116: 114-8.
21. Boruban MC, Altundag K, Kilic GS, et al. From endometrial hyperplasia to endometrial cancer: insight into the biology and possible medical preventive measures. Eur J Cancer Prev 2008; 17: 133–8.