Research Article

Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1653716

Association of PTEN expression with hormone receptor status, tumor subtype, histological grade, and clinicopathological parameters in endometrial carcinomas

Endometriyal karsinomlarda PTEN ekspresyonunun hormon reseptörü durumu, tümör alt tipi, histolojik derece ve klinikopatolojik parametrelerle ilişkisi

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Posted date:08.03.2025 Acceptance date:12.05.2025

Abstract

Purpose: This study investigates the relationship between PTEN expression and tumor characteristics and clinical outcomes in endometrial carcinoma (EC). EC is the most common malignancy of the female genital tract, typically classified into Type I (endometrioid, hormone-sensitive, favorable prognosis) and Type II (serous, aggressive, poor prognosis). PTEN is a tumor suppressor gene that regulates cell growth. Loss of PTEN expression is frequently observed in Type I EC and is associated with early tumorigenesis.

Materials and methods: A retrospective analysis was conducted on 186 EC cases. PTEN expression was evaluated immunohistochemically, and its association with tumor size, histological subtype, stage, hormone receptor status, and survival outcomes was analyzed.

Results: Loss of PTEN expression was detected in 81.2% of cases. While PTEN loss was more prevalent in tumors >3 cm in size, it did not show a significant correlation with stage, grading, myometrial invasion, or metastasis. p53 mutation and high-grade tumors were associated with poorer survival rates. Estrogen receptor (ER) and progesterone receptor (PR) expression were predominantly observed in endometrioid carcinoma.

Conclusions: Although PTEN loss is frequently observed in endometrioid EC, it does not directly impact survival outcomes. Hormone receptor status and genetic alterations play a crucial role in EC pathogenesis. Further studies on PTEN and other molecular markers may contribute to the development of personalized treatment strategies. These findings suggest that while PTEN loss plays a role in early tumor development, it is not a definitive prognostic factor in EC.

Keywords: Endometrial cancer, PTEN, tumor cells**.**

Arman Karakaya Y, Kosar Can O. Association of PTEN expression with hormone receptor status, tumor subtype, histological grade, and clinicopathological parameters in endometrial carcinomas. Pam Med J 2025;18:530-539.

Öz

Amaç: Bu çalışma, PTEN ekspresyonunun tümör özellikleri ve hastalık progresyonu ile ilişkisini incelemektedir. Endometriyal karsinom (EK), kadın genital sisteminin en yaygın malignitesidir ve genellikle Tip I (endometrioid, hormon duyarlı, iyi prognoz) ve Tip II (seröz, agresif, kötü prognoz) olarak sınıflandırılır. PTEN, hücre büyümesini düzenleyen bir tümör supresör genidir. PTEN ekspresyon kaybı özellikle Tip I EK'de sık görülmekte ve erken tümör gelişimi ile ilişkilendirilmektedir.

Gereç ve yöntem: Bu çalışmada 186 EK vakası retrospektif olarak analiz edilmiştir. PTEN ekspresyonu immünohistokimyasal olarak değerlendirilmiş ve tümör boyutu, histolojik alt tip, evre, hormon reseptör durumu ve sağkalım sonuçları ile ilişkisi araştırılmıştır.

Bulgular: PTEN ekspresyon kaybı olguların %81,2'sinde tespit edilmiştir. PTEN kaybı 3 cm'den büyük tümörlerde daha sık görülmesine rağmen, evre, derecelendirme, myometrial invazyon veya metastaz ile anlamlı bir ilişki göstermemiştir. p53 mutasyonu ve yüksek dereceli tümörler daha kötü sağkalım oranları ile ilişkilendirilmiştir. Östrojen (ER) ve progesteron (PR) reseptör ekspresyonu ise ağırlıklı olarak endometrioid karsinomda gözlenmiştir.

Sonuç: PTEN kaybı endometrioid EK'de sık görülmekle birlikte sağkalım üzerinde doğrudan bir etkisi bulunmamaktadır. Hormon reseptör durumu ve genetik değişiklikler EK patogenezinde önemli bir rol oynamaktadır. PTEN ve diğer moleküler belirteçler üzerine yapılacak ileri çalışmalar, kişiselleştirilmiş tedavi stratejilerinin geliştirilmesine katkı sağlayabilir. Bu bulgular, PTEN kaybının erken tümör gelişiminde rol oynadığını ancak EK için kesin bir prognostik faktör olmadığını göstermektedir.

Anahtar kelimeler: Endometrial kanser, PTEN, tümör hücreleri.

Arman Karakaya Y, Koşar Can Ö. Endometriyal karsinomlarda PTEN ekspresyonunun hormon reseptörü durumu, tümör alt tipi, histolojik derece ve klinikopatolojik parametrelerle ilişkisi. Pam Tıp Derg 2025;18:530-539.

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Introduction

Endometrial carcinoma (EC) is the most common cancer of the female genital tract and the fourth most commonly diagnosed cancer overall, after breast, lung, and colorectal cancers. Understanding the molecular genetic mechanisms that drive tumor progression is crucial for improving early diagnosis, assessing prognosis, and developing effective treatment strategies for endometrial carcinoma [1]. According to global data, approximately 420.368 women are diagnosed with endometrial carcinoma annually, with 97.723 deaths attributed to the disease [2].

Endometrial carcinoma is traditionally categorized into two subtypes based on their biological behavior and prognosis. Type I EC is commonly associated with risk factors such as obesity, hyperlipidemia, and hyperestrogenism, and predominantly consists of well to moderately differentiated endometrioid tumors. In contrast, Type II EC encompasses poorly differentiated tumors, including serous carcinoma, clear cell carcinoma, and carcinosarcoma. Type II tumors typically exhibit a more aggressive clinical course, with a greater propensity for deep myometrial invasion and are often diagnosed at more advanced stages. These tumors are characterized by a higher recurrence rate and are associated with a poorer prognosis [3].

Phosphatase and Tensin Homolog (PTEN) is a gene located at the 10q23.31 locus, composed of nine exons encoding a 403-amino acid protein product with phosphatidylinositol, tyrosine, and serine/threonine protein phosphatase activity [4]. PTEN protein produces a tumor-suppressor phosphatase that regulates cell division and inhibits oncogenesis. As a dual-specificity phosphatase, PTEN suppresses cell proliferation and induces apoptosis via an AKT-dependent pathway [5]. PTEN is the most frequently mutated tumor suppressor gene in endometrial carcinoma, with particularly high mutation rates in the endometrioid subtype. In contrast, PTEN mutations are rarely observed in serous carcinoma. PTEN loss of function serves as an indicator of early carcinogenesis in the endometrium and is associated with favorable prognosis [6]. Even a slight reduction in PTEN protein levels and activity can lead to increased cancer susceptibility and tumor malignancy [6]. PTEN exerts its effects through the Akt signaling pathway by inhibiting cell proliferation and inducing apoptosis. PTEN mutations or deletions have been identified in approximately 80% of endometrioid carcinoma cases. Functional inactivation of PTEN is linked to cancer progression and the development of a malignant phenotype [7]. The physiological fluctuation of PTEN levels throughout the menstrual cycle suggests that it is regulated by hormonal factors [8].

This study aims to explore the association between PTEN expression and tumor characteristics, as well as its impact on disease prognosis in endometrioid endometrial carcinoma. The findings are expected to provide valuable insights that can aid in clinical decision-making, particularly in determining the necessity of adjuvant therapy.

Materials and methods

Cases

This study presents a retrospective analysis of 186 cases of endometrial cancer, all diagnosed between 2018 and 2024. Histopathological data, including patient age, tumor type, histological grade, nuclear grade, tumor diameter, depth of invasion, lymphovascular invasion, perineural invasion, cervical stromal invasion, endocervical gland involvement, and uterine serosal involvement, were obtained from pathology reports. Additionally, immunohistochemical findings for markers such as p53, Ki-67, estrogen receptor (ER), progesterone receptor (PR), HER2, and PTEN, as well as treatment details, disease-free survival, and overall survival, were collected from the hospital automation system and patient follow-up records of the Department of Obstetrics and Gynecology.

The ethical approval for this study was granted by the Non-Interventional Clinical Research Ethics Committee of Pamukkale University in its meeting dated February 22, 2022 (meeting no: 04).

Immunohistochemistry

A representative tumor sample that best reflected the tumor tissue was selected for each case. From the selected paraffin blocks, 5-micron-thick sections were obtained and mounted on positively charged slides for PTEN antibody staining. The tissue samples were

incubated at 60°C overnight for deparaffinization and subsequently stained using an automated staining protocol with the VENTANA Benchmark XT system. Automated staining was performed using pre-diluted PTEN antibody (SP-218, Ventana, Rabbit Monoclonal Antibody) to visualize the targeted proteins.

The immunohistochemical expression of PTEN in tumor-dominant blocks was analyzed using a light microscope. When assessing PTEN expression in the endometrial carcinoma regions, the adjacent endometrial stroma was used as an internal positive control. PTEN reactivity was evaluated based on its extent and distribution through a semi-quantitative scoring system for nuclear staining. Cytoplasmic staining intensity was classified as either moderate to strong (positive) or faint (negative, indicating loss of expression) [9].

Statistical analysis

Statistical analyses were conducted using SPSS software (version 23.0, SPSS Inc., Chicago, IL, USA). Demographic and clinical data are presented as mean ± standard deviation (SD) or frequency (percentage). A *p*-value of <0.05 was considered statistically significant. Kaplan-Meier survival analysis, Cox regression analysis, Mann-Whitney U test, and Chi-square test were used for statistical assessment.

Results

Demographic and clinical data

A total of 186 endometrial cancer cases were included in the study. Histologically, 163 cases (87.6%) were diagnosed as endometrioid carcinoma, while 23 cases (12.4%) were classified into other subtypes, including serous carcinoma (n=11), mixed carcinoma (serous carcinoma + endometrioid carcinoma) (n=5), clear cell carcinoma (n=2), carcinosarcoma (n=3), and dedifferentiated carcinoma (n=2). Among these cases, 127 (68.3%) underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH+BSO), while 59 cases (31.7%) were diagnosed through curettage specimens. The patients' ages ranged from 31 to 89 years, with a mean age of 60.27±10.38 years. Tumor diameter ranged from 1 to 10 cm, with a mean size of 3.61±2.01 cm. 61 cases (32.8%) had tumors <3 cm, while 106 cases (57%) had tumors ≥3 cm. 123 cases (66.1%) were <65 years old, while 61 cases (32.8%) were ≥65 years old.

In the immunohistochemical analysis, the following marker expressions were observed: ER: 176/186 cases (94.6%), PR: 166/186 cases (89.2%), HER2, score 3: 1/181 cases (0.5%), p53 (mutant expression): 16/186 cases (16%), PTEN expression loss: 151/186 cases (81.2%), Ki-67 proliferation index >20%: 122/186 cases (65.6%).

In terms of tumor invasion, 53 cases (28.5%) exhibited invasion beyond the inner half of the myometrium. Serosal invasion was detected in 2 cases (1.1%), lymphovascular invasion in 19 cases (10.2%), and perineural invasion in 2 cases (1.1%). Malignant peritoneal fluid was identified in 3 cases (1.6%).

Staging analysis revealed that 74 cases (39.8%) were in early-stage (Stage I-II), while 9 cases (4.8%) were in advanced-stage (Stage III-IV). No recurrences were observed in the cohort. Six patients (3.2%) died during follow-up, with an overall survival duration ranging from 31 to 89 months and a mean survival of 26.5±14.88 months.

Association between tumor type and clinicopathological features

Endometrioid carcinomas were more frequently observed in patients younger than 65 years, whereas other tumor subtypes were predominantly found in patients older than 65 years (p=0.003). Perineural invasion was most commonly detected in the non-endometrioid group, with a statistically significant difference (p=0.000). Lymphovascular invasion was observed more frequently in endometrioid carcinoma compared to other subtypes (p=0.044) (Figure 1).

Immunohistochemical analysis showed that the Ki-67 proliferation index was higher in serous carcinoma, clear cell carcinoma, and mixed-type carcinomas than in endometrioid carcinoma, with a trend indicating it may exceed 20% (p=0.094) (Figure 2a, 2b). P53 mutation was most frequently detected in serous carcinoma, and this difference was statistically significant (p=0.000) (Figure 2c, 2d).

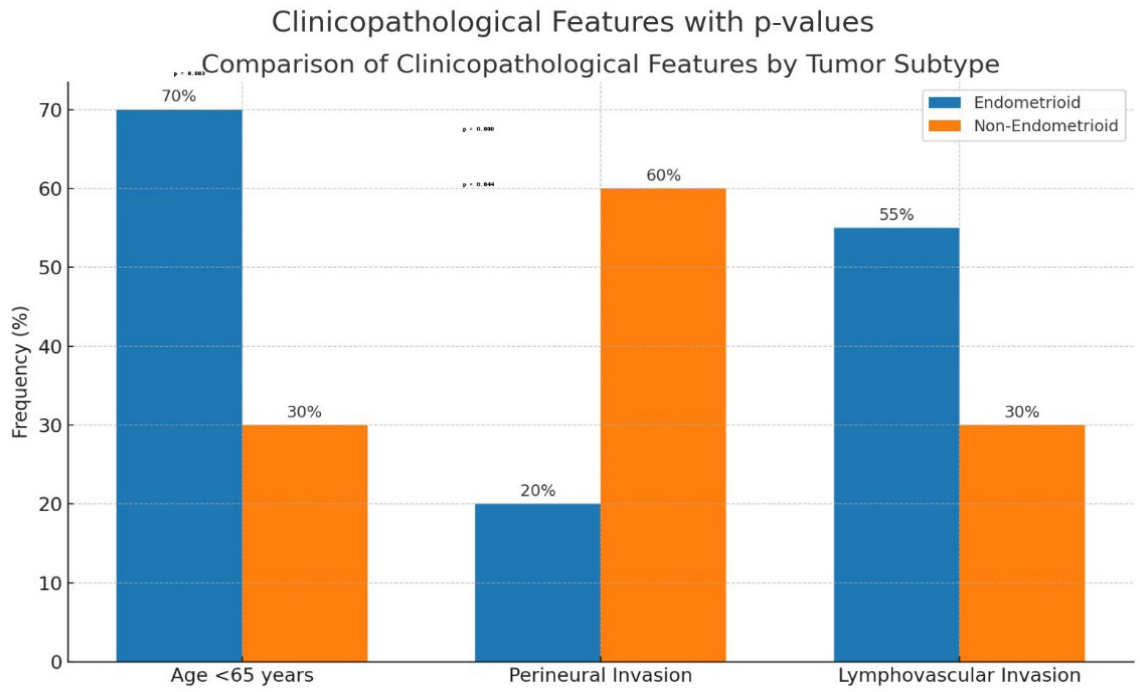

Figure 1. Comparison of clinicopathological features by tumor subtypes

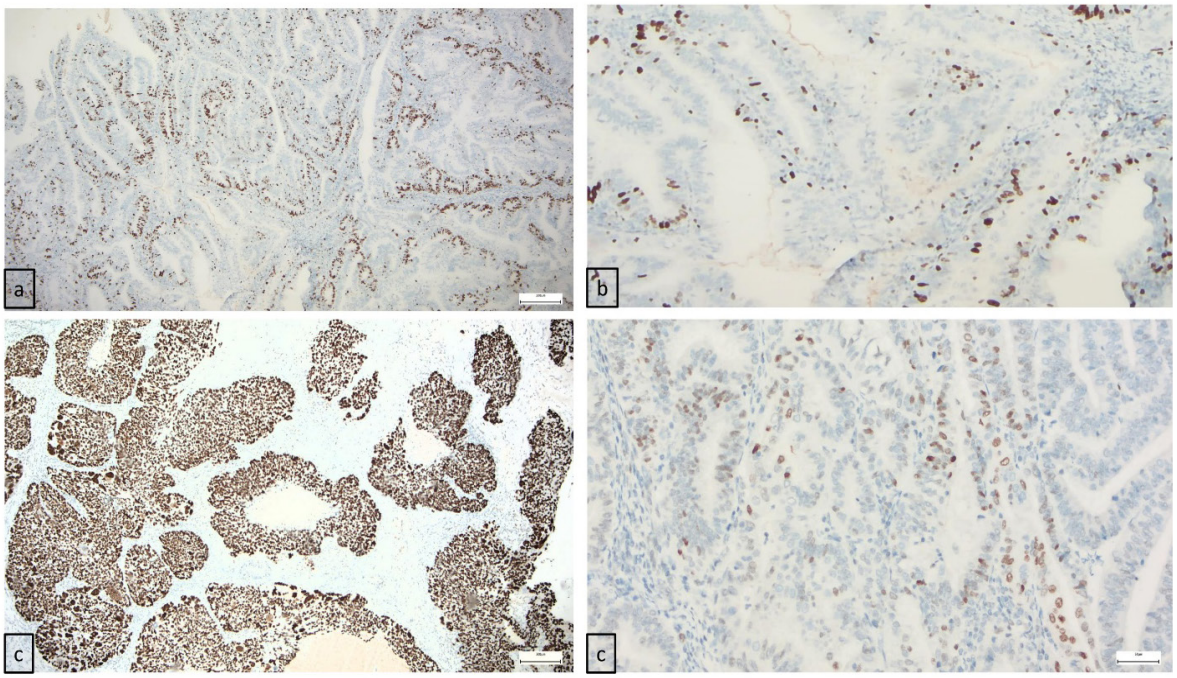

Figure 2. a. Immunohistochemically, Ki-67 proliferation index > 20% in a high-grade tumor, IHC, x100 b. Ki-67 proliferation index < 20%, IHC, x200 c. Strong nuclear p53 positivity, mutant, IHC, x100 d. Rare nuclear p53 positivity, wild-type, IHC, x200

HER2 positivity was identified in serous carcinoma (p=0.000). In contrast, estrogen receptor (ER) and progesterone receptor (PR) expression was most commonly observed in endometrioid carcinoma (p=0.000). The mortality rate was significantly higher in patients diagnosed with serous carcinoma and other aggressive subtypes, including carcinosarcoma and dedifferentiated carcinoma (p=0.004). The clinicopathological distribution of the cases is presented in Table 1.

Table 1. Distribution of cases according to their clinicopathological features

Clinicopathological Features	Number of Patients Endometrioid Carcinoma n=163 (87.6%)	Number of Patients Others n=23 (12.4%)	Total n=186 (10%)	*p*	**X^2 value
Age					
<65	115 (62.5%)	8 (4.3%)	123 (66.8%)	0.000*	12.195
≥65	46 (25%)	15 (8.2%)	61 (33.2%)		
Tumor diameter					
<3 cm	55 (32.9%)	6 (3.6%)	61 (36.5%)	0.634	0.194
≥3 cm	93 (55.7%)	13 (7.8%)	106 (63.5%)		
Histological grade					
Low grade	122 (70.1%)	0 (0%)	122 (70.1%)	0.000*	59.086
High grade	30 (17.2%)	22 (12.6%)	52 (29.9%)		
Myometrial invasion					
Inner half invasion	105 (62.1%)	11 (6.5%)	116 (68.6%)	0.161	1.960
Outer half invasion	44 (26%)	9 (5.3%)	54 (31.4%)		
Lymphovascular invasion					
No	142 (76.3%)	18 (9.7%)	160 (86.0%)	0.044*	6.249
Yes	17 (9.1%)	2 (1.1%)	19 (10.2%)		
Perineural invasion					
No	158 (88.3%)	19 (10.6%)	177 (98.9%)	0.000	3.702
Yes	1 (0.6%)	1 (0.6%)	2 (1.1%)		
Endocervical gland involvement					
No	142 (76.3%)	16 (8.6%)	158 (84.9%)	0.030*	7.014
Yes	7 (3.8%)	4 (2.2%)	11 (5.9%)		
Stage					
I-II	68 (81.9%)	6 (7.2%)	74 (89.2%)	0.375	0.787
III-IV	9 (10.8%)	0 (0%)	9 (10.8%)		
Patient survival					
Alive	160 (86%)	20 (10.8%)	182 (52.3%)	0.004*	8.103
Ex	3 (1.6%)	3 (1.6%)	166 (47.7%)		

*p<0.05 statistically significant difference; chi-square analysis

Correlation between PTEN expression and tumor characteristics

Loss of PTEN expression was most commonly observed in the endometrioid carcinoma subtype (Figure 3a-3d). PTEN expression loss was also observed in the other tumors (Figure 4a-4c). Additionally, Chi-square analysis revealed that loss of PTEN expression was more prominently observed in tumors with a diameter >3 cm (p=0.16). Loss of PTEN expression was not significantly associated with clinical-pathological parameters, such as age, perineural invasion, lymphovascular invasion, endocervical gland involvement, cervical stromal invasion, metastasis, recurrence, or immunohistochemical markers like Ki-67, p53, ER, PR, and HER2 (p>0.05) (Table 2) (Figure 5).

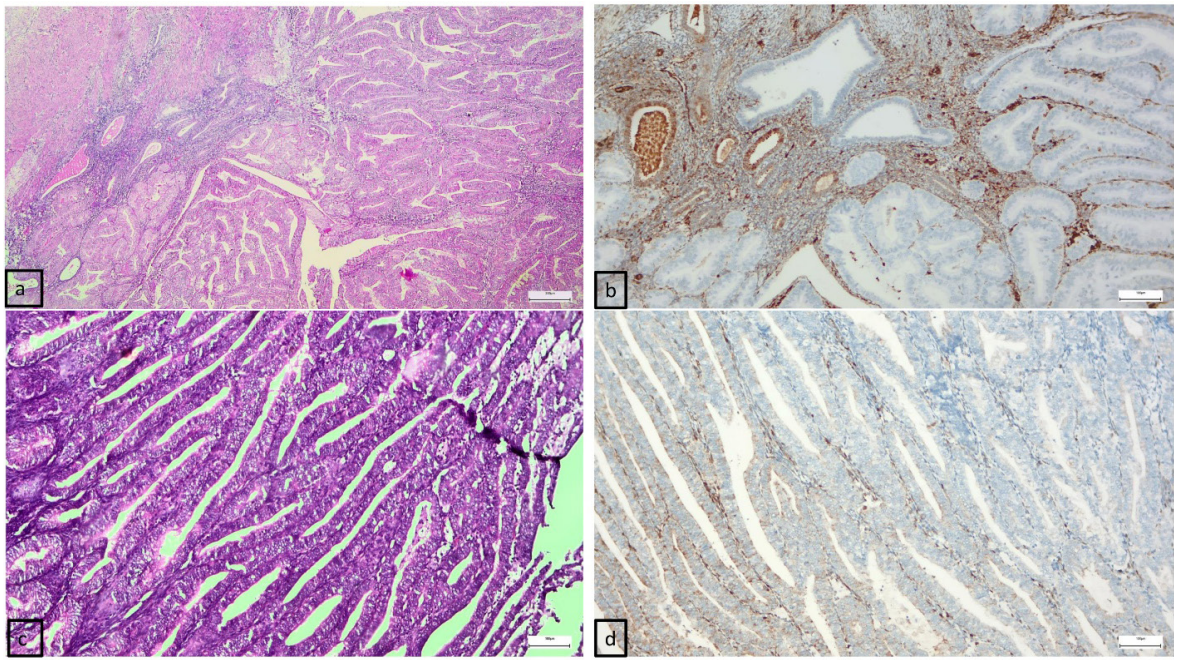

Figure 3. a. Endometrioid carcinoma, H&E, x100 b. Loss of PTEN immunoexpression observed in tumor areas, with no loss in normal glands, IHC, x200 c. Endometrioid carcinoma, H&E, x200 d. Weak staining areas with PTEN observed, but no loss, IHC, x200

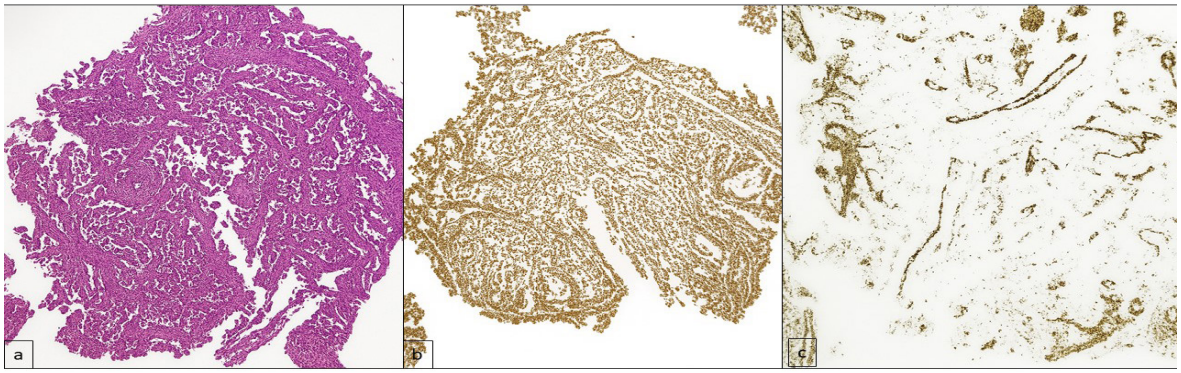

Figure 4. a. High-power microscopic image showing a papillary architecture with hierarchical branching, fibrovascular cores, and nuclear atypia, consistent with serous papillary carcinoma. H&E, x100. b. Immunohistochemical staining for p53 demonstrating strong and diffuse nuclear positivity in tumor cells, consistent with a mutant (aberrant) expression pattern, supporting the diagnosis of serous papillary carcinoma, IHC, x100. c. PTEN showing complete loss of cytoplasmic and nuclear expression in tumor cells, while surrounding stromal and inflammatory cells retain expression, IHC, x200

Table 2. Relationship of PTEN immunoexpression with clinicopathological features

Clinicopathological Features	Number of Patients Loss of PTEN Immunoexpression n=151 (81.2%)	Number of Patients No loss of PTEN Immunoexpression n=35 (18.8%)	*p*	**X^2 value
Age				
<65	100 (54.3%)	23 (12.5%)	0.874	0.025*
≥65	49 (50.5%)	12 (6.5%)		
Tumor type				
Endometrioid	135 (72.6%)	28 (15.1%)	0.128	2.319
Others	16 (8.6%)	7 (3.8%)		
Tumor size				
<3 cm	44 (26.3%)	17 (10.2%)	0.019*	5.506
≥3 cm	92 (55.1%)	14 (8.4%)		
Biopsy type				
Endometrial curettage	52 (28%)	7 (3.8%)	0.098	2.734
TAH+BSO	99 (53.2%)	28 (15.1%)		
Tumor grade				
Low grade	99 (56.9%)	23 (13.2%)	0.810	0.058
High grade	43 (24.7%)	9 (5.2%)		
Histological grade				
1	12 (14%)	5 (5.8%)		
2	41 (47.7%)	13 (15.1%)	0.822	0.392
3	12 (14%)	3 (3.5%)		
Lymphovascular invasion (LVI)				
No	128 (68.8%)	32 (17.2%)	0.578	1.096
Yes	17 (9.1%)	2 (1.1%)		
Myometrial invasion				
Inner half invasion	94 (55.6%)	22 (13%)	0.757	0.096
Outer half invasion	44 (26%)	9 (5.3%)		
Evre				
I-II	66 (79.5%)	8 (9.6%)	0.299	1.077
III-IV	9 (10.8%)	0 (0%)		
Patient survival				
Alive	144 (77.4%)	35 (18.8%)	0.194	1.437
Ex	7 (3.8%)	0 (0%)		

**p*<0.05 statistically significant difference; chi-square analysis

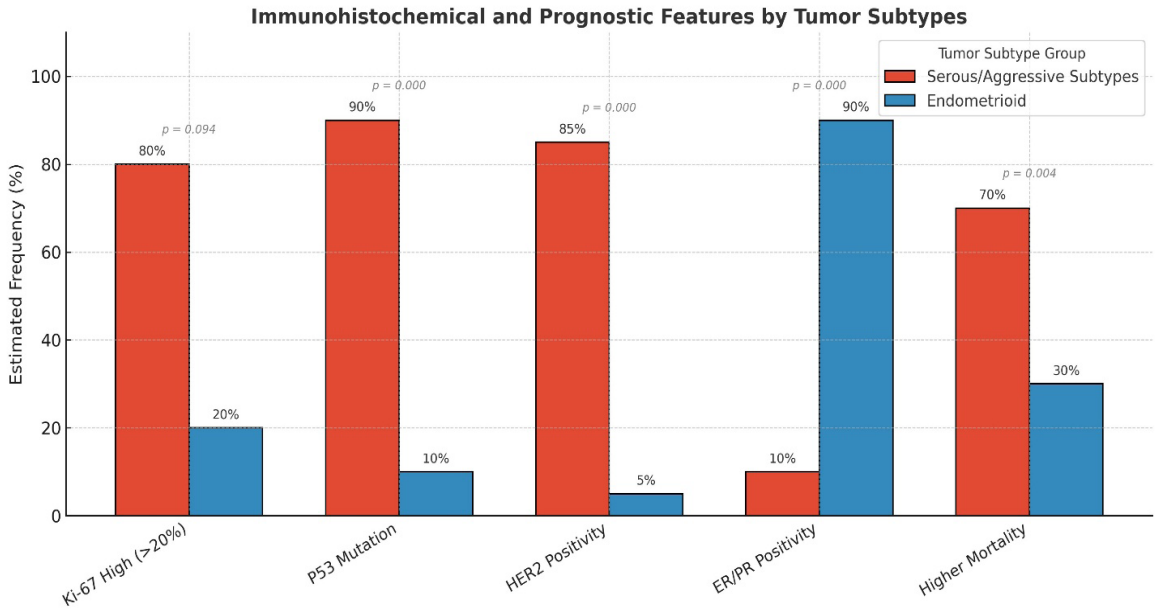

Figure 5. Immunohistochemical and prognostic features by tumor subtypes

In this study, various clinicopathological parameters were compared according to the group_pten variable using the Mann-Whitney U test. The analysis revealed a statistically significant difference between the groups only in terms of tumor size (U=1611.5, Z=-2.395, *p*=0.017). No significant differences were observed for the other variables (*p*>0.05). The effect size (Cohen's r) was also calculated for the tumor size variable and found to be r=0.176.

PTEN positivity and disease outcome

Kaplan–Meier survival analysis was conducted to evaluate the impact of various clinical and pathological parameters on overall survival (OS) and disease-free survival (DFS). The loss of PTEN expression did not exhibit a statistically significant association with either OS or DFS (*p*=0.219). However, patients with high-grade tumors demonstrated significantly lower survival rates compared to those with low-grade tumors (*p*=0.048; low-grade: 65.893±0.776 months vs. high-grade: 59.153±2.322 months). Furthermore, patients with perineural invasion exhibited markedly poorer survival outcomes (*p*=0.000; perineural invasion present: 29±4.950 months vs. absent: 65.509±0.737 months). Additionally, the presence of a p53 mutation was associated with a significant reduction in survival (*p*=0.033; wild-type p53: 65.373±0.803 months vs. mutant p53: 39.917±3.331 months).

Conversely, variables such as age, lymphovascular invasion, endocervical gland involvement, cervical stromal invasion, metastasis, recurrence, and immunohistochemical markers (including Ki-67, ER, PR, and HER2) were not found to have a significant impact on survival. Kaplan-Meier survival curves were generated for each of these parameters; however, statistical analysis using the log-rank test and Cox regression model revealed no significant association with survival time (*p*>0.05).

Discussion

This study aimed to evaluate the relationship between PTEN expression and various tumor characteristics in endometrial cancer, such as stage, grade, and patterns of invasion and recurrence. These findings will contribute to understanding disease prognosis and will aid in future targeted individualized therapies.

Loss of PTEN function is a significant event in endometrial carcinogenesis, which may develop in response to known endocrine risk factors. Additionally, PTEN is a useful immunohistochemical biomarker in the evaluation of premalignant diseases. In cases where PTEN expression is impaired, the underlying genetic modification is typically associated with mutations [2, 10]. Moreover,

PTEN IHC results showed positive staining in 9 of 33 endometrioid adenocarcinoma cases (27.27%) and negative staining in 24 cases (72.73%) [2, 9]. PTEN inactivation has been reported in 83% of endometrioid endometrial cancer cases and in 55% of precancerous lesions, characterized by loss of expression [11, 12]. PTEN inactivation driven by mutations is linked to early-stage disease and a more favorable prognosis. Patients with PTEN mutations have a 5-year survival rate of approximately 80%, while the survival rate is around 50% in patients without such mutations [11]. A study referencing The Cancer Genome Atlas (TCGA) database found that PTEN was mutated in 57% of 530 EC patients [13]. A similar finding was also observed with multigene next-generation sequencing (NGS) [14, 15]. In our study, PTEN inactivation was observed in 82.8% of endometrioid endometrial cancer cases, but it was not associated with survival.

In 2013, The Cancer Genome Atlas Research Network classified EC into four distinct molecular categories. In the 'ultramutated', 'hypermutated', and 'low copy number' categories, which are typically endometrioid, PTEN mutations were found in 94%, 88%, and 77% of cases, respectively. In the last category, mainly consisting of serous EC ('high copy number'), PTEN mutations were found in only 15% of cases [16]. In our study, PTEN inactivation was seen in 63.6% of other carcinoma cases, which is higher than reported in the literature, possibly due to the smaller sample size. A higher rate of PTEN loss was observed in stage III cancers [11], although no such relationship was found in our study.

The normal endometrium goes through cycles of growth and changes in response to hormonal fluctuations. Interestingly, studies from two different research groups have shown that during the proliferative phase of the menstrual cycle, when estradiol is more dominant, PTEN protein levels are highest in the uterine epithelial cells [17, 18]. Previous studies suggest that long-term exposure to high estrogen levels, along with the accumulation of genetic mutations, plays a key role in the progression of hyperplastic endometrium to type I endometrial carcinoma [19, 20]. However, PTEN mutations may contribute to the early development of atypical endometrial hyperplasia, and additional mutations in KRAS and PIK3CA are linked to the transformation of this hyperplasia into cancer [21]. It is important to note that PTEN mutations alone are not enough to cause cancer. In six out of eight cases, the carcinomas had mutations not found in surrounding healthy tissue, indicating that other mutations are also necessary for the cancer to develop [11]. However, this study did not assess the relationship between PTEN inactivation and hormone receptor status.

Tumor molecular biology research has supported the development of anti-tumor compounds. In the new approach to drug discovery, the selection of molecular targets has become a key issue. The mechanism of the PTEN gene and its associated signaling pathways has become a hot topic in targeted research. Further studies on the PTEN gene signaling pathway will provide new ideas and foundations for the diagnosis and treatment of tumors at the genetic level [6].

A limitation of our study is the smaller number of cases in the non-endometrioid group. Further studies with larger patient cohorts could yield different results. Moreover, PTEN was analyzed using immunohistochemistry, and genomic methods could provide more effective results.

In conclusion, our study found that the loss of PTEN expression did not have a significant direct effect on survival. However, other clinical and genetic factors, such as high-grade tumors, perineural invasion, and p53 mutations, significantly impacted survival. These findings suggest that to better understand the prognosis of endometrial cancer, other genetic and clinical factors should be considered. This highlights the need for personalized clinical management, where each patient is treated according to their genetic and clinical characteristics. Additionally, the prognostic significance of PTEN expression in EEC should be further investigated using genomic and proteomic approaches. A detailed study of PTEN status and metabolic conditions may improve the management of EEC patients in gynecological clinical settings.

Funding: None

Authors contributions: Y.A.K. formulated the study's main concept and hypothesis. Y.A.K. and Ö.K.C. developed the theoretical framework and organized the materials and methods. Y.A.K. conducted the data analysis. Both authors wrote and approved the discussion section. All authors participated in discussions and approved the final manuscript.

Conflict of interest: The authors declare no conflicts of interest.

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