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Research Article

Prognostic Importance of PTEN, p53, and MDM2 Expressions in Endometrioid and Serous-Type Endometrial Carcinomas

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Abstract

Aim: Endometrial carcinomas (ECs) are neoplasms with the highest rate of change in the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway. In this study, the relationship among PTEN, MDM2, and p53 protein expression in the PI3K/AKT/mTOR pathway with clinicopathological data in endometrioid endometrial carcinomas (EECs) and serous-type endometrial carcinomas (SECs) was evaluated.

Material and Method: A hundred and twenty cases of patients who underwent hysterectomy for EC between 2009 and 2021 were included in the study. Thirty cases of SEC and 90 cases of EEC were evaluated. EEC cases consist of grades 1-3 tumors, and each group includes 30 patients. p53 was examined in two groups as normal/wild type and abnormal/mutant type. PTEN and MDM2 were examined in two groups: positive and negative. The relationship among p53, PTEN, and MDM2 immunohistochemical expression status with histological grade, myometrial invasion, cervical invasion, lymphovascular invasion (LVI), metastatic lymph nodes, presence of tumor in peritoneal fluid, tumor stage, and overall and progression-free survival was evaluated.

Results: Loss of PTEN was associated with EEC compared to SEC (p<0.001). PTEN loss is mostly associated with p53 normal/wild type (p=0.038). MDM2 expression was associated with a lower histological grade (p<0.001) and stage (p=0.002). MDM2 expression was inversely associated with lymphovascular invasion (p=0.017), cervical invasion (p=0.040), and peritoneal fluid retention (p=0.018). In most cases showing MDM2 expression, p53 was found to be normal/wild type (p=0.011). p53 mutation was found to be associated with advanced age (p=0.002), SEC (p<0.001), high grade (p<0.001), high risk (p<0.001), advanced stage (p=0.002), adjuvant therapy (p=0.002), and peritoneal fluid involvement (p=0.002) and low overall (p=0.014) and progression-free survival (p=0.050).

Conclusion: MDM2 expression was found to be associated with positive prognostic parameters. PTEN loss can be used to distinguish between EEC and SEC. p53 remains a critical determinant of prognosis in ECs.

Keywords: Endometrial carcinomas, PTEN, MDM2, p53, immunohistochemistry

INTRODUCTION

ECs are the most common gynecological malignancy in the United States (1). Unlike most cancers, the incidence rates of ECs have been increasing over the past two decades and are expected to increase significantly. This increase has been attributed to obesity rates, the aging of the population, and the decreased use of combined menopausal hormone therapy (2).

Bokhman's classification system classifies ECs as type I (endometrioid type) or type II (serous type) based on clinical, demographic, and endocrine characteristics (3). Type I ECs have a good prognosis and are associated with hyperestrogenism and obesity. Type II ECs have a poor prognosis and are not associated with hyperestrogenism or obesity (4).

The PI3K/AKT/mTOR pathway is involved in numerous cancers. Endometrial cancers exhibit the highest frequency of alterations in this pathway, occurring in 80% of cases. Specifically, alterations in this pathway are observed in 92% of type I endometrial cancers and 60% of type II endometrial cancers. Loss of phosphatase tensin homolog (PTEN) and/or PI3K mutations are seen in type I ECs, whereas type II ECs are associated with a high

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mTOR expression and less PTEN loss (5). PTEN, a tumor suppressor gene found on chromosome 10, produces a protein that influences various cellular functions such as cell death and proliferation via the PI3K/AKT/mTOR pathway (6). PTEN enhances both the levels and activity of p53 by suppressing MDM2's transcription and its ability to bind to p53 (7). It also inhibits MDM2 from entering the nucleus, thus detaching it from p53 (8).

MDM2 functions as an oncoprotein regulating tumorigenesis. Its mRNA level is subject to transcriptional control by p53 following DNA damage, including oxidative stress (9). MDM2, functioning as a ubiquitin ligase, attaches ubiquitin to both p53 and itself when situated in the cytoplasm, consequently directing both proteins for proteasomal degradation. AKT regulates both the MDM2 protein itself and its cellular localization (10). PTEN suppresses MDM2 transcription, while PI3K/AKT signaling facilitates MDM2 translocation. When PTEN is absent in cells, MDM2 promoter activity becomes apparent, leading to elevated MDM2 expression. MDM2 plays a crucial role as the regulator of p53 (8).

The most prevalent somatic gene alteration observed in neoplasms is the mutation of p53 (11). The p53 protein is a stress-activated transcription factor that positively regulates the gene products required for cell cycle arrest or apoptosis (9).

This study will evaluate the relationship of PTEN, MDM2, and p53 expression with prognostic factors and other clinicopathological data in endometrioid and serous-type endometrial carcinomas. The importance of this pathway in treatment will be questioned, and this pathway may guide the development of targeted therapy agents.

MATERIAL AND METHOD

Following local ethics committee approval on November 18, 2020, reference number 2020/22, 120 consecutive cases diagnosed with EEC or SEC were included in the study. These cases were selected from specimens obtained after total abdominal hysterectomy + bilateral salpingo-oophorectomy (TAH+BSO) and/or regional lymphadenectomy performed between 2009 and 2021. EECs constitute 90 of these cases and SECs constitute 30 of them. Cases of EECs consisted of grades 1, 2, and 3 tumors, and each group included 30 patients (Figure 1). Data pertinent to patient records, including age, tumor size, tumor stage, lymph node metastasis, affected lymph node area, total number of lymph nodes, prognostic category, treatment status, involvement of peritoneal fluid, recurrence status, and survival, were extracted. Two pathologists reviewed hematoxylin-eosin-stained pathology slides to assess pathological prognostic factors including histological subtype, tumor grade, myometrial invasion, cervical invasion, and lymphovascular invasion.

The clinical and pathological staging of the cases were re-evaluated according to the WHO 2019 TNM and FIGO staging system.

The cases were examined in five groups as low, moderate, moderate-high, high, and advanced metastatic, according to the prognostic risk groups recommended by the International Society of Gynecological Pathologists (ISGyP) guidelines.

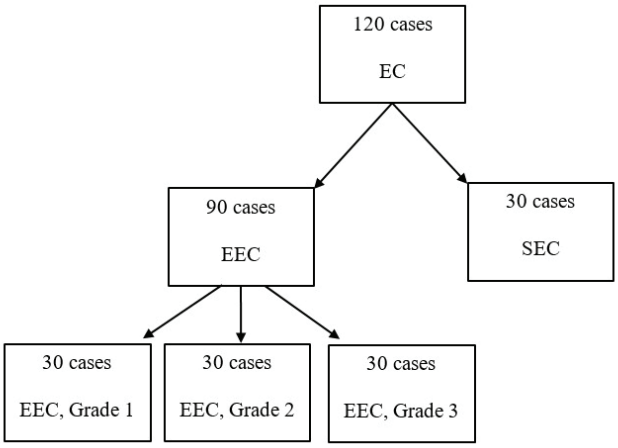

Figure 1. Flow chart of the distribution of groups

Evaluation and Scoring of Immunohistochemically Stained Slides

While evaluating PTEN immunohistochemical staining, a comparison with stroma was made. If there was no staining in the tumor, the score was 0; less than stroma, light brown staining, score 1 (+); less intense than stroma and moderate brown staining, score 2 (++); equal or more severe staining with the stroma was evaluated as score 3 (+++). A score of 0 was defined as PTEN negative and a score of 1–3 as PTEN positive (12).

In the evaluation of MDM2, the rate of positive staining were determined by photographing the cases with the most intense staining in a high-magnification area (with the AxioCam MRc5 camera connected to the Zeiss Imager.D1 brand microscope). Ten percent or more staining was accepted as positive expression and less than 10% staining as negative expression (11,13).

p53 staining is evaluated as normal/wild type and abnormal/mutant type. In the normal/wild type, heterogeneous staining is seen in the cells. In the abnormal/mutant type, there are three different staining patterns. The first is the overexpression pattern of p53, in which more than 80% of tumor cells show strong and diffuse nuclear staining. Another pattern is the null pattern, in which no staining is seen in the tumor cells. Internal control is essential when evaluating this pattern. The last pattern is the pattern in which cytoplasmic staining is seen in tumor cells. In this pattern, nuclear staining should be of the same or less intensity than the cytoplasm. If the nuclear staining is more intense than

the cytoplasm, this cannot be considered a cytoplasmic pattern. In addition to these staining patterns, the presence of a normal pattern with one or more abnormal patterns is called a subclonal staining pattern. The threshold for subclonal staining is the presence of a population of at least 12 cells with an abnormal staining pattern (14).

Statistical Analysis

The data underwent analysis within a computerized setting utilizing the SPSS 25.0 software. When the expected value was less than 5 in over 20% of cells within multi-well tables, Fisher's exact test was employed. The normal distribution of continuous data was assessed through Q-Q plots, skewness, and kurtosis. The multiple Cox proportional hazards model was used to examine the parameters affecting the survival time of the patients, and the Kaplan–Meier method was used to examine the lifetime curves. A significance level of $p<0.05$ was considered for all analytical findings.

RESULTS

One hundred and twenty patients diagnosed with EC were evaluated in this study. The mean age of the patients was 60 years (25–87). The mean follow-up period of the patients was 66.0±46.6 (1.0–140.0) months. At the end of the follow-up period, 72.5% (n=87) of the patients included in the study were alive and 27.5% (n=33) were dead. The mean tumor size was 4.8±2.1 (0.5–11.0) cm. The clinicopathological characteristics of the patients are summarized in Table 1.

Immunohistochemical analysis of p53, PTEN, and MDM2 is shown in Figures 2-4.

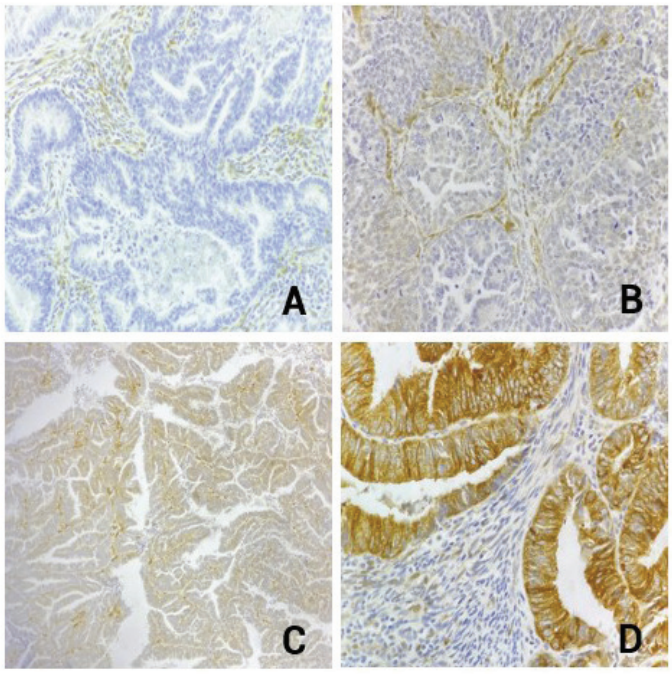

Figure 2. PTEN staining scores: A. Score 0 (x200); B. Score 1 (x100); C. Score 2 (x100); D. Score 3 (x400)

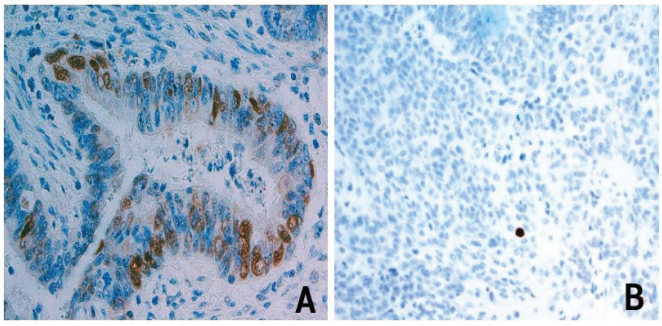

Figure 3. Positive (A) and negative (B) expression in tumor cells by MDM2 (x400)

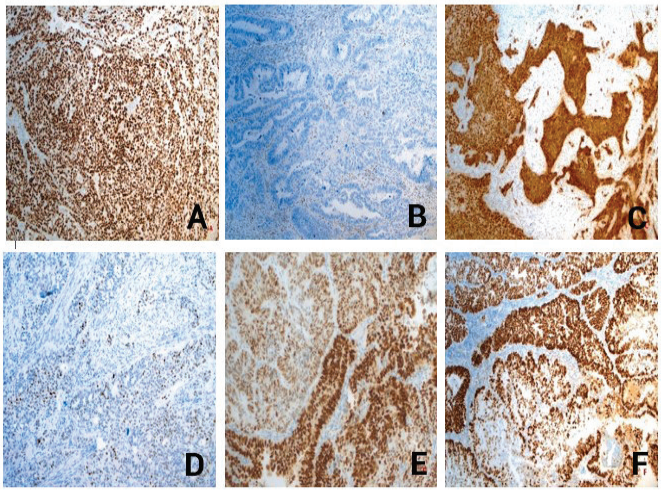

Figure 4. A. abnormal/mutant p53 overexpression pattern (x100); B. abnormal/mutant p53, null pattern (x200); C. abnormal/mutant p53, cytoplasmic pattern (x400); D. p53 normal/wild type (x100); E and F. subclonal pattern (x200).

Relationship between p53, PTEN, and MDM2 Expressions with Clinicopathological Data

p53 abnormal/mutant-type staining was higher in patients over 60 years of age ($p=0.002$), in SEC ($p<0.001$), in the high and advanced metastatic risk group, ($p<0.001$), in stage 4, ($p=0.002$), in those with retained peritoneal fluid ($p=0.002$) and in those receiving adjuvant therapy ($p=0.015$). No statistically significant correlation was found between p53 expression and other clinicopathological data ($p>0.05$) (Table 1).

Loss of PTEN was found to be higher in EEC than in SEC ($p<0.001$). No statistically significant correlation was found between PTEN expression and other clinicopathological data ($p>0.05$) (Table 1).

MDM2 expression was observed in grade 1 EEC ($p<0.001$), and low-risk group ($p=0.002$). MDM2 expression was inversely associated with adjuvant therapy ($p<0.001$), LVI ($p=0.017$), cervical invasion ($p=0.040$), and peritoneal fluid retention ($p=0.018$). No statistically significant correlation was found between MDM2 expression and other clinicopathological data ($p>0.05$) (Table 1).

Table 1. Relationship among PTEN, P53, and MDM2 expressions with clinicopathological data

			p53			PTEN			MDM2		
		(n/%)	N/W	A/M	p*	Negative	Positive	p*	Negative	Positive	p*
Age	**≤60 (n/%)**	59 (49.1)	45 (76.3)	14 (23.7)	**0.002**	31 (52.5)	28 (47.5)	0.713	41 (69.5)	18 (30.5)	0.25
	>60 (n/%)	61 (50.9)	30 (49.2)	31 (50.8)		30 (49.2)	31 (50.8)		48 (78.7)	13 (21.3)	
Histological type	**EEC (n/%)**	90 (75.0)	71 (78.9)	19 (21.1)	**<0.001**	54 (60.0)	36 (40.0)	<0.001	64 (71.1)	26 (28.9)	0.185
	SEC (n/%)	30 (25.0)	4 (13.3)	26 (86.7)		7 (23.3)	23 (76.7)		25 (83.3)	5 (16.7)	
Grade	**Grade 1 EEC (n/%)**	30 (25.0)	29 (96.7)[a]	1 (3.3)a	**<0.001**	20 (66.7)[a]	10 (33.3)[a]	0.005	12 (40.0)[a]	18 (60.0)[a]	**<0.001**
	Grade 2 EEC (n/%)	30 (25.0)	25 (83.3)[a.b]	5 (16.7)[a.b]		17 (56.7)[a.b]	13 (43.3)[a.b]		24 (80.0)[b]	6 (20.0)[b]	
	Grade 3 EEC (n/%)	30 (25.0)	17 (56.7)[b]	13 (43.3)[b]		17 (56.7)[a.b]	13 (43.3)[a.b]		28 (93.3)[b]	2 (6.7)[b]	
	SEC (n/%)	30 (25.0)	4 (13.3)[c]	26 (86.7)[c]		7 (23.3)b	23 (76.7)[b]		25 (83.3)[b]	5 (16.7)[b]	
Risk groups	**Low (n/%)**	29 (24.2)	27 (93.1)[a]	2 (6.9)[a]	**<0.001**	18 (62.1)	11 (37.9)	0.299	14 (48.3)[a]	15 (51.7)[a]	**0.002**
	Middle (n/%)	21 (17.5)	15 (71.4)[a.b]	6 (28.6)[a.b]		12 (57.1)	9 (42.9)		15 (71.4)[a.b]	6 (28.6)[a.b]	
	Middle-high (n/%)	15 (12.5)	11 (73.3)[a.b]	4 (26.7)[a.b]		6 (40.0)	9 (60.0)		14 (93.3)[b]	1 (6.7)[b]	
	High (n/%)	40 (33.3)	19 (47.5)[b.c]	21 (52.5)[b.c]		16 (40.0)	24 (60.0)		32 (80.0)[a.b]	8 (20.0)[a.b]	
	Advanced metastatic (n/%)	15 (12.5)	3 (20.0)[c]	12 (80.0)[c]		9 (60.0)	6 (40.0)		14 (93.3)[b]	1 (6.7)[b]	
Stage	**1 (n/%)**	68 (56.7)	49 (72.1)[a]	19 (27.9)[a]	**0.002**	34 (50.0)	34 (50.0)	0.844	45 (66.2)	23 (33.8)	0.092**
	2 (n/%)	9 (7.5)	7 (77.8)[a]	2 (22.2)[a]		5 (55.6)	4 (44.4)		8 (88.9)	1 (11.1)	
	3 (n/%)	28 (23.3)	16 (57.1)[a.b]	12 (42.9)[a.b]		13 (46.4)	15 (53.6)		22 (78.6)	6 (21.4)	
	4 (n/%)	15 (12.5)	3 (20.0)[b]	12 (80.0)[b]		9 (60.0)	6 (40.0)		14 (93.3)	1 (6.7)	
Survival	**Alive (n/%)**	87 (72.5)	59 (67.8)	28 (32.2)	0.051	45 (51.7)	42 (48.3)	0.751	62 (71.3)	25 (28.7)	0.238
	Ex (n/%)	33 (27.5)	16 (48.5)	17 (51.5)		16 (48.5)	17 (51.5)		27 (81.8)	6 (18.2)	
Recurrence	**No (n/%)**	112 (93.4)	72 (64.3)	40 (35.7)	0.131	57 (50.9)	55 (49.1)	0.961**	83 (74.1)	29 (25.9)	0.956
	Yes (n/%)	8 (6.6)	3 (37.5)	5 (62.5)		4 (50.0)	4 (50.0)		6 (75.0)	2 (25.0)	
Adjuvant therapy	**No (n/%)**	31 (25.8)	25 (80.6)	6 (19.4)	**0.015**	19 (61.3)	12 (38.7)	0.176	14 (45.2)	17 (54.8)	**<0.001**
	Yes (n/%)	89 (74.2)	50 (56.2)	39 (43.8)		42 (47.2)	47 (52.8)		75 (84.3)	14 (15.7)	
LVİ	**No (n/%)**	89 (74.2)	59 (66.3)	30 (33.7)	0.146	45 (50.6)	44 (49.4)	0.92	61 (68.5)	28 (31.5)	**0.017**
	Yes (n/%)	31 (25.8)	16 (51.6)	15 (48.4)		16 (51.6)	15 (48.4)		28 (90.3)	3 (9.7)	
Cervix invasion	**No (n/%)**	83 (69.2)	54 (65.1)	29 (34.9)	0.386	43 (51.8)	40 (48.2)	0.749	57 (68.7)	26 (31.3)	**0.04**
	Yes (n/%)	37 (30.8)	21 (56.8)	16 (43.2)		18 (48.6)	19 (51.4)		32 (86.5)	5 (13.5)	
Peritoneal fluid retention	**No (n/%)**	98 (83.1)	67 (68.4)	31 (31.6)	**0.002**	48 (49.0)	50 (51.0)	0.624	68 (69.4)	30 (30.6)	**0.018**
	Yes (n/%)	20 (16.9)	6 (30.0)	14 (70.0)		11 (55.0)	9 (45.0)		19 (95.0)	1 (5.0)	
Pelvic lymph node involvement	**No (n/%)**	87 (73.7)	56 (64.4)	31 (35.6)	0.348	44 (50.6)	43 (49.4)	0.834	62 (71.3)	25 (28.7)	0.308
	Yes (n/%)	31 (26.3)	17 (54.8)	14 (45.2)		15 (48.4)	16 (51.6)		25 (80.6)	6 (19.4)	
Paraaortic lymph node involvement	**No (n/%)**	96 (81.4)	62 (64.6)	34 (35.4)	0.204	48 (50.0)	48 (50.0)	>0.999	70 (72.9)	26 (27.1)	0.675
	Yes (n/%)	22 (18.6)	11 (50.0)	11 (50.0)		11 (50.0)	11 (50.0)		17 (77.3)	5 (22.7)	
Myometrium invasion	**<1/2 (n/%)**	65 (54.2)	41 (63.1)	24 (36.9)	0.887	33 (50.8)	32 (49.2)	0.988	45 (69.2)	20 (30.8)	0.179
	≥1/2 (n/%)	55 (45.8)	34 (61.8)	21 (38.2)		28 (50.9)	27 (49.1)		44 (80.0)	11 (20.0)	

* chi-square test; N/W: normal/wild; A/M: abnormal/mutant

Interrelationship of p53, PTEN, and MDM2 Expression

When the relationship among p53, PTEN, and MDM2 expressions was evaluated, it was observed that p53 normal/wild type staining was higher in those with MDM2 staining than in those without (p=0.005). In those with PTEN loss, p53 normal/wild-type staining was found to be high (p=0.038). It was observed that PTEN staining and MDM2 staining did not differ according to each other (p>0.999) (Table 2).

When the patients were grouped as EEC and SEC and the relationship between PTEN, p53, and MDM2 staining status was evaluated, it was observed that p53 normal/wild type staining was higher in those with MDM2 staining than in those without MDM2 staining (p=0.011). (Table 3).

Table 2. Interrelationship among p53, PTEN, and MDM2 expressions in whole patients

			p53		X^2	p*
			N/W	A/M		
MDM2	Negative	n (%)	49 (55.1)	40 (44.9)	8.145	**0.005**
	Positive	n (%)	26 (83.9)	5 (16.1)		
PTEN	Negative	n (%)	44 (72.1)	17 (27.9)	4.91	**0.038**
	Positive	n (%)	31 (52.5)	28 (47.5)		
			MDM2			
			Negative	Positive		
PTEN	Negative	n (%)	45 (73.8)	16 (26.2)	0.01	>0.999
	Positive	n (%)	44 (74.6)	15 (25.4)		

* chi-square test; N/W: normal/wild; A/M: abnormal/mutant

Table 3. Interrelationship of p53, PTEN, and MDM2 expression in separate groups of EEC and SEC

				p53		X^2	P
				N/W	A/M		
EEC	PTEN	Negative	n (%)	44 (81.5)	10 (18.5)	0.545	0.46*
		Positive	n (%)	27 (75.0)	9 (25.0)		
	MDM2	Negative	n (%)	46 (71.09)	18 (28.1)	6.544	**0.011***
		Positive	n (%)	25 (96.2)	1 (3.8)		
				MDM2			
				Negative	Positive		
	PTEN	Negative	n (%)	39 (60.9)	25 (39.1)	0.81	0.776*
		Positive	n (%)	15 (57.7)	11 (42.3)		
				p53			
				N	A/M		
SEC	PTEN	Negative	n (%)	0 (0.0)	7 (100.0)	-	0.548*
		Positive	n (%)	4 (17.4)	19 (82.6)		
	MDM2	Negative	n (%)	3 (12.0)	22 (88.0)	-	0.538**
		Positive	n (%)	1 (20.0)	4 (80.0)		
				MDM2			
				Negative	Positive		
	PTEN	Negative	n (%)	6 (24.0)	1 (76.0)	-	0.999**
		Positive	n (%)	19 (80.0)	4 (20.0)		

*chi-square test, ** Fisher's exact test

Effects of PTEN, p53, and MDM2 Expression on Overall and Progression-Rree Survival

It was observed that the survival time of patients with p53 normal/wild staining was higher than those with p53 abnormal/mutant staining (log-rank χ^2=8.438, p=0.004). It was observed that the progression-free survival time of patients with p53 normal/wild staining was higher than that of patients with p53 abnormal/mutant staining, but this difference closed toward the end of the observation period (log-rank χ^2=8.438, p=0.050; Breslow=3.964, p=0.046) (Figure 5). Among the low-grade patients, those with p53 normal/wild staining had a higher survival time than those with p53 abnormal/mutant staining (log-rank χ^2=6.053, p=0.014). When we observed the effect of p53 staining on overall survival in high-grade patients, the survival times did not differ between the groups (log-rank χ^2=5.070, p=0.079).

It was observed that the overall (log-rank χ^2=0.242, p=0.623) and progression-free survival times (log-rank χ^2=0.005; p=0.944) of patients with normal PTEN and loss of PTEN did not differ (Figure 6). It was observed that PTEN staining status did not affect overall survival in low- (log-rank χ^2=0.178, p=0.673) and high-grade (log-rank χ^2=0.021, p=0.885) patients.

It was observed that the overall (log-rank χ^2=2.354, p=0.125) and progression-free survival times (log-rank χ^2=0.050; p=0.824) of patients with and without MDM2 staining did not differ (Figure 7). It was observed that MDM2 staining status did not affect overall survival in low- (log-rank χ^2=0.538, p=0.463) and high-grade (log-rank χ^2=0.342, p=0.559) patients.

When the effects of risk group (log-rank χ^2=35.778, p<0.001) and grade (log-rank χ^2=19.661, p<0.001) on overall survival times were evaluated, it was seen that mean survival differed significantly between groups.

Eleven parameters that can be used to predict overall survival are age at diagnosis, p53, PTEN, MDM2, tumor grade (G1+G2=low-grade tumors; G3+serous=high-grade tumors), cervical invasion, myometrial invasion, peritoneal fluid involvement, pelvic lymph node involvement, paraaortic lymph node involvement, and LVI. The Cox regression model was found to be significant (log-rank x2=45.505, p<0.001). Age at diagnosis (B=0.056; p=0.002), peritoneal fluid involvement (HR=4.836; 95% CI=1.651–14.162; p=0.004), and pelvic lymph node involvement (HR=4.660; 95% CI=1.401–15.500; p=0.016) were found to be effective on survival (Table 4).

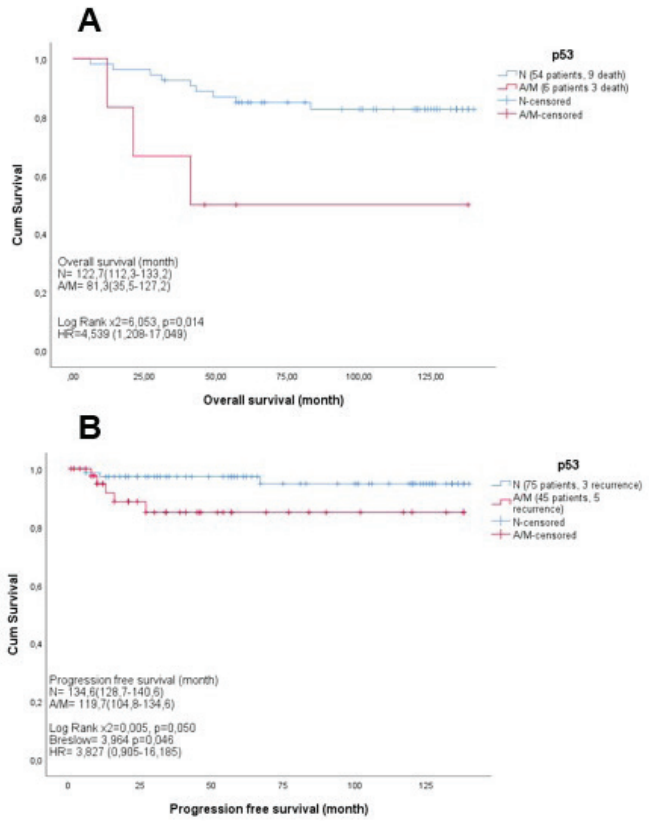

Figure 5. Effect of p53 expression on overall and progression-free survival

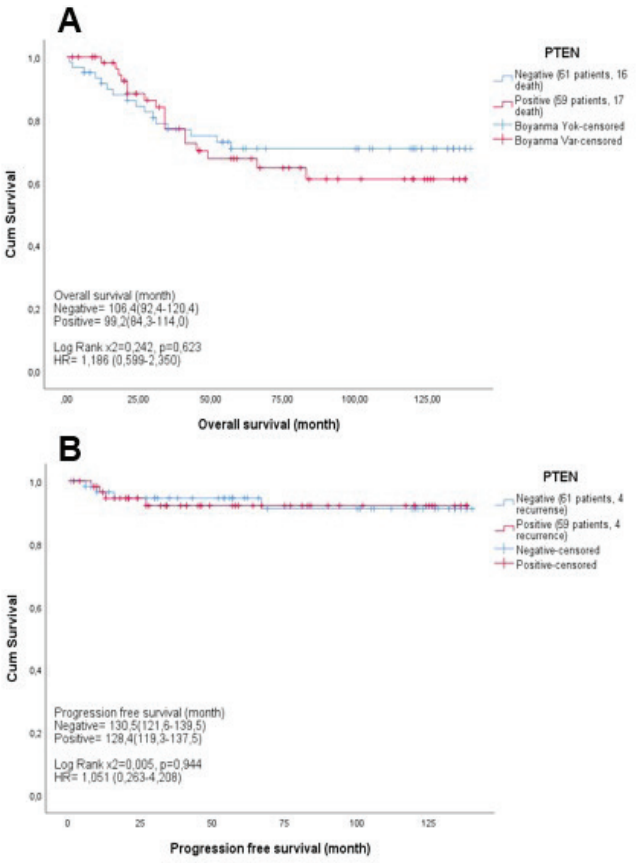

Figure 6. Effect of PTEN expression on overall and progression-free survival

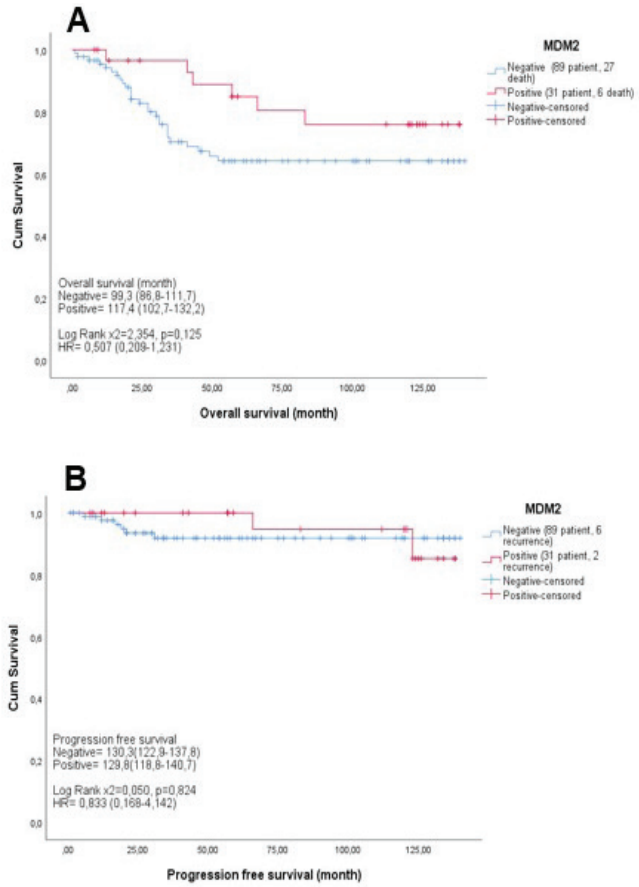

Figure 7. Effect of MDM2 expression on overall and progression-free survival

Table 4. Regression model to analyse the factors affecting the overall survival time of the patients.

							95.0% CI for Exp(B)	
	B	S.E.	Wald	df	p*	Exp (B)	Lower bound	Upper bound
Age	0.056	0.017	10.465	1	0.002	1.057	1.022	1.093
P53 (abnornal/mutant)	0.267	0.512	0.273	1	0.602	1.306	0.479	3.56
PTEN	-0.269	0.406	0.439	1	0.508	0.764	0.345	1.693
MDM2	-0.292	0.571	0.262	1	0.609	0.747	0.244	2.285
Grade (high)	0.238	0.631	0.142	1	0.706	1.268	0.368	4.371
Myometrium invasion	0.676	0.399	2.87	1	0.09	1.966	0.899	4.297
Lymphovascular invasion	-0.766	0.514	2.22	1	0.136	0.465	0.17	1.273
Cervix invasion	-0.587	0.498	1.385	1	0.239	0.556	0.209	1.477
Peritoneal fluid involvement	1.576	0.548	8.264	1	0.004	4.836	1.651	14.162
Pelvic lymph node involvement	1.539	0.613	6.3	1	0.012	4.66	1.401	15.5
Paraaortic lymph node involvement	-0.107	0.586	0.034	1	0.855	0.898	0.285	2.831

*Cox regression analysis

DISCUSSION

Loss of PTEN expression is associated with EEC rather than SEC in the literature (12). Djordjevic et al. and Sal et al. revealed no significant differences between the grades of EEC in terms of PTEN expression and PTEN mutation (15,16). In a study by Tao et al., the presence of the PTEN mutation was higher under 60 years of age than above 60. PTEN mutation was found to be more common in patients with EEC than SEC in patients with EC, in stages 1–2 than in stages 3–4, and in low grade than in high grade. In survival analyses, progression-free and overall survival times were found to be higher in cases with PTEN mutation (17). In a study by Sal et al., although PTEN expression was not associated with stage, LVI status, adjuvant therapy, metastasis, recurrence, survival status, or progression-free and overall survival, positive staining of PTEN was positively correlated with myometrial invasion (16). Akiyame-Abe et al. investigated the relationship among PTEN expression and age, LVI status, tumor stage, myometrial invasion, and histological type and found that PTEN loss was associated with EEC and inversely associated with LVI status. In survival analyses, the loss of PTEN expression was found to be an important and independent prognostic determinant of favorable survival in EC (18). Li et al. found that loss of PTEN was associated with EEC and that the overall survival time of these cases was higher than that of cases with PTEN expression (19). In a study by Stavropoulos et al., the relationship among PTEN expression and age, histological type, stage, histological grade, myometrial invasion, LVI, tubal-ovarian involvement, and tumor necrosis was not found (20). In a study by Daniilidou et al., PTEN staining was associated with grades 1 and 2 and stage 1B tumors, and PTEN loss was associated with grade 3 and stages 1C and 2C tumors (21). In this study, PTEN loss was more common in EECs than in SECs. It was concluded that PTEN loss can be used for diagnostic purposes in the differentiation of EEC and SEC. However, it should be kept in mind that PTEN loss can also be seen in SECs. We observed that PTEN expression did not affect survival. There is no common scoring system to evaluate PTEN expression in studies. This may explain the different results of PTEN expression on survival. A common scoring system should be established by looking at PTEN mutation and expression status in larger series.

In the series of 114 cases of high-grade endometrial cancer analyzed by Edmondson et al., it was observed that patients with high MDM2 expression had poorer overall survival compared to those with low or negative MDM2 expression. A study by Jeczen et al., consisting of 39 patients diagnosed with metastatic EC, found MDM2 overexpression to be more common in high grade tumors than low grades. No significant difference was found between overall survival and MDM2 overexpression alone. However, cases with both p53 and MDM2 overexpression had worse overall survival rates compared to those negative for both p53 and MDM2 (14). Soslow et al. found that MDM2 expression was associated with higher p53 expression in EEC than in SEC in a study of 41 patients diagnosed with high-grade EC (22). In a study by Ambros et al., p53 overexpression in EC was frequently associated with MDM2 overexpression. Liu et al. found MDM2 expression to be higher in EC than in the normal endometrium. It has been reported that MDM2 expression is associated with histological grade and lymph node metastasis but not with patient age, tumor size, and histological type. It was observed that MDM2 expression was higher in patients with stage 3 and 4 tumors and lymph node metastases (13). In the study by Buchynska et al. consisting of cases diagnosed with EC and endometrial hyperplasia, high p53 levels were found to be associated with low MDM2 levels. Their conclusion suggested that poorly differentiated endometrial cancer may be characterized by low MDM2 expression and high p53 expression levels (23). Soslow et al. found an inverse relationship between p53 and MDM2 expression in high-grade EEC versus SEC. In SEC, strong p53 immunoreactivity correlated with low MDM2 expression, while in EEC, weak p53 expression was linked with moderate MDM2 expression (22). In this study, MDM2 expression was observed more frequently in grade

1 EECs and the low-risk group. In contrast, no staining was observed in cases with cervical invasion, peritoneal fluid retention, and adjuvant treatment. We observed no effect of MDM2 expression on survival.

P53 mutations are almost exclusively present in high-grade tumors (24-26). Khalifa et al. determined that p53 positivity was associated with the non-endometrioid type (27). In a series of 100 cases diagnosed with EC by Lukes et al., p53 was found to predict recurrent or persistent disease (28). In the 221 cases of endometrial cancer studied by Hamel et al., strong p53 expression was linked to various prognostic factors, including stage, grade, depth of myometrial invasion, histological subtype, cytological findings, DNA ploidy, and HER-2/neu expression (29). Kohlberger et al. examined p53 overexpression in 92 cases diagnosed with stage 1 EC. In the study, it was concluded that immunohistochemically detected p53 protein overexpression in early-stage EC may have an impact on adjuvant and adjuvant therapy in predicting prognosis (30). p53 expression is associated with non-endometrioid, advanced high-grade, lymph node metastasis (31-33), peritoneal cytology (31,34), and deep myometrial invasion (35). Consistent with the literature, P53 abnormal/mutant type was associated with advanced age, SEC, high-grade EEC, high and advanced metastatic risk group, stage 3-4 tumor, adjuvant treatment, and peritoneal fluid retention.

CONCLUSION

MDM2 expression was found to be associated with positive prognostic parameters. This result can be clarified with further studies with larger series. PTEN loss can be used for diagnostic purposes differentiation of EEC and SEC. However, it should be noted that PTEN loss can also be seen in SECs. p53 remains a critical determinant of prognosis in ECs.

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