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The Impact of p53 and Ki67 Expression in Endometrial Cancer and its Effect on Survival

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ABSTRACT

OBJECTIVE: This study was conducted to evaluate the relationship of p53 and Ki67 expression with prognostic factors in patients who underwent surgery due to a diagnosis of endometrial cancer, and to evaluate their use as molecular markers that can help with survival prediction.

STUDY DESIGN: This retrospective cohort study included patients who underwent surgery for endometrial cancer indication at the Gynecologic Oncology Clinic of the University of Health Sciences Tepecik Training and Research Hospital between 2011 and 2019, and whose p53 and Ki67 from the dissected material were pathologically studied and who underwent pelvic/paraaortic lymph dissection between the relevant dates.

RESULTS: The study included 140 patients who met the inclusion criteria, 60% (n=84) of whom had endometrioid type endometrial carcinoma and 40% (n=56) had non-endometrioid type endometrial carcinoma. Estrogen and progesterone receptor positivity was significantly higher in the endometrioid type endometrial carcinoma group *(p*<0.001 and *p*<0.001, respectively). The non-endometrioid type endometrial carcinoma group had a high degree of positive staining (+3 and +4 staining) with p53 was 51.8%, while this rate was 11.9% in the endometrioid type endometrial carcinoma group. The non- endometrioid group also had a high degree of positive staining of Ki67 at 51.8%, whereas the endometrioid group had 25%. The total staining rate with *p*53 and Ki67 was significantly higher in the non-endometrioid type group (*p*<0.001 and *p*=0.001, respectively). The mean survival duration was less than six months in cases with high degree positive *p*53 [57.4±2.7, (52.1-62.8) vs 51.9±5.9, (41.8-61.9)] and the mean survival duration was less than eight months in cases with high degree positive Ki67 [59.6±2.9, (53.8-65.4) vs 51.6±4.3, (43.2-60.1)].

CONCLUSION: p53 and Ki67 can be new markers for the prediction of prognosis and duration in endometrial cancer. The results of this study pave the way for new studies: however, randomized controlled prospective and multi-center studies are needed for immunohistochemical measures to be used as a parameter.

Keywords: Endometrium cancer, Ki67, p53, Prognosis, Survival time

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Introduction

Endometrial cancer is the most common gynecological cancer among women in developed countries and can be diagnosed in the early period in many cases despite the absence of a screening test (1). Total hysterectomy, bilateral salpingo-oophorectomy, and large pelvic-paraaortic lymph node dissection are included in the staging and treatment in the early stages of this type of cancer. However, the morbidity of lymphadenectomy is quite high, and it can cause many complications such as vascular and neural damage, lymphedema and lymphocyte formation, and adhesion formation (2,3). Additionally, lymph node metastasis in patients with early-stage endometrial cancer is seen at 10%; thus, patients usually undergo unnecessary lymphadenectomy (4). Lymphadenectomy has recently become controversial due to these factors and has been removed from routine application in the early stages (5,6). However, this situation has compli-

cated prognosis prediction and the need for adjuvant chemotherapy because lymph node involvement is the most important factor in staging, while staging is the most important factor in prognosis and the need for adjuvant chemotherapy. All these developments have prompted researchers to look for new factors that direct the treatment and predict the prognosis. Two of the most recently discussed prognostic factors in endometrial cancer are p53 and Ki67.

TP53, a tumor-suppressing gene enabling the cell cycle to proceed and regulating cellular aging and apoptosis, mutates the most in human cancers, with mutations in the p53 protein existing in more than 50% of all cancers (7). Ki67 is a nuclear non-histone protein expressed during cellular division, thus indicating proliferation, and whose presence has been found to reflect bad prognoses in various tumors (8). This study was conducted to evaluate the relationship of p53 and Ki67 expression with prognostic factors in patients who underwent surgery due to a diagnosis of endometrial cancer and to evaluate their use as molecular markers that can help with survival prediction. As far as is known by the authors, this study has the largest sample size among studies on this subject in Turkey.

Material and Method

Study design

This retrospective cohort study included patients who underwent surgery for endometrial cancer at the Gynecologic Oncology Clinic of the University of Health Sciences Tepecik Training and Research Hospital between 2011 and 2019, whose p53 and Ki67 from extracted surgical material were pathologically studied, and who underwent pelvic/paraaortic lymph dissection between the relevant dates. Patient information and data were obtained from the hospital information management system (HIMS) and the patients' medical records. Patients whose post-operative follow-ups were conducted in external centers and those whose information could not be accessed and/or were missing from the records were excluded from the study. Power analysis was performed with G-power to determine the sample size, and the minimum number of patients required for each group was calculated as 42.

Surgical staging of the cases was evaluated based on FIGO 2009 classification (9). Histological typing of the cases was made based on the WHO 2014 classification (10). The Bokhman classification was used to group the cases and the cases were classified into two groups as type 1 (endometrioid) and type 2 (non-endometrioid) (11).

Immunohistochemical evaluation

The entire section was scanned at ×4, ×10, ×20, ×40 magnification of light microscope (Olympus Bx51) for each antibody in each case while evaluating the immunohistochemical staining. The ratio of nuclear positive-stained cells was calculated by counting 1000 cells in the tumor tissue at ×40 magnification in the areas with the most intense staining. The appropriate scoring was made for each antibody.

The quantitative grading system was used for p53 and Ki67 and the staining rates of the cells were investigated under five categories:

-: <5% cell staining
+: <25% cell staining
++: between 25% and 50% cell staining
+++: between 50% and 75% cell staining
++++: >75% cell staining

Additionally, material stained at the +3 and +4 levels with p53 was grouped as highly positive.

The study was approved by the University of Health Sciences Tepecik Training and Research Hospital Local Ethics Committee (approval number: 2019/17-11 date 28.11.2019). The research was conducted in accordance with the 1964 Helsinki Declaration. Informed consent is not required as it is a retrospective study.

Statistical analysis

Statistical Package for the Social Sciences 22.0 software program (IBM Corporation, Armonk, New York, US) was used for statistics. The normality distribution of the variables was made according to Kolmogorov-Smirnov (n>30), Shapiro-Wilk (n<30) tests, and Student T-test for parametric variables; Mann-Whitney U test was used for non-parametric variables. The chi-square test was used for categorical variables between groups. A 95% significance level (or α=0.05 margin of error) was used to determine the differences in the analyses, results with $p<0.05$ were considered significant. In our study, survival time analysis was calculated by Kaplan-Meier and Log-Rank methods.

Results

Of the 140 patients included in the study, 60% (n=84) had endometrioid type endometrial carcinoma while 40% (n=56) had non-endometrioid type endometrial carcinoma. The demographic and medical characteristics of the patients are presented in table I. Accordingly, there was no significant difference between the groups in terms of age, parity, and body mass index (BMI). While the presence of hypertension was similar between the groups, the prevalence of diabetes was significantly higher in the endometrioid type endometrial carcinoma group (p=0.031) (Table I).

The clinical and histopathological features of the cases are presented in table II. While most of the cases were at stage 1 in terms of surgical stage, grade 2 and grade 3 were more common in terms of the grade of the tumor. The cases with deep myometrial invasion and lymphovascular invasion constituted the majority. The tumor size was larger than 4 cm in most cases. Considering the peritoneal cytology taken, most were benign (Table II).

The immunohistochemical characteristics of the cases are presented in table III. Accordingly, estrogen and progesterone receptor positivity was significantly higher in the endometri-

oid type endometrial carcinoma group (p<0.001 and p<0.001, respectively). In intergroup comparisons, 50% of the cases with endometrioid type endometrial carcinoma had stained in terms of p53, while 84% of the cases with non-endometrioid type had stained. Of the non-endometrioid type group, 51.8% had high degree positive staining (+3 and +4 staining) with p53, while this rate was 11.9% in the endometrioid type group. In the comparison of K167 staining, high degree positive staining was 51.8% in the non-endometrioid type endometrial carcinoma group and 25% in the endometrioid type group. The total staining rate with p53 and Ki67 was significantly higher in the non-endometrioid type group (p<0.001 and p=0.001, respectively) (Table III).

The relationship between p53 and clinical and histopathological parameters is given in Table IV. Accordingly, advanced grade (grade 3) was observed at a high rate in the group with high degree positive staining (p<0.001) while there was no significant difference between the groups in terms of the surgical stage. Additionally, there were no differences between the groups in terms of myometrial invasion, lymphovascular invasion, lymph node metastasis, and tumor size (Table IV).

The relationship between Ki67 and clinical and histopathological parameters is given in Table V. Accordingly, advanced surgical stage (stage 4) and advanced grade (grade 3) was observed at a high rate in the group with a high degree of positive

Table I: *Demographic and medical characteristics of women involved in the study*

	Endometrioid n=84	Non-endometrioid n=56	*p*
Age (year) (mean±SD)	60±9	62±10	0.090
Parity (n,%)			0.874
Nulliparous	4 (4.8)	3 (5.4)	
Multiparous	80 (95.2)	53 (94.6)	
BMI at during diagnosis (kg/m2) (n,%)			0.319
≤30	29 (34.5)	24 (42.9)	
>30	55 (65.5)	32 (57.1)	
Presence of hypertension (n,%)	37 (44)	26 (46.4)	0.781
Presence of DM (n,%)	36 (42.9)	14 (25)	**0.031**

BMI: Body mass index, DM: Diabetes mellitus

Table II: *Clinical and histopathological features of women participating in the study*

Clinical and histopathological findings		n (%)
Surgical Stage	Stage 1	77 (55)
	Stage 2	21 (15)
	Stage 3	32 (22.9)
	Stage 4	10 (7.1)
Grade	Grade 1	21 (15)
	Grade 2	55 (39.3)
	Grade 3	64 (45.7)
Myometrial Invasion	No	3 (2.1)
	<%50	46 (32.9)
	≥%50	91 (65)
Lymphovascular Invasion	No	49 (35)
	Yes	91 (65)
Lymph Node Metastasis	No	101 (72.1)
	Pelvic involvement	17 (12.1)
	Paraaortic involvement	9 (6.4)
	Pelvic and paraaortic involvement	13 (9.3)
Tumor Size	≤4 cm	51 (36.4)
	>4 cm	89 (63.6)
Peritoneal Cytology	Benign	104 (74.3)
	Malignant	6 (4.3)
	Non-diagnostic	9 (6.4)
	Unspecified	21 (15)

Table III: *Immunohistochemical results*

	Endometrioid n=84 (%)	Non-endometrioid n=56 (%)	*p*
ER (n, %)			**<0.001**
Positive	71 (84.5)	28 (50)	
Negative	13 (15.5)	28 (50)	
PR (n, %)			**<0.001**
Positive	75 (89.3)	27 (48.2)	
Negative	9 (10.7)	29 (51.8)	
***p*53 (n, %)**			
(-)	42 (50)	9 (16.1)	**<0.001**
(+)	23 (27.4)	8 (14.3)	
(++)	9 (10.7)	10 (17.9)	
(+++)	4 (4.8)	9 (16.1)	
(++++)	6 (7.1)	20 (35.7)	
Ki67 (n, %)			**0.001**
(-)	11 (13.1)	2 (3.6)	
(+)	34 (40.5)	9 (16.1)	
(++)	18 (21.4)	16 (28.6)	
(+++)	14 (16.7)	21 (37.5)	
(++++)	7 (8.3)	8 (14.3)	

Table IV: *The relationship of p53 with clinical and histopathological parameters*

	Endometrioid n=84 (%)	Non-endometrioid n=56 (%)	*p*
ER (n, %)			**<0.001**
Positive	71 (84.5)	28 (50)	
Negative	13 (15.5)	28 (50)	
PR (n, %)			**<0.001**
Positive	75 (89.3)	27 (48.2)	
Negative	9 (10.7)	29 (51.8)	
***p*53 (n, %)**			
(-)	42 (50)	9 (16.1)	**<0.001**
(+)	23 (27.4)	8 (14.3)	
(++)	9 (10.7)	10 (17.9)	
(+++)	4 (4.8)	9 (16.1)	
(++++)	6 (7.1)	20 (35.7)	
Ki67 (n, %)			**0.001**
(-)	11 (13.1)	2 (3.6)	
(+)	34 (40.5)	9 (16.1)	
(++)	18 (21.4)	16 (28.6)	
(+++)	14 (16.7)	21 (37.5)	
(++++)	7 (8.3)	8 (14.3)	

Table V: *The relationship of Ki67 with clinical and histopathological parameters*

Clinical and histopathological findings		**p53 (-), 1+,2+ (n, %)**	**p53 3+, 4+ (High Grade Positive) (n, %)**	*p*
Surgical Stage	Stage 1	55 (54.5)	22 (56.4)	0.722
	Stage 2	15 (14.9)	6 (15.4)	
	Stage 3	25 (24.8)	7 (17.9)	
	Stage 4	6 (5.9)	4 (10.3)	
Grade	Grade 1	18 (17.8)	3 (7.7)	**<0.001**
	Grade 2	48 (45.5)	7 (17.9)	
	Grade 3	35 (34.7)	29 (74.4)	
Myometrial Invasion	No	3 (3)	0 (0)	0.254
	<%50	36 (35.6)	10 (25.6)	
	≥%50	62 (61.4)	29 (74.4)	
Lymphovascular Invasion	No	38 (37.6)	11 (28.2)	0.295
	Yes	63 (62.4)	28 (71.8)	
Lymph Node Metastasis	No	75 (74.3)	26 (66.7)	0.675
	Pelvic involvement	12 (11.9)	5 (12.8)	
	Paraaortic involvement	5 (5)	4 (10.3)	
	Pelvic and paraaortic involvement	9 (8.9)	4 (10.3)	
Tumor Size	≤4 cm	40 (39.6)	11 (28.2)	0.209
	>4 cm	61 (60.4)	28 (71.8)	
Peritoneal Cytology	Benign	76 (75.2)	28 (71.8)	**0.047**
	Malignant	5 (5)	1 (2.6)	
	Non-diagnostic	3 (3)	6 (15.4)	
	Unspecified	17 (16.8)	4 (10.3)	
Histological Type	Endometrioid	74 (88.1)	27 (48.2)	**<0.001**
	Non-endometriod	10 (11.9)	29 (51.8)	

staining of Ki67 (p=0.002 and p<0.001, respectively). While the lymphovascular invasion was at a higher rate in this group, tumor size was also larger (p<0.001 and p=0.023, respectively) (Table V).

The five-year survival analysis of p53 was calculated using the Kaplan-Meier and Log-Rank methods. Accordingly, the mean survival duration was less than six months in cases with high degree positive p53 [57.4±2.7, (52.1-62.8) vs 51.9±5.9, (41.8-61.9)] (Figure 1).

The same methods were used to calculate the five-year survival analysis of Ki67. Accordingly, the mean survival duration was less than eight months in cases with high degree positive Ki67 [59.6±2.9, (53.8-65.4) vs 51.6±4.3, (43.2-60.1)] (Figure 2).

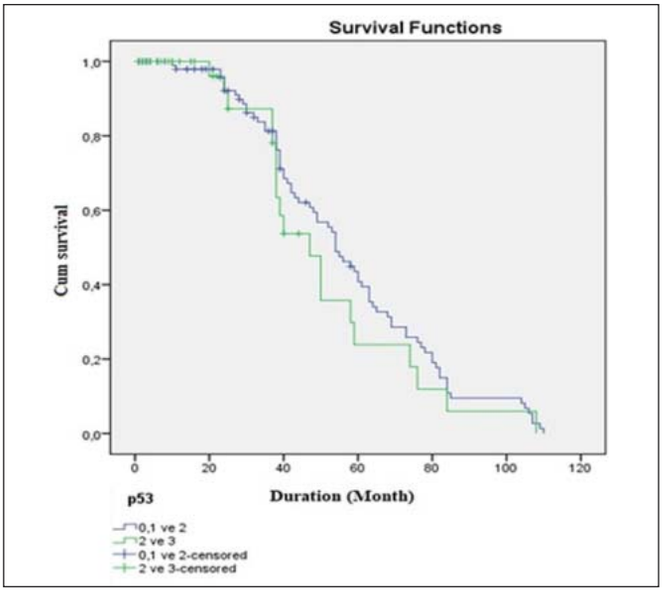

Figure 1: *p53 expression degree and mean survival time*

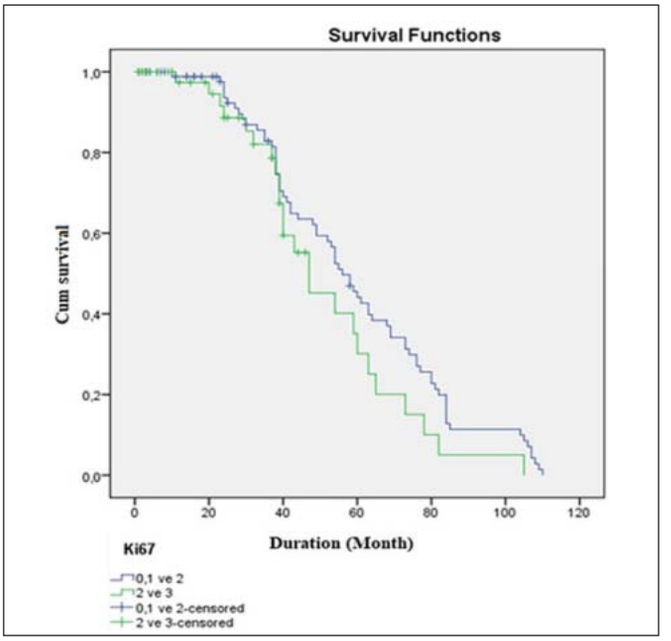

Figure 2: *Ki67 expression degree and mean survival time*

Discussion

Endometrial cancer is the primary malignant epithelial tumor of the endometrium and the most common malignancy of the female genital system (1). In recent years, the most important studies on endometrial cancer have been in the field of revealing the molecular properties of endometrial cancer, and knowledge on this subject is gradually increasing. The major research on this subject in recent years has been the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) study (12). Subsequently, a current meta-analysis of a total of 912 patients from 3 studies attempting to reveal the histopathological characteristics of ProMisE groups was published (13). This meta-analysis revealed that many patients receive under- or over-treatment when treated by looking at risk groups and clinical-pathological characteristics. It emphasized that molecular and histopathological features should be evaluated together.

A series of new molecular markers in this prevalent type of cancer is promising to show the prognostic value of cancer and could also act as a guide for the clinician in patient management during the post-operative period. p53 expression and Ki67 proliferation indices among these molecular markers are considered current research areas in terms of prognosis and survival prediction in endometrial cancer (14,15). Therefore, these markers were examined in this study, and it was found that the five-year survival duration was less than 6 months on average for p53 and 8 months on average for Ki67 in cases with high degree positive staining. Additionally, significant relationships were observed between high p53 expression and advanced grade, and high Ki67 proliferation and advanced surgical stage and advanced grade and showing lymphovascular invasion.

Salvesen et al. (1999) conducted a study with 141 cases and found a significant relationship between high Ki67 proliferation and p53 expression and short survival and histological grade. In this study, 35% and below were accepted as low staining and 35% and more were accepted as high staining for Ki67 expression (16). These results are similar to those obtained in the current study. Mariani et al. (2000) detected a significant relationship between high p53 expression and stage and no significant relationship between Ki67 proliferation and stage in a study of 125 patients. They showed that survival duration decreased with high p53 expression and Ki67 proliferation. The cut-off value for Ki67 and p53 positivity was taken as 33% in this study (17). In the present study, while the stage was shortened with Ki67 proliferation, no significant relationship was observed between p53 expression and stage. This may be due to the different classification of staining degrees in the current study. In terms of survival, the results of this study have similar findings with the present study.

Lundgren et al. (2002) conducted a study with 358 patients. In this study, the groups were divided into p53 expres-

sion and no p53 expression, then further sub-divided into three based on expression degree for Ki67 proliferation as 0-30%, 31-60%, and 61-100% (18). They observed that survival decreased with Ki67 proliferation and p53 expression, similar to our study. Finally, in 2003, Oreskovic et al. looked at 136 cases with endometrial cancer and set the cut-off value for Ki67 as 20% and 15% for p53 (19). They determined that Ki67 proliferation and p53 expression had an inverse relationship with survival, similar to the current study.

Suthipintawong et al. (2008) studied 65 patients and accepted cases with ≥50% nuclear staining for p53 and >35% nuclear staining for Ki67 as positive. While survival duration decreased with Ki67, no significant relationship was detected between p53 positivity and survival (20). In the present study, survival was reduced with Ki67 expression and p53 proliferation.

In a 2011 study by Yao et al., no significant relationship was observed between high Ki67 proliferation and high p53 expression and survival among 200 patients (21). Similarly, they found no significant relationship between these two markers and stage, myometrial invasion, and lymph node metastasis. A significant difference was only found between advanced grade and high Ki67 proliferation and high p53 expression. The cut-off value used for p53 and Ki67 positivity was 10% (21). The results of this study are different from the present research. These different findings may be due to the low cut-off value and/or the study population differences.

Budak et al. (2019) conducted a study with 49 patients and observed a significant relationship between Ki67 proliferation and advanced grade; however, they found no significant relationship between stage, lymphovascular invasion, myometrial invasion, lymph node involvement, and survival. A significant relationship was found between p53 expression and stage in the same study, while there was no significant relationship between grade, lymphovascular invasion, lymph node involvement, myometrial invasion, and survival. High Ki67 proliferation was observed in the non-endometrioid type endometrial cancer more in this group. The percentage of Ki67 and p53 positive cells was obtained for each case as the classification (22). Contrary to the present study, no significant relationship was found in survival. The most important difference with this study is that the present study's patient population is different in terms of grade, stage, myometrial, and lymphovascular invasion. In the current research, the patient population had a more aggressive course, whereas, in this study, less aggressive tumors with less metastasis constituted the majority of the population.

Overall, survival appears to be shortened by p53 expression and Ki67 proliferation. However, a variety of results have been observed in many studies on stage, grade, myometrial and lymphovascular invasion, and lymph node metastasis. Although the results of only a few studies seem insignificant, when the sample group of these studies is examined, it can be seen that they usually include low grade-low stage and less myometrial and lymphovascular invasion. This suggests that the difference was affected by the tumor aggressiveness of the study population. Apart from this, racial and geographical differences, number of cases, socio-economic levels of the patients, and the use of different staining classification ranges in different studies may cause these differences.

The main limitation of the present study is that it is a retrospective study. The strong aspects of this study are the number of patients, strict patient selection criteria, and sensitive percentage ranges used to determine the staining degree.

Conclusion

In conclusion, the most important studies on endometrial cancer in recent years are in the field of revealing the molecular features of endometrial cancer, and knowledge on this subject is gradually increasing. p53 and Ki67 may become new markers for the prediction of prognosis and survival in endometrial cancer. The results of this study pave the way for new studies, but randomized controlled prospective and multicenter studies are needed for immunohistochemical measures to be used as a parameter.

Declarations
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Ethics approval and consent to participate: Informed consent is not required as it is a retrospective study.
Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.
Authors' contributions: ZS raised the presented idea. ZS, BB, TK, and MS designed the study. BB conducted the analyses. All authors contributed to the writing of the paper, and have read and approved the final manuscript.

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