ORIGINAL RESEARCH

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# Relationship Between p53 and Recurrence in Endometrial Cancer

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## Abstract

### Objective
Tumor protein 53 (p53), were included in the new FIGO 2023 staging system. Tumor protein 53 (p53) was incorporated into the new FIGO 2023 staging system. This study aimed to assess recurrence rates, overall survival (OS), and progression-free survival (PFS) in endometrial cancer patients with p53 mutations treated in the radiation oncology clinic.

### Material and Method
260 patients were included in the study. The patients were divided into 2 groups according to the p53 mutation: p53 abnormal (p53 mutant) and p53 wild type. The Kaplan-Meier method was used to evaluate OS and PFS. Survival rates; were compared in terms of p53 mutations. Patients who underwent surgery for EC between January 1, 2008, and January 1, 2023, were included if their postoperative pathology reports evaluated p53 mutations, and they were referred to the radiation oncology clinic.

### Results
In our study; OS of EC was 84.2%, PFS was 88.8%. Total of 29 patients (%11.2) with recurrence were detected in the follow-up of the patients. The OS of p53 wild type patients was 88.6% and p53 mutant patients was 61% (p<0.001). The PFS of p53 wild type patients was 91.8% and p53 mutant patients was 73.2% (p<0.001). When risk calculation was made, we found a 4.094-fold increased risk of recurrence in cases with p53 mutation (95% CI: 1.763-9.508). Based on p53 status, 41 patients (15.8%) were classified as the p53 mutant group, while 219 patients (84.2%) were categorized as the p53 wild-type group.

### Conclusion
As a result, the most important point we want to emphasize in the study is that vaginal cuff recurrence was observed in 3 patients with p53 mutation despite brachytherapy. We found that endometrial cancer with p53 mutation were associated with increased recurrence rate and decreased OS and PFS.

**Keywords:** Endometrial carcinoma, p53, recurrence, survival

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## Introduction

The American Cancer Society reported that an estimated 61,880 new cases will be diagnosed in the United States in 2022, and 12,550 women will die from EC (2). As obesity increases worldwide and life expectancy increases, the incidence of EC is also increasing. (3). The Cancer Genome Atlas Research Network (TCGA) has made a new classification of EC based on sequence and sequencing technologies. POLE-ultramutated (POLEmut), mismatch repair defcient (MMRd), p53-abnormal (p53abn), and No Specific Molecular Profile Subgroup (NSMP) are the four subgroups of this molecular classifcation (4). Molecular markers were included in the staging system. Current changes to the endometrial staging system by FIGO have been made to further define the reported differences in prognosis and survival since the 2009 system was published. Patients with tumor protein 53 (p53) mutation are now considered stage 2c, regardless of myometrial invasion (5). There are studies on poor prognosis of endometrial cancer in p53 mutation. A better understanding of the molecular changes in the p53abn subgroup is necessary to identify better treatments for these most aggressive endometrial cancers (6,7) In our study, we aimed to evaluate recurrence rates, overall survival (OS) and progression free survival (PFS) in endometrial cancer patients with p53 mutations.Endometrial carcinoma (EC) is the sixth most commonly diagnosed cancer in women worldwide (1). Endometrial carcinoma (EC) ranks as the sixth most frequently diagnosed cancer among women worldwide (1). The FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) introduced a revised staging system for EC in 2023.

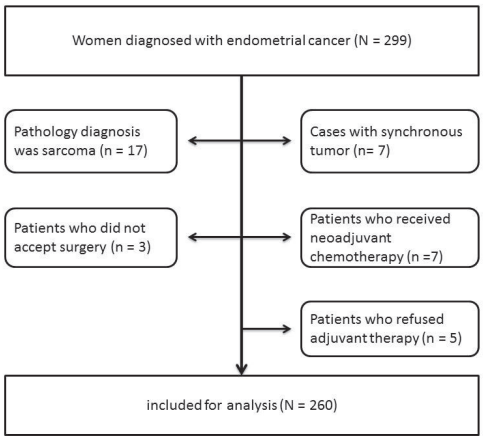
## Material and Method

### Patients

Cases with synchronous tumor or sarcoma detected in postoperative pathology diagnosis, patients who received neoadjuvant chemotherapy, those who did not accept the operation, and those who refused to receive adjuvant treatment were excluded from the study. As a result, 260 patients were included in the study (Supplemental Figure 1). Patients who underwent surgery for EC between January 1, 2008, and January 1, 2023, were included if their postoperative pathology reports evaluated p53 mutations, and they were referred to the radiation oncology clinic.

### Sample Evaluation

Data related with age, body mass index (BMI), grade, CA125 levels, histopathological type, stage, and survival were derived from hospital files.




**Supplemental Figure 1**
Flowchart

Vaginal examination, CA125 levels, transvaginal ultrasonography and imaging methods (MRI, CT, PET-CT) were used to detect recurrence. Staging was done according to FIGO 2009 criteria. P53 mutational status dichotomized as "wild type" vs "abnormal (mutated)". Patients were divided into 2 groups according to the p53 mutation: p53 abnormal (p53 mutant) and p53 wild type. In the evaluation of p53 immunohistochemical staining, diffuse strong staining in >80% tumor cell nuclei (overexpression) or complete loss of expression ("null" expression) or 25 diffuse cytoplasmic staining were evaluated as abnormal expression, other heterogeneous intensity staining was accepted as normal expression.

### Statistical Analysis

SPSS Version 26.0 was used for statistical analysis. Mean, median, and standard deviation were calculated for continuous variables. The relationship between qualitative variables was examined with Fisher Exact and Continuity Correction (Yates) Chi Square analysis. Two-tailed p values <0.05 were accepted to be statistically. Time-to-event analyses were conducted using the KaplanMeier method and log-rank test.

## Results

The mean age of the patients was 61.9±10.1 years. The mean BMI was calculated as 32.5±5.6 kg/m². The median CA 125 value was 17 IU/mL (3 IU/mL - 10655 IU/mL). According to the postoperative pathology results, the mean tumor size was 4.21 ± 2.13 cm. The most common stage was stage1b and endometrioid carcinoma was the most common histological type. The grades, myometrial invasion, histological type, lymphovascular space invasion (LVSI), cytology results, p53 mutations, staging of the postoperative

**Table 1** Postoperative pathology findings

| | No. of Patients | % |
|---|---|---|
| **Surgical stage** | | |
| IA | 85 | 32.7 |
| IB | 98 | 37.6 |
| II | 19 | 7.3 |
| IIIA | 18 | 6.9 |
| IIIB | 0 | 0 |
| IIIC1 | 16 | 6.2 |
| IIIC2 | 3 | 1.2 |
| IVA | 0 | 0 |
| IVB | 21 | 8.1 |
| **Histology** | | |
| Endometrioid adenocarcinoma | 223 | 85.7 |
| Clear cell carcinoma | 3 | 1.2 |
| Serous carcinoma | 26 | 10 |
| Malignant Mix Mullerian Tumor | 6 | 2.3 |
| Mucinous carcinoma | 2 | 0.8 |
| **Grade** | | |
| 1 | 76 | 29.2 |
| 2 | 108 | 41.6 |
| 3 | 76 | 29.2 |
| **Lymphovascular space invasion** | | |
| Negative | 183 | 70.4 |
| Positive | 77 | 29.6 |
| **Myometrial invasion** | | |
| <1/2 | 103 | 39.6 |
| ≥1/2 | 157 | 60.4 |
| **Cytology** | | |
| Positive | 38 | 14.6 |
| Negative | 222 | 85.4 |
| **P53** | | |
| Wild type | 219 | 84.2 |
| Abnormal (mutant) | 41 | 15.8 |

pathology results of the patients are summarized in Table 1. Based on p53 status, 41 patients (15.8%) were classified as the p53 mutant group, while 219 patients (84.2%) were categorized as the p53 wild-type group.

106 patients received only adjuvan radiotherapy, 30 patients received only adjuvan chemotherapy, and 54 patients received adjuvan chemo-radiotherapy. 70 patients are under follow-up with no treatment. A total of 160 patients received adjuvan radiotherapy. Of these, 109 patients received brachytherapy (BRT) alone, 20 patients received external beam radiotherapy (ERT) alone, and 31 patients received both BRT and ERT. Total of 29 patients (%11.2) with recurrence were detected in the follow-up (Table 2). The median time to recurrence was 30 months (range: 2-125 months). Three patients with vaginal cuff recurrence were p53 wild type. These patients are stage 1b grade 3 (adjuvant BRT), stage 2 grade 3 (adjuvant chemotherapy + ERT + BRT), stage 4b grade 2 (adjuvant chemotherapy + ERT + BRT), respectively. When the relationship between p53 and recurrence was evaluated, the p value was found to be significant ($p<0.001$). When risk calculation was made, we found a 4.094-fold increased risk of recurrence in cases with p53 mutation (95% CI: 1.763-9.508). A notable finding of this study is that vaginal cuff recurrence was observed in three patients with p53 mutations despite undergoing brachytherapy. In our study; OS of EC was 84.2%, PFS was 88.8%.

**Table 2** Recurrence location and no of patients with recurrence

| Recurrence site | No of Patients |
|---|---|
| Pelvic lymph node | 4 |
| Vaginal cuff | 3 |
| Adrenal gland | 2 |
| Pulmonary | 8 |
| Para-aortic lymph nodes | 3 |
| Hepatic | 4 |
| Bone (vertebral) | 3 |
| Bowel (sigmoid colon) | 2 |
| **Total** | 29 |

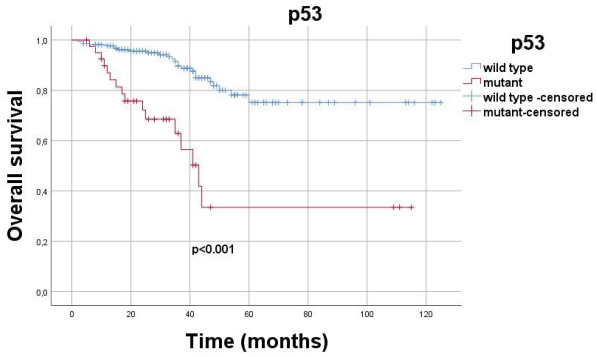



**Figure 1**
Overall survival rates with respect to p53 mutation

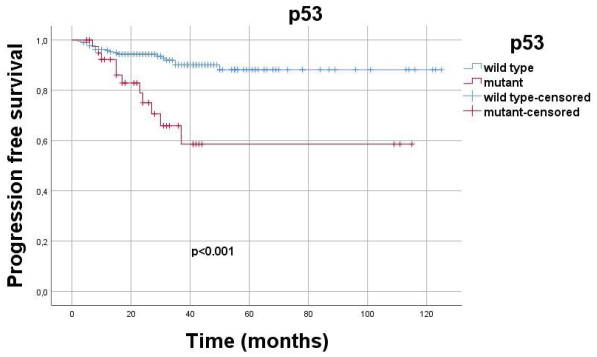



**Figure 2**
Progression-free survival rates with respect to p53 mutation

OS rates; were compared in terms of p53 mutation (Figure 1). Also PFS rates were compared in terms of p53 mutation (Figure 2). The OS of p53 wild type patients was 88.6% and p53 mutant patients was 61% (p<0.001). The PFS of p53 wild type patients was 91.8% and p53 mutant patients was 73.2% (p<0.001).

## Discussion

EC is usually detected between the ages of 50 and 65 years, with mean age of 60 years during diagnosis (8). Accordingly, the mean age of patients with endometrial cancer in this study was 61.9 years old.

A Turkish study reported that the OS of EC was 85% (9). In a study we conducted in Turkey and a region close to ours, the OS of EC was found to be 91.2% (10). Eltabbakh at al. showed that the 5-year PFS and OS rates of these patients were denoted as 95.2 and 96.4%, respectively (11). Chen at al. reported that 5-year relative survival rate was 81.0% in Germany (12). Although the 5-year survival rate changed between 74 and 91% for stage 1 and stage 2 tumors, this number decreased to 20 to 26% for stage 4 EC (13). Crosbie, E. J. et al. reported survival according to stages as 92% for stage 1, 74% for stage 2, 48% for stage 3, and 15% for stage 4, respectively (14). In line with previous studies, our study observed an OS rate of 84.2%.

The World Health Organization classification of obesity is non-obese (<30.0) and obese (≥30.0) (15).

Nowadays, obesity is known to be a risk factor for many types of cancer (16). In our study, we found the mean BMI value in the obese group.

Mutation of the p53 gene increases the uncontrolled proliferation of cells, causing aggressive tumor behavior. (17). In a study by Raffone et al. they found that the p53 mutant group had a prognosis approximately 2 times worse than the control group (18). PORTEC 3 trial showed that molecular classifcation of EC has a strong prognostic value in high-risk uterine cancer, and adjuvant chemotherapy and radiation signifcantly improved recurrence in p53abn tumors, regardless of histologic subgroup (19). Vermij, L et al. reported that abnormal p53 expression was observed in 131/408 (32%) tumors (20). Tresa, A et al. found that the 2-year OS of the p53 wild type and p53 mutant type was 97.2% and 91.7%, respectively (21). Shivkumar, V et al. concluded that p53 overexpression was associated with more aggressive behavior and poor survival outcome in EC cases (22). Consistent with these data in the literature, we found that it was associated with a 4,094-fold increased recurrence rate and decreased OS and PFS in those with p53 mutation. As it is known, FIGO published a new staging system for EC in 2023. p53 mutation has become part of the new staging system. Patients with p53 mutation are now considered stage 2c, regardless of myometrial invasion (5).

Most of patients has early stage endometrial cancer and our study is retrospective. Exclusion criteria for sarcoma or synchronous tumor in the postoperative pathology report results and exclusion of cases who did not receive postoperative adjuvant therapy may have led to differences in OS and PFS values. In addition, the fact that the study was conducted on radiation oncology data may have caused the low number of stage 1a cases who did not receive adjuvan treatment. The relatively small number of cases can be considered as another limitation of our study. This study is subject to several limitations.

## Conclusion

In conclusion, p53 mutation must be investigated in the postoperative pathological evaluation of endometrial cancer. We found that endometrial cancer with p53 mutation were associated with increased recurrence rate and decreased OS and PFS. A notable finding of this study is that vaginal cuff recurrence was observed in three patients with p53 mutations despite undergoing brachytherapy.

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**Conflict of Interest Statement**
The authors declare no conflict of interest.

**Ethical Approval**
The present study was approved by the Ethical Committee of Afyonkarahisar Health Sciences University Hospital (grant no: 2011-KAEK-2, 02/06/2023). The study was conducted in accordance with the Declaration of Helsinki. Consent was obtained from all patients during their hospitalization

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**Availability of Data and Materials**
All data are available from the corresponding author upon reasonable request.

**Authors Contributions**
DO: Conceptualization, Formal analysis, Project administration

CYO: Writing - Original Draft, Data Curation, Formal analysis

NC: Investigation, Validation, Review & Editing

CO: Data Curation, Visualization

BU: Validation, Formal analysis, Investigation

HD: Validation, Formal analysis, Investigation

DTA: Methodology, Supervision, Review & Editing

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