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ORIGINAL RESEARCH

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Evaluating molecular profiling and surgical factors influencing adjuvant therapy in patients with endometrial cancer

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Abstract

Background: Endometrial cancer (EC) staging is essential for effective treatment. Recent developments in molecular profiling have improved the management of EC through the identification of molecular subtypes that influence prognosis and the requirement for adjuvant therapies. This study aimed to evaluate clinical and diagnostic data together with immunohistochemical biomarker study related to molecular classification in patients with EC and to explore factors independently associated with the administration of adjuvant therapy. **Methods**: This retrospective study included 100 patients diagnosed with EC who underwent surgical intervention between October 2020 and October 2022. Data were obtained from clinical records and pathology reports. Patients were categorized based on whether they received adjuvant therapy. Multivariable logistic regression was used to identify independent factors associated with adjuvant therapy use. **Results**: Patients who received adjuvant therapy were older, had larger tumors, higher abnormal p53 staining (consistent with Tumor Protein 53 (TP53) mutation), and greater lymph node involvement. Independent predictors of adjuvant therapy included Stage IB (odds ratio (OR): 68.571, 95% confidence interval (CI): 10.540–446.114, $p < 0.001$), Stage II–IV (OR: 153.412, 95% CI: 15.048–1564.055, $p < 0.001$), and abnormal p53 stainings (OR: 8.572, 95% CI: 1.304–56.341, $p = 0.025$). Endometrioid carcinoma was negatively associated with adjuvant therapy (OR: 0.104, 95% CI: 0.012–0.911, $p = 0.041$). **Conclusions**: The results of this study indicate that abnormal p53 stainings, clinical staging, and the presence of endometrioid tumors are significant determinants for the administration of adjuvant therapy. Integration of clinical staging and exact diagnoses in addition to molecular profiling may improve treatment decisions.

Keywords

Endometrial cancer; Molecular profiling; Adjuvant therapy; p53; Neoplasm staging

1. Introduction

Endometrial cancer (EC), the second most common gynecological cancer worldwide [1], necessitates lymph node evaluation for staging and prognostic purposes. The sentinel lymph node mapping (identifying the first lymph node that drains from the primary tumor) is used in the staging of EC, particularly since sentinel lymph node mapping has been shown to be significantly superior to detailed lymphadenectomy in terms of reducing mortality and morbidity [2]. Adjuvant treatment strategies for EC are based on several known risk factors, and include external beam pelvic radiotherapy, vaginal brachytherapy, and combined chemotherapy and radiotherapy [3].

In the last decade, molecular testing in EC has become increasingly important for prognostication and management decisions. This has been made possible by advances in genomic profiling, which revealed that specific molecular markers could help identify the risk of recurrence, guide decisions regarding adjuvant treatments, and influence the need for more aggressive treatments [4]. The Cancer Genome Atlas (TCGA) project and confirmatory studies have identified four different molecular subclasses with considerable impact on EC prognosis: (i) Tumors with mutations in the DNA polymerase epsilon (POLE gene), which have an excellent prognosis and often do not require adjuvant therapy, even if they are high-grade. (ii) Microsatellite unstable cancers with defects in mismatch repair (MMR) genes (MutL Homolog 1 (MLH1), MutS Homolog 2 (MSH2), MutS Homolog 6 (MSH6), and Postmeiotic Segregation increased 2 (PMS2)), which are more likely to respond to immune checkpoint inhibitors and may benefit from specific targeted therapies. (iii) Copy-Number Low (Endometrioid) tumors that do not have POLE mutations or MMR defects, which generally have a moderate prognosis

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and often require standard adjuvant treatments like radiation or chemotherapy. (iv) Copy-Number High (Serous-like/P53 mutant) tumors with mutations in the *TP53* gene, which are more aggressive, demonstrate high recurrence rates, and often require adjuvant chemotherapy and radiation [5].

Current guidelines recommend routine molecular profiling for newly diagnosed EC patients, particularly those with high-grade or high-risk disease, to determine the best management approach [6, 7]. Integrating molecular and clinicopathological risk factors may enhance the selection of adjuvant treatments for women with high-intermediate risk EC. This study aims to evaluate the outcomes of molecular classification and sentinel lymph node dissection in EC patients, and to explore whether specific factors influence the need for adjuvant therapy.

2. Materials and methods

2.1 Setting and patient selection

Patients with EC who underwent surgery with sentinel lymph node dissection in the Gynecological Oncology Clinic of Ondokuz Mayıs University Hospital between October 2020 and October 2022 were eligible for study inclusion. Data collection was based on retrospective reviews of electronic medical records that were kept at all stages of management, including clinic notes, operation records, and pathologic reports. Ethical approval was obtained from the Clinical Research Ethics Committee of Ondokuz Mayıs University (Decision date: 28 April 2023, decision no: B.30.2.ODM.0.20.08/177), and the study was conducted in accordance with the principles of the Declaration of Helsinki. The Clinical Research Ethics Committee of Ondokuz Mayıs University waived the requirement for informed consent due to the retrospective nature of the study.

Inclusion criteria for the study were: being aged between 35–85 years, having preoperative imaging data, receiving a primary tissue diagnosis of EC, and undergoing intraoperative sentinel lymph node dissection as part of the surgical treatment of EC. Patients suspected of having Lynch syndrome (an autosomal dominant defect in the MMR pathway that predisposes individuals to early-onset EC and hereditary EC), those with a history of additional malignancy (or concurrent malignancy), and individuals for whom information access was not possible for any reason or whose records were incomplete were excluded from the study.

2.2 Diagnostic processes and adjuvant therapies

EC diagnosis was made according to histopathological findings obtained from endometrial biopsy. Grading was based on the International Federation of Gynecology and Obstetrics (FIGO) and the World Health Organization (WHO) recommendations [8, 9]. Briefly, each patient diagnosed with EC was assessed for tumor grade, histopathological type, lymphovascular space invasion (LVSI), and myometrial invasion (MI). Prognostic factors were evaluated based on the availability of molecular classification. Tumor grade was not determined in 13 patients (13%) as these cases had non-endometrioid histological subtypes for which FIGO grading is not applicable (including serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated carcinoma, and small cell neuroendocrine carcinoma), or the histopathological specimen was insufficient for definitive grading.

The decision regarding adjuvant therapy was made considering several factors, including disease stage, histopathological characteristics, molecular classification, and patient-specific considerations. Adjuvant therapy was defined as any therapy involving radiation or chemotherapy that was administered in conjunction with the primary treatment. Radiation therapy included either external beam radiation or brachytherapy (internal radiation) [1]. Chemotherapy was recommended for advanced or high-risk ECs, including those with spread beyond the uterus or high-grade histology [10]. A carboplatin and paclitaxel regimen was the most commonly used chemotherapy for EC at our center, either concurrently or sequentially with radiation therapy.

2.3 Procedures, data collection, and identification of molecular subclasses

All patients underwent endoscopic surgery employing an Olympus endoscopic device. Methylene blue or indocyanine green injections were used to facilitate sentinel lymph node sampling. Injections were performed into the cervix at two or four points (3-6-9-12 o'clock positions) at a depth of 1–3 mm, and the spread of the agents through the lymphatic channels was monitored. Ultrastaging was performed by assessing the presence of tumor cells within the lymph nodes based on the following criteria: isolated tumor cells: <0.2 mm, micrometastasis: 0.2–2 mm, macrometastasis: >2 mm.

Adjuvant therapy decisions were made by a multidisciplinary team, including gynecologic oncologists, radiation oncologists, and medical oncologists, within 4–6 weeks post-surgery. The decision-making process followed institutional guidelines based on National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) recommendations, considering tumor stage, histologic grade and subtype, depth of myometrial invasion, presence of lymphovascular space invasion, lymph node involvement, and available molecular markers. Patients with stage IA, grade 1–2 endometrioid tumors without adverse features typically did not receive adjuvant therapy, while those with higher stages, high-grade histology, or adverse molecular markers (particularly p53 mutations) were recommended adjuvant treatment. Although molecular profiling results were available to treating physicians, the integration of these findings into adjuvant therapy decisions varied during the study period as institutional guidelines were evolving. However, our analysis demonstrates that molecular markers, particularly p53 mutations, were significantly associated with adjuvant therapy administration, suggesting increasing incorporation of molecular data into treatment decisions.

The surgical specimens were sent to the pathology laboratory, and the tissue was processed into formalin-fixed, paraffin-embedded sections. Immunohistochemistry staining of tissue specimens was conducted to detect molecular subgroups identified by the TCGA project, including MMR (MLH1, MSH2, MSH6, PMS2) staining loss and abnormal

p53 expression. Due to limited availability of the necessary kits, analysis of POLE mutations could not be performed. Based on the test results, patients received genetic counseling by relevant departments and consultations were requested from appropriate clinics. Individuals with a suspected diagnosis of Lynch syndrome were referred to the genetics clinic as part of routine diagnostic procedures.

Relevant demographic and anthropometric data were recorded, including age, Body Mass Index (BMI), and menopausal status (pre/postmenopausal). Cancer-related information such as cervical involvement, lymph node involvement, sentinel node metastasis, histological cancer type (endometrioid, serous, clear cell, mixed, undifferentiated carcinoma, carcinosarcoma, small cell neuroendocrine carcinoma), tumor size, MI, LVSI, and molecular grouping data (MMR defects, p53 status), were also recorded.

It is important to note that this study was conducted during 2020–2022, when treatment decisions were transitioning from purely histopathology-based approaches to molecular-guided management. While initial adjuvant therapy decisions primarily followed conventional guidelines based on stage and histological factors, molecular profiling results were available to treating physicians and increasingly influenced treatment recommendations during the study period.

2.4 Statistics

Statistical significance was defined as $p < 0.05$ and analyses were performed by SPSS (v25, IBM, Armonk, NY, USA). Histograms and Quantile-Quantile plots (Q-Q plots) were examined to assess normality of distribution. Descriptive statistics for numerical data included "mean ± standard deviation" and "median (25th percentile–75th percentile)"—were used for parametric and non-parametric variables, respectively. Overall counts (n) and relative frequencies (%) were described for categorical variables. The test selection for the comparison of numerical variables was again based upon parametric assumptions, using the Student's *t*-test for parametric and the Mann-Whitney U test for non-parametric variables. Categorical distributions were compared using Chi-square tests or the Fisher's exact test (or the Freeman-Halton extension). Multivariable logistic regression was performed, with an initial model including all variables that demonstrated univariable significance in the comparison of recipients and non-recipients of adjuvant therapy. The model was subjected to the conditional forward selection, and significant parameters remaining at the final step were identified as factors independently associated with adjuvant therapy. Respective odds ratios (OR) and 95% confidence intervals (CIs), plus *p*-values were reported.

3. Results

A total of 100 patients were included in the study. The demographic, clinical, and tumor-related results of the patients are summarized in Table 1. Among the 34 patients who received adjuvant therapy, treatment modalities were as follows: radiation therapy alone in 16 patients (47.1%)—comprising external beam radiotherapy in 4 patients (11.8%), vaginal brachytherapy in 9 patients (26.5%), and combined external beam plus brachytherapy in 3 patients (8.8%); chemotherapy alone (carboplatin and paclitaxel) in 10 patients (29.4%); and combined chemoradiation in 8 patients (23.5%)—consisting of external beam radiotherapy plus chemotherapy in 3 patients (8.8%) and vaginal brachytherapy plus chemotherapy in 5 patients (14.7%). Of the 13 patients without tumor grade classification, 11 had non-endometrioid histology (4 serous, 2 clear cell, 2 mixed, 1 undifferentiated, 3 carcinosarcoma, 1 small cell neuroendocrine carcinoma) for which traditional FIGO grading is not applicable, and 2 had insufficient tissue for definitive grading.

TABLE 1. Demographic and cancer-related data of the study patients.

Variable	Value
Age, yr (n = 100)	61.27 ± 10.63
Body mass index, kg/m^2 (n = 100)	30.59 ± 4.16
Menopausal status (n = 100)	
Premenopausal	15 (15.00%)
Postmenopausal	85 (85.00%)
Histology (n = 100)	
Endometrioid carcinoma	87 (87.00%)
Serous carcinoma	4 (4.00%)
Clear cell carcinoma	2 (2.00%)
Mixed carcinoma	2 (2.00%)
Undifferentiated carcinoma	1 (1.00%)
Carcinosarcoma	3 (3.00%)
Small cell neuroendocrine carcinoma	1 (1.00%)
Adenomyosis (n = 99)	25 (25.25%)
Inferior uterine segment involvement (n = 99)	19 (19.19%)
Cervical involvement (n = 96)	5 (5.21%)
Adnexal involvement (n = 98)	3 (3.06%)
Uterine serosal involvement (n = 98)	1 (1.02%)
Abdomen metastasis (n = 99)	2 (2.02%)
Myometrial invasion, MR (n = 87)	
None	56 (64.37%)
<50%	10 (11.49%)
≥50%	21 (24.14%)
Myometrial invasion (n = 50)	
Restricted to endometrium	11 (22.00%)
Less than half invasion	28 (56.00%)
More than half invasion	11 (22.00%)
MELF pattern invasion (n = 99)	11 (11.11%)
Lymphovascular space invasion (n = 97)	32 (32.99%)
Positive cytology (n = 100)	1 (1.00%)
Tumor size, cm (n = 91)	3.38 ± 1.68
Grade (n = 87)	
Grade 1	37 (42.51%)
Grade 2	43 (49.42%)
Grade 3	7 (8.17%)

TABLE 1. Continued.

Variable	Value
Stage (n = 96)	
Stage IA	69 (71.88%)
Stage IB	14 (14.58%)
Stage II	3 (3.13%)
Stage IIIA	3 (3.13%)
Stage IIIB	1 (1.04%)
Stage IIIC	5 (5.21%)
Stage IV	1 (1.04%)
CA125 U/mL (n = 98)	15 (10–26)
Estrogen receptor, % (n = 86)	90 (80–100)
Estrogen receptor (n = 89)	
Negative	4 (4.49%)
Focal	3 (3.37%)
Diffuse	82 (92.13%)
Progesteron receptor, % (n = 74)	80 (40–90)
Progesteron receptor (n = 77)	
Negative	12 (15.58%)
Focal	9 (11.69%)
Diffuse	56 (72.73%)
Abnormal p53 staining (n = 99)	14 (14.14%)
MLH1 expression loss (n = 95)	25 (26.32%)
PMS2 expression loss (n = 95)	22 (23.16%)
MSH2 expression loss (n = 95)	2 (2.11%)
MSH6 expression loss (n = 95)	3 (3.16%)
Mismatch repair deficiency (n = 95)	28 (29.47%)
Total number of lymphadenectomies (n = 100)	7 (4–12)
Pelvic lymph node metastasis (n = 100)	0 (0.00%)
Paraaortic lymph node metastasis (n = 100)	0 (0.00%)
Lymph node metastasis (n = 97)	3 (3.09%)
Total number of sentinel lymph nodes (n = 100)	3 (2–6)
Sentinel lymph node status (n = 100)	
Non-metastatic sentinel lymph node	93 (93.00%)
Isolated tumor cell	2 (2.00%)
Micrometastasis, <2 mm	3 (3.00%)
Macrometastasis, >2 mm	2 (2.00%)
Staining material (n = 100)	
Methylene blue	45 (45.00%)
Indocyanine green	55 (55.00%)

TABLE 1. Continued.

Variable	Value
Type of staining (n = 99)	
None	5 (5.05%)
Unilateral	31 (31.31%)
Bilateral	63 (63.64%)
Adjuvant therapy (n = 100)	34 (34.00%)
Type of adjuvant therapy (n = 100)	
None	66 (66.00%)
Radiotherapy	16 (16.00%)
Chemotherapy	10 (10.00%)
Radiotherapy + Chemotherapy	8 (8.00%)
Detailed type of adjuvant therapy (n = 100)	
None	66 (66.00%)
External beam radiotherapy	4 (4.00%)
Vaginal brachytherapy	9 (9.00%)
External beam radiotherapy + Vaginal brachytherapy	3 (3.00%)
Taxol + Carboplatin	10 (10.00%)
External beam radiotherapy + Taxol + Carboplatin	3 (3.00%)
Vaginal brachytherapy + Taxol + Carboplatin	5 (5.00%)
Follow-up, months (n = 100)	10 (4–18)
Recurrence (n = 100)	3 (3.00%)
Mortality (n = 100)	2 (2.00%)

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile–75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables.
Grade was not applicable or available for 13 patients with non-endometrioid histology or insufficient tissue.
MR: Magnetic Resonance; CA125: Cancer Antigen 125; MLH1: MutL Homolog 1; MSH2: MutS Homolog 2; MSH6: MutS Homolog 6; PMS2: Postmeiotic Segregation increased 2.

Among the patients with endometrioid histology who did not receive adjuvant therapy, four had abnormal p53 staining. During the follow-up period, none of these p53-positive endometrioid patients experienced recurrence or mortality.

Adjuvant therapy recipients were significantly older and had higher rates of cervical, adnexal, and inferior uterine segment involvement, and were more likely to have microcystic elongated and fragmented pattern (MELF) invasion. Additionally, tumor size was significantly larger, progesterone receptor positivity and abnormal p53 staining were significantly more common, and the frequencies of lymph node metastasis and recurrence were higher (Table 2).

Multivariable logistic regression revealed that stage IB (OR: 68.571, 95% CI: 10.540–446.114, $p < 0.001$), stage II–IV (OR: 153.412, 95% CI: 15.048–1564.055, $p < 0.001$), and p53

TABLE 2. Univariate comparisons of all examined parameters with regard to adjuvant therapy.

	Adjuvant therapy		*p*
	No (n = 66)	Yes (n = 34)	
Age, yr (n = 100)	58.45 ± 10.41	66.74 ± 8.90	**<0.001**†
Body mass index, kg/m^2 (n = 100)	30.35 ± 4.36	31.07 ± 3.74	0.416†
Menopausal status (n = 100)			
Premenopausal	13 (19.70%)	2 (5.88%)	0.124§
Postmenopausal	53 (80.30%)	32 (94.12%)	
Histology (n = 100)			
Endometrioid carcinoma	64 (96.97%)	23 (67.65%)	**<0.001**#
Other	2 (3.03%)	11 (32.35%)	
Adenomyosis (n = 99)	16 (24.62%)	9 (26.47%)	1.000§
Inferior uterine segment involvement (n = 99)	8 (12.31%)	11 (32.35%)	**0.033**§
Cervical involvement (n = 96)	0 (0.00%)	5 (14.71%)	**0.005**#
Adnexal involvement (n = 98)	0 (0.00%)	3 (8.82%)	**0.039**#
Uterine serosal involvement (n = 98)	0 (0.00%)	1 (2.94%)	0.347#
Abdomen metastasis (n = 99)	0 (0.00%)	2 (5.88%)	0.116#
Myometrial invasion, MR (n = 87)			
None	48 (78.69%)	8 (30.77%)*	
<50%	6 (9.84%)	4 (15.38%)	**<0.001**§
≥50%	7 (11.48%)	14 (53.85%)*	
Myometrial invasion (n = 50)			
Restricted to endometrium	6 (18.18%)	5 (29.41%)	
Less than half invasion	22 (66.67%)	6 (35.29%)	0.111¶
More than half invasion	5 (15.15%)	6 (35.29%)	
MELF pattern invasion (n = 99)	3 (4.62%)	8 (23.53%)	**0.007**#
Lymphovascular space invasion (n = 97)	12 (19.05%)	20 (58.82%)	**<0.001**§
Positive cytology (n = 100)	1 (1.52%)	0 (0.00%)	1.000#
Tumor size, cm (n = 91)	2.96 ± 1.39	4.09 ± 1.88	**0.001**†
Grade (n = 87)			
Grade 1	32 (50.82%)	5 (21.74%)*	
Grade 2	29 (45.90%)	14 (56.52%)	**0.005**§
Grade 3	2 (3.28%)	5 (21.74%)*	
Stage (n = 96)			
Stage IA	60 (95.24%)	9 (27.27%)*	
Stage IB	2 (3.17%)	12 (36.36%)*	**<0.001**¶
Stage II–IV	1 (1.59%)	12 (36.36%)*	
CA125 U/mL (n = 98)	13.5 (10–27)	16.5 (12–26)	0.533‡
Estrogen receptor, % (n = 86)	90 (90–100)	90 (70–95)	0.106‡
Estrogen receptor (n = 89)			
Negative	1 (1.67%)	3 (10.34%)	
Focal	1 (1.67%)	2 (6.90%)	0.059¶
Diffuse	58 (96.67%)	24 (82.76%)	
Progesteron receptor, % (n = 74)	80 (70–90)	70 (0–90)	**0.039**‡

TABLE 2. Continued.

	Adjuvant therapy		*p*
	No (n = 66)	Yes (n = 34)	
Progesteron receptor (n = 77)			
Negative	5 (10.00%)	7 (25.93%)	
Focal	5 (10.00%)	4 (14.81%)	0.129¶
Diffuse	40 (80.00%)	16 (59.26%)	
p53 mutation (n = 99)	4 (6.15%)	10 (29.41%)	**0.004**#
MLH1 expression loss (n = 95)	18 (28.13%)	7 (22.58%)	0.744§
PMS2 expression loss (n = 95)	17 (26.56%)	5 (16.13%)	0.384§
MSH2 expression loss (n = 95)	1 (1.56%)	1 (3.23%)	0.548#
MSH6 expression loss (n = 95)	2 (3.13%)	1 (3.23%)	1.000#
Mismatch repair deficiency (n = 95)	20 (31.25%)	8 (25.81%)	0.760§
Total number of lymphadenectomies (n = 100)	7 (4–10)	8 (5–18)	0.063‡
Lymph node metastasis (n = 97)	0 (0.00%)	3 (8.82%)	**0.041**#
Total number of sentinel lymph nodes (n = 100)	4 (2–6)	3 (1–4)	0.053‡
Sentinel lymph node status (n = 100)			
Non-metastatic sentinel lymph node	64 (96.97%)	29 (85.29%)	**0.043**#
Metastatic sentinel lymph node	2 (3.03%)	5 (14.71%)	
Staining material (n = 100)			
Methylene blue	27 (40.91%)	18 (52.94%)	0.351§
Indocyanine green	39 (59.09%)	16 (47.06%)	
Type of staining (n = 99)			
None	1 (1.54%)	4 (11.76%)	
Unilateral	20 (30.77%)	11 (32.35%)	0.074¶
Bilateral	44 (67.69%)	19 (55.88%)	
Follow-up, months (n = 100)	7 (4–18)	11 (8–17)	**0.033**‡
Recurrence (n = 100)	0 (0.00%)	3 (8.82%)	**0.037**#
Mortality (n = 100)	1 (1.52%)	1 (2.94%)	1.000#

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile–75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables.
†*: Student's t test;* ‡*: Mann Whitney U test;* §*: Chi-square test;* #*: Fisher's exact test;* ¶*: Fisher-Freeman-Halton test; *: Significantly different category for variables with three or more categories. Statistically significant p-values ($p < 0.05$) are shown in bold.*
MR: Magnetic Resonance; CA125: Cancer Antigen 125; MLH1: MutL Homolog 1; MSH2: MutS Homolog 2; MSH6: MutS Homolog 6; PMS2: Postmeiotic Segregation increased 2.

mutation (OR: 8.572, 95% CI: 1.304–56.341, $p = 0.025$) were independently associated with adjuvant therapy use. Conversely, having a diagnosis of endometrioid carcinoma (OR: 0.104, 95% CI: 0.012–0.911, $p = 0.041$) was independently associated with a lower likelihood of adjuvant therapy. Other variables showed no significant association: age ($p = 0.105$), inferior uterine segment involvement ($p = 0.450$), cervical involvement ($p = 0.343$), adnexal involvement ($p = 0.571$), myometrial invasion ($p = 0.526$), MELF pattern invasion ($p = 0.094$), lymphovascular space invasion ($p = 0.761$), tumor size ($p = 0.826$), grade ($p = 0.945$), progesterone receptor ($p = 0.999$), lymph node metastasis ($p = 0.708$), and sentinel lymph node status ($p = 0.140$) (Table 3).

During the median follow-up period of 10 months (Interquartile range (IQR): 4–18), recurrence occurred in 3 patients (3.0%), all of whom had received adjuvant therapy. The recurrence rate was significantly higher in the adjuvant therapy group compared to those who did not receive adjuvant therapy (8.82% *vs.* 0.00%, $p = 0.037$). Mortality occurred in 2 patients (2.0%) during the follow-up period, one in each treatment group ($p = 1.000$). Due to the relatively short follow-up period and low event rates, formal survival analysis was not performed.

Abnormal p53 staining consistent with *TP53* mutation was

TABLE 3. Significant factors independently associated with adjuvant therapy, multivariable logistic regression analysis.

	β coefficient	Standard error	p	Exp(β)	95% CI for Exp(β)	
Histology, Endometrioid carcinoma	−2.259	1.105	**0.041**	0.104	0.012	0.911
Stage[(1)]						
Stage IB	4.228	0.955	**<0.001**	68.571	10.540	446.114
Stage II–IV	5.033	1.185	**<0.001**	153.412	15.048	1564.055
p53 mutation	2.148	0.961	**0.025**	8.572	1.304	56.341
Constant	−0.561	1.100	0.610	0.571		

Nagelkerke R^2 = 0.707. [(1)]*Reference category: Stage IA. Statistically significant p-values ($p < 0.05$) are shown in bold. CI: Confidence interval.*

detected in 14 patients (14%). Endometrioid cancer was significantly less likely to be associated with p53 mutations (35.71% *vs.* 95.29%, $p < 0.01$). Tumor size was larger in patients with p53 mutations (4.20 ± 1.84 cm *vs.* 3.23 ± 1.61 cm, p = 0.046) and adjuvant therapy was more frequently administered to patients with p53 mutations (71.43% *vs.* 28.24%, p = 0.004). MMR deficiencies were detected in 28 patients (28%). When patients were grouped according to their MMR status, no statistically significant differences were observed between those with and without MMR deficiency. When the patients were evaluated with respect to sentinel lymph node status, 7 patients (7%) were found to have metastatic nodes. Patients with metastatic sentinel lymph nodes were older (68.86 ± 7.29 *vs.* 60.70 ± 10.65 years, p = 0.049) and they also had a higher frequency of undergoing adjuvant therapy (71.43% *vs.* 31.18%, p = 0.043).

We examined whether p53 mutations were more common in advanced-stage tumors. p53 mutations occurred in 7/65 Stage IA cases (10.8%), 2/13 Stage IB cases (15.4%), and 2/11 Stage II–IV cases (18.2%). Although there was a slight increase with advancing stage, this difference was not statistically significant (p = 0.853). The small number of p53-positive cases and few patients with advanced disease likely limited our ability to detect a meaningful association.

4. Discussion

Our study examined the demographic, clinical, and tumor-related factors associated with the use of adjuvant therapy in patients with EC. A key finding was the significant association between adjuvant therapy and factors, such as tumor stage (IB and II–IV) and abnormal p53 staining. In contrast, patients with endometrioid carcinoma were less likely to undergo adjuvant therapy. Currently, adjuvant therapy decisions for EC are based upon cancer stage, histologic grade, subtype, and specific histopathologic markers. However, recent research has shifted focus toward new molecular features that enhance patient management by facilitating more precise assessment of prognosis and the possible benefits of different adjuvant therapies. These molecular features have been shown to identify subgroups that benefit from specific treatments [11]. In fact, studies examining these specific markers (p53 and MMR deficiency) have prompted the creation of molecular classification approaches that have improved risk assessment and management [12].

Disease stage, similar to its utility in other cancers, has long been accepted as a factor that determines the therapeutic approach in EC. The finding that stage IB and stage II–IV disease were independently associated with adjuvant therapy in our study aligns with existing literature in this respect. It has consistently been highlighted that advanced stage disease carries a greater risk for recurrence and aggressive disease [3]. We must note that the original adjuvant therapy decisions were made based on available guidelines; therefore, the detection of advanced stage as an independent variable was not surprising in our study. The exceedingly high effect sizes detected for stages IB and II–IV (68.57 and 153.41, respectively) indicate an escalating need for adjuvant therapy in more advanced cases.

The most common type of EC is endometrioid carcinoma, which constitutes approximately 80% of EC cases. Endometrioid carcinomas are often diagnosed in perimenopausal women, are usually low grade (grade 1 or 2), diagnosed at early stages, and have a good prognosis [9, 13]. Our data revealed that endometrioid carcinoma was independently associated with not receiving adjuvant therapy. This was a foreseeable result considering the well-established decision-making process for adjuvant therapies. The well-recognized favorable prognosis and lower recurrence rates of endometrioid carcinoma [14] usually result in a lower risk for patients, reducing the likelihood of recommending aggressive treatments.

In addition to stage, we detected a strong link between the use of adjuvant therapy and the presence of abnormal p53 staining. It is notable that the effect size for p53 in the multivariable model remained exceedingly high (8.57) despite being adjusted for stage (poor outcome) and endometrioid carcinoma diagnosis (good outcome). We believe this strong relationship highlights the aggressive biological behavior associated with this mutation, which is seen across multiple cancer types. The literature on this topic has shown that p53 mutations are often correlated with poor prognosis, an increased number of somatic copy number alterations, lower mutation rates, higher recurrence rates, and decreased survival [15]. These factors likely explain why p53 mutations are associated with more intensive treatment strategies [3]. This is particularly pertinent for patients with EC, in whom p53 mutations have been demonstrated to be associated with more aggressive cancer subtypes, such as serous and carcinosarcoma

[16]. The relationship between p53 mutations and metastatic lymph nodes appears to be consistent across multiple studies. For instance, a case control study of 76 patients with EC identified p53 as a independent predictor of metastatic nodes [17]. Although ECs with p53 mutations account for only 15% of all cases, they are responsible for 50%–70% of EC-attributed deaths [18]. Data from the Post Operative Radiation Therapy in Endometrial Carcinoma-3 (PORTEC-3) phase 3 trial provided insight into treatment effect by detailed examination of molecular classes. In this study, p53 status was one of the strongest indicators of poor outcomes in EC. In fact, even within a subgroup of patients classified as high risk, those with p53 aberrations were found to have worse outcomes compared to those without. The authors also determined that those in the p53 group were the only patients who experienced a clear benefit from the addition of chemotherapy to standard radiotherapy [19]. This finding has been corroborated by international cohorts showing that individuals with p53 mutations who received both chemotherapy and radiation achieved better outcomes than those treated with radiotherapy alone [20]. Taken together with the strong relationship shown in our study, we believe these findings suggest greater benefits from intensive treatment in patients with p53 mutations—even in early-stage disease. Such an approach to early-stage p53-positive disease could yield clinically-meaningful improvements and prolonged survival. Another interesting finding in our study is that, although p53 mutations are traditionally associated with non-endometrioid tumors [21], 35.7% of patients with such mutations had endometrioid histology in our study. This could be a confounding effect due to potential overlap between histologic and molecular classifications. It is therefore necessary to utilize and improve molecular profiling options to complement traditional histopathological diagnosis and understand how pathological p53 mutations might influence lesion development and disease progression in different EC subtypes.

A significant limitation was our inability to perform POLE mutation analysis due to resource constraints. POLE mutations define a molecular subclass with excellent prognosis, often eliminating the need for adjuvant therapy even in high-grade tumors. Including POLE analysis would have enabled a more comprehensive molecular classification and potentially identified additional patients who could safely avoid adjuvant therapy. Future studies with complete molecular profiling, including POLE mutations, would improve treatment precision and refine our understanding of factors influencing adjuvant therapy decisions.

Several factors showing univariable significance (age, cervical involvement, adnexal involvement, MELF pattern) did not remain significant in multivariable analysis, likely due to our relatively small sample size and heterogeneous population. Similarly, progesterone receptor expression lost significance after adjusting for other factors. Larger studies are needed to evaluate the complex role of hormone receptors in treatment decisions.

Our study was conducted during 2020–2022, when treatment was transitioning from histopathology-based to molecular-guided approaches. While adjuvant therapy decisions initially followed conventional guidelines, our analysis shows molecular markers like p53 mutations were already influencing treatment choices, suggesting early adoption of molecular data before formal guideline integration. However, we could not assess long-term outcomes for p53-positive patients who did not receive adjuvant therapy, which would help validate current molecular-guided recommendations. Future prospective studies comparing treatment patterns before and after routine molecular profiling would quantify the clinical impact of molecular classification.

5. Conclusions

In conclusion, the likelihood of receiving adjuvant therapy was strongly associated with p53 mutation status, as well as tumor stage (IB and II–IV) and endometrioid carcinoma diagnosis. Patients with higher stage (reference stage: IA) and patients with p53 mutations were found to be more likely to receive adjuvant therapy in our study. Conversely, patients diagnosed with endometrioid carcinoma were less likely to receive adjuvant therapy, most likely owing to the lower risk associated with these cases. The results highlight the importance of comprehensive examination of tumor characteristics (molecular and histological) to guide adjuvant treatment decisions in EC. Future research with larger cohorts would be beneficial to confirm these results and more reliably assess the impact of other factors on adjuvant therapy decisions.

ABBREVIATIONS

EC, Endometrial cancer; LVSI, Lymphovascular space invasion; MELF, Microcystic elongated and fragmented pattern; MI, Myometrial invasion; MMR, mismatch repair; POLE, Polymerase epsilon; TCGA, The Cancer Genome Atlas; WHO, World Health Organization; FIGO, International Federation of Gynecology and Obstetrics; TP53, Tumor Protein 53; OR, Odds Ratio; CI, Confidence Interval; MLH1, MutL Homolog 1; MSH2, MutS Homolog 2; MSH6, MutS Homolog 6; PMS2, Postmeiotic Segregation increased 2; NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology; IQR, Interquartile Range; PORTEC-3, Post Operative Radiation Therapy in Endometrial Carcinoma-3; Q-Q, Quantile-Quantile.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

MO, MFO—conceptualization, formal analysis, investigation, methodology, writing–original draft, writing–review & editing. IY—data curation, investigation, writing–original draft, writing–review & editing. MK—methodology, writing–review.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Clinical Research Ethics Committee of Ondokuz Mayıs University (Decision date: 28 April 2023, decision no: B.30.2.ODM.0.20.08/177), and the study was conducted in accordance with the principles of the Declaration of Helsinki. The Clinical Research Ethics Committee of Ondokuz Mayıs University waived the requirement for informed consent due to the retrospective nature of the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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