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Examination of Factors Affecting Prognosis and Treatment Choice in Patients with Endometrial Cancer: A Retrospective Single-Center Experience

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ABSTRACT Objective: The classification of endometrial cancer, based on histology, provides important prognostic information and is pivotal for assessing appropriate surgical and adjuvant therapy. However, molecular determinants could be incorporated to improve the current classification system. **Materials and Methods:** In our study,Seventy patients diagnosed with endometrial cancer between 2016 and 2021 were included. Pathological type, stage at diagnosis, the date of initiation of treatment, survival information, and molecular characteristics of the patients were recorded.The chi-square test was used to analyze categorical variables.Independent groups were compared using an independent sample t-test and Mann-Whitney-U test. Overall survival was estimated using the Kaplan-Meier method, and results were compared using the log-rank test. The independent prognostic risk factors were analyzed using the Cox regression model. **Results:** The primary findings obtained were as follows: (1) Median overall survival in de novo metastatic cases was significantly lower than that in patients with subsequent relapse; (2) The most common endometrioid type was observed based on the histopathological examination results. The undifferentiated endometrial cancer subtype demonstrated a highly aggressive course; (3) In the present study, p16 was positive at a significantly higher rate over 60 years of age ($p = 0.027$). **Conclusion:** Various prognostic factors were examined in this study. Molecular markers may have an important role in determining the prognosis of endometrial cancer. The positivity of molecular markers such as p16 may contribute to mortality, especially in the geriatric age group.

Keywords: Endometrial neoplasms; mortality; prognosis; human CDKN2A protein

Endometrial cancer (EC) is among the most common gynecological cancers in developed countries.[1,2] Owing to a slower course compared to other gynecological cancers, the curing possibility is high with early diagnosis and treatment. Adjuvant chemotherapy or radiotherapy is not needed in many cases with early surgery.[3] Two histological categories differ among EC in terms of incidence, response to hormones, and clinical behavior.[4] Type I tumors are generally Grade 1 and 2 tumors, with 80% of EC belonging to this category. These tumors generally have a good prognosis. Type II tumors constitute approximately 20% of EC. These include endometrioid Grade 3 and non-endometrioid tumors. Examples of these are serous, clear cell, mucinous, squamous, and undifferentiated histological types. Grade is extremely important in determining prognosis, and Grade 3 endometrioid EC is responsible for most deaths.[5] The serous is the second most common type of EC with a rather poor prognosis and high risk of metastasis.[6,7] The degree of myometrial invasion and cervical and lymph node involvement are critical considerations in staging. Although transvaginal ultrasonography and magnetic resonance imaging can be utilized for staging, they may be inefficient in detecting lymph node metastases. Therefore, a complete staging is achieved by comprehensive surgical staging. Thus, cervical, adnexal, peritoneal, and lymph node metastases can be evaluated more accurately. The clinicians decide the treatment based on the pathological prognostic factors used in risk classification systems.[8-10] This can be used to estimate the

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prognosis of the patients and for applying appropriate adjuvant treatment protocols. In studies of the Gynecological Oncology Group 33, surgical staging was demonstrated to be superior to clinical staging. In this study, 9%, 6%, 5%, and 6% of patients with clinical Stage I had pelvic nodal involvement, para-aortic involvement, adnexal involvement, and extrauterine metastasis, respectively.[11] It can be determined in patients requiring adjuvant radiotherapy and chemotherapy owing to detailed surgical staging. Consequently, patients with high-risk factors requiring adjuvant therapy can be distinguished from others.[12] The importance of detailed pathological evaluation in determining prognosis will further enhance with new developments in clinicopathological and molecular fields. Recognizing the molecular mechanisms involved in the etiology of EC will greatly contribute to the discovery of targeted therapies in the future. Here, we aimed to emphasize the subtypes of the emerging clinical features, clear determination of the factors affecting the prognosis, and the effects of all these on therapeutic options from a clinical perspective.

MATERIAL AND METHODS

Our study was designed based on the STROBE criteria.[13] The population of the study comprised 342 (n=342) patients with EC who reported to the Dokuz Eylül University Hospital Medical Oncology outpatient clinic for diagnosis and treatment between 2016 and 2021. One hundred and forty-two patients received treatment for concomitant ovarian cancer. The exclusion criteria were as follows: Patients whose information could not be obtained or limited, with a follow-up period of less than 12 months, pathological examination performed at an outside center, and those who received systemic therapy less than 6 months back. Patients who applied to our hospital for any reason and were diagnosed with EC but were not followed up were also excluded. A total of 70 patients were included in the study. Inclusion criteria were as follows: patients aged more than 18 years; those diagnosed with EC; and those diagnosed, treated, and followed up in the medical oncology outpatient clinic. Patient information was obtained retrospectively from patient files. Demographic patient data, laboratory findings at the time of admission, date of diagnosis, pathological type of the tumor, stage at diagnosis, date of initiation of treatment, and survival information were recorded. Concomitant diseases were noted from the patient history at the time of admission. The performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) performance status. Staging was performed based on the obstetrics [International Federation of Gynecology and Obstetrics (FIGO)]/Tumor, Node, Metastasis classification system, which was globally acceptable at the time of diagnosis. Survival was defined as the time from diagnosis to death or the last known date of the patient's life. The present study was conducted in accordance with the principles of the Declaration of Helsinki.

Dokuz Eylül University Non-Invasive Clinical Research Ethics Committee Ethical approval dated August 31, 2022, decision number 2022/28-26 has been completed.

Descriptive statistical analyses of patients' demographic, clinicopathological, and treatment characteristics were performed. The data was collected using IBM SPSS version v24.0 (IBM, NY, ABD). Descriptive statistics for participants are shown as percentages and (n), and mean±standard deviation for categorical and continuous data, respectively. The chi-square test was used to analyze categorical variables. Before performing the hypothesis tests, the Kolmogorov-Smirnov test to examine the normal distribution of data. Independent groups were compared using an independent sample t-test and Mann-Whitney U test. Overall survival (OS) was estimated using the Kaplan-Meier method, and results were compared using the log-rank test. The independent prognostic risk factors were analyzed using the Cox regression model. The results were evaluated at the 95% confidence interval, and the significance level was $p<0.05$.

RESULTS

The mean age of the patients was 61±11.02 years. Socio-demographics and characteristics of the patients are presented in Table 1.

It was determined that 30 (42.9%) patients were under 60 years and 40 (57.1%) were 60 years or older. Among all ECs, 31 (44%) patients were in the

TABLE 1: Clinical and pathological characteristics of the patients.

Variables	Number (n)	Ratio(%)	Variables	Number (n)	Ratio(%)
Tumor histological subtype			Number of metastases		
Endometrioid adenocarcinoma	31	44.3	No metastases	50	71.4
Serous	15	21.4	Single site metastasis	4	5.7
Mixt	7	10.0	Metastases to 2 sites	6	8.6
Clear cell	6	8.6	Metastases to 3 sites	2	2.9
Mucinous adenocancer	6	8.6	Metastases to 4 sites	3	4.3
Carcinosarcoma	4	5.7	Metastases to 5 or more sites	1	1.4
Undifferentiated	1	1.4			
TNM staging			Performance status		
Stage 1a	14	20	ECOG 0	38	54.3
Stage 1b	13	18.6	ECOG 1	22	31.4
Stage 2	15	21.4	ECOG 2	9	12.9
Stage 3a	12	17.1	ECOG 3	1	2.4
Stage 3b	1	1.4	ECOG 4	0	0
Stage 3c	13	18.6			
Stage 4b	2	2.9			
Metastasis site			Lymphovascular invasion		
Liver	5	7.1	No	28	40
Lung	10	14.3	Yes	42	60
Bone	4	5.7			
Other	16	22.9			
Metastasis status			Reason for application		
Metastasis at the time of diagnosis	9	12.9	Vaginal bleeding	52	74.3
Metastasis developed on follow-up	11	15.7	Abdominal pain	8	11.4
No metastases	50	71.4	Abdominal mass	2	2.9
Presence of progression			Other	8	11.4
Yes	13	18.6			
No	2	2.9			
Myometrial invasion			Operation		
No	10	14.3	Yes	68	97.1
Less than 50%	27	38.6	No	2	2.9
More than 50%	33	47.1			
Lymph node					
N0	50	71.4			
N1	9	12.9			
N2	11	15.7			

TNM: Tumor, Node, Metastasis; ECOG: The Eastern Cooperative Oncology Group.

endometrioid histological subtype. Undifferentiated EC are rare, and highly aggressive tumors.[14] In the present study, 1 (1.4%) patient had undifferentiated histology. Vaginal bleeding was the reason for admission in 52 (74.3%) patients. There were 19 (27.1%) patients with Stage 2 at the time of diagnosis. The stages of the patients in our study were as follows: 14 (20%) in Stage 1a, 13 (18.6%) in Stage 1b, 15 (21.4%) in Stage 2, 12 (17.1%) Stage 3a, 1 (1.4%) Stage 3b, 13 (18.6%) Stage 3c, and 2 (2.9%) in Stage 4b. In the peritoneal cytology results, malignant cells were observed in 10 (14.3%) patients. It was determined that 3 (30%) were in Stage 2, 1 (10%) in Stage 3b, 4 (40%) in Stage 3c, and 2 (20%) in Stage 4b. Lymphovascular invasion was present in 42 (60%) of the patients. No myometrial invasion was noted in 3 (7.1%) of these patients. In 12 (28.6%) patients, the invasion did not exceed 50% of the my-

ometrium, and in 27 (64.3%) invasion exceeded 50% of the myometrium. There were 60 (85.7%) patients with myometrial invasion. It was determined that 16 (22.9%) patients died. Six (37.5%) were found to have endometrioid type EC. Twelve (75%) of the patients who died were over the age of 60 years. The mean OS was 4±3.95 years. There was no significant relationship between pathological subtypes and age (p=0.071). Progesterone receptor (PR) was significantly more positive under 60 years of age (p=0.05). Median OS in de novo metastatic patients was shorter than that in those with relapse (p=0.001). The median OS of the patients was 79.5 months. This was 22.5 months in the median metastasis-free survival. In the comparative analysis of the mean and median values of the variables according to mortality, age was an important factor affecting mortality (p=0.020). The effect of the variables related to the Cox regression analysis on survival is shown in Table 2.

DISCUSSION

Endometrial cancer is generally diagnosed in postmenopausal women. More than 90% of the cases are observed in women over the age of 50 years, with the disease reaching the highest incidence in women over the age of 65 years.[15] In the present study, there was a patient weight in the geriatric population, which was consistent with the literature. Data and studies demonstrated the association of advanced age with poor prognosis and advanced disease in EC. Chi et al. stated the association of age with poor prognosis in patients with advanced EC.[16] In the present study, we demonstrated the relationship between age and prognosis in the comparative analysis of the mean and median values of the variables according to mortality (p=0.020). In contrast, Bristow et al. argued that advanced stage and prognosis were not related to age.[17] The parameters that are important in EC are the patient's age, tumor size, histopathological type, stage, and peritoneal cytology.[18] In the present study, tumor size, number and localization of lymph nodes involved, ECOG performance score, tumor grade, presence of lymphovascular invasion, size of myometrial invasion, and presentation as de novo metastases were demonstrated as factors directly affecting prognosis. The peritoneal cytology value in EC has been discussed for years. In FIGO 2009 staging, peritoneal cytology was excluded from the staging criteria. Peritoneal cytology is clinically more valuable, in particular, in the absence of extensive myometrial invasion or peritoneal implants. Obermair et al. reported that peritoneal cytology with the depth of myometrial invasion. In this situation, when a relationship between EC and peritoneal cannot be detected, it can spread.[19] The presence and depth of myometrial invasion is an important parameter in EC. Szumczyk et al. examined 137 of 420 patients with stage 1-4 EC who underwent pelvic lymph dissection and found 19.7% pelvic lymph node metastases (n=27), and consequently, stated that there was >50% myometrial invasion in all of these cases.[20] In patients with early-stage EC, the degree of myometrial invasion is decisive in terms of prognosis. Pelvic and para-aortic lymph node status associated with metastases to the cervix, adnexa, and peritoneum are important factors in terms of recurrence risk and prognosis. In our study, there were 60 (85.7%) patients with myometrial invasion. Burton et al. re-

TABLE 2: The effects of variables on survival by Cox regression analysis.

Patient characteristics	Factor	p value	HR	95% CI
Myometrial invasion	50%	0.006	6.715	1.741-25.896
Metastasis	De novo	0.001	12.543	2.954-53.259
Age	≥60	0.020	9.320	1.428-60.654
Histological subgroup	Pathology	0.031	6.083	1.182-31.317
Grade	Degree	0.005	6.366	1.745-23.230
ECOG	Score	0.004	8.591	1.980-37.269

HR: Hazard ratio; CI: Confidence interval; ECOG: The Eastern Cooperative Oncology Group.

ported that lymphovascular invasion was detected in 15% of early-stage EC, and the degree increases with increasing stage and myometrial depth.[21] In our study, lymphovascular invasion was present in 42 (60%) patients. Only three (7.1%) patients did not have myometrial invasion. In the present study, the risk of extrauterine metastasis was found to increase with the increase in depth of myometrial invasion. These results highlight the importance of surgical staging and dividing patients into prognostic groups to ensure adequate adjuvant therapy. In the study by Lachance et al., 396 patients with ERC were included, and 38% of the cases were above 65 years. Clear cell and serous histology were more common in this group. In the same population, higher histological degree and deeper myometrial invasion were detected in the advanced age. No difference between age groups was noted in terms of lymph node metastasis. Another finding was histological grades of 2 and 3 in 88% of patients over 75 years of age.[22] In our study, no correlation was found between the patients aged above and below 60 years and grade and myometrial invasion. Likewise, no significant relationship was found between histopathological types and age. The use of immunohistochemical markers, including tumor protein 53 (TP53), phosphatase and tensin homologous gene (PTEN), estrogen receptor (ER), and PR, is important for subtypes of EC. Hormone receptor status is an important molecular prognostic factor. Kim et al. reported that within type I EC, TP53 was found to be upregulated, together with downregulation of PTEN within higher EC grades.[23] Hormonal therapy should always be considered as complementary and palliative. In our study, although the ER receptor level was not significant in the group with a better prognosis, the PR receptor level was found to be significantly higher (p=0.05). Guan et al. argued that integrating ER/PR evaluation into clinical risk stratification may improve prognosis for grade I-II endometrioid endometrial adenocarcinoma patients.[24] Molecular genetic studies have proven EC to be a multistep event with oncogene activation and tumor suppressor gene inactivation. The most common genetic changes in endometrioid type EC, which have been detected in studies to date, are as follows: PTEN inactivation is beta-catenin mutation, microsatellite instability), Kirsten Rat Sarcoma Viral Oncogene Homologous Gene mutation, p53 mutation, E-cadherin changes, and p16 (Cyclin Dependent Kinase Inhibitor 2A) inactivation. P53 mutation, E-cadherin changes, p16 inactivation, increased expression of Nrf2 (Erythroid 2 associated nuclear factor 2), and PTEN inactivation are observed in serous adenocarcinoma, while p53 mutation is observed in clear cell adenocarcinomas.[25] Serous carcinoma (SC) can be distinguished from high-grade endometrioid adenocarcinoma, given their differences in prognosis and management. This distinction typically relies upon the use of a focused immunohistochemical panel, including p53, p16, and mismatch repair proteins. The p16 expression is characteristically strong and diffuse in SC, and weak and/or patchy in many high-grade endometrioid adenocarcinomas. Daniel et al. reported a subset of SC entirely negative for p16 immunostaining. In the context of an otherwise clinically and histologically classic example of SC, this negative p16 staining pattern was endorsed as an alternative aberrant staining pattern.[26] In our study, p16 was found to be positive at a significantly higher rate over 60 years of age (p=0.027). Dong et al. study demonstrated that p16 expression accompanies tumor progression and poor prognosis.[27] In our study, one of the reasons for the worse prognosis of patients aged 60 years and older might be the high p16 positivity rate. Yemelyanova et al., in their study, observed p16 positivity in all 49 endometrial serous adenocarcinoma cases, in the range of 30-38% in 101 endometrioid type EC cases. In this study, p16 was shown as an immunohistochemical marker in the differential diagnosis of endometrial serous adenocarcinoma and endometrioid type EC.[28] In our study, p16 endometrioid type EC was found to be positive in 11 (61.11%) of 18 cases. It was found positive in six (85.71%) of seven cases of serous adenocarcinomas and three (75%) of four cases of clear cell adenocarcinomas. Despite the significant increase in staining observed in serous adenocarcinomas, no significant association was found between p16 and endometrial serous adenocarcinoma, endometrioid type EC, and clear cell adenocarcinomas (p = 0.467). In contrast, in a study conducted on patients with high-grade EC, based on

the stage distributions and sites of recurrence, significant differences were found between high-grade endometrioid-type EC and serous carcinomas.[29] These differences are related to other conditions in the clinical course, and available biomarkers can be used to distinguish high-grade endometrioid-type EC from serous carcinomas. The limitation of this study was that it was retrospective with a limited number of patients.

CONCLUSION

Histopathological classification provides important prognostic information and guides the appropriate surgical and adjuvant therapy determination. The current classification system can be improved by including molecular determinants. More efficient and effective treatments for patients with EC will come to the fore with the understanding of the molecular basis of EC with prospective, randomized studies to be conducted in the coming years.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mehmet Uzun;* ***Design:*** *Eda Çalışkan Yıldırım;* ***Control/Supervision:*** *Aziz Karaoğlu;* ***Data Collection and/or Processing:*** *Aysu Usabbaylı, Mehmet Uzun;* ***Analysis and/or Interpretation:*** *Eda Çalışkan Yıldırım;* ***Literature Review:*** *Mehmet Uzun;* ***Writing the Article:*** *Mehmet Uzun;* ***Critical Review:*** *Aysu Usabbaylı;* ***References and Fundings:*** *Mehmet Uzun;* ***Materials:*** *Eda Çalışkan Yıldırım.*

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