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Research Article

Overview of Clinical, Pathological and Treatment Features of the Patients with Endometrium Cancer: A Single Center Study

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Abstract

Objectives: Endometrial cancer is the second most common gynecological cancer worldwide. Despite being usually diagnosed at an early stage with a better prognosis compared to other gynecological cancers, some cases can be aggressive. Obtaining data on independent prognostic factors correlated with survival and recurrence would be beneficial to control the disease and make informed systemic treatment decisions effectively. We aimed to review endometrial cancer's clinical and pathological features and determine the prognostic risk factors.

Methods: We conducted a retrospective study on 136 individuals with endometrial cancer who were followed up between 1997 and 2015. Prognostic factors with a p-value of less than 0.15 using the Long-rank test were included in multivariate analysis. Multivariate analysis was performed by the Cox regression test.

Results: Significant prognostic factors determining the overall survival in univariate analysis were disease stage, histological grade, age at diagnosis, histological type, lymph node metastasis, lymphatic and vascular invasion, depth of myometrial invasion, cervical stromal invasion, tumor diameter, the positivity of peritoneal cytology, and pre-op serum CA-125 levels. In multivariate analysis, advanced stage and high preoperative CA-125 levels were detected as factors reducing overall survival (p=0.012, p=0.005, respectively).

Conclusion: The two most important factors for endometrial cancer survival were stage and pre-op serum CA-125 level, independent of other parameters. As our study was retrospectively done with a limited number of patients, more extensive prospective, randomized studies with a larger number of patients are necessary to apply the information obtained from this study to our clinical practices.

Keywords: Endometrial cancer, prognosis, CA-125 antigen

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Uterine cancer is the second most common gynecological cancer worldwide, regardless of the development level of countries.[1] Endometrial cancer accounts for over 90% of all uterine cancers and arises from the epithelium. The remaining cases, which are less common, are mesenchymal and originate from the myometrial muscle or endometrial stroma.[2] Endometrial cancer affects around 3% of females in the United States.[3] 75% of the cases are in the postmenopausal period; the mean age of onset is 61.[3] Because EC shows early symptoms, it is usually diagnosed

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at an early stage and its prognosis is better than other gynecological cancers. At the time of diagnosis, the disease is limited to the uterus in 68%, metastases to neighboring organs and lymph nodes are seen in 20%, and distant metastases are seen in 8%. 75-90% of the cases present with abnormal uterine bleeding.[4]

The most common pathological type of endometrial cancer is endometrioid-type adenocarcinoma, and long-term endogenous or exogenous estrogen stimulation that is not met with adequate progesterone has a role in its development. Although most are sporadic, a small proportion are associated with hereditary syndromes such as Lynch Syndrome.[5]

The definitive diagnosis of endometrial cancer is made histologically by examination of endometrial biopsy, fractionated dilatation, and curettage (D&C) or hysterectomy material.[5]

The most commonly used staging system in endometrial cancer is the "International Federation of Gynecology and Obstetrics" (FIGO) staging system, which is mainly based on surgical findings.[6]

Surgery alone may be an appropriate treatment option for early-stage and low-risk endometrial cancers, while advanced-stage and high-risk patients benefit from adjuvant chemotherapy and radiotherapy. While the five-year survival rate is around 90% in patients diagnosed at an early stage, this rate decreases to 20% in advanced stages.[7] The most important factors in the treatment decision; the clinical features of the patient, the performance status and the extent of the tumor.[8] The basis of surgical treatment is total abdominal hysterectomy and bilateral salpingoopherectomy (TAH+BSO).[4,9] Pelvic and paraaortic lymph node dissection or surgical cytoreduction are performed selectively. The decision for adjuvant treatment after surgery is made according to the patient's risk of persistent and relapsed disease. This risk is determined by the stage at the time of diagnosis and prognostic factors.[9] Radiotherapy, chemotherapy or a combination of both are used in adjuvant treatment. Recently, the use of neoadjuvant chemotherapy has attracted attention for patients who are initially unsuitable for surgery. Although there are no randomized controlled studies on this strategy, it seems to have lower toxicity than primary surgery for stage IVb disease.[10]

The most important prognostic indicator in endometrial cancers is stage.[11] Prognostic indicators other than stage are age, histological type, histological and nuclear grade, myometrial and lymphovascular invasion status, presence of lymph node metastasis, tumor size, peritoneal cytology, hormone receptor status, and type of treatment.[11] Detection of independent prognostic factors related to survival and recurrence will be essential data for the control of the disease and for making systemic treatment decisions. In this single-center study, we aimed to review the clinical and pathological features of this cancer type and determine the prognostic risk factors.

Methods

In this single-center study, patients with endometrial cancer who applied to Trakya University Medical Faculty, Medical Oncology Clinic between 1997 and 2015 with the diagnosis of endometrial cancer were evaluated retrospectively. The study was conducted in accordance with the Principles of the Declaration of Helsinki. The Ethics Committee of Trakya University approval was granted before the study (TUTF-BAEK 2015/05).

File records of 430 patients were reviewed before the study. When all the files were examined, 136 patients with complete file records were included in the study due to insufficient data records of some files. Patients' complaints, age at diagnosis, menopausal status, age at menopause, age at menarche, number of children, age at first birth, presence of HT and DM in their history, diagnosis method, operation conditions, and operation types, tumor histopathological type, tumor grade, and stage, tumor location, tumor diameter, number of lymph nodes removed and lymph node metastasis status, presence of lymphatic, vascular, myometrial invasion, cervical and cervical stromal invasion status, peritoneal cytology results, preoperative CA-125 and hemoglobin (Hb) levels, CT regimens, the number of chemotherapy cycles, first and last chemotherapy dates, CT-related toxicities, RT type, frequency and doses, RT start and end dates, relapse status and final status of the patients were evaluated. The recurrence status of the disease, date of recurrence, site of recurrence, all metastasis sites, disease-free and overall survival were determined from the file records. Medical Oncology archive records, hospital files, Trakya University Medical Faculty Hospital automation system, and pathology laboratory records were used during data collection. The patients, whose last follow-up was over six months, were contacted by phone, and information about their latest status was obtained. Death records were obtained from the death notification system of the Ministry of Health. The date of diagnosis was taken as the time of pathological diagnosis or the time of operation in patients without a preoperative diagnosis.

The time between the tumor's first pathological diagnosis and the disease's first recurrence (local/regional, distant) was calculated as disease-free survival, and the time from the first diagnosis to the date of death was calculated as the overall survival time. Follow-up periods were determined by taking into account the time between the date of the first diagnosis and the date of the last control or death.

The comparison of the parametric variables between

groups was made with the Independent Samples t-test. The relationships between non-parametric variables were evaluated with the Chi-square test. Overall survival and disease-free survival analyses and survival curves were obtained using the Kaplan-Meier method. The comparison of survival curves was made with the Long-rank test. Prognostic factors with a p-value of less than 0.15 using the Long-rank test were also included in multivariate analysis. Multivariate analysis was performed by the Cox regression test. The confidence interval was 95%, and a p-value <0.05 was considered for statistical significance. All data was coded and entered in the SPSS 16.0 program.

Results

136 patients were included in the study population, and the descriptive characteristics of the population are presented in Table 1.

The median follow-up period in the study population was 37.6 (19.9-65.4) months, and recurrence was detected in 9 (6.6%) cases during the follow-up of the patients. At the end of the follow-up, 11 (8.1%) cases were observed as exitus. While the median overall survival time in the entire population was 192.6 months (95% CI: 177.4-207.8), the median disease-free survival time was 185.8 months (95% CI: 169.8-201.9). 1-year cumulative survival was calculated as 96% (SH:0.02), 2-year cumulative survival 91% (SH:0.03), 5-year cumulative survival 89% (SH:0.03), and 10-year cumulative survival 85% (SH:0.05).

It was determined that the recurrence rate increased statistically with age at diagnosis >55 years, non endometrioid histological type, presence of lymphatic invasion, tumor diameter greater than 2.5 cm, advanced disease stage, presence of high histological grade, and Hb level below 10 g/dl at the time of diagnosis. (p=0.024, p=0.001, p=0.032, p=0.029, p=0.025, p<0.001, p=0.013, respectively).

Age at diagnosis >55, non-endometrioid histological type, lymphatic, vascular, and cervical stromal invasion, myometrial invasion depth >1/2, high grade, malignant abdominal wash cytology, presence of lymph node and distant metastases and tumor diameter >2.5 cm were found to be factors that statistically significantly reduced the median disease-free survival time (Table 2).

It was observed that the overall survival time decreased statistically with increasing stage (p<0.001). While the 5-year survival was 98% in stage IA, there were no patients whose survival time reached 5 years during the follow-up period in stage IVB. Moreover, the median overall survival time of patients with normal preoperative CA-125 values was 201.5 months (CI%95=186.50-216.41), while those with high CA-125 values were 86.2 months (CI%95=10.60-161.86) (p<0.001). In addition, age at diagnosis >55 years, non-endometrioid histological type, presence of lymph node and distant metastases, lymphatic and vascular inva-

Table 1. Descriptive characteristics of the study population

	n (%)
Age at diagnosis (years)	58.0 (54.0-63.5)*
Age groups	
≤55 years	47 (34.6)
>55 years	89 (65.4)
Presence of menopause	111 (81.6)
Histological type	
Endometrioid	122 (89.7)
Non-Endometrioid	14 (10.3)
Histological grade	
Grade 1	61 (44.9)
Grade 2	52 (38.2)
Grade 3	23 (16.9)
Tumor diameter (n:122)	
≤2.5 cm	54 (45.3)
>2.5 cm	68 (55.7)
Presence of invasion	
Lymphatic invasion	35 (25.7)
Vascular invasion (n:130)	15 (11.5)
Cervix invasion (n:135)	30 (22.2)
Cervical stromal invasion(n:133)	13 (9.8)
Myometrial invasion	131(96.3)
Myometrial invasion depth (n:131)	
<1/2	73 (55.7)
>1/2	58 (44.3)
Stage	
I A	55 (40.4)
I B	38 (27.9)
II	17 (12.5)
III A	11 (8.1)
III B	1 (0.7)
III C	8 (5.9)
IV B	6 (4.4)
Cytologic evaluation of peritoneal washing (n=98)	
Benign cells	90 (66.2)
Malignant cells	8 (5.9)
Presence of lymph node metastasis	12 (8.8)
Presence of distant metastases	6 (4.4)
Serum CA-125 levels (U/mL)	13.0 (9.0-19.2)*
High preoperative CA-125 levels (n:104)	15 (11)
Hemoglobin (mg/dl)	12.3 (11.5-13.4)*
Hematocrit (%)	37.1 (35.2-40.3)*
ALT (U/L)	18.0 (13.0-26.0)*
Adjuvant Chemotherapy	22 (16.2)
Radiotherapy	87 (64.0)

* Median (25^{th}-75^{th} percentile); ALT: Alanine Aminotransferase.

sion, cervix and cervical stromal invasion, myometrial invasion depth >1/2, high nuclear grade, and malignant peritoneal cytology were identified as statistically significant reducing factors of overall survival (Table 3).

As a result of multivariate analysis for overall survival, statistically significant results were obtained regarding tumor stage and preoperative CA-125 level. The advanced stage had a statistically significant decrease in overall survival (p=0.012). Likewise, preoperative CA-125 levels above the normal range decreased overall survival (p=0.005).

Table 2. Effects of various parameters on disease-free survival

	DFS (/months) Median (95%CI)	DFS 2nd year (%)	DFS 5th year (%)	p
Age groups				0.030
≤55 years	207.9 (194.4-221.5)	95	95	0.047*
>55 years	126.8 (109.3-144.3))	87	79	
Presence of menopause				0.179
(-)	208.3 (189.8-226.8)	95	95	0.210*
(+)	152.9 (137.1-168.7)	88	83	
Histological type				0.002
Endometrioid	165.7 (154.4-176.9)	91	88	0.006*
Non-Endometrioid	115.2 (50.6-179.8)	76	63	
Histological grade				0.007
Grade 1	166.0 (147.9-184.1)	94	88	0.016*
Grade 2	130.7 (120.2-141.3)	91	91	(1-3)
Grade 3	121.3 (60.3-182.3)	76	67	0.018*
				(2-3)
Tumor diameter (n=122)				0.004
≤2.5 cm	156.4 (149.6-163.3)	100	100	0.020*
>2.5 cm	161.9 (133.0-190.7)	94	94	
Lymphatic invasion				0.001
(-)	171.2 (159.6-182.8)	95	91	0.002*
(+)	148.8 (112.5-185.1)	75	71	
Vascular invasion (n:130)				0.036
(-)	190.7 (174.6-206.8)	91	88	0.048*
(+)	127.3 (82.2-172.4)	76	65	
Cervix invasion (n:135)				0.054
(-)	197.4 (183.3-211.4)	92	89	0.064*
(+)	77.9 (65.8-90.0)	83	75	
Cervical stromal invasion (n:133)			0.019	
(-)	190.4 (174.2-206.6)	92	88	0.029*
(+)	65.9 (47.3-84.5)	68	68	
Myometrial invasion				0.480
(-)	-**	100	-	0.641*
(+)	-**	89	85	
Myometrial invasion depth (n:131)			0.032	
<1/2	146.1 (136.8-155.5)	92	92	0.043*
>1/2	167.3 (140.2-194.5)	85	77	
Cytologic evaluation of peritoneal washing (n:98)			0.017	
Benign cells	184.2 (164.5-203.9)	88	86	0.029*
Malignant cells	64.1 (15.7-112.4)	45	45	
Lymph node metastasis				0.019
(-)	193.2 (178.6-207.7)	91	87	0.028*
(+)	71.8 (48.5-95.1)	71	71	
Distant metastasis				0.001
(-)	192.3 (177.0-207.6)	93	89	0.001*
(+)	19.7 (16.8-22.6)	20	-	
Adjuvant Chemotherapy				0.036
(-)	193.9 (179.2-208.6)	92	87	0.047*
(+)	66.4 (52.4-80.4)	78	78	
Radiotherapy				0.359
(-)	171.4 (157.5-185.3)	93	93	0.366
(+)	180.6 (160.8-200.5)	88	83	

*Univariate Cox Regression analysis; DFS:Disease-free survival; ** Median survival times unavailable due to insufficient subgroup events.

Discussion

Endometrial cancers account for 3% of cancer-related fatalities in women.[1] While many instances are identified at an early stage, some cases can be exceedingly aggressive.[11] Identifying autonomous prognostic factors linked to survival and recurrence will offer valuable insights into managing the illness.

The prognosis of endometrial cancers is mainly based on

Table 3. Effects of various parameters on overall survival

	OS (/months) Median (95%CI)	OS 2nd year (%)	OS 5th year (%)	p
Age groups				0.026
≤55 years	213.2 (203.4-222.9)	98	98	0.057*
>55 years	131.7 (114.3-149.1)	87	83	
Presence of menopause				0.316
(-)	208.6 (190.2-227.0)	95	95	0.336*
(+)	159.2 (143.9-174.6)	90	88	
Histological type				0.005
Endometrioid	171.3 (162.2-180.5)	93	93	0.011*
Non-Endometrioid	122.95 (58.0-187.9)	81	63	
Histological grade				0.044
Grade 1	176.7 (166.6-186.7)	96	96	0.036*
(1-3)				
Grade 2	130.8 (119.7-141.8)	91	91	
Grade 3	142.1 (87.8-196.5)	83	72	
Tumor diameter (n:122)				0.004
≤2.5cm	-**	100	100	0.124*
>2.5cm	-**	85	82	
Lymphatic invasion				0.002
(-)	176.7 (168.5-184.9)	96	96	0.008*
(+)	161.0 (126.4-195.7)	81	76	
Vascular invasion (n:130)				0.006
(-)	198.5(183.6-213.4)	93	93	0.013*
(+)	125.7 (79.4-172.0)	76	61	
Cervix invasion (n:135)				0.028
(-)	203.5 (190.4-216.6)	95	92	0.039*
(+)	81.9 (70.8-92.9)	82	82	
Cervical stromal invasion (n:133)			0.002	
(-)	198.3 (183.3-213.3)	94	92	0.006*
(+)	65.4 (45.9-85.0)	66	66	
Myometrial invasion				0.566
(-)	-**	100	-	0.704*
(+)	-**	91	89	
Myometrial invasion depth (n:131)			0.022	
<1/2	151.3 (144.6-157.9)	96	96	0.039*
>1/2	174.0 (147.5-200.5)	85	81	
Cytologic evaluation of peritoneal washing (n:98)			0.005	
Benign cells	188.9 (168.2-209.6)	92	88	0.013*
Malignant cells	67.4 (20.8-113.9)	42	42	
Lymph node metastasis				0.003
(-)	201.7 (189.5-213.8)	94	91	0.009*
(+)	76.5 (54.9-98.1)	71	71	
Distant metastasis				0.001
(-)	199.8 (185.6-213.9)	95	93	0.001*
(+)	24.7 (16.8-32.6)	13	-	
Adjuvant Chemotherapy				0.003
(-)	202.8 (190.6-215.0)	94	92	0.008*
(+)	71.6 (58.2-84.9)	77	77	
Radiotherapy				0.928
(-)	167.8 (148.9-186.7)	92	92	0.928*
(+)	190.9 (172.3-209.5)	91	89	

*Univariate Cox Regression analysis; OS:Overall survival; ** Median survival times unavailable due to insufficient subgroup events.

the disease's stage, grade, and histology.[6] The stage of the tumor is a critical factor that affects survival rates in cases of endometrial cancers.[4,6,11] Several studies have demonstrated that survival rates decline as the stage of the disease advances in endometrial cancers.[7,11–13] Generally, the five-year survival rates are 95% for localized disease, 70% for regional disease, and 18% for distant disease.[3] Our study revealed that 5-year survival rates dropped to 0% in stage IVB, while it was 98% in stage IA, and the difference was significant in terms of survival time between the stages. Furthermore, it was observed that there was a statistically significant rise in the number of recurrences as the stage progressed. Additionally, our multivariate analysis revealed that tumor stage was an independent prognostic factor in determining overall survival. This finding aligns with the existing literature and highlights the importance of early detection and timely intervention in cancer management.

Different studies found that as the tumor grade increased, the 5-year survival rates decreased, and the recurrence rate increased.[11–13] Additionally, a study revealed that the grade was the most crucial factor in predicting prognosis for stage I cases.[14] Similarly, our study found it statistically significant that as the tumor grade increased, the median overall survival and median disease-free survival time decreased, and the recurrence rates increased. These results support considering tumor grade when determining patients' prognosis and treatment plan.

Numerous studies have revealed that patients who are diagnosed at a younger age tend to have a more favorable clinical outcome.[11,13,15,16] However, whether it means an independent predicting factor is contentious. There are also opinions claiming that the reason for the relationship between advanced age and poor prognosis is that histopathological types or grade 3 tumors with poor prognosis are more common in older age cases.[11] Moreover, a less aggressive chemotherapy approach may cause poorer outcomes in the geriatric population. Mundt et al.[17] demonstrated that age was not a prognostic factor for recurrence in a large cohort of 455 endometrial carcinoma patients. In our study, patients diagnosed at 55 or younger had longer survival rates. In addition, patients over 55 had lower disease-free survival rates and higher recurrence rates. However, in multivariate analysis, age was not an independent prognostic factor. These outcomes suggest that while age may have some impact on survival rates, it is not the only determining factor.

We found that patients with endometrioid type had higher disease-free survival and overall survival times. Although there is no definite consensus on the relationship between histopathological type and prognosis in endometrial cancers, in many studies, it has been emphasized that endometrioid adenocarcinomas show a better clinical course than the non-endometrioid type.[18,19]

Lymph node metastasis adversely affects prognosis and is associated with increasing tumor grade and stage.[11] Our research aligns with previous studies that have found a connection between lymph node metastasis and overall survival. However, it should be underlined that it could not be shown as an independent prognostic factor in multivariate analysis In addition, the reason the recurrence rate is proportionally lower in our cases with lymph node metastases compared to studies in the literature can be explained by the fact that the total number of recurrent cases is very low.

Studies have shown that the existence of lymphovascular space invasion is a risk factor for lymph node metastasis and the recurrence of the disease. It can impact the classification of the disease and the decision on which adjuvant therapy to choose.[20–22] Based on our research, it was found that an increase in lymphatic invasion and vascular invasion led to a decrease in disease-free and overall survival time and an increase in recurrence.

The extent of myometrial invasion is a crucial factor that affects the prognosis of individuals with endometrial cancer.[4,11] A deeper invasion is linked to lower survival rates and higher chances of recurrence.[11] In our study, both disease-free and overall survival were observed to be lower in the group with myometrial invasion depth >1/2. Furthermore, patients with a myometrial invasion rate above 1/2 had more recurrences, but no statistically significant relationship was detected. These findings may emphasize the importance of assessing the depth of myometrial invasion in endometrial cancer to make informed decisions about treatment and follow-up care.

Tumor size has been implicated as an independent prognostic factor for overall survival in endometrial cancers; it is also closely related to lymph node metastasis.[11,23,24] In the current study, the rate of lymph node metastasis was 3.7% in the group with a tumor diameter of 2.5 cm or less; It was found to be 11.7% in the group over 2.5 cm. It is compatible with the literature regarding tumor size and lymph node metastasis. The recurrence was less, and disease-free survival was higher with tumor diameter ≤2.5 cm. However, it was not an independent parameter determining prognosis.

The predictive importance of positive peritoneal washings without extrauterine spread is contentious. In an examination of 14,704 individuals with endometrial cancer determined from the Surveillance, Epidemiology, and End Results (SEER) registry, malignant peritoneal cytology was found as an independent predictor of mortality, regardless of other prognostic factors.[25] However, another sys-

tematic review found that the prognosis associated with malignant peritoneal washing ranged depending on the presence of other predictive factors.[26] Our study revealed that positive peritoneal cytology is a prognostic factor in univariate analysis, but not an independent prognostic factor, that can compromise disease-free and overall survival. Therefore, it may be important to consider the presence of positive peritoneal washings in the treatment planning of endometrial cancer patients, especially in those with other high-risk features.

Although it is controversial to consider isthmus and cervix spread as an independent prognostic factor in endometrial cancer, it is associated with deep myometrial invasion, increased lymph node metastasis, and poor prognosis.[11] In our univariate analysis, cervical invasion stood out as a parameter that only reduces overall survival, while cervical stromal invasion was identified as a predictor that reduces both overall and disease-free survival.

Measuring serum CA-125 levels is a useful clinical tool for predicting the extrauterine spread of endometrial cancer. Some studies suggest that metastatic endometrial cancers have significantly elevated CA-125 levels, and it can be used to detect and follow up with recurrent disease.[27,28] Nevertheless, this has yet to be fully proven. Additionally, some studies have linked high CA-125 levels with advanced stage and lymph node metastasis, but the threshold value for CA-125 remains unclear.[27–29] In our study, high serum CA-125 levels were associated with advanced-stage and lymph node metastasis. In addition, our findings show that high CA-125 levels are associated with decreased overall survival. Moreover, although it is challenging to reach a definite conclusion in a retrospective study with a limited number of patients, the relationship between CA-125 levels and overall survival continued as a result of the multivariate analysis for survival.

Conclusion

In our study, the most important prognostic indicators determining the survival time of the patients were disease stage, histological grade, age at diagnosis, histological type, presence of lymph node metastasis, presence of lymphatic and vascular invasion, depth of myometrial invasion, presence of cervical stromal invasion, tumor diameter, the positivity of peritoneal cytology, and pre-op serum CA-125 levels. Besides, the most critical factors determining survival independently without being affected by other parameters were stage and pre-op serum CA-125 level. However, since our study was retrospective and was conducted with a relatively small number of patients, prospective randomized studies with a large number of patients are needed in order to transfer the information obtained from this study to our clinical applications, especially to distinguish patients with a high risk of systemic spread and who genuinely deserve adjuvant treatment.

Disclosures

Ethics Committee Approval: The study was conducted in accordance with the Principles of the Declaration of Helsinki. The Ethics Committee of Trakya University approval was granted before the study (TUTF-BAEK 2015/05).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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