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Determining the Factors That Affect Survival and Recurrence Rate in Patients with Endometrial Cancer

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ABSTRACT

Background and Objective: Endometrial cancer is the sixth most common cause of cancer-related death in women. Out of 320,000 women diagnosed with endometrial cancer, 76,000 die each year. Considering the prevalence and mortality rate of this disease in Iran, the present study was conducted to determine the factors affecting survival and the recurrence rate in patients with endometrial cancer.

Methods: In this cohort study, all patients who referred to the Oncology Clinic of Ayatollah Rouhani Hospital and the Gynecological Cancer Center from 2008 to 2020 with endometrial carcinoma undergoing surgical and chemoradiotherapy treatment were studied. Demographic and clinical data were recorded in a checklist, and survival, recurrence, and recurrence-free survival rates were assessed during follow-up 1-5 years after surgery by telephone or based on available information, and finally, the findings were statistically analyzed and reported.

Findings: The follow-up period was 42.32±72.5 months, the mean age was 56.63±8.83 years, and 82.3% of patients had no recurrence after surgery. The median overall survival was 122.46±7.30 months and was significant based on disease grade (p=0.001). The effect of age, stage, and grade on survival was significant (p=0.004). The risk of death in high-risk individuals was 6.48 times higher than low-risk individuals (p=0.004), and most deaths (81.2%) occurred in the surgery-radiotherapy group. Compared with chemoradiotherapy, surgery and surgery-radiotherapy significantly reduced the risk of death by 98% and more than 80%, respectively (p=0.002, p=0.024). Recurrence was significant based on stage and was more frequent in high-risk patients (p=0.01), and the majority of those without recurrence were low-risk patients. Most recurrences were abdominal in high-risk individuals, and pelvic and vaginal in low-risk individuals.

Conclusion: According to the results of this study, tumor stage and grading, age, and treatment methods are among the factors affecting the survival of patients with endometrial cancer, and appropriate follow-up of patients with endometrial cancer can lead to timely identification of recurrence and treatment of these patients.

Keywords: *Endometrial Cancer, Recurrence, Survival, Radiotherapy.*

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Introduction

Endometrial cancer is the sixth most common cause of cancer death among women. Each year, 320,000 women are diagnosed with endometrial cancer, and 76,000 of them die (1). Endometrial cancer is more common in developed countries and has been increasing in recent years due to obesity, increased life expectancy, and declining birth rates (2). The risk of endometrial cancer in the general population is 2-3% (3), and it occurs most frequently in the perimenopausal age group (50-65 years) (4), and 75% of cases occur after menopause (5). The global median age of onset is 63 years (6). Despite the high prevalence, there are few warning signs, which is leading to delayed diagnosis or underdiagnosis (7). The 5-year survival rate with treatment is 80% (8). The best prognosis is associated with stage I of the disease (70%) and the worst with stages III and IV, which are quite rare. Tumors with high progesterone receptor expression have a better prognosis (9). The primary treatment for endometrial cancer is surgery, during which the disease can also be staged (10). In stage IV, when there is distant metastasis, palliative surgery is used (6). Surgery is also contraindicated in certain circumstances (5-10%), including obesity, high surgical risk, inoperable tumor, and the desire to preserve fertility (6, 11). In high-risk individuals or high-grade tumors, chemotherapy or radiotherapy is performed as adjuvant therapy following surgery (12). In stages III and IV, adjuvant radiotherapy is more effective than radiotherapy in increasing survival (12, 13). In cases where surgery is not indicated, palliative chemotherapy is an option, and survival increases as the dose increases (13).

Palliative chemotherapy is also used in recurrent endometrial cancer. Adjuvant radiotherapy is used in stages I and II, although its benefit is questionable, as it reduces pelvic recurrence but does not improve survival or the number of metastases (14). In situations where hysterectomy is contraindicated, radiotherapy alone or in combination with chemotherapy may be considered (15).

Considering that no study has been conducted in this region (Babol) regarding long-term follow-up of patients with endometrial cancer after initial treatment, we followed up patients with endometrial cancer who underwent surgery and chemoradiotherapy and examined the factors related to long-term survival. Therefore, the results can be used to plan the follow-up of these patients in oncology centers and to employ people to counsel these patients during and after treatment.

Methods

In this cohort study, after approval by the Ethics Committee of Babol University of Medical Sciences with the code IR.MUBABOL.REC.1399.123, 90 women with endometrial cancer were included via convenience sampling. All patients referred to the Pathology Unit and Oncology Clinic of Ayatollah Rouhani Hospital and a Private Cancer Clinic during 2008-2020 with endometrial cancer who underwent surgical-chemoradiotherapy treatment were selected as the research sample. Patients with a final diagnosis of endometrial cancer based on pathology sample were included in the study and were excluded if the patient's information was not available and the patient could not be followed up. The sample size for patient survival with $\alpha = 0.05$ and a power of 90% was determined as 68 people using SPSS 22. Considering the 30% drop out rate in studies with long-term follow-up (5 years), a sample size of 90 people was considered. Demographic and clinical information of the patients (including: patient age, number of births, history of internal diseases, date of surgery, type of surgery, type of pathology, stage and grade of disease, history of chemotherapy and radiotherapy, number of chemotherapy and radiotherapy sessions, number of postoperative visits and measures performed at each visit, possible recurrence, method of diagnosing recurrence, surgeries and treatments related to recurrence) were reviewed and recorded in a researcher-made

checklist. The validity of the measurement tool in this study (checklist) was reviewed by several trained individuals. To implement the plan, the files of patients with endometrial cancer pathology were used. If the patients' referral was incomplete, a telephone call was made for follow-up and referral if possible. Patients were first given sufficient explanation that all personal information of the patients would remain confidential, and finally informed consent was obtained from all patients. Moreover, the survival rate after recurrence and the survival rate without recurrence were also reviewed in this follow-up of patients during 1-5 years after surgery by telephone call or information available in the file, and the above findings were analyzed and reported after the end of the study. The follow-up method at the clinic of Ayatollah Rouhani Hospital was every 4 months for the first two years, then every 6 months until 5 years, and then every 1 year until 10 years. At each visit, abdominal and pelvic examination and vaginal cuff smear testing were done, and CXR and CA125 were requested annually. Ultrasound and CT scan of the abdomen and pelvis were also requested periodically if necessary.

Analysis was performed using SPSS 22 software. Quantitative data were reported as mean and standard deviation, and qualitative data were reported as frequency and percentage. Chi-square, t-test, Kaplan-Meier, and log-rank tests were also used to examine relationships, and Cox regression was used to examine factors affecting patient survival, and $p<0.05$ was considered significant.

Results

In this retrospective cohort study, 113 patients were included in the study from among 138 patients who had been referred to the Gynecological Oncology Clinic affiliated with Babol University of Medical Sciences with a primary diagnosis of endometrial cancer between 2008 and 2020. The mean age of the subjects was 56.63±8.83 years. 47.4% of the subjects were illiterate, 39.7% had a high school diploma, and 12.8% had academic education. The mean number of births was 3.23±2.36. The mean BMI of the subjects was 31.05±6.07. In addition, 18.8% of the subjects had a normal BMI, 24.6% were overweight, and 56.5% were obese.

The mean follow-up rate was 96.53%. The mean follow-up period was 72.42±32.5 months. 94 patients (83.2%) survived until the end of the study. 16 patients (14.2%) died of endometrial cancer and 3 patients (2.7%) died of other causes. 6 patients (5.3%) died in the first year after the start of treatment and 15 patients (13.2%) died in the first five years.

Patients were divided into two groups based on pathology: low-risk (stage 1A, grade I, II, no lymph node involvement, endometrioid pathology, no ectopic involvement) and high-risk (other pathologies). 56.5% of patients were low-risk, of whom 3 died, and 43.5% were high-risk, of whom 13 died. Of these patients, 26% were disease-free, 31.2% had hypertension, 19.5% had diabetes and hypertension, 10.4% had diabetes, and the rest had other diseases. In the evaluation of treatment methods, 45 patients (40.2%) were treated with surgery, 64 patients (57.1%) with surgery and radiotherapy, and 3 patients (2.7%) with chemoradiotherapy. 93 patients (82.3%) had no recurrence after surgery. 9 patients (8%) had recurrence in the abdomen, 6 patients (5.4%) in the pelvis and vagina, 2 patients (1.8%) in the lung, and 2 patients (1.8%) in the bone marrow.

The median overall survival was 122.46±7.30 months. The median survival in patients with low grade was 136.02±10.69 months and in patients with high grade was 78.71±8.21 months, which was significantly different according to the Log-Rank test ($p=0.001$) (Table 1 and Figure 1).

Table 1. Comparison of median survival in individuals with low and high grade of the disease

Pathological involvement	Number	Mean	Standard error	95% confidence interval	p-value
Low grade	61	136.02	10.69	115.05-156.99	0.001
High grade	47	78.71	8.21	62.61-94.82	0.001
overall	108	122.46	7.30	108.14-136.77	0.001

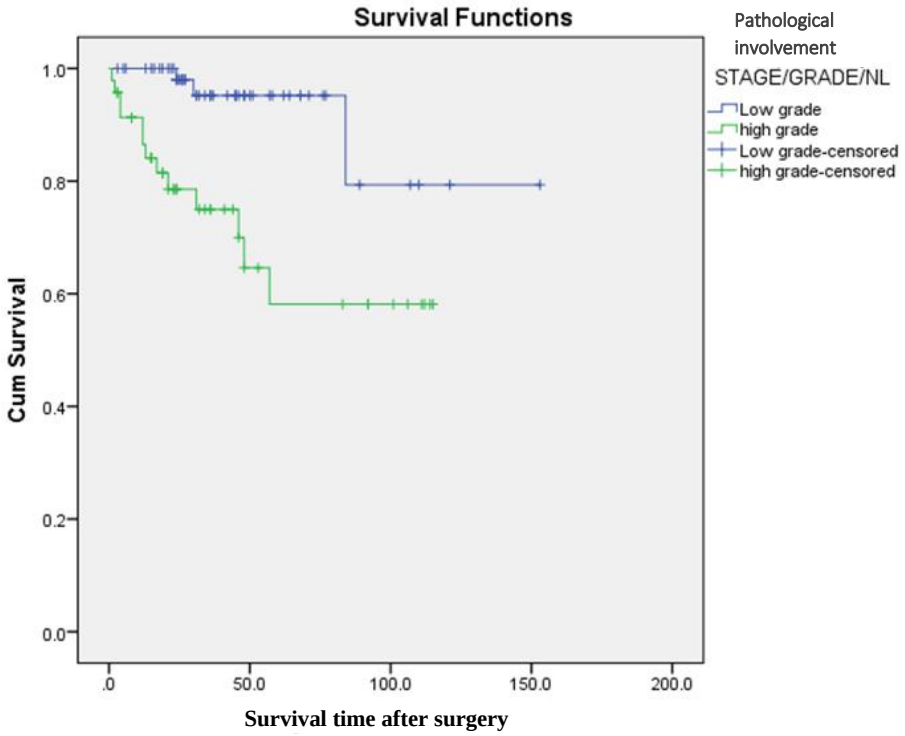

Figure 1. Estimation of patient survival based on low and high grade

For evaluating the effect of age, education, number of births, etc. on patient survival, multivariate analysis and Cox regression were used. The effect of age on patient survival was significant. For each year of increase in age, the risk of death increased by 8% (p=0.004). Although education level reduced the risk of death by 12%, this was not significant (p=0.82). Number of births and BMI increased the risk of death by 7% and 1% with a one-unit increase, but this value was not significant in number of births (p=0.47) and BMI (p=0.8). People with comorbidities showed more than 3-fold increased risk of death, but it was not significant (Table 2).

Surgery reduced the risk of death by 98% and surgery with radiotherapy reduced the risk by more than 80% compared to chemoradiotherapy, which was significant in both cases (p=0.002, p=0.024). Stage and grade of the disease had a significant effect on patient survival. The risk of death in high-risk patients was 48.6 times higher than in low-risk patients (p=0.004). Of the 16 deaths, 13 (81.2%) were in the surgery and radiotherapy group, 2 (12.5%) in the chemoradiotherapy group, and 1 (6.2%) underwent surgery alone.

The recurrence rate was significant according to stage. The recurrence rate in high-risk patients was higher than in low-risk patients. Among those who did not have recurrence, the low-risk group was more likely to have recurrence. The location of recurrence was more likely in the abdomen in high-risk groups and the pelvis and vagina in low-risk groups (p=0.01) (Table 3).

Table 2. Estimated coefficients of significant variables in the Cox regression model (univariate)

Variable	Estimated coefficient	Standard error	Risk ratio	p-value
Age	0.08	0.03	1.088	0.004
Education	-0.19	0.5	0.82	0.82
Number of births	0.075	0.10	1.078	0.47
BMI	0.014	0.055	1.014	0.803
Comorbidity	1.35	1.03	3.86	0.19
Stage and grade	1.86	0.64	6.48	0.004
Treatment method				
Chemoradiotherapy	–	–	1	0.008
Surgery	-3.74	1.23	0.02	0.002
Surgery and radiotherapy	-1.73	0.78	0.17	0.02

Table 3. Evaluating the relationship between recurrence rate based on stage

	Low risk Number(%)	High risk Number(%)	p-value
Recurrence-free	57(93.4)	33(71.7)	0.01
Pelvis and vagina	2(3.3)	3(6.5)	0.01
Lung	1(1.6)	1(2.2)	0.01
Abdomen	0(0)	8(17.4)	0.01
Bone marrow	1(1.6)	1(2.2)	0.01

The survival time based on the surgical and radiotherapy treatment method was 48.1±35.5 months, the surgical treatment method was 35.7±27 months, and the chemoradiotherapy method was 22.7±18.9 months, which was borderline significant (p=0.08). In the final (adjusted) model, for each year of age, the risk of mortality increased by 18% (HR=1.18, p=0.01). For each additional birth, the risk of mortality decreased by 37% (HR=0.63, p=0.07). In the high-risk group, the risk of death was 1.5 times that of the others (HR=2.58, p=0.04). The association between comorbidity and survival was not significant (Table 4).

Table 4. Estimated coefficients of significant variables in the Cox regression model (multivariate)

Variable	Multivariable Cox Regression		Univariable Cox Regression	
	p-value	AHR	p-value	HR
Age	0.015	1.180	0.004	1.080
BMI	0.870	0.980	0.800	1.010
Education			0.820	0.820
Number of births	0.074	0.638	0.473	1.070
Stage and grade	0.045	2.580	0.004	6.480
Comorbidity			0.192	3.860
Chemoradiotherapy			1.000	0.008
Surgery			0.002	0.020
Surgery and radiotherapy			0.002	0.170
Recurrence by stage	0.040	2.580		

Discussion

In the present study, the results showed that out of 16 deaths, 13 (81.2%) were in the surgery and radiotherapy group, 2 (12.5%) in the chemoradiotherapy group, and 1 (6.2%) in the surgery group. Therefore, surgical treatment reduced the risk of death by 98% and surgical treatment by more than 80% compared to chemoradiotherapy. The results of this study were not consistent with some studies that aimed to evaluate the effect of cytoreductive surgery and adjuvant chemotherapy on recurrence-free survival and overall survival in stage III. The results of the studies showed that the mean 5-year recurrence-free survival for patients receiving chemoradiotherapy, radiotherapy, and chemotherapy was 69.1%, 37.5%, and 23.8%, respectively. The 5-year overall survival for chemoradiotherapy, radiotherapy, and chemotherapy was 83%, 35.7%, and 25%, respectively (16-18). Among the reasons for the inconsistency of these studies, it can be noted that in these studies, all patients were in stage III of the disease. Therefore, the severity of the disease and the extent of involvement were greater in these people, which led to a decrease in the survival rate of patients. Moreover, people who only undergo surgical treatment are in a lower stage of the disease, so they were in a better condition considering the conditions of these patients. However, it can be concluded that cytoreductive surgery is the most important prognostic factor and it seems that chemoradiotherapy is associated with a significant reduction in the risk of recurrence in stage III. Furthermore, the results of our study showed that the stage and grade of the disease have a significant effect on the survival of patients. Therefore, the risk of death in people who were high-risk was 48.6 times higher than in low-risk people. The recurrence rate was significant based on stage. Thus, recurrence was more in high-risk people than in low-risk people. Among people who did not have recurrence, the number of low-risk people was higher. The site of recurrence in high-risk patients was mostly the abdomen, and in low-risk patients, the pelvis and vagina.

The results of this study were consistent with the studies of Rauh-Hain et al., Hochreiter et al., and AlHilli et al. (19-21). In the study by AlHilli, the results showed that the mean age at diagnosis was 65 years and 58% were in the early stages of the disease. The mean time from diagnosis to surgery was 3.7 weeks. The 5-year survival rate was 57%. The strongest predictor of survival was the stage of the disease, with a 15-20% reduction in 5-year survival for each stage. Stage, age, and the presence of comorbidities were independent predictors of survival. In our study, the effect of age on patient survival was also significant. For every year of age, the risk of death increased significantly by 8%. However, this rate did not show a significant difference in relation to education, number of births, and BMI, although it reduced the risk of death by 12% (21). Adjuvant chemoradiotherapy was associated with improved survival. Multidrug chemotherapy was better than single-drug chemotherapy, especially in advanced stages of the disease. Also, the strongest measurable predictor of death was the stage of the disease at diagnosis. In addition, surgical treatment, lymph node dissection, fewer underlying diseases, and higher socioeconomic status are associated with improved survival.

In the present study, patients were divided into two groups based on pathology: low-risk (stage 1A + grade I and II + no lymph node involvement + endometrioid pathology + no ectopic involvement) and high-risk (other pathologies). 56.5% of patients were low-risk, of whom 3 died, and 43.5% were high-risk, of whom 13 died. The median overall survival was 122.46±7.30, with the mean survival being 136.02±10.69 months in low-grade patients and 78.71±8.21 months in high-grade patients, which was significant according to the Log Rank test. The results of this study were consistent with the study of Gadducci et al. (22). In the study by Gadducci et al., the results showed that 36 recurrences were reported after 13.5 months with vaginal (5 cases), pelvic (8 cases), para-aortic (16 cases) and distant (17 cases) involvement. The progression-free survival rate was 51.1% and the 5-year survival rate was 59.8% (22). These results indicate that the absence of lymph node involvement can lead to higher patient survival. Therefore, diagnosing the

disease at an early stage is of great importance. In the present study, the survival time based on the surgical and radiotherapy treatment method was 48.1±35.5, the surgical treatment method was 35.7±27, and the chemoradiotherapy method was only 22.7±18.9, which was not a significant difference. The results of this study were in line with the study of Miao et al. (23), who evaluated the survival rate of 224 intermediate and high-risk endometrial cancer patients who underwent surgery and staging and adjuvant treatment (chemotherapy, radiotherapy, or both) in a 5-year study. The survival rate in the chemoradiotherapy group was 80.6% compared with 63.8% in the other group. In 110 high-risk endometrial cancer patients, the survival rate in the chemoradiotherapy group was very comparable when compared with the other group. In 83 intermediate-risk endometrial cancer patients, the survival and recurrence rates in the chemoradiotherapy or radiotherapy or chemotherapy alone groups were not significantly different. Finally, it was concluded that adjuvant chemoradiotherapy in high-risk endometrial cancer is effective in reducing recurrence rates and increasing survival, while patients with intermediate risk do not benefit as much from chemoradiotherapy.

The results of the present study showed that stage, type of treatment, and age were among the factors affecting patient survival. In this way, the risk of death in high-risk individuals was 6.48 times higher than in low-risk individuals. The majority of individuals had no recurrence after surgery, and the highest recurrence rate was in the abdominal area. The study also showed that increasing age and BMI lead to an increased risk of death.

Conflict of Interest: The authors declare that they have no competing interests.

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