

TREATMENT OUTCOMES OF UTERINE CARCINOMA: A SINGLE INSTITUTION RETROSPECTIVE STUDY



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ABSTRACT

Background

Endometrial cancer has a lifetime risk of 2.6% for women living in industrialized countries and it is the most prevalent kind of cancer diagnosed in those regions. In terms of gynecologic cancer-related deaths, it ranks after ovarian and cervical cancer as the third most common cause.

Objectives

To evaluate endometrial cancer patients' long-term treatment outcomes, including disease-free survival and overall survival, as well as to pinpoint independent predictive markers.

Materials and Methods

At the Zhianawa Cancer Center, a retrospective analysis was conducted. All patients who had been referred for radiation therapy between March 2009 and January 2019 were included in the research, except those who had distant metastases. In the end, 89 patients were included. Using the Kaplan-Meier technique, overall survival and disease-free survival were calculated, and the significance of the variations across curves was evaluated using the log-rank test.

Results

All patients underwent surgery, 96.6% received adjuvant radiotherapy, and 42.7% received concomitant chemotherapy. The 5-year and 10-year disease-free survivals were 62.9% and 56.2%, and the overall 5-year and 10-year survivals were 74.2% and 66.3% respectively. The statistically significant variables impacting disease-free survival were lymphovascular invasion and marginal status, and the only statistically significant prognostic variable affecting overall survival was the FIGO stage.

Conclusion

In this analysis, we concluded that uterine cancer has a good prognosis, and its outcome was influenced by stage, lymphovascular space invasion, and surgical marginal status.

Keywords: *Uterine cancer, radiotherapy, survival outcomes*

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INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in developed countries and has a lifetime risk of 2.6%, it is also regarded as the third most common cause of gynecologic cancer-related mortality after cervical and ovarian cancer, and the average diagnostic age is 61 years old ⁽¹⁾. A risk factor for this malignancy is long-term unopposed estrogen exposure, which typically causes the start of the disease's premalignant phase ⁽²⁾. Endometrial cancer risk is also enhanced by obesity and nulliparity.

The two primary histological subtypes of uterine cancer are uterine carcinomas and uterine sarcomas. Endometrial carcinomas account for the bulk of uterine cancer cases, with uterine sarcomas accounting for 4.2% of all instances. Uterine carcinomas are categorized into type I and type II carcinomas based on the pathophysiology of the illness. Type I endometrial cancer frequently manifests in perimenopausal women who are hyperestrogenic.

The prototypes of type I endometrial adenocarcinoma include mucinous carcinoma and endometrioid carcinoma and their variations (3-5), which account for 80% of endometrial carcinoma ⁽⁶⁾. Ten percent of uterine carcinoma, which includes papillary serous carcinomas, clear cell carcinomas, and carcinosarcomas, are type II endometrial adenocarcinomas, which are highly aggressive, high-grade tumours that are not induced by estrogen and typically affect older, postmenopausal women ^(3,4,7-9). The three primary subtypes of uterine sarcoma are endometrial stromal sarcoma (ESS), leiomyosarcoma (LMS), and adenosarcoma ⁽¹⁰⁾.

In a study performed in 2017, 67 percent of individuals with endometrial adenocarcinomas had uterine involvement at the time of diagnosis. Regional illness accounted for 21% and distant disease for 8% of patients, respectively ⁽¹¹⁾. Since endometrial adenocarcinomas frequently appear with early signs of vaginal bleeding that generally urge patients to seek treatment when the condition is still treatable, so many doctors believe that these cancers are more treatable ⁽¹²⁾. SEER data suggests younger individuals, who have the early-stage disease, and lower-grade disease have a better chance of survival ⁽¹³⁾.

In addition, to grade, other risk factors associated with poor prognosis include depth of myometrial invasion, age, lymph node status, tumor size, lymphovascular space invasion (LVSI), and tumor involvement of the

lower uterine segment ^(14,15). The primary treatment modality for endometrial cancer is surgery, which includes total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO) ⁽¹⁶⁾.

The main controversial topic in endometrial cancer treatment concerns the therapeutic role of lymphadenectomy ⁽¹⁷⁾. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) introduced the concept of the surgical staging of endometrial cancer ⁽¹⁸⁾, and in 2005, the American College of Obstetricians and Gynecologists (ACOG) recommended surgical staging as an essential part of its management. The ACOG committee suggested that adjuvant therapy should be recommended for patients with positive nodes, while the use of adjuvant radiation therapy in women with disease confined to the uterus based on systematic surgical staging remains debatable ⁽¹⁹⁾.

Post-operative radiotherapy (RT), either external beam radiotherapy (EBRT) and/or vaginal brachytherapy (VBT), is recommended for patients with early-stage illness based on the existence of adverse risk features ⁽²⁰⁻²²⁾. The results of multiple randomized trials revealed improved locoregional control with adjuvant RT over observation alone, but its impact on survival is controversial ^(23, 24). Contrarily, several studies have shown that chemotherapy alone improves survival ⁽²⁵⁾ as well as improved survival for a combination of adjuvant chemotherapy and radiotherapy for defined high-risk groups ⁽²⁶⁾.

Since there is little population-based research on uterine cancer in Eastern nations (including Iraq) that provides survival estimates by prognostic factor, we aimed to evaluate long-term treatment outcomes including disease-free survival (DFS) and overall survival (OS) of patients with uterine cancer, as well as to determine independent factors affecting the prognosis.

MATERIALS AND METHODS

This research was approved by the Kurdistan Higher Council of Medical Specialties. It was based on recorded data from Zhianawa Cancer Center, the data was anonymous and approval has been obtained from the administrator of the targeted centre. Approval of the patients or their family has been achieved via a phone call and they were informed regarding their participation in our study. A retrospective chart review was performed on all patients diagnosed with uterine cancer and referred for radiation treatment at the

Zhianawa Cancer Center during a period of our study design (March 2009-January 2019).

All cases of uterine cancer including sarcoma (stage I-IVA) were included & and those patients who presented with a distant metastatic disease (Stage IVB) who were not eligible for curative radiotherapy were excluded. Our search identified 95 patients with uterine cancer. Medical data including presentation, treatment, histological details and outcome were extracted. All patients underwent surgery and staged using the International Federation of Gynecology and Obstetrics (FIGO) 2008 operative staging system for endometrial cancer.

Survival was calculated from the date of the last treatment until the date of recurrence, death, or last follow-up. The acquired data were entered into the Microsoft Excel program, in which clearing of data and coding were performed. Then, the data was transferred to Statistical Package for the Social Sciences software 25.0 to conduct data analysis. In the data analysis, two methods—the analytical method and the descriptive method—were employed. The data were examined and provided as frequency, percentage, mean, and standard deviation in the descriptive methodology.

In the analytical method, relationships between variables were evaluated using specific statistical tests, such as the t-test and Chi-square test. By using the Kaplan-Meier technique and the log-rank test to determine the significance of the differences between the curves, actuarial overall survival and disease-free survival were determined. In this study, a p-value of < 0.05 was considered significant, while a p-value of ≤ 0.001 was considered highly significant.

RESULTS

A total of 95 patients with endometrial cancer were reviewed during the study period, but 6 of these were excluded from the analysis because they were lost from our follow-up.

The study population consisted of 89 patients, with a mean (standard deviation [SD]) age of 52 (15) years. In 53.9% history of comorbidities including DM& HTN was recorded. 59.6% were overweight at the time of diagnosis (with BMI>25), only 10.1% of patients were smokers, 28.1% were nulliparous, and the most presenting symptom was vaginal bleeding (n=77) patients.

All patients underwent an operation (TAH with BSO), while only 8 patients had pelvic lymph node dissection done, and only 1 patient had positive LN. Adjuvant radiation therapy was given to 86 (96.6%) patients that were delivered in >3 months in 76.4% of patients. Among these patients, 37 (43.1%) patients were treated by external beam radiation therapy (EBRT) + brachytherapy, 23 (26.7%) by EBRT with a dose of 45 Gy in 31 patients and >45 Gy in 30 patients, and 26 (30.2%) received only vaginal brachytherapy.

Adjuvant CTX was given in 38 (42.7%) patients, while others didn't receive it. The majority of patients (83.1%) had endometrioid histology. Low-grade (I&II) disease was more detected in the specimens (67.4%). 58 out of the 89 patients (65.1%) had Stage I disease. In 79 (88.8%) patients the disease invaded more than half of the myometrium. In 64 patients lymphovascular space invasion was evaluated. 18 patients had a lymphovascular space invasion; the margin was assessed in 73 patients with only 3 having a positive margin, Tables 1 and 4.

At the end of this study, 59 patients (66.3%) were alive and 30 patients (33.7%) had died, among them 7 patients died due to other causes. 39 (43.8%) patients had disease recurrence, among those 51.3% were locoregional and 48.7% were distant. The mean time+/- SD for death was 39.69±26.65 months and for recurrence were 28.58±25.13 months. The 5-year and 10-year disease-free survivals were 62.9% and 56.2%, and the overall 5-year and 10-year survival were 74.2% and 66.3% respectively (Figure 1).

Lymphovascular invasion (LVI) and marginal status were prognostic factors that substantially affected disease-free survival (DFS), with DFS being 26 percent for patients with positive LVI and 58 percent for those with negative LVI (p=0.013). Regarding marginal status, all patients with positive surgical margin had local recurrence at the time of our study, while those with a negative margin had a DFS of 88 % (p=0.025), and those who received CTX had a lower DFS (p=0.002), though other prognostic factors like age, myometrial invasion, histologic type, grade, and stage did not differ statistically.

The only statistically significant prognostic variable affecting overall survival was a stage, 10-year overall survival was 72.4%, 59.3%, and 25% for stages I, and III respectively (p=0.01) all shown in Table 2. Differences in disease-free survival and overall survival in terms of

FIGO stage and tumour grade are shown in Figures 2 and 3 respectively.

with locoregional recurrence died, while the death rate among those with distant recurrence was 94.7% (p=0.002), as shown in Table 3.

In patients with recurrent disease, 45% of those

Table 1. Patients, disease, and treatment characteristics.

Variables	Frequency (percentage)
Age diagnosis years	
Mean±SD	52.55±15.61
Age of diagnosis	
≤60 years	59(66.3)
>60 years	30(33.7)
Comorbidity	
Yes	48(53.9)
No	41(46.1)
Obesity	
Overweight	53(59.6)
Normal weight	36(40.4)
Smoking	
Yes	9(10.1)
No	80(89.9)
Parity	
Nulliparous	25(28.1)
Multiparous	64(71.9)
Presenting symptoms	
Vaginal bleeding (Menorrhagia)	77(86.5)
Other	12(13.5)
Way of diagnosis	
Surgery	55(61.8)
Biopsy	22(24.7)
DC	12(13.5)
Type of surgery	
TAH+BSO	81(91)
TAHSO+LND	8(9)
Interval between surgery and radiotherapy (month)	
≤3	21(23.6)
>3	68(76.4)
Myometrial	
>1/2	79(88.8)
≤ 1/2	10(11.2)
Pathology	
Type 1	74(83.1)
Type 2	10(11.2)
Sarcoma	5(5.7)
Grade	
Low(I&II)	60(67.4)
High(III)	27(30.4)
Unknown	2(2.2)
Stage	
I	58(65.2)
II	27(30.3)
III	4(4.5)
LV1	
+Ve	18(20.2)
-Ve	46(51.7)
Unknown	25(28.1)
Margin	
+Ve	3(3.4)
-Ve	70(78.6)
unknown	16(18)

Table 1. Continued.

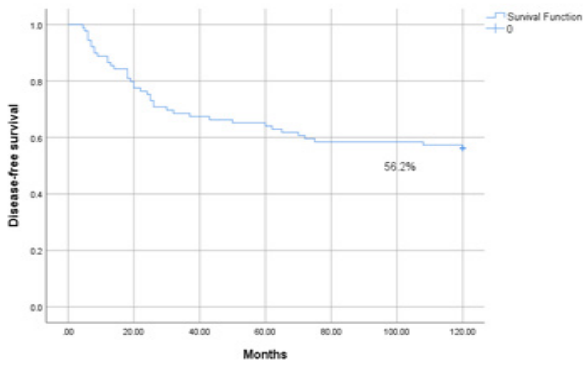
LN status	
Unknown	81(91)
Not involved	7(7.9)
Involved	1(1.1)
Chemotherapy	
Yes	38(42.7)
No	51(57.3)
Radiotherapy	
Yes	86(96.6)
No	3(3.4)
Dose of radiotherapy	
45 GY	31(50.8)
>45 GY	30(49.2)
Type of radiotherapy	
EBRT+brachy	37(43)
ERBT	23(26.7)
Brachy	26(30.2)
Recurrence	
Yes	39(43.8)
No	50(56.2)
Recurrence time (month) Mean±SD	28.58±25.13
Recurrence site	
Locoregional	20(51.3)
Distant	19(48.7)
Recent status	
Alive	59(66.3)
Death	30(33.7)
Death causes	
Cancer-related	23(76.6)
Nonrelated	7(23.4)
Death time (month) Mean±SD	39.69±26.65

Table 2. Disease-free survival and overall survival at 10 years for the variables analyzed.

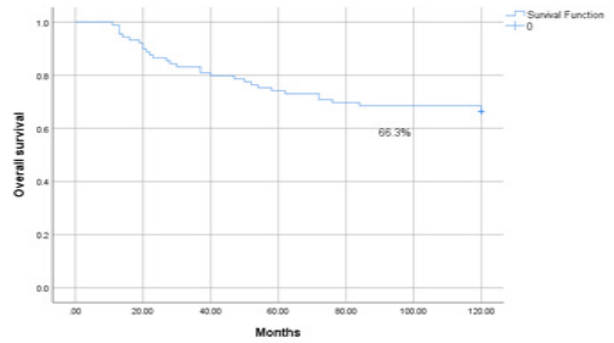
Variable	Disease-free survival N (%)	p.value	Overall survival N (%)	p.value
Age diagnosis				
≤60 years	31(62)	0.332	39(66.1)	0.957
>60 years	19(38)		20(33.9)	
Myometrial				
≤1/2	43(86)	0.350	52(88.1)	0.792
>1/2	7(14)		7(11.9)	
Pathology				
Type 1	44(88)	0.208	52(86.4)	0.471
Type 2	5(10)		5(8.5)	
Sarcoma	1(2)		3(5.1)	
LVI				
+Ve	13(26)	0.013	12(20.3)	0.057
-Ve	29(58)		35(59.4)	
Unknown	8(16)		12(20.3)	
Margin				
+Ve	0(0)	0.025	1(1.7)	0.422
-Ve	44(88)		48(81.4)	
unknown	6(12)		10(16.9)	
Chemotherapy				
Yes	14(28)	0.002	21(35.6)	0.057
No	36(72)		38(64.4)	
Radiotherapy				
Yes	49(98)	0.417	58(98.3)	0.219
No	1(2)		1(1.7)	

Table 3. Death rate in recurrent disease.

Recurrence	Recent status			p.value
	Alive	Death	Total	
Locoregional	11 (55)	9 (45)	20 (100)	0.002
Distant	1 (5.3)	18 (94.7)	19 (100)	

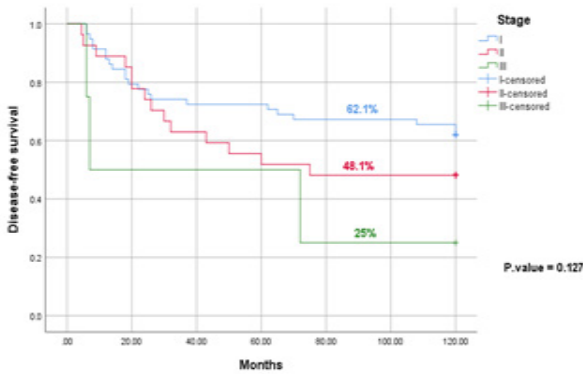


A

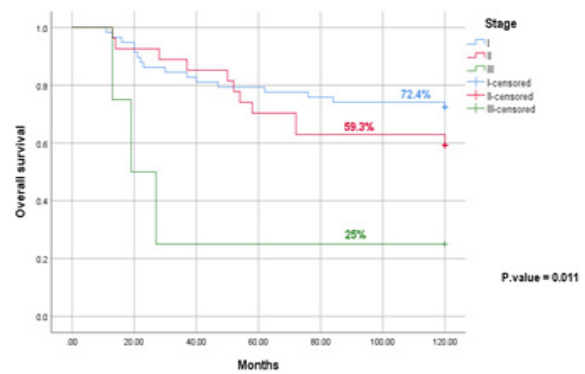


B

Figure 1. (A) Disease-free survival and (B) overall survival in the study population.

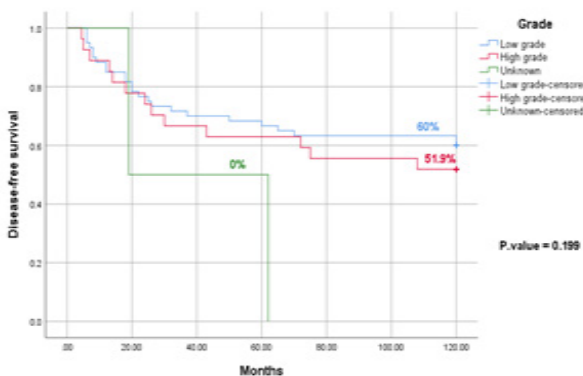


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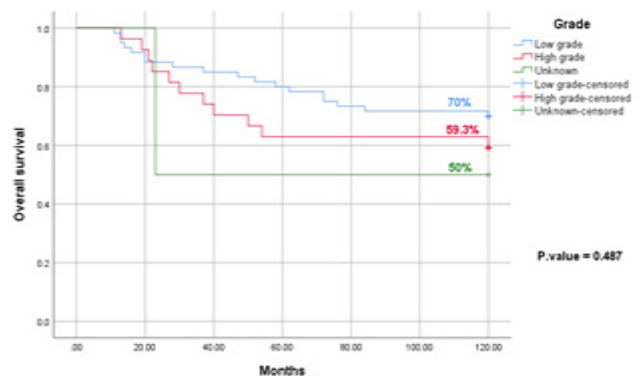


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Figure 2. difference in (A) disease-free survival and (B) overall survival between stages.



A



B

Figure 3. difference in (A) disease-free survival and (B) overall survival according to grade.

DISCUSSION

In this study, all patients underwent surgery, in most of our patients adequate surgical staging was not performed. Only 3 cases didn't receive any kind of adjuvant therapy since they had FIGO IA, low grade without other poor prognostic factors. It was previously described that adjuvant therapy (radiotherapy or chemotherapy) should be delivered within 90 days⁽¹⁸⁾, but the majority of our patients received radiotherapy after 3 months of surgery.

The 5-year and 10-year disease-free survivals were 62.9% and 56.2%, which is not similar to data reported by other authors⁽²⁷⁾ since in the majority of our patient adequate surgery was not performed, and in the majority of our patients selective pelvic and para-aortic LND not performed. Also, the 5-year and 10-year overall survivals of 74.2% and 66.3% respectively were found in our study near the result found by Creasman et al in a study of 8110 patients, in which 5-year overall survival was 80%⁽¹⁸⁾.

The stage of cancer at initial presentation is an important prognostic factor and lower stages have a favorable prognosis⁽³⁾. In this study, overall survival significantly was different between patients with stages I, II, and III, as 5-year overall survival was 80% for stage I as compared to 25% for stage III ($p=0.01$), although both 5-year and 10-year DFS was different among different FIGO stage in our study, but it was not statistically significant ($p=0.1$).

The multivariate analysis indicated that the chance of tumour recurrence was 7.5 times greater in patients with FIGO stage II, III, or IV than in those with FIGO stage I, demonstrating the effect of the FIGO stage on the fate of endometrial cancer patients. Furthermore, Kosary showed that the FIGO stage affected the likelihood of survival in an examination of data on 41120 cases of endometrial cancer from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute that was diagnosed between 1973 and 1987.

The overall survival rate at 5 years was 48.8% in patients with advanced stages in contrast to 90.2% in patients with early disease⁽²⁸⁾.

According to Gal et al., lymphovascular space involvement was a significant risk factor for Stage I endometrial cancer 5-year survival⁽²⁹⁾. In our analysis, we didn't assess among different FIGO stages but in

general, it has a significant effect on DFS ($p=0.013$) in terms of overall survival, although those with positive LVI have a lower survival rate but are statistically not significant, in 18% of patients LVI status was not assessed in histopathology report and this may be the cause for the limitation of our results. Although the depth of invasion and Grade 3 histopathology are typically thought to be important risk factors⁽¹⁸⁾, they were statistically insignificant in our analyses.

Although it was noted that individuals under 60 years old had a longer survival duration than those over 60⁽¹⁴⁾, there was no significant correlation between age at diagnosis and overall survival ($p=0.9$), endometrial cancer's worse prognosis in the oldest age group may be partially due to co-morbidities and a lack of access to new treatment developments.

In a group of 181 patients with endometrial cancer described by Steiner et al., the effect of the histopathologic tumour type as an independent prognostic factor for recurrence-free survival and death was revealed, and these investigators found that patients with adenocarcinoma or adenoacanthoma had considerably higher overall survival and recurrence-free survival rates when compared to patients with other tumour forms like (papillary, clear-cell carcinoma, and others)^(30,31).

In our study, patients with endometrioid tumours had a disease-free survival rate at 10 years of 88%, which was significantly higher than the 10% for patients with other tumour types, such as serous-papillary, clear cell, and undifferentiated carcinomas. Moreover, 10-year overall survival was 86.4% vs. 8.5% among unfavourable histology, but it was not statistically significant in our analysis for either recurrence or survival, which may be explained by the low number of patients, limiting the statistical power of the analysis. Giving adjuvant CTX in our study harmed DFS since CTX was prescribed in those patients with advanced stage, high grade or unfavourable histology, and these factors made them have poor prognosis.

In conclusion, his retrospective study we concluded that our estimated overall survival and disease-free survival were acceptable, and it is crucial to evaluate any patient with endometrial cancer before doing surgery by a multidisciplinary team to identify those with poor prognostic factors and the need for selective pelvic/ para-aortic lymph node dissection which was not performed in the majority of our patients.

Our outcomes were influenced by stage, lymphovascular space involvement, and marginal status after surgery. Adjuvant chemotherapy hurt disease-free survival, but Radiotherapy significantly didn't affect survival, although this may need a larger study sample.

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