RESEARCH ARTICLE

# Endometrial Adenocarcinoma: Clinicopathologic and Survival Characteristics in Yazd, Iran

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## Abstract

**Background: Endometrial adenocarcinoma is the most common gynecological cancer in the Western world and its incidence appears to be rising. However, population-based studies on endometrial cancer providing survival estimates by age, histology, and stage in Asia have been sparse. The aim of this study was to evaluate the clinicopathological data and survival for patients with endometrial adenocarcinoma treated at three institutions in Yazd, Iran. Materials and Methods: Medical and anatomicopathological records at the Department of Pathology and Radiotherapy of the Shahid Sadoughi University of Medical Sciences and Madar private hospital, between 2005 and 2012 were reviewed. All cases of endometrial adenocarcinoma were included. The Kaplan-Maier method was used for survival analysis and Cox proportional hazards model for multiple regression analysis. Results: The study included 84 patients. Stages I, II, III, and IV were identified in 65.4%, 21.5%, 11.9% and 1.2%, respectively. Disease-free survival rate was 73.9±3.77 months (95% confidence interval, 64.51-83.22 months) and relapse occurred in 12.3% of the patients. The overall survival rate was 78. 2±3.65 months (95% confidence interval, 71.0-85.3 months). A multivariate analysis revealed that stage and grade were associated with overall survival. Conclusions: In this survival analysis of patients with endometrial cancer, we found that the prognosis of endometrial cancer was fair but strongly varied by stage and grade, and moderately varied by histology and age.**

**Keywords:** Cancer stage - endometrial adenocarcinoma - prognosis - survival - Yazd, Iran

*Asian Pac J Cancer Prev,* **15 (6)**, 2797-2801

## Introduction

Carcinoma of the endometrium is the most common gynecologic malignancy in developed countries (Rosai et al., 2011). An estimated 8,010 deaths were reported in 2012 (Oaknin et al., 2012). Long time unopposed estrogen exposure is often responsible for initiation of the premalignant phase of the disease and is the risk factor for this cancer. Fortunately, this is also one of the most curable cancers when detected in the early stages. Most cases of endometrial cancer are diagnosed when the disease is confined to the uterus. Because of this, most women with endometrial cancer have an excellent prognosis (Oaknin et al., 2012). It typically occurs in elderly individuals; however, it can occur into younger age group (Park et al., 2013). It is currently believed that endometrial carcinomas can be divided in two distinct types on the basis of their pathogenesis (Rosai et al., 2011). Type I endometrial adenocarcinoma usually develops in perimenopausal women in the setting of hyperestrogenism. Endometrioid carcinoma and its variants, as well as mucinous carcinoma, are the prototypes of type I endometrial adenocarcinoma. Type II endometrial adenocarcinomas are very aggressive neoplasms unrelated to estrogen stimulation that usually occur in postmenopausal, elderly women. Type II endometrial adenocarcinomas are high-grade and deeply invasive. From the pathologic viewpoint, they encompass the non-endometrioid carcinomas, including papillary serous, clear cell, squamous cell, and undifferentiated carcinoma. Obesity and nulliparity increase the risk of endometrial cancer (Colombo et al., 2011). In this article we provide detailed (stratified by age, histology, stage and treatment) survival estimates of endometrial cancer patients in Yazd from3 major institutes, covering 84 patients.

## Materials and Methods

This research was approved by the university ethics committee. A retrospective chart review was performed on all patients who were diagnosed as endometrial adenocarcinoma and treated at Madar and Shahid sadoughi hospitals and Ramazanzadeh radiotherapy center. All cases of endometrial adenocarcinoma were included. Our search identified 84 patients with endometrial adenocarcinoma. Medical charts, including admission and discharge notes,

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as well as surgical pathology reports and treatment records (chemotherapy and radiation therapy) were reviewed, and epidemiological data (age at diagnosis, gravity, and parity), clinical data (past medical history, hormone or tamoxifen use, personal or family history of other malignancies) , pathologic and histological data (grade ,stage, lymphovascular space involvement, positive peritoneal washings and lymph nodes metastases) as well as survival data (disease-free and overall survival) were extracted. Seventy nine patients underwent surgery and staged using the International Federation of Gynecology and Obstetrics (FIGO) 1988 operative staging system for endometrial cancer. Disease-free survival was calculated from date of the termination of the treatment until date of recurrence, death, or last follow up. Overall survival was calculated from date of diagnosis until death or date of last follow up. Survival data were analyzed using Kaplan-Meier estimates, and multivariate analysis was performed using the Cox regression method. A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS.16.

## Results

There were 84 patients. Their mean age at the time of diagnosis was 58±12.51 years (range: 43 to 90 years).The most common presenting symptom was post menopausal bleeding (70.2%). Medical comorbidities at the time of diagnosis included hypertension (33.3%) and diabetes (32.1%). Of these patients, 11.9% were nullipar. 8 patients (9.52%) had a history of other malignancies. 4 patients (4.76%) had a history of breast cancer and 4 (4.76%) patients had the gastrointestinal malignancies .A family history of malignancy in a first-degree relative was found in 17 (20.2%) patients. Two (2.4%) patients had used hormone-replacement therapy .8 patients (9.5%) had a history of oral contraceptive use, and one case (1.2%) had used tamoxifen. Surgery (total abdominal hysterectomy and bilateral salpingooophorectomy) had been performed on 79 (94%) patients and endometrial curettage was done for 5 (6%) patients. Majority of patients (85.7%,) had endometrioid histology. Grade I was the most common grade (45.2%). 55 of the 84 patients (65.4%) had Stage I disease, 18 (21.5%) had Stage II, 10 (11.9%) had Stage III, and 1 (1.2%) had Stage IV disease. Peritoneal washing results were available for 21 patients. Among these patients 3 patients had positive peritoneal washings .Lymphovascular space invasion was evaluated in 30 patients. Ten patients had a lymphovascular space invasion. Adjuvant radiation therapy was given to 40 (47.6%) patients. Among these patients, 28 (33.3%) patients were treated by external beam radiation therapy and one case (1.2%) received only vaginal brachytherapy. 11 (13.1%) patients received external beam radiation therapy along with vaginal brachytherapy. Twenty four patients (28.6%) received chemotherapy (platinum-based chemotherapy) in the adjuvant or metastatic/recurrent setting. 15 (17.9%) patients who received chemotherapy also had radiation therapy (Table 1). Hormone therapy was given to only 2 (2.5%) patients. At the end of this study, 66 patients (78.6%) were alive and 17patients (20.2%) had died. A total of 10 patients (11.9%) locally recurred with 5 still alive and 5 succumbing to their disease. Distant metastases had occurred in 10 (11.9%) patients. The overall survival was 78.17±3.65 months (95% confidence interval, 71.00-85.34 months) and disease free survival was 73.86±3.77 months (95% confidence intervals, 64.51-83.22 months) (Figure 1, 2). In this study patients were divided into several groups according to their age (age group 30-39 years,40 to 49 years,50 to 59 years and more than 60 years). Patients in age group less than 60 years survived longer than patients in age group more than 60 years but this difference was not statistically significant (p=0.06). Tumor's histology didn't have a significant relationship with overall survival (p=0.17), but, patients with endometrioid type histology had a longer survival period. Regarding grade and overall survival there was a significant relationship between grade and overall survival (p=0.00) (Figure 3). Overall survival was different between patients with early stage (stages I&II) and advanced stages (stages III and IV) (p=0.01). All patients with lymphovascular space invasion were alive so we were unable to evaluate the relationship between survival and

**Table 1. Result Of Study. (stratified by Comorbidities, histology, stage, grade and treatment)**

| | | |
|---|---|---|
| Comorbidities | DM (%) | 32.1 |
| | HTN (%) | 33.3 |
| Histologic type | Endometrioid (%) | 85.7 |
| | Non-endometrioid (%) | 14.3 |
| Grade | I (%) | 45.2 |
| | II (%) | 40.5 |
| | III (%) | 14.3 |
| Stage | I (%) | 65.4 |
| | II (%) | 21.5 |
| | III (%) | 11.9 |
| | IV | 1.2 |
| Treatment | TAH+BSO (%) | 94% |
| | Curettage (%) | 6% |
| Radiotherapy+ (%) | | 47.6 |
| | External (%) | 33.3 |
| | Internal (%) | 1.2 |
| | Both (%) | 13.1 |
| Chemotherapy (%) | + (%) | 28.6 |
| | - (%) | 71.4 |
| Chemotherapy and Radiotherapy | | |
| | + (%) | 17.9 |
| | - (%) | 82.1 |

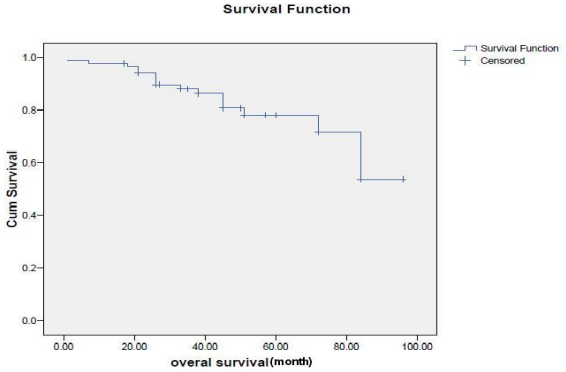


**Figure 1. Overall Survival in Patient with Endometrial Adenocarcinoma**

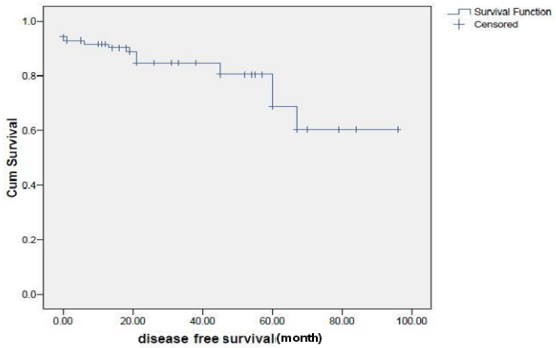


**Figure 2. Disease Free Survival in Patient with Endometrial Adenocarcinoma**

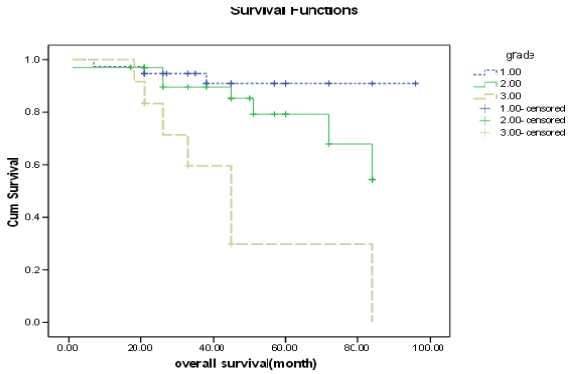


**Figure 3. Overall Survival Estimated by Grade**

presence of lymphovascular space invasion. It was true in the case of patients with positive peritoneal washing. The patients who had received radiation therapy had lower median survival than those who did not receive this treatment, but this difference was not significant (p=0.31). Chemotherapy had a significant negative impact on overall survival (p=0.00). Combination of radiation therapy plus chemotherapy had a negative effect on overall survival (p=0.06) although this difference was not statistically significant. A multivariate analysis revealed that grade and stage were associated with overall survival.

## Discussion

The aim of this study was to assess the relationship between selected clinical and pathological factors, disease free survival and overall survival in endometrial cancer patients at three institutions in Yazd,Iran. Approximately 90% of women with endometrial cancer have abnormal uterine bleeding which is the only presenting complaint leading to the diagnosis of the disease (Colombo et al., 2011) and this fortunately leads to the early diagnosis of the majority of the cases. It was true about our patients. Most cases of endometrial carcinoma occur in the sixth and seventh decades of life (Huang et al., 2012) .The mean age at diagnosis was 58±12.51 years in the current study.

Stage of cancer at initial presentation is an important prognostic factor and lower stages have a favorable prognosis (Colombo et al., 2011). Although only 3-13% of all endometrial cancers are stage IV, these account for 23% of cancer-related deaths in the first year following diagnosis (Bristow et al., 2000). In this study overall survival was different between patients with early stages (stages I, II) and advanced stages (stages III & IV) (p=0.01). Lambrou et al. (2004) showed that overall survival was lower and morbidity was higher in patients with advanced endometrial cancer (mainly stage III). They suggested that alternative treatment options should be considered in patients with surgically unresectable disease. There was not a significant relationship between age at diagnosis and overall survival (p=0.06), nevertheless patients in age group <60 years had a longer survival period than patients in age group >60 years, consistent with a previous report (Assaad Semaana et al., 2012). The less favorable prognosis of endometrial cancer in the oldest age group might be in part attributable to co morbidities and less access to therapeutic innovations. It was interesting that in the current study in the age group <60 years, the best survival belonged to patients in the age range 50-59 years (78 months). To explain this we should say that endometrial adenocarcinoma is biologically and genetically heterogeneous among women of different ages and ethnicities.

Non- endometrioid histologies are not a rare event in young endometrial adenocarcinoma patients and it is less likely that younger patients undergo radical surgery as part of their treatment. On the other, hand one study found that advanced age was not a poor prognostic factor for overall survival after adjusting for other significant variables (Nicole et al., 2011). In our study, the endometrioid type of tumor demonstrated better prognosis compared with other cell types; also consistent with another study (Huang et al., 2012), however, this tendency was not statistically significant. The overall survival of the present study was much better than those of some previous reports, which found a median overall survival of 19-51 months (Ayhan et al., 2002; Thomas et al., 2007). This difference may be due to a lower frequency of non-endometrioid-type tumors in our population group and that majority of our cases were in stage I. In the current study there was a significant relationship between grade and overall survival (p=0.00). It was consistent with the previous study (Zhang et al., 2012). While the primary treatment for localized endometrial carcinoma has always been total abdominal hysterectomy and bilateral salpingooophorectomy, the role of postoperative radiotherapy as an adjunct to surgery has not been as clearly defined. The present lack of clarity about the optimal clinical management of these patients is due in part to inconsistencies in the scientific evidence and in part to recent modifications of the FIGO classification. Adjuvant radiotherapy as an adjunct to surgery has long been used in the management of endometrial carcinoma with the intent to improve local tumor control as well as to achieve excellent survival rates.

In the present study patients with stage IA&B did not receive radiation therapy unless those with grade III or non-endometrial histology. The entire patients with stage II and III received radiation therapy. Although stage I endometrial cancer has a favorable prognosis with an 80% 5-year survival, as high as 20% of the patients with early-stage disease will experience relapses and ultimately dies of the disease (Papadia et al., 2013). For these early-stage diseases with high risk of recurrences, radiation therapy certainly plays a major role as an adjuvant

treatment (Stanojević et al., 2006). There is no consensus for the adjuvance of cancer of the endometrium stage IA; histological grades 1 and 2 patients. In one study there was no difference in disease free survival and overall survival in patients with stage IA endometrioid adenocarcionoma of endometrium, histological grades 1 and 2 regarding different radiotherapy regimens, even when compared to no radiotherapy at all (Zuliani et al., 2011). It is worth noting the use of radiation therapy for FIGO stages IB, IC and II still remains controversial. Several authors agree on the adjuvant radiotherapy indication for the old FIGO stage IB and grade 3 subgroup, giving preference to teletherapy in these cases (Lukka et al., 2006; Kong et al., 2008). The GOG 99 (Keys et al., 2004) study showed that the patients with FIGO stages IB, IC and II which submitted to external radiotherapy had a reduction in recurrence risk by 58% (p=0.007). The authors concluded that radiation therapy reduces the risk of recurrence, but should be used only in women aged more than 70 years, in tumors with lymphovascular invasion, stage IC and histological grades 2 and 3. Most recurrence of initial tumors was limited to vagina, which, added to low toxicity of this treatment and encouraged the use of adjuvant brachytherapy in these cases, however there is no strong evidence in the literature.

It seems that primary radiation therapy for clinical stage I and II endometrial adenocarcinoma is a feasible option for medically inoperable patients and provides disease control, with fewer than 16% of surviving patients experiencing recurrence (Podzielinski et al., 2012). Some authors now propose pelvic radiotherapy only for intermediate prognosis tumours (such as IA >50% of myometrium invasion with grade 3 and IB stages), if patients did not have any lymphatic surgery, or for bad prognosis tumours (Moreau-Claeys et al., 2011). Although radiation therapy in intermediate and high risk patients increases local control, effect on overall survival is not clear such as the current study that radiation therapy did not increase the overall survival (p=0.31).

Chemotherapy is increasingly integrated into management of advanced-stage endometrial cancer and may have a role in intermediate and high risk early-stage disease. Combination therapy with radiation and chemotherapy is under evaluation (Mehasseb et al., 2012). A review published by the Japan Society of Gynecologic Oncology. Nagase et al. (2010) has shown some benefits for the addition of systemic chemotherapy in the management of endometrial cancer patients. However, this analysis could not identify how best to select the patients who would benefit from this systemic treatment. The benefit of adjuvant chemotherapy or combined radio- and chemotherapy in stages I and II has yet to be demonstrated in clinical trials. A study of patients who had undergone optimal surgical treatment for stage III and IV endometrial carcinoma without any hematogenous metastases revealed a survival advantage from adjuvant chemotherapy (adriamycin/cisplatin) compared to whole abdominopelvic radiotherapy (Randall et al., 2006). Another study showed that postoperative platinum based chemotherapy is associated with a small benefit in progression-free survival and overall survival irrespective of radiotherapy treatment (Johnson et al 2011). Combined treatment with radiation and chemotherapy may improve overall survival in patients with FIGO stages III and IV endometrial cancer (Nakayama et al., 2010). One study revealed that concomitant paclitaxel plus carboplatin and radiation was feasible and well tolerated and resulted in excellent local-regional control in high risk or advanced endometrial adenocarcinoma (Wen et al., 2013). Again in the current study chemotherapy and combination of RT plus chemotherapy had significant negative impact on overall survival (p=0.00 and 0.06 respectively). To explain these findings we must say that since chemotherapy and radiation therapy were used in advanced stages of the disease, higher grade tumors and non endometrial histologies it would seems logical that these patients would have worse prognosis.

Endometrial cancer is a hormone-dependent disease, and, therefore, adjuvant hormonal therapy might improve the outcome in the early stages of the disease. In this study only 2 patients had received hormone therapy. Peritoneal washing results were available for 21 patients. Among these patients 3 patients had positive peritoneal washings. All patients with positive peritoneal washing result were alive so we were unable to evaluate relationship between survival and malignant peritoneal washing. Lymphovascular space invasion was present in10 patients and since all patients with lymphovascular invasion were alive so we were unable to evaluate relationship between survival and lymphovascular space invasion. Recently, Akbayir et al. (2012) stated that the combination of lymphovascular space invasion and cervical glandular and stromal involvement were superior to Gynecologic Oncology Group's (GOG's) criterion (Creasman et al., 1987) (tumor grade and myometrial invasion) for predicting pelvic lymph node metastasis. Weaknesses of our study are its retrospective nature and the lack of information regarding lymphovascular space invasion and peritoneal cytology results in all of the patients which have influenced the interpretation of the data. In addition the average follow-up for survival was relatively short.

In conclusion, regarding the new staging system, future research should be focused on developing individualized risk models in endometrial cancer. The use of adjuvant therapy did not affect overall survival in our series .This points to the need for further studies that include both therapy for local control and distant control.

In this survival analysis of patients with endometrial cancer we found out that prognosis of endometrial cancer strongly varied by grade and stage, and moderately varied by histology and age. The prognosis is fair.

## Acknowledgements

The authors of this article would like to thank the staff of Pathology ward of Shahid Sadoughi hospital and Ramazanzadeh radiotherapy center, especially Mrs Hosseini for their support and help.

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