Comparison of Outcomes in Patients with Early-stage Mucinous Endometrial Cancer and Those with Endometrioid Endometrial Cancer, With and Without Adjuvant Therapy

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OBJECTIVE: To compare risk factors, treatment, and outcomes in patients with stage I/II mucinous endometrial cancer (MEC) relative to those of patients with endometrioid endometrial cancer (EEC).

STUDY DESIGN: We conducted a case-control study of patients with MEC and EEC. Patients with stage IA, IB, or II MEC treated at the 2 institutions between 01/01/1996 and 01/01/2007 were identified. Each MEC case was matched with 2 EEC controls by age, stage, grade, and year of diagnosis. The Kaplan-Meier method was used to generate overall survival (OS) data. Factors predictive of outcome were compared using the log-rank test and Cox proportional hazards model.

RESULTS: A total of 34 patients with MEC were compared to 68 controls with EEC. All patients were treated by hysterectomy and bilateral salpingo-oophorectomy. Use of adjuvant radiation therapy was similar between cases and controls. The 5-year disease-free survival (DFS) rates were not significantly different in patients with MEC when compared to those with EEC (89% vs. 92%, respectively, p = 0.2). The 5-year OS rates for patients with MEC and the control group were 95% and 96%, respectively (p = 0.1).

CONCLUSION: Patients with early-stage MEC and EEC have similar DFS and overall survival. (J Reprod Med 2014;59:527–533)

…the outcome for patients with stage I and II MEC is similar to that of patients with early-stage EEC lesions.

Keywords: endometrial cancer, endometrioid endometrial cancer, gynecological malignancies, hyperestrogenism, mucinous endometrial cancer.

In the United States endometrial cancer remains the most prevalent of all gynecological malignancies. It is estimated that in 2013 49,560 new cases of endometrial cancer will be diagnosed. Endometrial cancer will account for an estimated 8,190 deaths in 2013.[1] Endometrial cancer traditionally has been categorized into type I and type II. Type I cancers

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account for an estimated 80% of cases, tend to occur in the setting of hyperestrogenism, and are usually early-stage, low-grade tumors with a favorable prognosis. These tumors are of endometrioid histology, grade 1 or 2, and can be preceded by an intraepithelial neoplasm, atypical and/or complex endometrial hyperplasia. Type II cancers account for an estimated 10–20% of endometrial cancers and include grade 3 endometrioid tumors, as well as those of nonendometrioid histology. The latter group comprises serous, clear cell, mucinous, squamous, transitional cell, mesonephric, and undifferentiated endometrial cancers.[2,3]

In most cases the prognosis for patients with endometrial cancer is favorable. However, certain poor prognostic factors have been identified which are predictive of recurrence and risk of death. Most of these factors, like presence of lymph-vascular space involvement, depth of myometrial invasion, and status of nodal involvement, are determined after hysterectomy and lymphadenectomy.[4,5] Preoperative prognostic factors such as tumor histology and grade are equally important and often are independent predictors of survival and help determine the optimal surgical management of the disease. For example, for patients with serous uterine cancer, the risk of recurrence is estimated to be 50% and survival is decreased.[6]

Pure mucinous endometrial cancer (MEC) is a rare histologic nonendometrioid type of endometrial cancer accounting for < 10% of endometrial tumors.[6-9] Mucinous cancer of the endometrium was first described in 1983 and requires that greater than one-half of the cells in the tumor contain periodic acid-Schiff–positive diastase-resistant intracytoplasmic mucin.[7-10] The available literature to inform clinicians as to the optimal management of patients with this histology is further compromised by the fact that it was collected prior to the practice of comprehensive surgical staging for endometrial cancer and is complicated by the use of radiation therapy preoperatively. Some data suggest that MECs represent well-differentiated tumors with prognosis similar to low-grade endometrioid adenocarcinomas.[11] However, the information pertinent to mucinous histology as a prognostic factor in endometrial cancer remains limited and was obtained mostly from retrospective studies.

The aim of the present case-control study was to describe the experience at two large academic institutions with respect to demographic, treatment, and outcome of patients with early-stage MEC and to compare them to those of patients with early stage endometrioid endometrial cancer (EEC).

Materials and Methods

An institutional review board–approved retrospective analysis of the Cancer Registry database at the 2 participating institutions was performed. Patients with stage IA, stage IB, or stage II MEC who underwent treatment at the 2 participating institutions between January 1, 1996, and January 1, 2007, were identified from the institutional cancer registry databases. Assignment to stage was in accordance with the 2009 International Federation of Gynecology and Obstetrics (FIGO) criteria for staging.[12] Patients were excluded from the study for any of the following: surgical exploration/staging for endometrial cancer at another institution, incomplete clinicopathologic data, history of an additional primary cancer within the 5 years before or during the period after endometrial cancer diagnosis, and advanced-stage disease (FIGO stages III or IV).

For MEC diagnosis in all study cases at least 50% of the tumor had to comprise mucinous histology. Each MEC case was matched with 2 controls diagnosed with EEC, without local mucinous, serous or clear cell differentiation. Cases (MEC) were matched with controls by age (±5 years), stage (IA vs. IB vs. II), grade (1 and 2 vs. 3), and year of diagnosis (±3 years). Controls were selected without knowledge of outcome. In all patients (cases and controls) the diagnosis had to be histologically confirmed by a dedicated gynecologic pathologist following postsurgery pathology review. Once patients were selected, individual subject data were collected retrospectively from inpatient and clinical records. The medical records were reviewed for demographic information, medical history, treatment, and outcome parameters.

Statistical Analysis

Continuous variables were evaluated by Student's *t* test or Wilcoxon-Mann-Whitney test, as appropriate. Categorical variables were evaluated by χ^2 test or Fisher's exact test as appropriate for category size. Survival estimates were plotted utilizing the Kaplan-Meier method. The log-rank test was utilized to statistically quantify these survival differences on univariate analysis. Multivariate analyses were performed with a Cox proportional regression method. For continuous variables the cutoff level chosen was their median value unless otherwise specified. Length of survival was calculated

from the date of initial surgery to the date of death; surviving patients were censored at the date of last contact. All statistical tests were two-sided, and differences were considered statistically significant at $p < 0.05$.

Statistical analyses including Kaplan-Meier curves were plotted using SPSS statistical software version 16.0 (SPSS, Inc., Chicago, Illinois). All other data analyses were performed with Stata statistical software version 9.2 (Stata Corp LP, College Station, Texas).

Results

During the study period a total of 1,898 patients diagnosed with early stage (stage I or II) endometrial carcinoma were treated at our institutions and identified from the cancer registry cancer database. Of these, 34 patients (1.8%) with a diagnosis of MEC were identified. Sixty-eight cases of EEC were identified as controls. The criteria for which the groups had been matched—age, substage, grade, and year of diagnosis—were similar between cases and controls (Table I). Cases and controls were also similar with respect to ethnicity, predominantly Caucasian, and reflecting the characteristic patient population at our institutions. There was no difference in the rates of diabetes and hypertension between the groups. All the patients in the study underwent a total hysterectomy with bilateral salpingo-oophorectomy (BSO). A total of 87% of the surgeries were performed abdominally. The remaining 13% were performed vaginally. The rate of lymph node dissection was similar between the groups (44.1% vs. 42.6%, $p = 0.8$). The median number of lymph nodes resected was not significantly different between MEC and EEC (11 ± 5 vs. 9 ± 7, $p = 0.3$). Patients did not undergo surgical staging for their tumors because of operating surgeon's preference, results of intraoperative frozen section, patient's age and/or medical comorbidities, morbid obesity, or patient's anatomy. Patients whose tumors were not staged surgically were categorized as having clinical stage IA, IB, or II. Among the cases and controls undergoing comprehensive surgical staging, the mean number of pelvic and paraaortic lymph nodes retrieved was similar between cases and controls. There was no statistically significant difference with respect to the use of adjuvant radiation therapy between cases and controls. None of the patients underwent adjuvant chemotherapy.

Table I *Demographic and Clinical Characteristics of the Study Population*

Characteristic	Mucinous (N = 34)	Endometrioid (N = 68)	p Value
Age (yr)	63 (±9)	63 (±9)	0.8
Race, no. (%)			
White	30 (88.2)	54 (79.4)	0.4
Asian	0	2 (2.9)	
Hispanic	0	2 (2.9)	
African-American	0	1 (1.5)	
Unknown	4 (11.8)	9 (13.3)	
Comorbidity, no. (%)			
Diabetes	4 (11.8)	7 (10.3)	0.7
Hypertension	9 (26.5)	30 (44.1)	0.1
Hypercholesterolemia	10 (29.4)	19 (27.9)	0.6
Grade, no. (%)			
1 and 2	32 (94.1)	64 (94.1)	0.9
3	2 (5.9)	4 (5.9)	
Stage, no. (%)			
IA	31 (91.2)	62 (91.2)	0.9
IB	2 (5.9)	4 (5.9)	
II	1 (2.9)	2 (2.9)	
Procedure, no. (%)			
Total hysterectomy	34 (100)	68 (100)	0.9
Bilateral salpingo-oophorectomy	34 (100)	68 (100)	0.9
Lymph node dissection	15 (44.1)	29 (42.6)	0.8
Radiotherapy	7 (20.6)	7 (10.2)	0.1

The median follow-up time for the entire study population was 90 months. Of the 34 patients in the MEC group there were 4 recurrences, and of the 68 patients in the EEC group there were 3 recurrences (11.7% vs. 4%, $p = 0.1$). All the recurrences were local and isolated to the vagina. The 5-year disease-free survival (DFS) was not significantly different in patients with MEC as compared to those with EEC: 89% vs. 95%, respectively ($p = 0.1$) (Figure 1). In a crude analysis of prognostic factors associated with time to recurrence, only radiotherapy was significantly associated with improved DFS. Age older than 65 years, lymph node dissection, grade, and stage were not significantly associated with decreased DFS. In a Cox proportional hazards model only radiotherapy was an independent predictor of DFS. All the patients in the MEC group who had recurrences were treated with external beam radiotherapy (EBRT) and vaginal brachytherapy. One of the recurrences in the EEC group was treated only with vaginal brachytherapy. The rest were treated with both EBRT and brachytherapy. None of the patients with recurrences in either group received adjuvant radiotherapy after their initial diagnosis.

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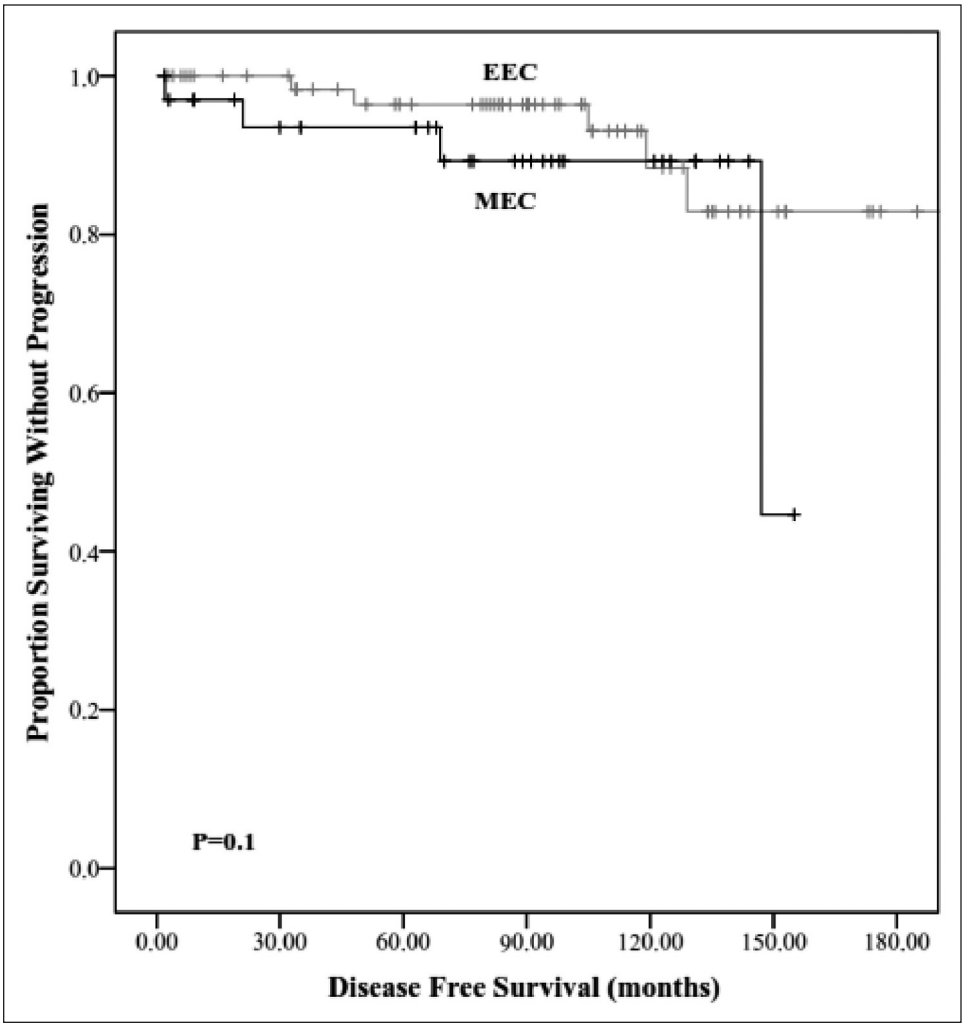

Figure 1
A comparison of DFS in patients with MEC versus those with EEC.

5 deaths, and among the 68 patients in the EEC group there were 4 deaths (14.7% vs. 5.8%, p = 0.1). Kaplan-Meier survival curves for patients with MEC and EEC are displayed in Figure 2. The 5-year overall survival (OS) rates for the MEC and control groups were 95% and 96%, respectively (p = 0.1). In a crude analysis of prognostic factors associated with time to death, age beyond 65 years, lymph node dissection, myometrial invasion > 50%, or adjuvant radiotherapy were not significantly associated with overall survival. In addition, in a Cox proportional hazards model none of these variables were independent predictors of OS.

Discussion

Endometrial cancers of mucinous histology represent a rare entity. Consequently, there is significant paucity of peer-reviewed literature to inform clinical outcomes and optimal treatment strategies for these patients. The relevance of mucinous histology as a prognostic factor in endometrial cancer also remains elusive. Traditionally, patients with MEC have been managed similarly to patients with EEC. In our study we identified 34 patients with early-stage MEC and 68 matched controls with EEC. Patients were diagnosed with stage IA, stage IB, or stage II disease. Based on review of the English literature reporting on patients with stage I–IV MEC, the present study represents one of the largest series to date documenting demographic and treatment outcomes of women with early-stage MEC.[7,9,11,13-27] Our data supports previous findings that patients with FIGO stage I/II MEC have an excellent prognosis, similar to what is reported

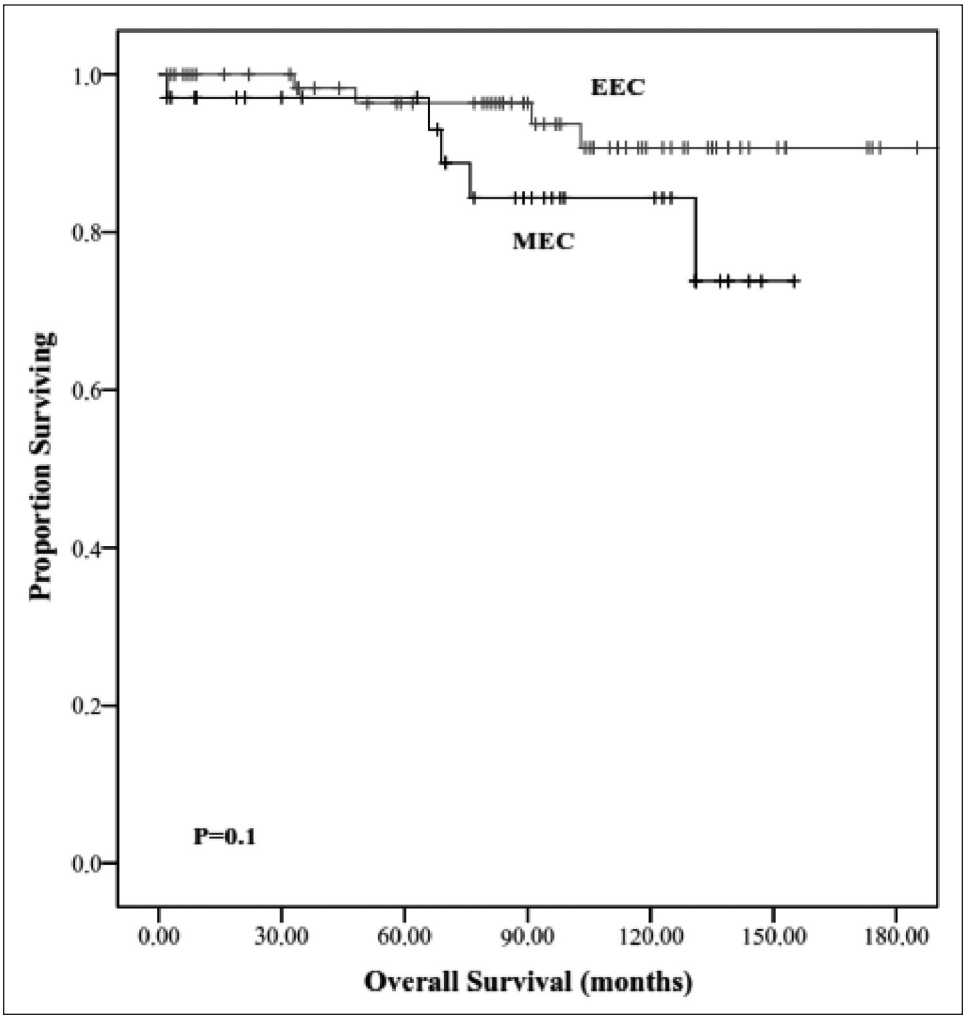

Figure 2
A comparison of overall survival in patients with MEC versus those with EEC.

for patients with similar stage and low-grade EEC, with surgical treatment alone. In our study we did not find any difference between DFS and OS between patients with MEC and those with EEC.

In the present study patients' mean age at diagnosis was 63, consistent with what has been reported in the literature.[11,13,15,26,28] There was no difference in the incidence of diabetes and hypertension between cases and controls in our study, as has been reported in other studies.[18,26] We did not have sufficient data documenting other potential risk factors such as body mass index, gravidity, or parity in the medical records to make meaningful comparisons between the incidence of these variables in the 2 groups.

Most patients with MEC in our series were also Caucasian and had low-grade tumors, with a low incidence of lymphovascular space involvement, as previously noted by other authors.[7,13,26] We did not find age >65 years, lymph node dissection, myometrial invasion >50%, or adjuvant radiotherapy to impact overall survival. The 5-year DFS rates were not significantly different in patients with MEC as compared to those with EEC. In the study by Ross et al,[7] of the 256 patients with corpus-confined uterine cancer 98 (21%) cases were found to have focal intracytoplasmic mucin production, and 21 (9%) were noted to have predominantly mucinous tumors (>50% mucinous features). In that study, consistent with our findings, the frequency of myometrial invasion and recurrence rates were similar for patients with MEC and patients with EEC tumors. The authors concluded that mucinous histology did not independently

impact prognosis. One of the study limitations is that an estimated 25% of patients were treated with preoperative radiation therapy. Patients in the study had tumors that were clinically staged so that rates of lymph nodal metastases were not reported. In the study by Czernobilsky et al,[16] all 10 patients with MEC had < 50% myometrial invasion. No recurrences were reported. In that series treatment among all 10 patients consisted of hysterectomy and BSO. Lymph node dissection was omitted.

Given the rarity of MEC, it is difficult to draw definitive conclusions from the small number of studies with respect to overall clinical outcomes.[26] While some authors have reported overall prognosis for patients with MEC to be superior to outcomes in patients with EEC, others have found no difference between these 2 different histologies of endometrial cancer.[7,11,13,26,27,29] In the present study 5-year OS for patients with MEC was similar to survival in patients with EEC. Similarly, Musa et al[27] documented mean OS for patients with MEC compared to patients with EEC to be similar. In that case-control study each of 41 cases of MEC was matched with 2 controls diagnosed with EEC. Thirty-four (85%) patients with MEC had stage I or II lesions. Among the patients with MEC tumors 70% underwent comprehensive surgical staging. The authors did not find any differences in adjuvant treatment, recurrence rate, or survival between the 2 groups. Jalloul et al[26] reported a series of 31 patients, all with MEC tumors surgically staged. Twenty-six (83.9%) patients had stage IA disease. Median follow-up was 62 months. The authors reported the 5-year OS to be 86.3%, concluding that the outcome of patients with stage I and II MEC is excellent with surgical treatment alone.

In our study there was no statistically significant difference between cases and controls with respect to adjuvant radiation therapy. There were 3 vaginal recurrences in each group. Others have reported similar findings. Melhem and Tobon[13] documented 3 recurrences among 18 patients with stage IA and IB MEC, all treated initially by hysterectomy and BSO only. Two of the patients had grade 3 tumors and 40–50% had myometrial invasion. One patient developed metastatic disease in the paraaortic area and the other one in the lung. The third patient developed recurrent disease in the bladder and vagina 4.5 years after the hysterectomy. Four of 18 patients in that series received adjuvant radiation therapy. In the study by Jalloul et al[26] 4 of 31 patients (13%) developed recurrent disease. Median time to recurrence was 13.5 months. All 4 patients had stage III disease and developed tumor recurrence either in the pelvic or paraaortic lymph nodes or both. None of the patients in that study received adjuvant radiation therapy. Ross et al[7] did not offer details on the number of recurrences in their study. Seven of 21 patients received adjuvant radiation therapy. All of these studies are limited by their sample size, inconsistency in regards to comprehensive surgical staging, and adjuvant radiation therapy, making it difficult to draw definitive conclusions with respect to the role of adjuvant radiation therapy on risk of local recurrence.

There are several limitations to this current study that must be considered in interpreting the data. First, our Tumor Registry database provides no information regarding previous or subsequent care at nonaffiliated institutions. Information regarding postsurgical follow-up care was limited to information obtained from our institution's electronic medical records. Lastly, this was a small, retrospective study, a problem echoed in all studies of rare tumors. The limitations imposed by these attributes have to be borne in mind when interpreting or using the findings of this study.

In conclusion, our study represents one of the largest retrospective series of patients with stage I and II MEC tumors. Our data support previous findings that the outcome for patients with stage I and II MEC is similar to that of patients with early-stage EEC lesions. These findings warrant validation from future studies.

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