A Clinical and Pathologic Comparison Between Stage-Matched Endometrial Intraepithelial Carcinoma and Uterine Serous Carcinoma: Is There a Difference?

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Abstract

Endometrial intraepithelial carcinoma (EIC) is a rare pathologic variant of uterine serous carcinoma (USC). Our aim is to distinguish patterns of clinic–pathologic outcomes in patients with EIC and USC for disease limited to the endometrium (stage 1A) as well as with distant metastasis (stage 4B). Surgically staged patients were retrospectively identified and relevant variables were extracted and compared. Kaplan-Meier was used to generate the survival data. More USC ($n = 29$) exhibited lymphovascular invasion (stage 4, $P = .01$) and expressed higher levels of estrogen receptor- α than EIC ($P = .0009$ and $.063$ for stages 1 and 4, respectively). The survival is comparable, with 1 recurrence in each group for stage 1A disease. For stage 4 EIC and USC, the progression-free survival (14 vs 10 months) and overall survival (19 vs 20 months) are similar to what is previously published. In conclusion, EIC, whether limited to the endometrium, or widely metastatic, imparts similar outcomes and should be treated comparably with stage-matched USC.

Keywords

EIC, uterine serous carcinoma, serous intraepithelial carcinoma, USC

Introduction

Endometrial cancer is the most common gynecologic malignancy in women in the United States, with an estimated 49 560 cases diagnosed in 2013.¹ While the incidence and mortality rates of other gynecologic cancers have plateaued or decreased in the last decade, the death rates for endometrial cancer continue to rise.² In 2011, there will be approximately 8190 deaths in women attributable to endometrial cancer. While the exact reason for this increased mortality is unknown, it is likely to be multifactorial, and epidemiological studies suggest an association with a rising incidence of uterine serous carcinoma (USC)^{3,4}

The USC is relatively uncommon and represents approximately 10% of all endometrial cancers, but it accounts for approximately 39% of endometrial cancer–related death.⁵ It has a predilection to occur in African Americans and white Hispanics.⁶ Among these patients, USC is associated with 53% of the mortality related to endometrial cancer.⁷ Clinically, USC is a subtype of endometrial cancer that has a distinct morphology and an aggressive tumor biology.⁸ It appears to have a predilection for lymphovascular invasion (LVI) and distant metastasis, irrespective of tumor burden in the uterine corpus, and is independent of estrogen-driven mitogenesis.⁹ After controlling for

stage and adjuvant treatment, early stage USC is associated with a high recurrence rate and poor survival. This is true even when it is compared to other known aggressive histologic subtypes such as clear cell endometrial carcinoma.¹⁰⁻¹²

Due to its poor prognosis, the pathogenesis of USC is a topic of ongoing research. Unlike endometrioid endometrial adenocarcinoma, which has an established precursor pathologic entity—glandular hyperplasia with nuclear atypia—USC usually arises from an atrophic endometrium.¹³ The term

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endometrial intraepithelial carcinoma (EIC) was first described as cells closely resembling serous carcinoma observed on the surface of endometrium and often occurring adjacent to invasive tumors.¹³ This entity has been proposed as a probable precursor to USC, although longitudinal studies that track the development and progression of invasive USC are lacking. Histopathologically, EIC does not invade the endometrial stroma, the lymphovascular channels, or the myometrium.¹⁴ Despite minimal uterine involvement, EIC has been associated with extrauterine metastasis in 33% to 67% of cases.¹⁵⁻¹⁷ This is a vexing clinical and management issue. There is no consensus regarding the optimal management of EIC in the literature to date.

Currently, the clinical-pathologic potential of EIC remains ambiguous. The high association with extrauterine spread, together with a high recurrence rate, argues against EIC being a precursor to USC.^{18,19} However, the clinical distinction, if any, between EIC limited to the uterus and stage 1A USC as well as EIC with extra-uterine spread and advanced stage USC, is not clear. Furthermore, although the standard of care for USC is evolving based on primarily retrospective and 1 small prospective experience from single and multi-institutions,^{20,21} there is even less consensus on optimal treatment for EIC.³ The objective of this retrospective study is to compare treatment and outcomes of patients with comparable tumor burden diagnosed with EIC and USC (ie, stage 1 EIC vs stage 1A USC; stage 4 EIC vs stage 4 USC), in order to gain a better understanding of serous-type carcinogenesis in the uterine corpus.

Methods

Cases of USC were obtained by searching the tumor registry databank within the Division of Gynecologic Oncology at Albert Einstein School of Medicine/Montefiore Medical center between 2000 and 2010. Consecutive cases of EIC were identified when the tumor satisfies the published and accepted histopathologic criteria of Wheeler et al¹⁶: EIC is defined as a replacement of the surface epithelium and/or underlying superficial glands of the endometrium, or an endometrial polyp lined by cells resembling serous carcinoma, and stromal invasion is absent. An endometrial polyp is defined histologically as a focal proliferation of endometrium in polypoid fashion with sclerosing stroma and thickened wall vessels. Due to the retrospective nature of this article, International Federation of Gynecology and Obstetrics (FIGO) staging definition prior to 2009 were used, defining stage 1A disease to be serous carcinoma limited to the endometrium only, with stromal invasion and possible LVI. The EIC with myometrial invasion were excluded from stage 1 group. Cases with mixed histologies in the endometrium or synchronous cancer (ie, ovary) were excluded.

All cases were diagnosed preoperatively by dilation and curettage or office endometrial biopsy. All patients underwent standard surgical staging procedure at a single institution, which included total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, bilateral pelvic and para-aortic lymph node sampling, and infracolic omentectomy or omental biopsy.

These EIC cases were matched by stage with the consecutive USC cases diagnosed at the same institution in the same time period. Clinical data were collected from patients' charts and included age at diagnosis, body mass index (BMI), stage of disease, histopathologic features such as hormonal receptor status and lymphovascular space invasion, treatment, and follow-up. Receptor and growth factor expression was determined by immunohistochemistry analysis. Absent or weak staining is designated as 0 or 1, and moderate to strong staining is designated as 2 or 3.

Statistical Analysis

The χ^2 goodness-of-fit test was used performed for age and BMI covariates, while Fisher exact test was used when comparing categorical variables with cell counts ≤ 5 . The Mann-Whitney *U* test was used to compare continuous data, because normality was not assumed and of its robustness toward outliers. Kaplan-Meier survival curves were obtained for progression-free survival (PFS) and overall survival (OS). The PFS was calculated starting from the time of their surgery to the time of their first documented recurrence, and the OS until the patient expired. The log-rank test was used to compare survival distributions among both PFS and OS for both sets of patients. An α level of .05 was used to determine significance for all tests. Statistical analysis was performed in R v 2.12.2.

Results

Table 1 summarizes the relevant clinical parameters between USC and EIC in patients with stages 1 and 4 disease. A total of 29 patients with EIC were diagnosed in the 10-year time span; 15 were limited to the uterine corpus (stage 1 EIC), while 15 had stage 4 disease. In the same time period, 15 stage 1A USC and 29 stage 4B USC were diagnosed.

Compared to the stage matched USC controls, there were no significant differences in the mean age, BMI, or ethnicity distribution. The majority of stage 4 USC patients received chemotherapy as their primary adjuvant treatment, significantly more than the stage-matched patients with EIC. The CA-125 at diagnosis (prior to surgical staging), LVI, and size of uterine tumor have all been previously suggested to impact prognosis in patients with USC.¹⁵ In our cohort, there is no difference in largest tumor size within the uterus, or CA-125 levels between EIC and USC when tumor is limited to the uterus (stage 1) or in stage 4 patients prior to surgical staging. The difference in LVI was statistically significant only in the stage 4 group, where more patients with stage 4B USC had LVI than staged-matched EIC patients.

Hormonal receptor expression has often been correlated with a favorable outcome or prognosis in endometrial carcinoma, while p53 expression suggested a poor prognosis and aggressive biology. Table 2 compares the distribution of moderate to strong estrogen and progesterone receptor (ER and PR, respectively) expressions as well as p53 expression between the stage-matched patients with EIC and USC. Of the 15

Table 1. Demographic Distribution and Clinical Variables in Stage-Matched EIC and USC.

Variable	Stage 1 EIC (n = 15)	Stage 1A UPSC (n = 15)	Stage 4 EIC (n = 14)	Stage 4B UPSC (n = 29)	P Value ^{a/b}
Age, years (SD)	65.67 (4.6)	66.13 (7.6)	66.8 (8.9)	66 (10.2)	NS
BMI (SD), kg/m ²	33.83 (9.1)	29.85 (6.9)	32.69 (9.9)	29.48 (5.4)	NS
Race, n (%)					
White	2 (13.3)	2 (13.3)	4 (28.5)	4 (13.8)	NS
Hispanic	3 (20.0)	3 (20.0)	2 (14.3)	8 (27.6)	
Asian	0	2 (13.3)	0	1 (3.4)	
AA	8 (53.3)	7 (46.7)	7 (50.0)	15 (51.7)	
Other	2 (13.3)	1 (6.7)	1 (7.2)	2 (6.9)	
LVI, n (%)					
None	13 (86.7)	10 (66.7)	5 (35.7)	1 (6.9)	NS/0.1
Present	0	3 (20.0)	6 (42.9)	23 (79.3)	
Missing	2 (13.3)	2 (13.3)	3 (21.4)	5 (17.2)	
Largest uterine tumor size (SD), cm	2.6 (1.4)	2.7 (0.91)	4.9 (2.3)	4.7 (2.6)	NS
Baseline CA-125 (SD), U/mL	8.7 (8.4)	11.7 (9.7)	664.2 (1655)	626.5 (848)	NS
Treatment, n (%)					
None	6 (40.0)	8 (53.3)	3 (21.4)	0	NS/0.2
Chemotherapy	0	1 (6.7)	6 (42.9)	24 (82.7)	
RT	0	2 (13.3)	0	1 (3.4)	
Chemo/RT	9 (60.0)	4 (26.7)	5 (35.7)	4 (13.8)	

Abbreviations: NS, not significant; AA, African American; BMI, body mass index; EIC, endometrial intraepithelial carcinoma; LVI, lymphovascular invasion; RT, radiation therapy; SD, standard deviation; UPSC, uterine papillary serous carcinoma.

^{a/b} (P value for stage 1 comparison)/(P value for stage 4 comparison). First value denotes P value comparing stage 1 EIC to stage 1A USC, and second value denotes P value comparing stage 4 diseases.

Table 2. Expression Profiles of ER, PR, and p53 in Stage-Matched EIC and USC.

	Stage 1 EIC (n = 15)	Stage 1A UPSC (n = 15)	Stage 4 EIC (n = 14)	Stage 4B UPSC (n = 29)	P Value ^{a/b}
ER n (%)					
Positive	6 (46)	7 (70)	4 (36)	13 (50)	.0009/
Negative	7 (54)	3 (30)	7 (64)	13 (50)	.063
Unknown	2	5	3	3	
PR n (%)					
Positive	7 (54)	5 (50)	4 (36)	9 (35)	
Negative	6 (46)	5 (50)	7 (64)	17 (65)	NS/NS
Unknown	2	5	3	3	
p53 n (%)					
Positive	14 (100)	13 (93)	12 (100)	25 (96)	NS/NS
Negative	0	1 (7)	0	1 (4)	
Unknown	1	0	2	3	

Abbreviations: NS, not significant; EIC, endometrial intraepithelial carcinoma; LVI, lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor; UPSC, uterine papillary serous carcinoma.

^{a/b} (P value for stage 1 comparison)/(P value for stage 4 comparison). First value denotes P value comparing stage 1 EIC to stage 1A UPSC, and second value denotes P value comparing stage 4 diseases.

patients with stage 1 EIC, 5 (33%) expressed ER compared to 7 (46.7%) of 15 patients with stage 1A USC. Similarly, 8 (57.1%) of the 14 patients with stage 4 EIC and 10 (34.5%) of 29 patients with stage 4 USC expressed ER in their tumor. Although the overall immunohistochemistry (IHC) expression of ER is similar among the groups, there is a statistically significant differential in moderate to strong ER expression (2 or 3 on IHC staining score) in stage 1 patients (0% in stage 1 EIC vs 33.3% in stage 1A USC; $P = .042$). There are no differences comparing PR expression in the USC and EIC stage-matched groups. In addition, the vast majority of tumor samples expressed p53 protein

in similar frequency throughout the comparison groups, even in stage 1 disease (93.3% in EIC vs 66.6% in stage 1A USC).

Overall, the stage stratified recurrence rates among the groups were not statistically significant. A similar proportion (6.7%) of patients showed recurrence in both stage 1 groups. Of the patients with stage 4 disease, 60% of EIC recurred within the follow-up period ($n = 9$), compared to 79% of USC ($n = 23$). Table 3 summarizes the survival data. Due to the small number of recurrences and the lack of significant mortality events, 2- and 5-year survival rates were calculated for the stage 1 patients only. As reflected in the Kaplan-Meier curves

Table 3. Survival of Stage-Matched Patients with EIC and UPSC.^a

	Median PFS, months (Range)	Median OS, months (Range)	P Value, PFS/OS
Stage 1 EIC	— (15-137)	— (15-137)	.5/.64
Stage 1A USC	— (31-135)	128 (26-135)	
Stage 4 EIC	14 (1-48)	19 (8-48)	.5/.4
Stage 4B USC	10 (1-38)	20 (3-53)	

Abbreviations: EIC, endometrial intraepithelial carcinoma; OS, overall survival; PFS, progression-free survival; UPSC, uterine papillary serous carcinoma.

^a The variance calculation for each Kaplan-Meier Survival curve was done using "Greenwoods Formula," and if the confidence interval could not attain a median survival it was reported as a blank.

(Figure 1A-D), the survival is excellent for stage 1 patients. Stage 1 USC had consistently superior survival rates at both 2 and 5 years. Interestingly, for stage 4 patients, it appears that the USC cohort have a shorter PFS, although not statistically significant. After approximately 12 months, the survival curve for patients with USC exceeds EIC.

Discussion

Our data is the first to evaluate the survival of patients with pure EIC and USC. In this small retrospective analysis, patients with stage 1 pure EIC have poorer 2- and 5-year survival rates than those with stage 1 USC, despite similar treatment. Once the disease presents with extrapelvic metastasis or carcinomatosis, the survival for these patients with advanced stage appears to be similar. To the best of our knowledge, this is the largest series of patients with EIC, and the only one that compares the clinical and pathologic parameters in EIC and USC as distinct disease entities. These patients were stage-matched due to a previous report suggesting that stage, not LVI or myometrial invasion, is the only factor impacting survival in patients with USC.^{22,23} Our findings suggest that EIC does not behave like a precursor of USC, even in stage 1 disease. In fact, EIC may be a pathologic variant, with similar clinical aggressiveness, as their stage-matched serous carcinoma counterpart.

Following the original description of USC by Hendrickson and Kempson in 1980,²⁴ Sherman first coined the term intraepithelial carcinoma to describe multifocal malignant serous cells on the epithelial surface next to invasive tumor.¹⁴ Since then, the idea of EIC being a precursor or in situ lesion of fulminant USC evolved from subsequent reports.^{13,16,25} Once the morphology of EIC was described and established, confluent glands made of abnormal cells without myometrial, stromal, or LVI, pathologic synonyms of EIC appeared in literature: *uterine surface carcinoma*, *minimal serous uterine carcinoma* (EIC and superficial USC measuring less than 1 cm), and *intraepithelial serous carcinoma*.^{14,16,26-28} Despite the nomenclature differences, noninvasive isolated clusters of serous cells in the uterine corpus share one biologic phenomenon: they have been reported, not infrequently, to be associated with peritoneal carcinomatosis and/or distant metastasis. Due to these reports, the concept of EIC being a precursor lesion of USC has

recently been challenged. It has been replaced as a morphologic variant of USC, with a noninvasive growth pattern in the uterus but similar metastatic potential. If this is true, the biologic behavior between the 2 pathologies should be similar. While this hypothesis may be true, there has been no published literature comparing outcomes of patients with pure EIC and USC when their disease is either limited to the uterine corpus or associated with extrapelvic spread.

Numerous investigators have previously studied stage 1 USC. Most reports show that adjuvant treatment, involving chemotherapy and/or radiation therapy, decreases the likelihood of recurrence for patients with stage 1 disease. Whether this benefit carries over to disease limited to the endometrium (ie, stage 1A) is more controversial, with some studies suggesting no benefit²⁹⁻³¹ and therefore recommending clinical observation or individualizing the adjuvant therapy based on the presence or absence of residual tumor in the uterus.²⁶ Similar to prior studies, we also report a low recurrence rate for EIC and USC (6.7%).^{11,30,32} Our data suggests that stage 1 EIC is associated with lower 2- and 5-year survival rates. The reason for this is unclear, but it should be noted that in this small cohort of patients, 2 patients in the stage 1 EIC group were lost to follow up. It is interesting to keep in mind that although both groups had similar rates of receiving adjuvant treatment, more patients in the stage 1 EIC group received combination platinum and taxane-based chemotherapy and radiation (60%) compared to stage 1A USC (26%). While the goal of this study is not to establish the optimal treatment regimen for stage 1 serous disease, our study corroborates the idea that EIC limited to the uterus does not behave like a serous precursor lesion and that its treatment should be consistent with that for stage 1A USC.

Looking at traditional molecular and pathologic markers for prognosis in our cohort, it is interesting to note that while serous carcinoma is not traditionally considered to be a hormone receptor-expressing tumor, more patients in the stage 1A USC group expressed some degree of ER (46.7%) compared to stage 1 EIC (33.3%). Furthermore, a significantly higher percentage of patients with stage 1A USC expressed moderate to strong staining for ER when compared to patients with stage 1 EIC. In stage 4 disease, more patients with USC had LVI, which may be related to tumor volume, as stage 4 USC typically presents with abdominal carcinomatosis. Our patient population was also predominantly African American, which has been shown in previous studies to be associated with poorer survival in endometrial cancer.³³ In our multivariate analysis, LVI, hormone receptor expression, and African American race were not significantly associated with survival. The correlation between prognosis and the reported and known clinic-pathologic features in endometrioid adenocarcinoma may not be true in uterine serous tumors. This is somewhat surprising, since ER expression is known to be associated with better outcome.³⁴ However, the biology of membrane-bound ER, and its activity in a cancer type (such as USC) that may be dependent on growth survival pathways other than that mediated by estrogen, remains unclear.

There are several limitations in our study. It is retrospective and is therefore inherent to biases in analysis. The individual

Figure 1. Progression-free survival comparison between stage 1 (A) and stage 4 (B) uterine papillary serous carcinoma (UPSC) and endometrial intraepithelial carcinoma (EIC). Overall survival comparison between stage 1 (C) and stage 4 (D) UPSC and EIC.

patient cohort is small in each group, making generalizing patterns or conclusions difficult. Specific treatment modalities for patients within each group also differed despite being similar. However, we believe that this study also has several strengths. All these patients had comprehensive surgical staging in a center practicing the same standard of care. In addition, all slides were reviewed by dedicated gynecologic pathologist. Both EIC and stage 1A USC are rare pathologies associated with good overall survival, which makes them extremely difficult to study even in multi-institutional prospective trials. Combining an increasing understanding of the molecular pathogenesis of USC and its clinical behaviors may help to optimize the surgical and clinical care of these women with this disease.

Declaration of Conflicting Interests

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