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Comparison of Outcomes in Early-Stage Uterine Clear Cell Carcinoma and Serous Carcinoma

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Abstract

PURPOSE: The treatment paradigm for uterine clear cell carcinoma is often linked to serous carcinoma. This study compares oncologic outcomes between women with uterine clear cell and serous carcinoma.

MATERIALS AND METHODS: We reviewed 114 women with stage I-II uterine clear cell carcinoma (n=17, 15%) or serous carcinoma (n=97, 85%) who underwent hysterectomy and salpingo-oophorectomy at our institution from 04/1992–12/2011; 86 (76%) had stage IA, 14 (12%) had stage IB, and 14 (12%) had stage II disease. Median follow-up was 57 months.

RESULTS: Patients with uterine clear cell and serous carcinoma did not differ significantly by age, 60, stage, or rate of lymphovascular invasion. There was no difference in the number of patients with clear cell or serous histology who received adjuvant radiotherapy (71% vs. 84%, respectively; $p=0.31$); however, significantly fewer clear cell patients received adjuvant

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chemotherapy (35% vs. 67%, respectively; $p=0.02$). At 5 years, there were no significant differences in disease-free survival (94% vs. 84%, respectively; $p=0.27$), disease-specific survival (100% vs. 92%, respectively; $p=0.20$), or overall survival (100% vs. 89%, respectively; $p=0.34$). The differences in chemotherapy utilization did not impact pattern of relapse, specifically peritoneal spread (7% vs 6%, respectively; $p = 0.92$) or other distant sites (0% vs 9%, respectively; $p= 0.17$).

CONCLUSIONS: Oncologic outcomes and recurrence patterns of women with stage I-II uterine clear cell carcinoma compared favorably to those of women with serous carcinoma, despite significantly less adjuvant chemotherapy use. Potential reduction in adjuvant therapy in women with clear cell carcinoma should be studied prospectively.

Keywords

uterine clear cell carcinoma; uterine serous cell carcinoma; early-stage endometrial cancer; radiation therapy; chemotherapy

INTRODUCTION

Uterine clear cell carcinoma is a rare histology. In the Gynecologic Oncology Group (GOG)/NRG 210 protocol, clear cell carcinomas accounted for only 3.5% (129/3,715) of all endometrial cancers [1]. The rate is even lower when considering early-stage disease. Of the 2,600 patients with early-stage uterine cancer enrolled in the GOG LAP2 trial, only 42 (1.6%) had clear cell carcinoma [2]. This histology has been associated with more aggressive tumor biology and poor outcomes [3–7], and is felt to be also associated with higher likelihood of occult metastases even with disease apparently clinically confined to the uterus [8]. As a result, patients with early-stage disease often receive aggressive adjuvant therapy, including systemic treatments. However, optimal adjuvant management for uterine clear cell carcinoma remains undefined given its rarity. In 2014, the Gynecologic Cancer InterGroup (GCIG) published a consensus review for uterine clear cell carcinoma that noted the limited evidence base supporting the use of adjuvant treatments in women with International Federation of Gynecology and Obstetrics (FIGO) stage I-II clear cell carcinoma [9]. One of the confounding factors regarding the optimal adjuvant therapy is that the treatment paradigm for stage I-II clear cell is often linked to that of serous carcinoma [4, 10, 11]. Although selected studies focused on patients with only clear cell histology [3, 6, 12, 13], most provided limited information on the adjuvant therapy administered, and the majority of these studies predated contemporary practice patterns. While the available data suggest that adjuvant radiotherapy may improve local control in this patient population [14], the benefit of chemotherapy is less evident.

The purpose of this study was to compare the types of adjuvant therapies given to patients with stage I-II clear cell carcinoma of the uterus to those given to patients with serous carcinoma to determine the potential impact of these therapies on outcomes.

MATERIAL AND METHODS

After obtaining Institutional Review Board approval, we retrospectively analyzed 114 consecutive patients with FIGO 2009 stage I-II uterine clear cell or serous carcinoma who underwent hysterectomy and salpingo-oophorectomy at our institution between April 1992 and December 2011. Patients with positive pelvic washings (n=19) were excluded from the study.

Pathologic specimens were evaluated by gynecologic pathologists at the time of presentation. Patients were considered to have uterine clear cell histology if pathology demonstrated clear cell carcinoma only (n=17), or serous carcinoma if pathology demonstrated serous carcinoma only (n=97). Patients with mixed clear cell carcinoma and endometrioid adenocarcinoma (n=18), serous carcinoma and endometrioid adenocarcinoma (n=31), and mixed serous carcinoma and clear cell carcinoma (n=6) were excluded. Standard clinical follow-up consisted of vaginal examination every 3 months and a Pap smear and computed tomography of the chest/abdomen/pelvis every 6 months for the first 2 years, followed by graded decreases in frequency.

Comparisons of patient and treatment characteristics were performed using the chi-square test. Follow-up was measured from the date of surgery to the last known visit or death. Kaplan-Meier estimates were used to assess actuarial rates of disease-free survival (DFS), disease-specific survival (DSS), overall survival (OS), and site-specific recurrence rates. DFS was defined as survival without any locoregional and distant recurrences. Site-specific recurrences were calculated regardless of prior relapse(s) in other sites. Multivariate Cox regression analysis including age (<60 vs. ≥60 years), stage (IA vs. IB-II), histology (clear cell vs. serous), lymphovascular invasion (yes vs. no), adjuvant radiation therapy (yes vs. no), and adjuvant chemotherapy (yes vs. no) was performed to evaluate significant clinical prognostic factors.

RESULTS

Patient and Surgical Characteristics

From April 1992 to December 2011, 114 women with stage I-II uterine clear cell (n=17, 15%) or serous carcinoma (n=97, 85%) underwent hysterectomy and salpingo-oophorectomy at our institution. Patient characteristics are detailed in Table 1. Overall median age was 66 years (range, 44-88 years). Overall median body mass index (BMI) was 30 kg/m² (range, 18-55 kg/m²); 49 patients (43%) had a BMI >30 kg/m². Cohort characteristics were not significantly different between women with clear cell and serous carcinoma with regards to age (median age, 65 vs. 66 years, respectively; $p=0.21$), postmenopausal status (88% vs. 97%, respectively; $p=0.16$), history of diabetes (0% vs. 13%, respectively; $p=0.21$), obesity (BMI >30 kg/m², respectively; 24% vs. 46%, $p=0.11$), rates of hormone replacement therapy use (18% vs. 9%, respectively; $p=0.38$), rates of oral contraceptives use (6% vs. 30%, respectively; $p=0.07$), or rates of anti-estrogen therapy use (6% vs. 11%, respectively; $p=0.69$).

All patients underwent surgery at our institution, and rates of open vs. minimally invasive surgery were similar between cohorts (clear cell: 71% vs. 29%, serous: 51% vs. 49%; $p=0.18$). Lymphovascular invasion (LVI) was present in 27 patients (24%) overall, with no difference between the two histologic cohorts (clear cell 24% vs. serous 24%; $p=1.0$). Peritoneal cytology was obtained in 15 patients (88%) with clear cell carcinoma and 93 patients (96%) with serous carcinoma ($p=0.22$). All patients demonstrated negative cytology. Omentum sampling was performed in 15 patients (88%) with clear cell carcinoma and 80 patients (82%) with serous carcinoma ($p=0.73$). There was no difference in pelvic and para-aortic nodal sampling or stage distribution between the two groups (Table 1).

Adjuvant Therapy

Of the 114 total patients, 97 (85%) went on to receive adjuvant therapy. Of the 17 patients (15%) who did not receive adjuvant therapy, 5 were patients with clear cell and 12 with serous carcinoma ($p=0.13$). The reasons for omitting adjuvant therapy were patient refusal ($n=9$) and physician preference ($n=8$).

Adjuvant radiation therapy was given to 12 patients (71%) with clear cell and 81 patients (84%) with serous carcinoma ($p=0.31$). Platinum and taxane-based adjuvant chemotherapy was given to 71 (62%) of all patients; 69 patients received carboplatin/paclitaxel, 1 received carboplatin/docetaxel due to pre-existing neuropathy, and 1 received carboplatin alone due to advanced age and comorbidities. The median cycles of chemotherapy received was 6 (range, 3-6 cycles), with 60 (85%) of 71 patients receiving 6 cycles. In contrast to adjuvant radiotherapy, significantly fewer patients with clear cell carcinoma (35%) received adjuvant chemotherapy compared to those with serous carcinoma (67%; $p=0.02$). There was no significant difference in the number of patients with clear cell carcinoma compared with serous carcinoma who received less than 6 cycles of chemotherapy (17% vs. 15%, respectively; $p=0.9$) or required chemotherapy dose reduction (17% vs. 23%, respectively; $p=0.9$).

Treatment Outcomes

The median follow-up time was 57 months (range, 6-231 months). At last follow-up, 17 patients had recurred and 15 had died (9 deaths were due to endometrial cancer). The 5-year actuarial DFS, DSS, and OS rates of the entire study population were 86% (95% confidence interval [CI]: 79%-93%), 93% (95% CI: 88%-98%), and 91% (95% CI: 85%-97%), respectively. There were no significant differences in DFS, DSS, and OS rates between patients with clear cell compared with serous carcinoma: DFS 94% (95% CI: 83%-100%) vs. 84% (95% CI: 76%-92%; $p=0.27$; Figure 1A), DSS 100% vs. 92% (95% CI: 86%-98%; $p=0.20$; Figure 1B), and OS 100% vs. 89% (95% CI: 82%-96%; $p=0.34$; Figure 1C). Other potential prognostic factors of outcome are shown in Table 2. Disease stage was found to be significantly associated with 5-year DFS and OS. The 5-year DFS rates for those with stage IA vs. stage IB-II disease were 91% and 68%, respectively ($p=0.002$). While the presence of LVI demonstrated a trend toward worse 5-year DFS (72% in patients with LVI vs. 90% in those without LVI; $p=0.06$), on multivariate Cox regression analysis, only stage (IA vs. IB-II) retained its significance (HR=0.27, $p=0.02$). For OS, stage was the only significant

predictor on multivariate analysis ($HR=0.31$, $p=0.04$). Tumor histology was not predictive of survival outcomes.

Of the 17 patients with disease recurrence, 2 had a vaginal recurrence, 10 had a pelvic recurrence, 4 had a para-aortic lymph node recurrence, 7 had a peritoneal recurrence, and 10 had non-peritoneal distant metastases. Only one patient with clear cell carcinoma developed an isolated peritoneal recurrence, which was surgically resected; patient had no evidence of disease at last follow up. The 5-year actuarial site-specific relapse rates for the entire patient cohort were as follows: vaginal 2% (95% CI: 0%-5%), pelvic 9% (95% CI: 3%-15%), para-aortic lymph nodes 3% (95% CI: 0%-6%), peritoneal 6% (95% CI: 1%-11%), and non-peritoneal distant sites 8% (95% CI: 3%-12%). The 5-year locoregional and distant recurrence rates in all sites were not significantly different between the two cohorts, as shown in Table 3.

DISCUSSION

Given the rarity of uterine clear cell carcinoma, there have been no prospective studies evaluating treatment strategies solely in women with this disease. Our limited understanding of uterine clear cell carcinoma is further compounded by the frequent reporting of outcomes in the combined patients with clear cell and serous carcinoma [9]. In general, aggressive adjuvant therapy has been recommended but lacks strong evidence [9, 15]. In this study, we investigated treatments and outcomes differences between women with early-stage clear cell or serous carcinoma who underwent surgery at our institution.

In this study, survival outcomes for patients with stage I-II uterine clear cell carcinoma were better, albeit not statistically significant, than those of serous carcinoma. The 5-year DFS rates were 94% vs. 84% ($p=0.27$), the 5-year DSS rates were 100% vs. 92% ($p=0.20$), and the 5-year OS rates were 100% vs. 89% ($p=0.34$) for the 17 patients with clear cell carcinoma and 97 patients with serous carcinoma, respectively. Age, stage distribution, and presence of LVI were comparable between the two cohorts. There was no difference in the extent of surgery performed (i.e., extent of pelvic and para-aortic node sampling). Despite the comparable high-risk patient characteristics, we found significantly less use of adjuvant chemotherapy in the clear cell group compared to the serous group (35% vs. 67%; $p=0.02$), while the rate of adjuvant radiation therapy use was similar.

In addition to the equivalent survival outcomes of the patients in the two cohorts, we also demonstrated the similar patterns of relapse in patients with clear cell and serous carcinoma, indicating the less use of adjuvant chemotherapy among women with clear cell carcinoma did not adversely impact disease control. At 5 years, a similar proportion of patients with clear cell and serous carcinoma had peritoneal (7% vs. 6%; $p=0.92$) and non-peritoneal distant metastasis (0% vs. 9%; $p=0.17$). The rates of vaginal, pelvic, and para-aortic lymph metastasis were also comparable in the two cohorts. Stage (IA vs IB-II) was the only predictor for DFS ($HR=0.27$; $p=0.02$) and OS ($HR=0.31$; $p=0.04$) for the whole cohort.

Accounting for the lower rates of adjuvant chemotherapy received, patients with early-stage uterine clear cell carcinoma did not experience worse oncologic outcomes compared to

serous patients, arguing for the potentially less aggressive nature of clear cell disease. In 2008, Thomas et al. reported on a multi-institutional retrospective analysis of 22 patients with stage I-II uterine clear cell carcinoma, of whom only 8 received adjuvant radiotherapy and 4 received adjuvant chemotherapy. At 44 months, no patient with early-stage disease experienced lymphatic or distant failure. The authors concluded that given the low rate of distant failure, adjuvant chemotherapy did not appear to be necessary for patients with early-stage clear cell disease. [14] Creasman et al. reported similar findings and conclusions [7]. It is still unclear whether clear cell carcinomas generally respond to chemotherapy as well as serous carcinomas. In 2007, McMeekin et al. [16] investigated the relationship between histology and outcomes in patients with advanced and recurrent endometrial cancer enrolled in GOG chemotherapy trials. Although the authors did not find histologic type to be a statistically significant predictor of response, patients with clear cell carcinoma had the lowest chemotherapy response rate (32%) compared to patients with endometrioid carcinoma (44%) and serous carcinoma (44%).

Molecular studies have demonstrated genetic distinctions between clear cell and serous carcinomas [15]. While greater than 90% of patients with serous carcinoma harbor *TP53* mutations, typically accompanied by loss of heterozygosity and nuclear protein over-expression [17], only 30-40% of patients with clear cell carcinoma harbor p53 mutations [18]. Furthermore, the frequency of microsatellite instability (MSI; 15%) and PTEN (30%) mutations in clear cell carcinoma are higher than in serous carcinoma (5% and 10%, respectively) [19, 20]. Moreover, DeLair et. al. recently evaluated the genetic heterogeneity of clear cell carcinomas and showed that it can be classified into the previously demonstrated 4 molecular subtypes for endometrioid and serous carcinomas [21]. Patients with clear cell carcinomas showing abnormal p53 expression by immunohistochemistry (11/32) had the worst DFS compared to those with POLE mutations (2/32), mismatch repair (MMR) deficiency (4/32), or wild-type p53 (15/32). Hierarchical clustering also demonstrated similar findings. Together, this suggests that clear cell carcinoma as a histologically defined entity is genetically variable, and this may account for the similar outcomes between clear cell and serous carcinomas despite differences in adjuvant treatment; although, this will need to be further evaluated in larger patient cohorts.

Prior reports from our institution addressed the outcome of early-stage serous endometrial cancer treated with intravaginal brachytherapy and carboplatin/paclitaxel [22], as well as patterns of relapse based on type of adjuvant therapy given [23]. The intent of this study was not to test the merit of adjuvant therapy within each histology, but rather to determine if the less use of adjuvant chemotherapy in clear cell carcinoma affected the outcome. A limitation of our study is the retrospective nature of the analysis. Only patients with pure serous and pure clear cell carcinoma were included to limit the potential confounding effect of mixed histologies on outcome. While we accounted for the well-recognized risk factors in women with endometrial malignancies in this investigation, it is possible we did not account for all confounding factors that could contribute to our outcome analyses. Furthermore, given the smaller number of patients with clear cell compared to serous disease, it is possible that some analyses were underpowered to detect a true statistical difference.

In conclusion, our experience demonstrated that while no significant difference in survival outcomes and relapse patterns were observed between women with early-stage uterine clear cell and serous carcinoma, almost twice as many patients with serous disease received adjuvant chemotherapy. This study suggests that uterine clear cell carcinoma is a distinct histology, with potentially less aggressive behavior than that of serous carcinoma. Prospective, multi-institutional studies are needed to delineate the best treatment paradigm and to assess potential reduction in chemotherapy for women with early-stage uterine clear cell carcinoma.

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Figure 1.

There were no significant differences in disease-free survival (A), disease-specific survival (B), or overall survival (C) between patients with uterine clear cell carcinoma and serous carcinoma.

Table 1.

Patient characteristics by histology

	Total (n=114)		Clear cell carcinoma (n=17)		Serous carcinoma (n=97)		
Characteristics	N	%	N	%	N	%	<i>p</i>
Age							
< 60	31	27%	7	41%	24	25%	0.24
60	83	73%	10	59%	73	75%	
LVI							
Yes	27	24%	4	24%	23	24%	1.0
No	87	76%	13	76%	74	76%	
Stage (FIGO 2009)							
IA	86	76%	14	82%	72	74%	0.67
IB	14	12%	2	12%	12	12%	
II	14	12%	1	6%	13	13%	0.46
PLN Sampling	98	86%	16	94%	82	85%	
Median Nodes	13	-	17	-	13	-	0.59
PALN Sampling	71	62%	12	71%	59	60%	
Median Nodes	3	-	4	-	2	-	0.02
Adjuvant Therapy							
Radiotherapy	93	82%	12	71%	81	84%	0.31
Chemotherapy	71	62%	6	35%	65	67%	

Abbreviations: LVI= lymphovascular invasion; FIGO=International Federation of Gynecology and Obstetrics; PLN= pelvic lymph node; PALN= para-aortic lymph node.

Table 2.

5-year DFS, DSS, and OS by clinical characteristics

Characteristics	DFS (95% CI)	<i>p</i>	DSS (95% CI)	<i>p</i>	OS (95% CI)	<i>p</i>
Age (years)						
< 60	89% (77%-100%)	0.24	97% (91%-100%)	0.20	97% (91%-100%)	0.12
60	84% (76%-92%)		92% (85%-99%)		88% (80%-96%)	
LVI						
No	90% (83%-97%)	0.06	93% (87%-99%)	0.50	91% (84%-98%)	0.37
Yes	72% (54%-90%)		92% (82%-100%)		89% (77%-100%)	
Histology						
Clear Cell	94% (83%-100%)	0.27	100% *	0.20	100%	0.34
Serous	84% (76%-92%)		92% (86%-98%)		89% (82%-96%)	
Stage						
IA	91% (85%-97%)	0.002	93% (87%-99%)	0.11	93% (87%-99%)	0.01
IB-II	68% (49%-87%)		92% (82%-100%)		82% (65%-99%)	
Radiation Therapy						
No	89% (79%-99%)	0.64	89% (72%-100%)	0.55	89% (74%-100%)	0.82
Yes	85% (77%-93%)		94% (89%-99%)		91% (84%-98%)	
Chemotherapy						
No	90% (81%-99%)	0.20	95% (88%-100%)	0.26	89% (78%-100%)	0.87
Yes	83% (74%-92%)		92% (85%-99%)		92% (85%-99%)	

Abbreviations: CI= confidence interval; DFS= disease-free survival; DSS= disease-specific survival; OS= overall survival; LVI=lymphovascular invasion.

*. One patient with clear cell carcinoma developed an isolated peritoneal relapse, which was resected; the patient had no evidence of disease at last follow-up.

Table 3.

Comparison of 5-year recurrence rates between women with uterine clear cell vs. serous carcinoma

Relapse Sites	Total (n=114)		Clear cell carcinoma (n=17)		Serous carcinoma (n=97)		<i>p</i>
	N	5-year actuarial % (95% CI)	N	5-year actuarial % (95% CI)	N	5-year actuarial % (95% CI)	
Vaginal	2	2% (0%-5%)	0	0%	2	2% (0%-5%)	0.55
Pelvic	10	9% (3%-15%)	1	6% (0%-17%)	9	10% (4%-16%)	0.64
Para-aortic lymph nodes	4	3% (0%-6%)	0	0%	4	7% (3%-11%)	0.40
Peritoneal	7	6% (1%-11%)	1 [*]	7% (0%-20%)	6	6% (1%-11%)	0.92
Non-peritoneal distant sites	10	8% (3%-12%)	0	0%	10	9% (3%-15%)	0.17
All distant sites	13	11% (5%-17%)	1	7% (0%-20%)	12	12% (5%-19%)	0.40

^{*}One patient with clear cell carcinoma developed an isolated peritoneal relapse, which was resected; the patient had no evidence of disease at last follow-up.