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Prevalence and clinicopathologic profiles of patients with high-grade serous and clear cell carcinoma of the endometrium

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Abstract:

OBJECTIVES: This study aims to determine the prevalence and clinicopathologic characteristics of patients with endometrial serous and clear cell carcinoma in a tertiary referral center in the Philippines. It will identify and review patients' clinical profiles, tumor characteristics, management approaches, and determine their associations with treatment outcomes.

MATERIALS AND METHODS: This 5-year retrospective cross-sectional study reviewed all women diagnosed with serous and clear cell endometrial carcinoma in a tertiary cancer referral center in the Philippines from January 2018 to December 2022. Statistical analysis with univariate and multivariate analysis was done to determine association of clinical and tumor characteristics with treatment outcomes. Odds ratios and *t*-test were used to determine significant relationships among variables.

RESULTS: One thousand new endometrial cancer cases were identified during the study. Prevalence for serous carcinoma was 6.8% and 3.5% for clear cell carcinoma. Both were commonly encountered in the postmenopausal age, with a mean age of presentation of 62 years. Surgery was performed through open surgery for all cases, and included lymphadenectomy and omentectomy. Adjuvant systemic chemotherapy alone was given for 48.5% of serous cases, and in combination with radiotherapy in 42.86% of clear cell cases. Lymphovascular space invasion was significantly associated with treatment outcome for serous carcinoma while depth of invasion was significant for clear cell carcinoma. Among the cases, 41.8 % of serous and 28.57% of clear cell had extrapelvic metastasis, with omentum and lymph nodes as the the more common sites. Adjuvant chemotherapy and multimodal approach of radiation with external pelvic radiotherapy and vaginal brachytherapy impacted treatment outcome.

CONCLUSIONS: High-grade endometrial histologies are less common and tend to have more aggressive and less predictable behavior. Surgery is the mainstay of treatment followed by combination adjuvant therapy. Our study shows that the omentum is a common site of extrapelvic metastasis. This supports the need for omentectomy for both serous and clear cell cases, even in early stages. Prognosis tends to be less favorable and recurrences and distant metastasis may occur even for earlier stages. Thus, it is important to identify any clinical factors that may aid in better counseling and giving tailored management for these patients.

Keywords:

Clear cell endometrial carcinoma, high-grade endometrial cancer, serous endometrial carcinoma

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Introduction and Significance of the Study

Endometrial cancer is a common gynecologic malignancy affecting

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thousands of women worldwide. According to the 2022 World Health Organization Global Cancer observatory statistics, it ranks 15th among newly diagnosed cases for all types of cancer.

The Bokhman classification for endometrial cancer postulates that there are two different histopathogenic types. Type 1 includes the estrogen-dependent tumors with endometrioid pathologies. Type 2 includes the nonestrogen dependent tumors, which are generally more aggressive and carry poorer prognosis.[1] Uterine serous and clear cell carcinoma belong to the latter and are classified as high grade histologic types and a tendency for earlier metastasis, often to the upper abdomen.[2] Serous tumors tend to develop lymph node, adnexal and peritoneal metastasis, while clear cell tumors are often associated with lymph node metastasis.[3]

In the Philippines, the prevalence of high grade endometrial cancers of the serous and clear cell histologic type is not known. No recent studies have been done to determine the clinicopathologic profiles of these types of tumors. This study aims to describe the prevalence and clinicopathologic characteristics of patients with endometrial serous and clear cell carcinoma in a tertiary referral center in the Philippines. It will review the patients' clinical profiles and tumor characteristics, and their relations with the different approaches in management and treatment outcomes. With further knowledge and better understanding on the characteristics and behavior of these types of tumors, we can be guided with our different treatment strategies especially in the local setting and give adequate counseling on treatment options and disease prognosis. Tailored recommendations for the Filipino population can also be updated and applied from the study's results.

Objectives

General objective

To determine the prevalence and clinicopathologic characteristics of patients with endometrial serous and clear cell carcinoma in a tertiary referral center in the Philippines.

Specific objectives

1. To determine the prevalence of endometrial serous and clear cell carcinoma in a tertiary referral center in the Philippines
2. To describe the clinical profiles of patients histologically diagnosed with endometrial serous and clear cell carcinoma
3. To identify tumor characteristics and patterns associated with type of treatment received and clinical outcomes
4. To determine the different approaches and details of treatment
5. To determine outcomes from the different treatments received.

Materials and Methods

Study design

This study employed a cross-sectional design using retrospective chart reviews. The study group consisted of women with a histological diagnosis of endometrial serous or clear cell carcinoma, diagnosed from January 2018 to December 2022 at a tertiary cancer referral center in the Philippines.

Inclusion criteria were as follows: (1) patients with histological diagnosis of serous carcinoma or clear cell endometrial carcinoma, diagnosed from January 2018 to December 2022, (2) patients with only one primary gynecologic malignancy, and (3) patients of any clinical stage (FIGO Clinical Stage I – IV). Patients with biopsy results showing endometrioid carcinomas exhibiting clear cell features were excluded from this study.

Sample size

Since this is a cross-sectional study, all cases who satisfied the eligibility criteria within the specified time period were included.

Description of the study procedure

Approval of the Institutional Review Board was sought prior to data collection. On approval, the weekly census reports from January 2018 to December 2022 of the institution's division of gynecologic oncology were reviewed by the principal investigator. These were used to identify patients with biopsy-proven endometrial serous and clear cell carcinomas.

Only the principal investigator was given access to these compilations and patients' charts. Patients handled by the Division are made aware that their cases are presented to and discussed weekly with all Division consultants, in the interest of providing the best possible individualized cancer care.

Clinical and surgicopathologic features from the patient records were reviewed. Patients with more than one primary gynecologic malignancy were excluded from the study. Collated data were encoded into a file, where patients were assigned study numbers and anonymized.

Data analysis

Statistical tests and data analysis were obtained using the R Statistical Software (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.). Descriptive statistics on the attributes of the study patients were generated for sociodemographic and clinicopathologic characteristics of patients, tumor characteristics, and different management approaches.

The prevalence rates of endometrial serous and clear cell carcinoma were determined by getting the ratio of the number of patients with serous and clear cell carcinoma to the total number of endometrial cancer patients seen at the tertiary hospital from January 2018 to December 2022. A 95% confidence interval (CI) was derived.

The mean and standard deviation of the ages of the patients were determined. Data for clinical profiles of the patients, tumor characteristics and patterns, management approaches, treatment details and outcomes were shown as frequencies and percentage distributions. Univariate analysis was done through percentages and standard deviations.

Multivariate analysis was performed using logistic regression to identify the clinical profiles and tumor characteristics of the patients, and association with treatment outcomes. The Wald's test was used to test for significance of the resulting logistic regression coefficients and for deriving 95% CIs.

Odds ratios were derived to compare the relative odds of the occurrence of the treatment outcome given exposure to the variable of interest. 95% CI and *P* values were used to estimate the precision of the resulting Odds ratios.

The associations of the outcomes from the different management approaches and treatments received were analyzed using contingency tables. The *f*-test at a 5% level of significance was used to test for the significance of the relationships among the variables.

Results

Clinical characteristics

Of all new cases of gynecologic malignancies consulting during the 5-year study period, a total of 1000 new endometrial cancer cases were identified. Of these, 68 patients were diagnosed with serous histology, while 35 patients had clear cell histologies. This corresponds to a prevalence rate of 6.8% and 3.5%, respectively.

Table 1 summarizes the frequencies, percentages, means and standard deviations of the clinical characteristics of the study patients.

The mean age of the study population was 62 years for both serous and clear cell groups. The youngest age at diagnosis was 31 and 39 years old for the serous and clear cell groups respectively. Majority were postmenopausal.

Most cases were diagnosed with other comorbidities, the most common of which were hypertension (47%), obesity (26%), and diabetes mellitus (9%). Several patients also had a history of nongynecologic malignancies such as breast and colon cancer.

Table 1: Clinical characteristics of patients diagnosed with serous and clear cell endometrial carcinoma from January 2018 to December 2022

	Serous carcinoma (*n*=68), number of patients (%)	Clear cell carcinoma (*n*=35), number of patients (%)
Age, mean±SD	62.31±8.01	62.26±7.81
≤40 years old	1 (1.47)	1 (2.86)
Above 40 years old, premenopausal	2 (2.94)	0
Above 40 years old, postmenopausal	65 (95.59)	34 (97.14)
Presence of comorbidities		
Diabetes	9 (13.24)	5 (14.29)
Obesity	26 (38.24)	13 (37.14)
Hypertension	32 (47.06)	16 (45.71)
Other malignancies	4 (5.88)	1 (2.86)
Other illnesses	12 (17.65)	9 (25.71)
None	26 (38.24)	15 (42.86)
Parity, mean±SD	2.92±1.97	2.77±2.03
Parity=0	12 (17.65)	5 (14.29)
Parity=1	7 (10.29)	5 (14.29)
Parity >1	49 (72.06)	25 (71.43)
BMI (Asia-Pacific Classification), mean±SD	24.67±4.62	23.83±4.46
Underweight (<18)	3 (4.41)	3 (8.57)
Normal (18–22.9)	25 (36.76)	15 (42.86)
Overweight (23–24.9)	14 (20.59)	4 (11.43)
Obese class I (>25)	26 (38.24)	13 (37.14)
Clinical stage, mean±SD	2.68±1.21	2.51±1.17
I	19 (27.94)	11 (31.43)
II	5 (7.35)	3 (8.57)
III	22 (32.35)	13 (37.14)
IV	22 (32.35)	8 (22.86)

BMI: Body mass index, SD: Standard deviation

At the time of diagnosis, serous endometrial cancer cases often presented at the advanced stage of Stage III (32.35%) to Stage IV (32.35%), while clear cell carcinomas were mostly diagnosed at Stage III (37.14%).

Tumor characteristics

Study patients were analyzed for their tumor characteristics [Table 2]. Stage III disease was highest among serous carcinomas (25.67%) and Stage I (28.57%) for clear cell carcinoma.

Tumors were > 2 cm in most cases (73.53% in the serous group, 71.43% in the clear cell group) and had deep myometrial invasion (58.82% and 51.43% respectively).

Of the cases for which lymphovascular space invasion (LVSI) presence was specified, more cases presented with positive LVSI (36.76% in the serous group, 42.86% in the clear cell group).

Metastasis was common in both groups and were often located in extrapelvic sites. In the serous group, 41.18%

Table 2: Tumor characteristics of patients diagnosed with serous and clear cell endometrial carcinoma from January 2018 to December 2022

	Serous carcinoma (*n*=68), number of patients (%)	Clear cell carcinoma (*n*=35), number of patients (%)
Final stage		
I	15 (22.06)	10 (28.57)
II	4 (5.88)	2 (5.71)
III	18 (26.47)	9 (25.71)
IV	15 (22.06)	5 (14.29)
Not otherwise specified/ inadequately staged	0	4 (11.43)
N/A (no treatment received)	16 (23.53)	5 (14.29)
Depth of invasion		
Superficial (<50% myometrial invasion)	21 (30.88)	12 (34.29)
Deep (> 50% myometrial invasion)	40 (58.82)	18 (51.43)
Not specified	7 (10.29)	5 (14.29)
LN involvement		
Pelvic lymph nodes only	8 (11.76)	7 (20.00)
Paraaortic lymph nodes only	3 (4.41)	2 (5.71)
Both pelvic and paraaortic lymph nodes	11 (16.18)	3 (8.57)
Not specified	10 (14.71)	9 (25.71)
None	36 (52.94)	14 (40.00)
LVSI		
Present	25 (36.76)	15 (42.86)
Absent	18 (26.47)	11 (31.43)
Not specified	25 (36.76)	9 (25.71)
Extrauterine metastasis		
Pelvic	20 (29.41)	9 (25.71)
Extrapelvic	28 (41.18)	10 (28.57)
None	20 (29.41)	16 (45.71)

LVSI: Lymphovascular space invasion, LN: Lymph node

had extrapelvic metastasis. The most common sites included the omentum, paraaortic lymph nodes, and abdominal carcinomatosis. 29.4% had pelvic metastasis, particularly to the adnexa, pelvic lymph nodes, and parametria [Figure 1]. For the clear cell group, 28.57% of the cases had extrapelvic metastasis, mostly to the omentum and paraaortic lymph nodes. 25.71% had pelvic metastasis, often to the pelvic lymph nodes and parametria [Figure 2].

Management approaches

Data on management approaches are summarized in Table 3. All cases who underwent surgery were approached via open laparotomy. The main type of surgery performed was an extrafascial hysterectomy with bilateral salpingo-oophorectomy. The addition of pelvic and paraaortic lymphadenectomy was done in 10.29% (serous) and 11.43% (clear cell) of cases. Extended surgical staging (i.e., addition of infracolic omentectomy) was performed in 45.59% of serous cases and 25.71% of the clear cell cases. Advanced cases deemed suitable for surgery underwent tumor debulking (11.76% of serous and 20% clear cell cases). Some cases of advanced disease necessitated neoadjuvant treatment as initial management (13.24% serous, 14.29% clear cell group).

After surgery, 48.5% of serous cases received further adjuvant treatment, whether in the form of chemotherapy or radiotherapy (pelvic external beam radiotherapy [EBRT]/vaginal brachytherapy [VB]) alone, or a combination of both modalities. For the clear cell cases, only 42.86% received adjuvant treatment, most of whom received a combination of both modalities.

Status of treatment and treatment outcomes

Although most patients were advised adjuvant treatment, only 25% of the serous cases and 28.57% for the clear cell cases completed the recommended treatment [Table 4]. After completing treatment, majority are alive with no evidence of disease [Table 5].

Among all cases of serous carcinoma included in the study, 54.41% expired from progressive disease [Table 6]. Tumor recurrence was noted as early as 1 month after surgery and as late as 1 year and 6 months after surgery. Among all cases of clear cell carcinoma, 48.57% expired from disease progression [Table 6]. The earliest time to recurrence was 3 months while the longest time was at 2 years and 1 month after treatment.

The association between certain clinical characteristics, tumor characteristics, and management approaches with treatment outcomes is summarized in Table 7. Clinical stage, final stage, and adjuvant treatment were all associated with treatment outcome for both groups. In addition, LVSI and tumor depth of invasion were associated with treatment outcomes for the serous and clear cell groups, respectively.

Tables 8 and 9 show the result of the multivariate analysis to identify which of the clinical profiles, tumor characteristics and management approaches of the study patients affected their treatment outcomes. The characteristics listed in the table do not significantly affect treatment outcome based on the logistic regression done.

Similarly, the analysis of tumor characteristics and their effect on treatment outcomes [Tables 10 and 11] show that LVSI appears significant among the cases of serous carcinoma while depth of invasion is significant for clear cell carcinoma.

Analysis of management approaches and their effect on treatment outcomes is summarized in Tables 12 and 13. For the cases of serous carcinoma, those who underwent pelvic/paraaortic lymphadenectomy and omentectomy

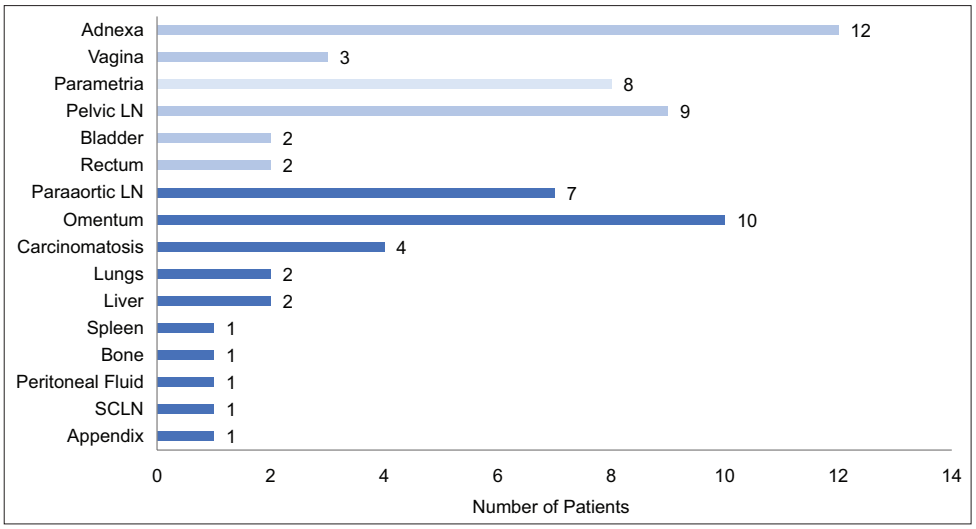

Figure 1: Sites of pelvic and extrapelvic metastasis in the cases of serous endometrial cancer. Sites of pelvic metastasis include adnexa, vagina, parametria, pelvic lymph nodes (LN), bladder, rectum; extrapelvic sites include paraaortic LN, omentum, carcinomatosis, lungs, liver, spleen, bone, peritoneal fluid, supraclavicular lymph nodes, appendix

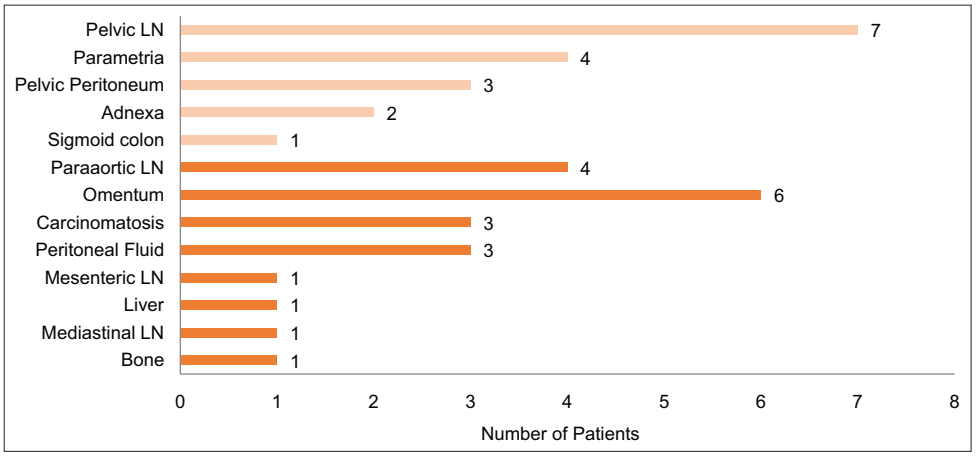

Figure 2: Sites of pelvic and extrapelvic metastasis in the cases of clear cell endometrial cancer. Sites of Pelvic Metastasis include pelvic lymph nodes (LN), Parametria, pelvic peritoneum, adnexa, sigmoid colon; Extrapelvic sites include paraaortic LN, omentum, carcinomatosis, peritoneal fluid, mesenteric LN, liver, mediastinal LN and bone

had a significant effect on treatment outcome. For adjuvant treatment, chemotherapy and multimodal approach of chemotherapy with pelvic EBRT and VB impacted treatment outcome for the serous group, while a multimodal approach of chemotherapy and VB, with or without pelvic EBRT, had a statistically significant effect on treatment outcome.

Discussion

Endometrial serous carcinomas comprise 5%–10% of all endometrial cancer cases, but account for up to 39% of disease-specific deaths.[4] Clear cell endometrial tumors comprise 1%–5.5% of all endometrial cancers, with a 5-year overall survival rate below 50%.[1] This study shows a similar prevalence for both histologies. Of the 1000 newly diagnosed endometrial cancer cases in the 5-year study period, we report a prevalence of 6.8% serous and 3.5% clear cell endometrial carcinomas.

Serous carcinomas are thought to arise from polyps or precursor lesions developing in atrophic endometrium.[4] They are more common among older women[3] and tend to have deeper myometrial invasion with a more extensive metastatic spread.[4] The overall survival rate is around 30%–40%, and highest among clinically Stage I diseases. Risk factors include personal history of breast cancer, tamoxifen use, hereditary cancer syndromes, older age, higher stage at the time of diagnosis, and presence of p53 mutation.[4]

This study shows that serous endometrial carcinomas were more common among older women of postmenopausal age. A few cases had a history of other nongynecologic malignancies such as breast cancer and colon cancer. At present, uterine serous carcinomas are not features of any known hereditary cancer syndrome, though other studies suggest that they may be overlooked components of a BRCA 1/2-associated hereditary breast and ovarian syndrome. For those patients with a positive first degree

Table 3: Management approaches for the patients diagnosed with serous and clear cell endometrial carcinoma from January 2018 to December 2022

	Serous carcinoma (*n*=68), number of patients (%)	Clear cell carcinoma (*n*=35), number of patients (%)
Surgical approach		
Exploratory laparotomy	52 (76.47)	28 (80.00)
Minimally invasive surgery	0	0
None	16 (23.53)	7 (20.00)
Type of surgery		
EHBSO	1 (1.47)	0
EHBSO with pelvic lymphadenectomy only	2 (2.94)	5 (14.29)
EHBSO with pelvic and paraaortic lymphadenectomy	7 (10.29)	4 (11.43)
EHBSO, LN dissection, omentetomy	31 (45.59)	9 (25.71)
EHBSO, tumor debulking	8 (11.76)	7 (20.00)
None	16 (23.53)	7 (20.00)
Others	3 (4.41)	3 (8.57)
Neoadjuvant treatment received		
Yes	9 (13.24)	5 (14.29)
No	59 (86.76)	30 (85.71)
Type of neoadjuvant treatment received		
Chemotherapy alone	9 (13.24)	3 (8.57)
Radiotherapy alone	0	1 (2.86)
Chemotherapy with radiotherapy	0	1 (2.86)
None	59 (86.76)	30 (85.71)
Adjuvant treatment		
Systemic chemotherapy only	15 (22.06)	3 (8.57)
Pelvic EBRT only	0	0
VB only	0	1 (2.86)
Chemotherapy + pelvic EBRT	3 (4.41)	2 (5.71)
Chemotherapy + pelvic EBRT + VB	13 (19.12)	6 (17.14)
Chemotherapy + VB	2 (2.94)	3 (8.57)
None	35 (51.47)	20 (57.14)

EBRT: External beam radiation therapy, VB: Vaginal brachytherapy, EHBSO: Extrafascial hysterectomy with bilateral salpingo-oophorectomy, LN: Lymph node

Table 4: Status of adjuvant treatment of the patients diagnosed with serous and clear cell endometrial carcinoma from January 2018 to December 2022

	Serous carcinoma (*n*=68), number of patients (%)	Clear cell carcinoma (*n*=35), number of patients (%)
Completed	17 (25.00)	10 (28.57)
Ongoing treatment	3 (4.41)	1 (2.86)
Interrupted	12 (17.65)	5 (14.29)
Not completed due to progression	7 (10.29)	3 (8.57)
Advised but not started	28 (41.18)	14 (40.00)
None advised	1 (1.47)	2 (5.71)

Table 5: Treatment outcomes after completing the recommended course of adjuvant treatment of the patients diagnosed with serous and clear cell endometrial carcinoma from January 2018 to December 2022

	Serous carcinoma (*n*=17), number of patients (%)	Clear cell carcinoma (*n*=10), number of patients (%)
Alive with no evidence of disease	11 (64.71)	9 (90.00)
Alive, with recurrence	5 (29.41)	0
Died of disease	1 (5.88)	1 (10.00)

Table 6: Treatment outcomes for the patients diagnosed with serous and clear cell endometrial carcinoma from January 2018 to December 2022

	Serous carcinoma (*n*=68), number of patients (%)	Clear cell carcinoma (*n*=35), number of patients (%)
Alive, with no evidence of disease	16 (23.53)	11 (31.43)
Alive, with disease recurrence/progression	8 (11.76)	0
Died of disease	37 (54.41)	17 (48.57)
Died of other causes	1 (1.47)	1 (2.86)
Lost to follow up	6 (8.82)	6 (17.14)

family history of breast and/or ovarian cancer, screening for germline BRCA 1/2 mutations may be considered.[5]

Among the different clinical and tumor characteristics analyzed, only preoperative clinical stage of the tumor and presence of LVSI were deemed associated risk factors with treatment outcomes. Thus, we advise that LVSI be routinely reported in pathologic reports.

Clear cell endometrial carcinomas appear similar to their ovarian counterparts. Prognosis-related factors

Table 7: Association of treatment outcomes for the patients diagnosed with serous and clear cell endometrial carcinoma from January 2018 to December 2022

Patient characteristics	Serous carcinoma (*n*=68)		Clear cell carcinoma (*n*=35)	
	P	Association	*P*	Association
Clinical stage versus treatment outcome	0.00216	Associated	0.00038	Associated
Tumor characteristics				
Final stage versus treatment outcome	0.00494	Associated	0.00458	Associated
Tumor size versus treatment outcome	0.06899	Independent	0.73026	Independent
Depth of invasion versus treatment outcome	0.13935	Independent	0.04438	Associated
Pelvic LN involvement versus treatment outcome	0.32358	Independent	0.51437	Independent
Paraaortic LN involvement versus treatment outcome	0.52491	Independent	0.85870	Independent
LVSI versus treatment outcome	0.01387	Associated	0.26054	Independent
Treatment outcomes				
Neoadjuvant treatment versus treatment outcome	0.94905	Independent	0.57960	Independent
Adjuvant treatment versus treatment outcome	0.00006	Associated	0.00236	Associated

LN: Lymph node, LVSI: Lymphovascular space invasion

Table 8: Multivariate analysis of clinical characteristics with treatment outcomes for the cases of serous endometrial carcinoma

Clinical profile	Categories (if categorical variable)	Coefficient	SD	*P*	OR	95% CI of OR
Age		−0.04739	0.03598	0.18777	0.95371	0.88877–1.02340
Gravidity		0.11712	0.13328	0.37952	1.12426	0.86580–1.45986
Parity		0.11220	0.13788	0.41579	1.11874	0.85381–1.46587
Educational attainment	No formal education					
	Elementary undergraduate	−21.60836	40192.99109	0.99957	0.00000	0.00000–0.00000
	Elementary graduate	−21.53937	40,192.99108	0.99957	0.00000	0.00000–0.00000
	High school graduate	−22.14116	40,192.99108	0.99956	0.00000	0.00000–0.00000
	Vocational course	−21.89604	40,192.99110	0.99957	0.00000	0.00000–0.00000
	College graduate	−20.10428	40,192.99108	0.99960	0.00000	0.00000–0.00000
Family history of malignancy	Without history					
	With history	1.32914	0.76483	0.08224	3.77778	0.84374–16.91462
Menopausal status	No					
	Yes	−21.76929	23205.42312	0.99925	0.00000	0.00000–0.00000
Comorbidities	Without comorbidities					
	With comorbidities	−0.10228	0.54440	0.85097	0.90278	0.31059–2.62405
BMI		0.04776	0.06525	0.46416	1.04892	0.92300–1.19202
Clinical stage	I					
	II	0.62861	1.28776	0.62545	1.87500	0.15026–23.39629
	III	−1.02962	0.72210	0.15391	0.35714	0.08673–1.47060
	IV	−1.69378	0.76408	0.02664	0.18382	0.04112–0.82185

OR: Odd ratio, CI: Confidence interval, BMI: Body mass index, SD: Standard deviation, BMI: Body mass index

are still controversial due to the scarcity of data relating to these tumors. Some studies suggest that age, tumor size, myometrial invasion, stage, and distant metastasis carry poorer prognosis.[1] In our study, almost all cases of clear cell carcinoma were above 40 years old and menopausal. Although age seems to be a risk factor for both histologic types, statistical analysis shows that differences in age was not a statistically significant factor impacting treatment outcome.

Stage and depth of invasion were risk factors associated with the outcomes of these cases. Tumor size, pelvic and paraaortic lymph node involvement, and LVSI were all independent variables in relation to patients' treatment outcomes.

Though immunohistochemistry (IHC) studies were not done for the study patients, studies have reported serous tumors to have abnormal p53 staining and clear cell cases to be HNF1B-positive and Napsin-A positive.[6]

Surgery (total hysterectomy with bilateral salpingo-oophorectomy, pelvic washings, and pelvic with or without paraaortic lymphadenectomy) is the recommended treatment. This may be done through open surgery or minimally invasive techniques (MIS), with MIS having reduced surgical morbidity, faster recovery, and similar overall survival. Though none of our patients in this study underwent MIS approach, it is acceptable for high grade histological types when the disease is confined to the uterus.[4]

Table 9: Multivariate analysis of clinical characteristics with treatment outcomes for the cases of clear cell endometrial carcinoma

Clinical profile	Categories (if categorical variable)	Coefficient	SD	*P*	OR	95% CI of OR
Age		0.01673	0.04668	0.72009	1.01687	0.9279–1.114
Gravidity		−0.02646	0.17988	0.88306	0.97389	0.6845–1.385
Parity		−0.07719	0.19519	0.69251	0.92572	0.6314–1.357
Educational attainment	No formal education					
	Elementary undergraduate	−21.60836	40,192.875	0.99957	0.00000	0.0000–0.000
	Elementary graduate	−21.76251	40,192.875	0.99957	0.00000	0.0000–0.000
	High school graduate	−42.40579	56,841.376	0.99940	0.00000	0.0000–0.000
	Vocational course	−21.60836	40,192.875	0.99957	0.00000	0.0000–0.000
Family history of malignancy	Without history					
	With history	0.19783	0.88615	0.82335	1.21875	0.2146–6.921
Menopausal status	No					
	Yes	20.82820	40,192.962	0.99959		0.0000–0.000
Comorbidities	Without comorbidities					
	With comorbidities	1.09861	0.83333	0.18739	3.00000	0.5858–15.36
BMI		0.11757	0.10445	0.26031	1.12476	0.9165–1.380
Clinical stage	I					
	II	20.35560	28,420.721	0.99943		0.0000–0.000
	III	−1.94591	1.06904	0.06872	0.14286	0.0175–1.161
	IV	−22.05019	14,210.360	0.99876	0.00000	0.0000–0.000

OR: Odd ratio, CI: Confidence interval, BMI: Body mass index, SD: Standard deviation

Table 10: Multivariate analysis of tumor characteristics with treatment outcomes for the cases of serous endometrial carcinoma

Tumor characteristics	Categories (if categorical variable)	Coefficient	SD	*P*	OR	95% CI of OR
Final stage	I	2.04122	0.96632	0.03465	7.70000	1.15867–51.17057
	II	22.90764	23,205.42175	0.99921		0.00000–0.00000
	III	1.70475	0.90174	0.05869	5.50000	0.93929–32.20501
	IV	0.31845	1.00378	0.75105	1.37500	0.19226–9.83382
	No treatment received					
Tumor size		−0.03508	0.07056	0.61905	0.96553	0.84082–1.10873
Depth of invasion	Deep	−0.47000	0.59861	0.43236	0.62500	0.19335–2.02031
	Not specified	−1.60944	1.20416	0.18136	0.20000	0.01888–2.11842
	Superficial					
Pelvic LN involvement	No					
	Not specified	−1.89712	1.11679	0.08937	0.15000	0.01681–1.33877
	Yes	−0.13613	0.58149	0.81490	0.87273	0.27920–2.72800
Paraaortic LN involvement	No					
	Not specified	−1.25276	0.86494	0.14751	0.28571	0.05244–1.55657
	Yes	−1.29928	0.72767	0.07417	0.27273	0.06551–1.13533
LVSI	Negative					
	Not specified	−2.04307	0.80178	0.01083	0.12963	0.02693–0.62400
	Yes	−0.25131	0.64856	0.69839	0.77778	0.21817–2.77277

OR: Odd ratio, CI: Confidence interval, SD: Standard deviation, LVSI: Lymphovascular space invasion, LN: Lymph node

Pelvic and paraaortic lymphadenectomy appears important in early uterine disease.[4] The SEPAL study for early stage endometrial cancer at high intermediate risk of recurrence (including uterine serous carcinoma) demonstrated improved overall survival among patients undergoing pelvic and paraaortic lymphadenectomy compared to those undergoing pelvic lymphadenectomy alone.[7] Sentinel lymph node (SLN) mapping may also be an acceptable alternative to systematic lymphadenectomy.[4] However, further studies are still needed to determine its impact on survival. With our results showing pelvic and paraaortic lymph nodes as common metastatic sites, we recommend routine comprehensive lymphadenectomy, whether through SLN mapping or systematic lymphadenectomy.

Extended surgical staging is often done for high grade tumors. However, some studies do not support routine omentectomy, given the relatively low incidence of microscopic metastasis and lack of impact on overall survival in clinically Stage I patients.[8] Other studies report up to 9% omental metastases

Table 11: Multivariate analysis of tumor characteristics with treatment outcomes for the cases of clear cell endometrial carcinoma

Tumor characteristics	Categories (if categorical variable)	Coefficient	SD	*P*	OR	95% CI of OR
Final stage	I	22.45566	20,096.48654	0.99911		0.00000–0.00000
	II	42.40579	44,937.10677	0.99925		0.00000–0.00000
	III	20.79743	20,096.48655	0.99917		0.00000–0.00000
	IV	0.00000	26,962.26511	1.00000	1.00000	0.00000–0.00000
	No treatment received	20.10428	20,096.48656	0.99920		0.00000–0.00000
	Not specified/inadequately staged					
Tumor size		−0.55147	0.31062	0.07583	0.57610	0.31340–1.05900
Depth of invasion	Deep	−2.15948	0.95407	0.02361	0.11538	0.01778–0.74861
	Not specified	0.00000	1.41421	1.00000	1.00000	0.06255–15.98751
	Superficial					
Pelvic LN involvement	No					
	Not specified	−0.44183	0.94491	0.64008	0.64286	0.10088–4.09661
	Yes	−2.10006	1.20515	0.08141	0.12245	0.01154–1.29951
Paraaortic LN involvement	No					
	Not specified	0.25131	0.86831	0.77225	1.28571	0.23444–7.05106
	Yes	−20.95158	23,205.42211	0.99928	0.00000	0.00000–0.00000
LVSI	Negative					
	Not specified	−1.20397	1.13284	0.28788	0.30000	0.03257–2.76312
	Yes	−1.42712	0.93986	0.12890	0.24000	0.03804–1.51433

OR: Odd ratio, CI: Confidence interval, SD: Standard deviation, LVSI: Lymphovascular space invasion, LN: Lymph node

Table 12: Multivariate analysis of management approaches with treatment outcomes for the cases of serous endometrial carcinoma

Management approaches	Categories (if categorical variable)	Coefficient	SD	*P*	OR	95% CI of OR
Surgical approach	Exploratory laparotomy	1.53769	0.82148	0.06123	4.65385	0.93018–23.28385
	None					
Surgical treatment	None					
	EHBSO	−19.4981	40,192.97010	0.99961	0.00000	0.00000–0.00000
	EHBSO with pelvic lymphadenectomy only	−19.4981	28,420.72172	0.99945	0.00000	0.00000–0.00000
	EHBSO with pelvic and paraaortic lymphadenectomy	2.62104	1.13618	0.02106	13.75000	1.48314–127.47423
	EHBSO, LN dissection, omentetomy	1.77886	0.85980	0.03855	5.92308	1.09820–31.94573
	EHBSO, tumor debulking	1.19392	1.06030	0.26016	3.30000	0.41303–26.36607
	Others	−19.4981	23,205.42212	0.99933	0.00000	0.00000–0.00000
Neoadjuvant treatment	None					
	Chemotherapy	−0.30368	0.76150	0.69004	0.73810	0.16593–3.28322
Adjuvant treatment	None					
	Systemic chemotherapy only	1.54490	0.76267	0.04280	4.68750	1.05137–20.89911
	Chemotherapy+pelvic EBRT	2.52573	1.33791	0.05905	12.50000	0.90799–172.08383
	Chemotherapy+pelvic EBRT+VB	3.03655	0.85049	0.00036	20.83333	3.93387–110.33091
	Chemotherapy+VB	23.03548	28,420.72127	0.99935		0.00000–0.00000

EBRT: External beam radiation therapy, VB: Vaginal brachytherapy, EHBSO: Extrafascial hysterectomy with bilateral salpingo-oophorectomy, OR: Odd ratio, CI: Confidence interval, BMI: Body mass index, SD: Standard deviation, LN: Lymph node

among high-grade endometrial cancer. Some have shown 4% of cases of grossly normal omentum as microscopically positive.[9] Currently, there is no uniform recommendation across societies on omentectomy for early stage high grade endometrial cancers. It has been considered for serous types, regardless of stage. Our study demonstrated that the omentum is the most common site of extrapelvic metastasis for both histologic types. We suggest that routine omentectomy be recommended for both early stage serous and clear cell carcinomas.

Advanced stages are managed with a multimodal approach (surgery, adjuvant chemotherapy, and possible radiotherapy) due to the high propensity for recurrence. Combination therapy has been shown to improve recurrence-free survival and overall survival.[4] This study showed that adjuvant treatment was associated with treatment outcome for both histologic types. The use of adjuvant systemic chemotherapy alone and the multimodal approach of chemotherapy with pelvic EBRT and VB were both statistically significant and predictive of treatment outcome.

Table 13: Multivariate analysis of management approaches with treatment outcomes for the cases of clear cell endometrial carcinoma

Management approaches	Categories (if categorical variable)	Coefficient	SD	*P*	OR	95% CI of OR
Surgical approach	Exploratory laparotomy	0.7621	1.22669	0.53440	2.14286	0.19357–23.72
	None					
Surgical treatment	None					
	EHBSO	2.4849	1.60728	0.12210	12.0000	0.51412–280.0
	EHBSO with pelvic lymphadenectomy only	22.301	23,205.4	0.99923		0.00000–0.000
	EHBSO with pelvic and paraaortic lymphadenectomy	0.4054	1.44338	0.77878	1.50000	0.08861–25.39
	EHBSO, LN dissection, omentectomy	−20.104	15,191.5	0.99894	0.00000	0.00000–0.000
	EHBSO, tumor debulking	0.4054	1.68325	0.80965	1.50000	0.05537–40.63
	Others	−1.0986	1.15470	0.34139	0.33333	0.00000–0.000
Neoadjuvant treatment	None					
	Chemotherapy	−21.115	23,205.4	0.99927	0.00000	0.00000–0.000
	Radiotherapy	−21.115	40,192.9	0.99958	0.00000	0.00000–0.000
	Chemotherapy with radiotherapy	−21.115	40,192.9	0.99958	0.00000	0.00000–0.000
Adjuvant treatment	None					
	Systemic chemotherapy only	−18.637	28,420.7	0.99948	0.00000	0.00000–0.000
	VB only	23.767	40,192.9	0.99953		0.00000–0.000
	Chemotherapy + pelvic EBRT	23.767	28,420.7	0.99933		0.00000–0.000
	Chemotherapy + pelvic EBRT + VB	4.1743	1.50895	0.00567	65.0000	3.37672–1251.21500
	Chemotherapy + VB	3.2581	1.60528	0.04240	26.0000	1.11830–604.4

EBRT: External beam radiation therapy, VB: Vaginal brachytherapy, EHBSO: Extrafascial hysterectomy with bilateral salpingo-oophorectomy, OR: Odd ratio, CI: Confidence interval, BMI: Body mass index, SD: Standard deviation, LN: Lymph node

For advanced stage diseases warranting neoadjuvant treatment, this was primarily given via systemic chemotherapy due to widespread disease. Best outcomes are achieved when neoadjuvant treatment is followed by cytoreductive surgery with the goal of a complete gross resection. Studies have reported a significant difference in median time to recurrence and median survival among those optimally cytoreduced Stage IIIC or IV uterine serous carcinoma cases.[10]

Although none of the study patients underwent molecular profiling, recent studies have recognized the role of molecular characterization in furthering the development and application of targeted therapies for the different types of endometrial cancer, especially in the setting of recurrent and high-grade endometrial cancer. Through identification of mutational pathways, more opportunities arise to explore the use of targeted therapies such as mTOR, PARP and EZH2 inhibitors for these rare types of endometrial cancers. If available, molecular profiling may pave the way for more individualized treatment strategies to improve outcomes.[11]

Conclusions

Serous and clear cell endometrial carcinomas are high grade histological type whose behavior differs from the more common endometrioid type. Their risk factors and clinical behavior patterns are affected by different clinical and tumor characteristics. Management approaches should be tailored to individual cases. The standard of treatment remains to be surgery, followed by a multimodal approach of adjuvant treatment, regardless of stage of disease. The omentum, despite being grossly normal, has been identified as one of the most common extrapelvic sites of metastasis. This supports the performance of extended surgical staging for both serous and clear cell carcinomas, even in clinically early stages. Prognosis tends to be less favorable and recurrences and distant metastasis may occur even for earlier stages. Thus, it is important to identify any clinical factors that may aid in better counseling of patients with their disease and administering appropriate management for their cases.

Limitations

This study is limited to identifying and correlating possible associations between certain patient and tumor characteristics with treatment outcomes. It cannot directly determine any cause-and-effect relationships among the variables being studied. Furthermore, it covers only a 5-year period of data collection, during which, only a few patients with high-grade endometrial tumors were identified and there was a high dropout rate. Many patients were lost to follow-up, especially during the years affected by the COVID-19 pandemic. This may have impacted compliance and access to recommended treatment, thereby limiting our data on the possible treatment outcomes, had they received the treatment as advised.

Recommendations

Molecular characteristics now play a significant role in the behavior of tumors. This study lacks any molecular data on the cases that were included. Knowledge on the molecular profiles of the different tumors may help in better understanding their behavior and tailoring their individualized management later on. For cases of recurrent disease, improved knowledge on the molecular profiles can broaden treatment options and allow the use of targeted therapies for different individuals. We recommend that further studies incorporate and report molecular characteristics of these tumors. These should be analyzed in terms of associations with treatment outcomes.

Authorship contributions

Maria Angelica B. Arada-Garcia – Involved in the conceptualization, methodology, formal analysis, data curation, writing of the original draft, review and editing, visualization.

Maria Constancia Y. Wylengco - Involved in conceptualization, methodology, review and editing of the draft, supervision.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, M.A.B.A.G.

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