Comparative study of ovarian clear cell carcinoma with and without endometriosis in People's Republic of China

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Objective: To analyze and compare the clinicopathological features and prognosis of ovarian clear cell carcinoma (CCC) with or without endometriosis in Chinese patients.
Design: Comparative study based on a retrospective review of medical charts.
Setting: A general university hospital.
Patient(s): Two hundred ten patients diagnosed and treated with ovarian CCC between 2000 and 2012.
Intervention(s): Patients were divided into two groups depending on coexisting endometriosis. A comparison of clinicopathological characteristics was performed. The Kaplan-Meier model and Cox regression were employed in survival analysis.
Main Outcome Measure(s): Clinicopathological parameters and survival outcomes.
Result(s): Of 210 patients, 79 (37.6%) were confirmed to have concurrent endometriosis. Patients with endometriosis were 8 years younger than those without. They were more likely to present at early stage (78.5%) with resectable tumors in primary surgery (with optimal cytoreduction rate at 89.9%) and platinum-sensitive disease (51.7%). Median overall survival for patients with endometriosis was 115 months, an increase of 52 months when compared with 63 months for patients without endometriosis. The 5-year survival rate in patients with endometriosis was 70.2%, while it was 52.6% for those without. Univariate and multivariate analysis showed that coexisting endometriosis was not an independent predictor of survival outcome. Tumor stage and optimal debulking were the independent prognostic factors for both overall survival and progression-free survival.
Conclusion(s): Patients with ovarian CCC and coexisting endometriosis had distinct clinicopathological features and better survival outcome. However, endometriosis per se did not confer improved survival. (Fertil Steril® 2014;102:1656–62. ©2014 by American Society for Reproductive Medicine.)
Key Words: Epithelial ovarian cancer, clear cell adenocarcinoma, endometriosis, clinicopathological features, prognosis

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Endometriosis is a common gynecologic disorder, which is characterized by ectopic growth of endometrial glands and stroma. Previous publications pointed out that immune response abnormality and alteration as well as inflammation in women with endometriosis might predispose them to have cancer and infections (1–3). In a large cross-sectional study involving 4,331 women with surgically diagnosed endometriosis, a higher prevalence of ovarian cancer was noted (3). A pooled analysis of case-control studies included 13,226 controls and 7,911 women with ovarian malignancy and concluded that endometriosis is associated with certain histology subtypes including clear cell carcinoma (CCC) (20.2%), endometrioid carcinoma (13.9%), and low-grade serous carcinoma (9.2%) (4).

Emerging studies have shown that endometriosis-associated ovarian carcinoma (EAOC) might deviate from the non-EAOC in many key biological

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characteristics (5–7). However, most studies aggregated ovarian cancer cases with different histological subtypes, making comparisons between various studies suboptimal (4–6, 8–10).

Our previous retrospective studies aimed to analyze the clinical features of ovarian carcinoma with coexisting pelvic endometriosis (6) and endometriosis-associated endometrioid carcinoma (7). Based on our data, CCC is the most common histology (47.1%), and patients with EOAC tend to be younger and diagnosed at an earlier stage when compared with patients with non-EOAC. Up to now, two different studies, one from Japan (11) and the other from the United States (12), have been undertaken to investigate the possible prognostic implication of endometriosis in ovarian CCC. However, the published studies that mainly concentrate on endometriosis-associated ovarian CCC in Chinese patients are comparatively few. Therefore, in the present study, we aimed to evaluate and compare the clinical and pathologic characteristics as well as survival outcomes of ovarian CCC patients with or without endometriosis in China.

MATERIALS AND METHODS

Study Subjects

The Ovarian Clear Cell Carcinoma Database was set up and maintained by research faculty members in our department. All the CCC patients diagnosed and treated in our hospital since 1982 were included, and basic information was recorded in the database. After obtaining Institutional Review Board approval, we identified all the patients between the years 2000 and 2012. Case selection was based on original diagnosis by the pathologists via pathology reports in the medical documentation. To be included in this study, patients had to fulfill the following criteria: [1] patients underwent primary comprehensive staging surgery or cytoreductive surgery (CRS) in our hospital; [2] diagnosis of ovarian CCC was confirmed by histopathology; [3] a complete medical record and pathology report were available.

Data Collection

Data collection included age at diagnosis, menopausal state, personal history, family cancer history, serum level of cancer antigen 125 (CA 125), ascites, date and type of primary surgery, primary tumor size, International Federation of Gynecology and Obstetrics (FIGO) stage, lymph node metastasis, endometriosis, residual disease, adjuvant chemotherapy, date of disease progression or recurrence, and tumor status at the date of last contact. All patients with stage I and II ovarian CCC underwent complete staging surgery, and patients with stage III and IV ovarian CCC received CRS. Adjuvant chemotherapy was routinely administered after primary surgery with few exceptions. In the study period, all the patients received a platinum-based chemotherapy regimen, including paclitaxel and carboplatin and paclitaxel and cisplatin. Specific chemotherapy dosage was listed as follows: TC regimen (paclitaxel 175 mg/m^2 + carboplatin area under curve 5) or TP regimen (paclitaxel 175 mg/m^2 + cisplatin 70 mg/m^2). Both were repeated every three weeks. The number of cycles ranged from six to nine after tailoring to different individuals.

Microscopic slides were reviewed and confirmed by a single experienced gynecologic pathologist (Dr. You). Pathological features of ovarian CCC with and without endometriosis are shown in Figure 1. Specifically, EAOC was defined as follows: [1] presence of CCC and endometriosis in the same ovary, [2] presence of endometriosis in one ovary and of CCC in the contralateral ovary, [3] presence of CCC and extraovarian endometriosis.

All the patients were staged by the FIGO 1999 staging system according to CRS and pathological findings. They were further divided into two groups for statistical analysis: early stage (FIGO I-II) and advanced stage (FIGO III-IV). Optimal CRS was defined as residual disease less than (or including) 1 cm after primary debulking. The tumor size was measured by gynecologic oncologists during operation and recorded in a surgery note. Patients were considered to have platinum-sensitive disease if the interval time was >6 months from the completion of the last platinum-based chemotherapy to disease recurrence. The normal upper limit of serum CA 125 was 35 U/mL.

Progression-free survival (PFS) was defined as the time interval from the date of primary surgery to the date of disease progression or recurrence. Overall survival (OS) was defined as the time interval from the date of the primary surgery to the date of death or last contact. Patients with incomplete follow-up information were excluded from the survival analysis.

Statistical Analyses

Statistical analyses were performed using SPSS, version 17.0 (SPSS, Inc.), and GraphPad Prism, version 5.0 (GraphPad Software, Inc.). Comparisons between the two groups (CCC with or without endometriosis) were performed by using the χ^2-test and parametric Student's t tests. PFS and OS times were estimated using the Kaplan-Meier model, while Cox regression was used for multivariate analysis. Variables with statistical significance in univariate analyses were included in the multivariate one. All P values reported were two tailed, and $P<.05$ was considered statistically significant.

RESULTS

During the study period 2000–2012, a total of 210 patients fulfilled the inclusion criteria. Of them, 79 (37.6%) patients were associated with endometriosis and allocated to group 1, while the other 131 (62.4%) without endometriosis were assigned to group 2. In group 1, 20 (25.3%) had been diagnosed with endometriosis before admission. Among them, 17 patients had a surgical history of ovarian endometriosis (cystectomy) and three were clinically diagnosed with endometriosis on the basis of dysmenorrhea, pelvic mass detected by bimanual exam or ultrasound, painful nodularity in the pouch of Douglas, and slightly elevated serum CA 125.

Comparison of Clinical and Pathological Features

The clinical and pathological variables between the two groups are shown in Table 1. For all patients, the mean age at the time of diagnosis was 51 ± 10.9 years (range, 30–