Gynecologic Oncology 143 (2016) 526–531

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Prognostic value of endometriosis in patients with stage I ovarian clear cell carcinoma: Experiences at three academic institutions☆

Huimin Bai, M.D., PhD. [a,b,1], Dongyan Cao, M.D. [b,1], Fang Yuan, M.D. [c], Guihua Sha, M.D. [b], Jiaxin Yang, M.D. [b], Jie Chen, M.D. [d], Yue Wang, M.D. [e], Zhenyu Zhang, M.D., PhD. [a,*], Keng Shen, M.D., PhD. [b,**]

[a] Department of Obstetrics and Gynecology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
[b] Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[c] Department of Obstetrics and Gynecology, The Affiliated Hospital Qingdao University, Beijing, China
[d] Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[e] Department of Pathology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

HIGHLIGHTS

- OCCC patients with EAOC had significantly improved survival than those without EAOC.
- EAOC was not an independent prognostic predictor for patients with stage I OCCC.
- The intrinsic relationship between EAOC and OCCC warrants further investigation.

ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form 2 October 2016
Accepted 5 October 2016
Available online 13 October 2016

Keywords:
Clear cell carcinoma
Ovary
Stage I
Prognosis
Endometriosis

ABSTRACT

Objectives. To investigate the prognostic value of endometriosis in patients with stage I ovarian clear cell carcinoma (OCCC).

Methods. The medical records of patients with stage I OCCC who had undergone complete staging surgery followed by systemic chemotherapy were retrospectively reviewed.

Results. A total of 237 women were included in this study. Univariate analysis revealed that the patients with endometriosis-associated ovarian carcinoma (EAOC) had significantly improved recurrence-free survival (RFS) and overall survival (OS) than those without EAOC (5-year RFS: 91.4% vs. 73.0%, respectively, and 5-year OS: 97.5% vs. 89.9%). However, EAOC was not identified as a significant prognostic predictor in multivariate analysis. The potential risk factors determined to be associated with EAOC included the pretreatment CA-125 level, FIGO stage, lymphovascular space invasion (LVSI), and menopausal status ($P < 0.001$, $P = 0.0031$, $P = 0.020$, and $P = 0.038$, respectively).

Conclusions. Endometriosis was not independently associated with the prognosis of the OCCC patients, even when the tumor was confined to stage I. However, the intrinsic relationship between endometriosis and OCCC warrants further investigation.

1. Introduction

Ovarian clear cell carcinoma (OCCC) is a comparatively rare tumor that accounts for 10% of all epithelial ovarian cancers [1,2], and its incidence may be higher among Asian women [3]. OCCC has distinct clinical characteristics. This tumor type is known for its aggressive nature and is associated with an adverse prognosis, particularly in advanced or recurrent cases [4–7]. OCCC is likely to be diagnosed at an early stage, rarely occurs bilaterally, and is frequently associated with endometriosis, hypercalcemia, and thromboembolic complications [8–10].

The presence of endometriosis may increase the risk of ovarian cancer, especially OCCC or endometrioid carcinoma [11,12]. Endometriosis

Abbreviations: OCCC, Ovarian clear cell carcinoma; RFS, recurrence-free survival; OS, overall survival; FIGO, Federation of Gynecology and Obstetrics; WHO, World Health Organization; LVSI, Lymphovascular space invasion; EAOC, Endometriosis-associated ovarian carcinoma.

☆ Source of the study: 1 Peking Union Medical College Hospital, Chinese Academy of Medical Sciences Peking Union Medical College;2 Beijing Chao-Yang Hospital, Capital Medical University;3 The Affiliated Hospital Qingdao University, Beijing, China.

* Correspondence to: Z. Zhang, Department of Obstetrics and Gynecology, Beijing Chao-Yang Hospital, Capital Medical University. No.8, north road of Workers Stadium, Chaoyang District, Beijing 100020, China.

** Correspondence to: K. Shen, Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. No. 1 Shuai Fu Yuan, Eastern District, Beijing 100730, China.

E-mail addresses: zhenyuzhang2000@163.com (Z. Zhang), skpumch@126.com, shenkeng@vip.sina.com (K. Shen).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ygyno.2016.10.009
0090-8258/

has been consistently reported to be more common in early-stage OCCC [13–16] and to be associated with improved recurrence-free survival (RFS) and overall survival (OS) in our previous studies [17,18] and in studies published by other authors [19,20]. However, endometriosis has never been identified as an independent predictor of recurrence or survival in OCCC patients, and Lee [13] and Takano [21] have demonstrated that endometriosismay not affect the tumor response or prognosis in OCCC patients. These conflicting results may be due to the rarity of the disease and the heterogeneity of these previously published studies. The majority of these studies have included patients with tumors with different Federation of Gynecology and Obstetrics (FIGO) stages, which differ in whether cytoreductive surgery is an optimal treatment. FIGO stage and the optimality of cytoreductive surgery are common and significant risk factors for recurrence and survival in many subtypes of epithelial ovarian cancer, including OCCC. Therefore, these heterogeneous factors might have biased previous conclusions to some extent.

In the present study, we focused exclusively on stage I OCCC and attempted to determine the prognostic value of endometriosis in the target patients. Clarifying the intrinsic relationship between endometriosis and OCCC may improve the current understanding of the tumorigenesis of OCCC.

2. Materials and methods

The medical records and clinical follow-up data for women diagnosed with and treated for OCCC at 3 hospitals from January 1993 to January 2013 were reviewed. These hospitals included Peking Union Medical College Hospital (PUMCH), Beijing Chao-Yang Hospital, Capital Medical University, and the Affiliated Hospital of Medical College Qingdao University. The inclusion and exclusion criteria used were generally consistent with those described in one of our previous studies [4]. Briefly, patients with pure OCCC who had undergone complete staging surgery and subsequent systemic chemotherapy as the primary treatment were included in our previous study [4]. Patients with stage IA-IC3 disease were selected for further analysis in the present study. Patients were excluded from this study if they had insufficient data or were lost to follow-up within one month after surgery. Patient information, including the demographic and pathological characteristics, surgery and subsequent systemic chemotherapy received, and disease status at last contact, was collected and evaluated.

All patients were surgically staged by gynecologic oncologists, and staging was performed according to existing practices at the time of surgery. The predominant initial surgical procedure consisted of total hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and omentectomy, in addition to multiple-site random peritoneal biopsies. Ascites or washings were routinely collected before surgery, and cytological data were evaluated for all patients. If any abnormalities were found during surgery, the appropriate peritoneal multiple-site biopsies were performed. Two independent pathologists with extensive experience in gynecological pathology reviewed all pathological slides. These pathologists were blinded to the patient outcomes. The histological cell types were determined according to the criteria of the World Health Organization (WHO). Pure OCCC was defined as the presence of typical clear or hobnail cells in a papillary, solid or tubulocystic pattern, with each individual epithelial component comprising no <90% of the tumor. Lymphovascular space invasion (LVSI) was defined as the presence of a cluster of tumor cells within a lymphatic or vascular lumen. Endometriosis-associated ovarian carcinoma (EAOC) was defined as the co-existence of OCCC and endometriosis in the same and/or contralateral ovary and/or the co-existence of OCCC and extraovarian endometriosis [18,20,21]. Disease staging was re-assessed according to the following FIGO staging criteria [22]: stage IA (tumor limited to one ovary), stage IB (tumor limited to both ovaries), stage IC1 (surgical spill), stage IC2 (capsule ruptured before surgery or tumor on ovarian surface), and stage IC3 (malignant cells in ascites or peritoneal washing).

Taxane/platinum or conventional cis/carboplatin-based chemotherapy (6 to 8 cycles) was administered as the postoperative first-line treatment. The main chemotherapy regimens consisted of TC (paclitaxel/carboplatin), TP (paclitaxel/cisplatin), weekly TC, weekly TP, PC (cisplatin/cyclophosphamide), PAC (cisplatin/adriamycin/cyclophosphamide), CC (carboplatin/cyclophosphamide), or PAF-C (cisplatin/adriamycin/5-fluorouracil/cyclophosphamide).

After the initial treatment was completed, the patients were followed-up monthly for the first half-year, every 3 months for the second half-year, and every 6 months thereafter. Clinical examinations performed at each visit included pelvic examination, ultrasonographic scan, and CA-125 evaluation, in addition to CT, MRI and/or PET-CT scans when necessary. An effort was made to contact patients by telephone or letter to obtain regular follow-up information when it was not available. Recurrence was documented by histologic evidence of disease in tumor biopsy or fine-needle biopsy and/or the appearance of new lesions on imaging examination. RFS was calculated as the period from the date of initial surgery to the date of recurrence. Women who were disease-free at the time of their last visit were censored. OS was calculated as the number of months from the date of initial surgery to the date of patient death from the disease. Patients who died from other conditions or who were survivors at the time of their last visit were censored.

Patient records/information was made anonymous and de-identified prior to analysis. Thus, consent was not required. The study protocol was approved by the ethics committees of Peking Union Medical College Hospital, Beijing Chao-Yang Hospital, the Affiliated China Capital Medical University, and the Affiliated Hospital of Medical College Qingdao University. This study was performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

2.1. Statistical analysis

All statistical analyses were performed using SAS® Version 9.2 (SAS Institute, Cary, NC). All of the tests were 2-sided, and a $P < 0.05$ was considered to indicate statistical significance. The Kaplan-Meier method was used in univariate analysis of recurrence and survival. The log-rank test was used to compare different survival curves. The Cox proportional hazards model was applied to evaluate all parameters that were significant in univariate analysis. Chi-square tests and logistic regression analyses were performed to identify risk factors associated with EAOC.

3. Results

During the study period, 375 consecutive women with pure OCCC underwent complete staging surgery and subsequent systemic chemotherapy at PUMCH and Beijing Chao-Yang Hospital, Capital Medical University, as previously described [4]. Stage I disease was identified in 180 patients. An additional 57 patients who were diagnosed and treated at the Affiliated Hospital of Medical College Qingdao University during the same period also met the eligibility criteria and were included in the present study. Ultimately, a total of 237 eligible patients were included in this study. The patient demographics and clinicopathological characteristics are shown in Table 1. The mean patient age at initial diagnosis was 48.9 ± 11.0 years, and 146 of the patients (61.6%) were premenopausal. More than half (65.7%) of the patients presented with symptoms. The majority (84.4%) of the surgeries were performed using a laparotomic approach. All 237 women underwent pelvic and para-aortic lymphadenectomy for complete disease staging. The mean number of removed lymph nodes was 28.1 ± 8.5 (range, 10–66) per patient. EAOC and LVSI were present in 105 (44.3%) and 49 (20.7%) patients, respectively. IC1 (38.4%) was the most common stage, followed by IA (29.5%) and IC3 (23.2%). Stage IB was very rarely observed and