Original Article
Clinicopathologic features of ovarian carcinosarcoma: a report of 17 cases

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Abstract: Background: Ovarian carcinosarcoma (OCS) is a rare and aggressive type tumor of the ovary. The present study was to evaluate the clinicopathologic features and prognosis of OCS patients. Methods: 17 OCS patients who were diagnosed and treated in the Obstetrics and Gynecology Hospital of Fudan University between 2004 and 2014 were collected. The clinical data, treatment regimens and prognosis information were extracted from medical records. Results: The median age at diagnosis was 56 years old (range from 43~76 years) and 14 (82.35%) cases were diagnosed at advanced stage. For those who were tested for Vimentin antibody which is a biomarker of stromal components, 100% (15/15) were positive. For CK7 antibody, all patients (15/15) were positive except for 2 patients who were not detected. 13 (76.47%) cases were treated with optimal primary cytoreductive procedures and all patients received platinum-based chemotherapy regimens. The overall one-year survival rate was 79.4% and three-year survival rate was 57.8%. Patients with optimal cytoreductive surgery had three-year survival rate of 64.8% versus 33.3% in those with nonoptimal cytoreductive surgery. No statistical significance was found when we compared the overall survival rate of the two groups with Log-Rank test. Conclusions: From our study, CK7 combined with Vimentin staining deserves to be studied further for its histopathologic diagnostic value in OCS. OCS patients have very poor prognosis. Radical cytoreductive surgery to no visible disease may be associated with better survival in OCS patients. Optimal chemotherapy regimens are still unclear.

Keywords: Ovarian carcinosarcoma, clinicopathologic features, treatment regimens

Introduction

Carcinosarcomas, also called malignant mixed müllerian tumors, are rare, aggressive malignances and can be found in the whole female reproductive tract [1, 2]. It is mostly can be seen in the uterus followed by ovaries where it accounts for only 1~4% of ovarian cancers [3, 4]. Ovarian carcinosarcoma (OCS) consists of two types of histologic components, carcinomatous and sarcomatous. In ovaries, the carcinomatous component can be clear cell, serous or squamous epithelium, endometrioid cell while the sarcomatous component can be classified as homologous and heterologous according to whether they can be found in the uterus or ovaries or not. OCS patients always are diagnosed between the age of 50 and 70 and have higher rates of advanced International Federation of Gynecology and Obstetrics (FIGO) stage at presentation [5]. Similar to epithelial ovarian cancers (EOC), most OCS patients complain of pelvic mass, lower abdominal pain and abdominal distention. However, the prognosis of OCS patients is worse than that of EOC patients with similar FIGO stages [1, 6]. It is reported that the age of patients and FIGO stage are related to prognosis [7, 8].

Evidence of optimal treatment obtained from prospective studies are absent because of the rarity of OCS [9]. Until now almost all data on management of OCS come from limited retrospective case series. Some published retrospective studies indicated that optimal cytoreductive surgery followed by platinum-based chemotherapy regimens are associated with the benefit of OCS. Overall, appropriate treatment regimens of OCS haven’t been reached. The objective of this study was to analyse the
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Materials and methods

This study was approved by the Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University, Shanghai, PR of China.

In the present study, we analyzed clinical data of 17 OCS patients who were diagnosed and treated in the Obstetrics and Gynecology Hospital of Fudan University between 2004 and 2014. We extracted the age at diagnosis, main complaints, menstruation status, serum tumor biomarkers, surgery regimens, stage, pathology information, adjuvant chemotherapy from medical records. The histologic type of tumors were determined by two experienced pathologists specializing in gynecologic oncology randomly. Immunohistochemical staining was performed with the following antibodies: CK7, Vimentin, Ki-67, P53, WT-1, Desmin, EMA and CA-125. The result was assessed by semi-quantitative evaluation of the number of positively stained cells as follows: -, no staining; + (weakly positive), 1~25% of cells stained; ++ (moderate positive), 26~50% of cells stained; +++ (strongly positive), 51~100% of cells stained. The Ki67 labeling index was determined by the percentage of positive nuclei stained with MIB-1 antibody. The stages at diagnosis were referred to the FIGO criteria. We followed up those patients from the date of diagnosis by pelvic examination, serum bio-markers, X-ray and ultrasonography of pelvic and abdominal.

All analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA) statistical software version 16.0. A P-value <0.05 was considered statistically significant. The survival between groups was analyzed by Log-Rank Test.

Results

Clinical characteristics

Among those 17 OCS patients, the median age at diagnosis was 56 years old (range from 43~76 years) and 10 (58.82%) of them had experienced natural menopause. 15 (88.24%) cases complained of abdominal distention and/or mass at presentation. 1 case complained of weight loss, vesical tenesmus and 1...
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11 (64.71%) patients had ascites at diagnosis. As for FIGO stage, 3 were diagnosed at stage I or II and 14 patients were at stage III or IV. In other words, 14 (82.35%) cases were diagnosed at advanced stage. According to medical records, 13 (86.67%) patients had high level of CA-125 (median: 240.6 U/ml, range: 36–3074 U/ml) preoperatively except for 2 cases who didn’t accept the test (Table 1).

Histopathologic features

All patients presented with both carcinomatous and sarcomatous components (Figure 1). 13 (86.67%) patients occurred in one side ovary. Heterologous components were found in 8 (47.06%) patients including osteosarcoma, rhabdomyosarcoma and chondrosarcoma. According to immunohistochemistry staining, the Ki-67 labeling index as determined by MIB-1 antibodies (%) was positive in 15 patients (the other 2 cases were not detected). About 53.3% (8/15) of them expressed Ki-67 for ≥50% positive. As for P53 antibody, 72.72% (8/11) were positive (6 of 17 were not detected). For those case complained of only lower abdominal pain. 11 (64.71%) patients had ascites at diagnosis. As for FIGO stage, 3 were diagnosed at stage I or II and 14 patients were at stage III or IV. In

Figure 1. Representative histological and immunohistochemical manifestations of ovarian carcinosarcoma. Scale bar: 20 μm.

Table 2. Immunohistochemical staining of 17 patients

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<th>CK7</th>
<th>CA-125</th>
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who were tested for Vimentin antibody which is a biomarker of stromal components, 100% (15/15) were positive. We concluded that Vimentin can be defined as a sensitive biomarker of carcinosarcomas. For CK7 antibody, all patients (15/15) were positive except for 2 patients who were not detected (Table 2). Also, it may indicate that CK7, a biomarker of carcinomatous components, could be a sensitive marker of carcinosarcomas. From our study, CK7 combined with Vimentin staining deserves to be studied further for its histopathologic diagnostic value in ovarian carcinosarcomas.

Treatment

All of these 17 patients were treated with cytoreductive surgeries followed by chemotherapies, of which 2 cases accepted TP (paclitaxel + cisplatin) for two cycles before cytoreductive surgery. 13 (76.47%) cases were treated with optimal primary cytoreductive procedures (maximal residual disease diameter ≤1.0 cm). All patients received platinum-based chemotherapy regimens such as paclitaxel/carboplatin, carboplatin/epirubicin, ifosfamide/carboplatin/etoposide and cisplatin/dacarbazine/epirubicin. The overall response rate was 76.47% (13/17). However, no statistical difference was found in overall survival between TP group and non-TP group (P>0.05) (Figure 2). That may due to our small sample size and short time of follow-up.

Follow-up

These patients were followed up until 1st, 10, 2016. Among the 17 cases, 7 of them died of...
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OCS and 6 are alive. Another 4 patients lost follow-up. The median follow-up time of the alive was 91.5 months. The overall one-year survival rate was 79.4% and three-year survival rate was 57.8% (Figure 3). Recurrence occurred in 9 (7 within 2 years, the other 2 beyond 2 years) patients after operation.

Among the 13 cases with high level of CA-125 preoperatively, 10 of them presented with normal level of CA-125 within 1–3 cycles of chemotherapy except for 3 who lost follow-up. We compared the survival rate of 14 patients of advanced FIGO stage. Patients with optimal cytoreductive surgery had three-year survival rate of 64.8% versus 33.3% in those with non-optimal cytoreductive surgery. However, there was no statistical significance when we compared the overall survival rate of the two groups with Log-Rank test (Figure 4). It is probably due to few cases available for analysis and high rate of loss to follow-up.

Discussion

OCS is a kind of rare histology type cancer accounting for about 1% of ovarian cancers. It is reported that nearly 70% OCS patients are diagnosed with advanced stages [10]. In our study, 82.35% cases were diagnosed at stage III/IV. Similar to EOC, OCS usually occurs in postmenopausal women with a median age of 66.8–71 [11, 12], and the median age in our 17 patients is 56 years old. The most common complaints are abdominal mass, lower abdominal pain and abdominal distention. However, these symptoms usually happen to women with advanced stages. Notably, high level of CA-125 can be tested in more than 70% OCS patients [13] which is in accordance with our study (86.67%).

Carcinosarcomas are composed of both carcinomatous and sarcomatous tissue type. Currently, two main theories have been proposed on the origin of carcinosarcoma: 1. The collision theory: carcinosarcoma originated from two kinds of stem cells which differentiated into epithelial and stromal malignant cells respectively; 2. The conversion theory: both carcinomatous and sarcomatous components were from a common pluripotent stem cell. Until now most studies are in favor of the latter one [14, 15].

The prognosis of OCS is very poor. The overall median survival is only 13-27 months [16]. A large retrospective study found that women with OCS had a worse five-year survival rate, 26.63% vs. 43.61%, than those with high-grade papillary serous carcinoma [3]. In our study, the overall one-year survival rate is 79.4% and three-year survival rate is 57.8%. The consensus management treatment of OCS hasn’t been determined mostly because of the scarcity of prospective studies. Limited treatment regimens are extrapolated from EOC or other histologic types of ovarian cancer. Almost all retrospective studies suggested that optimal cytoreductive surgery was associated with a better survival for OCS patients. Jernigan, et al [17] analyzed 47 cases retrospectively to define the prognostic factors of OCS. They found that compared to microscopic residual, women with >1 cm diameter of residual disease after primary surgery had an HR of 4.71 (95% CI 1.16-12.09, P=0.001). It was also conformed in another study [18]. Among 51 OCS patients who were treated with primary cytoreductive surgery, 18 had no visible disease, 20 had ≤1 cm of residual disease and 13 had >1 cm of residual disease. Median progression-free survival varied significantly among groups: 29 vs. 21 vs. 2 months (P=0.036), so did the median overall survival. In the current study, patients with optimal cytoreductive surgery has a three-year survival rate of 64.8% versus 33.3% in those with nonoptimal cytoreductive surgery. However, there was no statistical significance when we compared the overall survival rate of the two groups with Log-Rank test. It is probably due to few cases available for analysis and high rate of loss to follow-up. Generally, primary cytoreductive surgery to no visible disease should be confirmed as a goal for OCS patients.

The most effective chemotherapy regimen for OCS hasn’t been determined. In the present, the treatment of paclitaxel/platinum has been defined as optimal chemotherapy for EOC and this combination is utilized in most OCS patients. It has been reported that a response rate of 72% was reached with carboplatin plus paclitaxel in reproductive tract carcinosarcomas [19], Duska LR, et al [16] retrospectively analyzed 28 cases treated with adjuvant carboplatin/paclitaxel and indicated that complete response rate was 55%, and partial response rate 23%. However, significant difference
wasn’t detected in the survival benefit between platinum-based and nonplatinum-based chemotherapy in Jernigan’s study (P=0.08) [17]. It is uncertain whether this is due to small samples or not. In our study, all 17 patients received platinum-based chemotherapy (14 were given TP and 3 were given other platinum-based regimens). The overall response rate was 76.47% (13/17). However, we did not find statistical difference in overall survival between TP group and non-TP group (P>0.05). Altogether, prospective randomized controlled clinical trials are strongly necessary for optimal chemotherapy regimens.

Many limitations can be detected in our study. Firstly, it is a retrospective study and we can’t determine any causation from it. Secondly, we accrued too small samples mainly due to the scarcity of OCS. Thirdly, high rate of loss to follow-up probably lead to no statistical significance between groups. However, it is one of the largest single-institution series of OCS in China. We described clinicopathologic features, treatment regimens and prognosis of OCS in our hospital.

OCS a rare kind of ovarian cancer, which shows high invasive and poor prognosis. Clinical guidelines of treatment management for OCS patients haven’t been reached. A large amount of retrospective studies indicated that optimal cytoreductive surgery with no gross residual disease should be the goal [17-19]. The optimal chemotherapy regimens are still questionable although some case series suggested platinum-based regimen be benefit for OCS [17]. One possible solution to promote prospective studies may be cooperation of multiple centers to recruit more patients.

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Disclosure of conflict of interest

None.

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