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Case analysis of fertility-preserving treatment in female patients with malignant ovarian cancer

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Summary

The aim of this study was to evaluate the impacts of fertility-preserving surgery and chemotherapy on the fertility and ovarian functions in malignant ovarian cancer. The clinical data of 52 female patients with malignant ovarian cancer and performed fertility-preserving treatment (FPT) in the present hospital between June 2004 and December 2014 were retrospectively analyzed. The 52 cases included 25 cases of germ cell carcinoma (GCC) (48.07%), 12 cases of epithelial ovarian carcinoma (EOC) (23.07%), and 15 cases of borderline carcinoma (28.84%), among which one case recurred (1.92%) and one died (1.92%). Forty-five cases had normal menstruation after the treatment (86.53%), and 16 cases out of the 27 cases with fertility requirement successfully achieved pregnancy (59.26%). FPT in female patients with malignant ovarian cancer was effective and feasible; although chemotherapy might affect ovarian function, it could also be reversed. Ovarian tumor resection or adnexectomy may be the best way for fertility preserving treatments; however, further investigation is warranted.

Key words: Ovarian cancer; Fertility-preserving treatment; Surgery; Chemotherapy.

Introduction

Ovarian cancer is the most lethal gynecologic malignancy claiming about 160,500 deaths in 2010, which increased from 113,600 in 1990 and 140,200 in 2008 [1, 2]. Efforts of early detection and new therapeutic approaches to reduce the mortality were largely unsuccessful because the origin and pathogenesis of epithelial ovarian carcinoma (EOC) were poorly understood [3].

The gold standard for the treatment of any suspected ovarian cancer included intact removal of the involved adnexa with intraoperative pathological evaluation [4-6]. In ovarian carcinoma, EOC comprises 90-95% of all cases, and the most common EOC type is the serous tumor followed by endometrioid, mucinous, and clear-cell cancers representing 50-60%, 25%, 4%, and 4% of all ovarian tumors, respectively [7]. While sex cord-stromal tumors, malignant ovarian germ cell carcinoma (GCC), and ovarian carcinosarcoma were uncommon [8, 9]. Until now, all EOC cases have been treated in a similar fashion, namely the upfront debulking surgery, staging and/or tumor reduction, and adjuvant chemotherapy for all but early stage diseases, and usually a taxane and a platinum agent might be supplemented [10]. Despite the improvements in managing the patients with ovarian cancer over the last 30 years, there had been only a minimal improvement in the overall survival [11].

Approximately, 30% of ovary tumors affect women under 40 years of age, and traditional management is total hysterectomy with bilateral salpingo-oophorectomy (BSO). Fertility-preserving surgery (FPS) depends on the histology, disease stage, and pre-existing ovarian reserve [12]. The improvements of surgical approaches and optimization of chemotherapy make it possible for the patients with malignant cancer to preserve their fertility. This study analyzed the clinical data of 52 patients with malignant ovarian cancer after their fertility preservation treatment, aiming to summarize and evaluate the feasibility, effectiveness, and safety of fertility preservation treatment.

Materials and Methods

Fifty-two female patients with malignant ovarian cancer were performed fertility-preserving treatment (FPT) in the present hospital between June 2000 and December 2014, aged 10~40 years old, among which 16 cases were in 10~18-year-old age segment, 27 cases in 18~30-year-old age segment, seven cases in 30~35-year-old age segment, and two cases in 35~40-year-old age segment. This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of the People's Hospital of Hainan Province. Written informed consent was also obtained from all participants.

First, a comprehensive abdominal exploration was performed, and the peritoneal washing fluid was maintained for cytological assay. The suspected site was sampled for biopsy. No comprehensive and accurate staging surgery was performed, and the disease stage was determined based on the exploration and postoperative pathologies.

Fifty patients underwent the surgery in the present hospital for the first time, including six cases of ovarian cystectomy on the diseased side (the contralateral ovary had normal appearance):

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one case of left ovarian papillary cystadenocarcinoma, two cases of left ovarian borderline mucinous cystadenoma, one case of right ovary borderline serous cystadenoma, one case of left ovarian immature teratoma, and one case of right ovary multilocular mucinous cystadenoma (borderline to low-grade malignant). Twenty-nine patients underwent adnexectomy on the diseased side, including 13 cases without contralateral ovarian exploration (one case underwent greater omentectomy) and 16 cases with contralateral ovarian exploration (three cases underwent greater omentectomy); 15 cases underwent the comprehensive staging surgery, namely adnexectomy + appendectomy + bilateral pelvic lymph node biopsy or dissection (or contralateral ovarian biopsy) on the diseases side.

Two cases underwent a second surgery in the present hospital for left ovarian tumor resection, among which one case was admitted because of recurrence ten months after the first surgery, and the other case underwent surgery after recovery from the first surgery.

Twenty-five cases of GCC, including ten cases of dysgerminoma (five cases in Stage Ia, three cases in Stage I, one case in Stage IIb, and one case in Stage IIc), seven cases of immature teratoma (seven cases in Stage Ia), nine cases of yolk sac tumor (three cases in Stage Ia, two cases in Stage Ic, two cases in Stage IIIc, and two cases in Stage IV).

Twelve cases of epithelial carcinoma (nine cases in Stage Ia and three cases in Stage Ic), 15 cases of borderline carcinoma (12 cases in Stage Ia, one case in Stage Ic, one case in Stage IIc, and one case in Stage IIIc); one case of mixed GCC (dysgerminoma combined with endodermal sinus tumor). Fifteen cases underwent pelvic lymph node biopsy or dissection; 14 cases had lymph node metastasis and one case had metastasis.

Fourteen cases did not undergo postoperative chemotherapy while 38 cases were, including 24 cases were administered the PEB protocol, three cases the TP or TC protocol, nine cases with the PAC or PC protocol, and two cases with other protocols.

All the patients were followed up; the follow-up periods ranged from nine months to nine years; the follow-up contents included postoperative recovery, periodic review, menstruation restoration, and pregnancy conditions.

Data were archived with the use of Numbers. Categoric variables were compared by means of chi-square test. Statistical calculations were performed with the use of the Statistical Package for the Social Sciences version 13.0 (SPSS). $P < 0.05$ was considered to be statistically significant.

Results

Until December 2010, 51 cases still survived and one case died, with a survival rate of 98.07%, among which 42 cases survived two or more years.

One case with ovarian endodermal sinus tumor underwent the first surgery outside the present hospital for left ovarian cystectomy, and recurred six months later on the diseased side. She did not visit hospital regularly for personal reasons; therefore, widespread pelvic growth appeared which also extended to the contralateral ovary and with abdominal metastasis. This patient underwent conservative surgery for the second time, namely partial left ovarian cystectomy + right adnexectomy + pelvic tumor resection + pelvic lymphadenectomy + para-aortic lymph node biopsy + abdominal wall-metastatic lesion debridement. The pathology indicated the recurrence of ovarian endodermal sinus tumor, so she was combined with the PEB chemotherapy twice, and the disease conditions were under control. Due to the failure of in-time chemotherapy, the patient suffered from the recurrence and died of systemic metastasis.

Forty-five patients out of the 51 patients had menstrual onset, and the menstrual period and amount had no significant change, among of which two cases had normal menstrual onset during and after the chemotherapy while the remaining experienced menopause one to two times after the chemotherapy, but had restored normal menstruation after the chemotherapy was discontinued for one to ten months. Twenty-seven patients had the fertility requirements, and 18 of them achieved pregnancy; except for two cases of abortion, the remaining 16 cases had normal pregnancy period and delivery.

There was no significant difference in the two-year survival rate among the patients that underwent comprehensive staging surgery, tumor resection, or adnexectomy ($p > 0.05$, Table 1).

There was no significant difference in the two-year survival rate among the patients that underwent fertility-preserving adnexectomy, regardless if the tumor type was epithelial carcinoma or GCC ($p > 0.05$, Table 2).

Whether the postoperative chemotherapy was performed or not did not affect the pregnancy success rates of the patients ($p > 0.05$, Table 3).

Discussion

Malignant GCC derives from the primordial germ cells and occurs more in young women and girls with high malignant degree and poor prognosis. In the past 20 years, the application of platinum-based combined chemotherapy made the malignant GCC become the malignant ovarian cancer with the best treatment effects, and the sustained remission rate of the patients in clinical Stage III could reach 50~100%. In the past, the average survival period of endodermal sinus tumor was only one year, and the five-year survival rate was increased to more than 90% currently. Young patients could undergo FPT regardless of early or later stage; the treatment model of FPT combined with normative postoperative chemotherapy had been widely used in clinical practice and achieved good consensus. The study enrolled 25 cases of malignant GCC, and except for one case of recurrence and death caused by non-tumor disease; the remaining all achieved tumor-free survival. Furthermore, the two cases in Stage III ovarian endodermal sinus tumor also achieved tumor-free survival after regular chemotherapy, among which one case was followed up for two years and became pregnant once, and the case was followed up for six months from the end of the chemotherapy and no abnormality was found.

Currently, there still exists the controversy whether ad-

Table 1. — *Two-year survival rates of different surgical types.*

	Cases	2-year survival rate
Comprehensive staging surgery	12	12 (100%)
Tumor resection or adnexectomy	32	30 (93.75%)

Note: Chi-square test, $p > 0.05$.

Table 2. — *Two-year survival rates of malignant ovarian tumors with different pathological types.*

	Cases	2-year survival rate
Malignant epithelial carcinoma	11	11 (100%)
Malignant GCC	20	19 (95%)

Note: Chi-square test, $p > 0.05$.

Table 3. — *Relationships of postoperative chemotherapy and pregnancy success rate.*

	Cases (with fertility requirements)	Pregnancy cases
With postoperative chemotherapy	17	10 (58.82%)
Without postoperative chemotherapy	10	6 (60%)

Note: Chi-square test, $p > 0.05$.

juvant chemotherapy should be performed after the surgery of Stage I malignant GCC; some scholars suggested close follow-up instead of chemotherapy [13]. The more accepted view was that unless supported by the comprehensive accurate staging, all other patients except for those in Stage Ia of G1 needed chemotherapy.

American Society of Clinical Oncology recommendations on fertility preservation in cancer patients were [14]: patients should undergo comprehensive accurate staging surgery and meet the following conditions [1] young and eager to give birth; [2] in Stage Ia; [3] with good cell differentiation (G1); [4] the contralateral ovary shows no abnormal appearance or negative biopsy; [5] with negative peritoneal cytology; [6] with negative results in both high-risk area exploration and biopsy; [7] could be followed up; [8] could undergo hysterectomy or contralateral adnexectomy according to the situations after completing fertility. Patients in late ovarian cancer stage normally had high recurrence rate and poor prognosis; therefore, patients with ovarian cancer later than Stage II would not be suitable for the conservative surgical treatment [15]. Presently, the currently best-available data suggest that the use of FSS for invasive epithelial ovarian cancer seems safest in FIGO Stage IA/Grade 1 and FIGO Stage IC/Grade 1 in completely staged patients, which corresponds with the lowest common denominator of the current German and international guidelines [16]. According to another literature data, conservative surgery should be considered in the treatment of young women with Stage IA, Grades 1 and 2. FSS in clear cell cancer and high risk patients with FIGO Stage ≥IA G3 is still under debate [17].

To treat Stage IC, a multi-institutional study about recurrence-predicting prognostic factors for patients with EOC confined to intraoperative rupture (IC1), FSS may be proposed, if without tumor-associated dense adhesion. However, those with preoperative rupture, surface invasion (IC2), and positive cytology (IC3) showed a greater risk of recurrence, suggesting that they are not recommended candidates [18].

The 12 cases of malignant epithelial carcinoma in this study all preserved their fertility and tumor-free survived until now; the two-year survival rate was 100%, showing no significant difference in fertility-preserving rate with those with malignant ovarian GCC, indicating that it was feasible to preserve the fertility of patients with early ovarian cancer. In this study, one case in Stage Ic of poorly differentiated serous adenocarcinoma did not suffer from recurrence in the five-year follow-up; therefore, it provided information for exploring the conservative surgical indications of EOC. Whether the conservative surgical indications of EOC could be widened still needs to be certified by multi-center large-sample evidence-based medicine.

Ovarian borderline carcinoma (OBC) is also known as low-grade malignant potential ovarian tumor and normally undergoes surgical treatment methods, including conservative surgery and radical surgery. A systematic review of literature and meta-analysis was preformed. Given BOT general good prognosis, low mortality rates, and general short-follow-up of most studies [19], it was reported that the five-year survival rate was nearly 100%, and the patients that died of OBC were rare. A series of 572 women with Stage I EOC showed no differences in five-year overall survival (OS) or disease-free survival between those having undergone radical hysterectomy or fertility-sparing surgery [20]. Currently, it was widely recognized that the postoperative recurrence rate of conservative surgery towards OBC was higher than that of non-conservative surgery, but it did not increase the mortality rate caused by the postoperative recurrence; furthermore, the majority of the recurrent tumors were still OBC, which could still be resected surgically [21], so FPT was also feasible.

Presently, most scholars advocated the patients in Stage I that were young and wanted to preserve the fertility to undergo FPT, and the chemotherapy should only be used for the patients with residual lesions and recurrence [22]. A retrospective analysis of 339 OBC cases showed no significant difference in the recurrence or progression rate between the patients with or without postoperative adjuvant chemotherapy [23]. In this study, the 15 OBC cases preserved their fertility function, and no recurrence oc-

curred; one case in Stage IIIc with bilateral ovarian serous borderline papillary fibroadenoma underwent staging adnexectomy on one side and ovarian biopsy on the contralateral side, with no postoperative chemotherapy; the 33-month follow-up showed no recurrence. Therefore, the author of this study thought that the indications of FPT towards OBC could be extended.

The main purpose of FPT aimed at post-FPT childbearing and had obtained increasing attention. The impacts of chemotherapy on ovarian functions were mainly reflected in two aspects: menstruation and pregnancy. A study showed that chemotherapy affected the ovarian functions, resulting in reversible menopause, while exhibited no adverse effect on pregnancy outcome. Of course, the impacts of chemotherapy on ovarian functions were related with the type, drug dosage, and administration time of chemotherapeutic drugs, as well as age [24]. The 38 cases with postoperative supplementary chemotherapy reported in this study restored their menstruation one to ten months after the chemotherapy, the younger the patient, the relatively faster the menstruation recovery, among which two cases (12- and 18-years-old) restored normal menstruation during and after the chemotherapy, respectively. The pregnancy rate in this study was 59.26%, consistent with most foreign studies, and there was no significant difference in the impacts on pregnancy between the chemotherapy and non-chemotherapy group, indicating that chemotherapy did not affect the ovarian functions; however, it still requires multi-center large-sample studies for its verification.

It has been always controversial whether staging surgery should be performed during FPT in patients with malignant ovarian tumors. As for OBC, Fauvet *et al.* [25] suggested that there was no significant relationship between the staging surgery and recurrence rate of OBC. NIH [26] reported that if there existed larger residual lesion(s), the surgery should be performed firstly followed by the staging; otherwise, staging surgery should not be encouraged. As for malignant ovarian GCC, Billmire *et al.* [27] reported 131 cases of surgery plus chemotherapy, and only three cases underwent comprehensive staging surgery; 21% did not undergo peritoneal washing fluid examination, 36% did not undergo greater omentectomy, and 97% did not undergo bilateral lymph node biopsy; the overall six-year survival rate reached more than 95%. As for malignant EOC, some scholars believed that the lymph node metastasis rate in late ovarian cancer was high and it was not sensitive to chemotherapy; therefore, comprehensive staging surgery should be performed as much as possible, namely the retroperitoneal lymph node dissection and at least lymph node biopsy; the conservative surgery normally selected early cases, which had low lymph node metastasis rate, so if the careful exploration showed no significantly swelled lymph node, the lymph node dissection could also not be performed. Fifteen cases in this study underwent the dissection or biopsy, and the intraoperative exploration found no case of celiac growth; all the lymph node pathologies were negative; one case with wide abdominal metastasis exhibited positive lymph nodes, while the statistical analysis showed no significant difference in the impacts between the comprehensive staging surgery and simple surgical tumor debulking/resection on the diseased side towards the survival rate. Therefore, this study showed that since the staging surgery towards OBC and GCC did not affect the recurrence rate, and the indications for selecting the conservative surgery towards EOC were much more stringent together with extremely low lymph node metastasis rate, the non-staging surgery of malignant ovarian cancer that could shorten the operation time and reduce the surgical trauma should firstly be considered unless other suspicious lesions have been found.

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