Prognosis of primary peritoneal carcinoma: effect of cytoreductive surgery combined with neoadjuvant chemotherapy after laparoscopic diagnosis and evaluation: a multi-center trial

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Summary

Objective: To evaluate the clinical outcome and prognosis of patients with primary peritoneal carcinoma (PPC) treated with cytoreductive surgery and neoadjuvant chemotherapy after laparoscopic diagnosis. *Material and Methods:* We retrospectively reviewed 29 patients with PPC, treated between March 2001 and June 2009 at three hospitals. All patients underwent laparoscopy to diagnose and evaluate whether they were good candidates for optimal cytoreductive surgery. After confirmed to be PPC histologically, the patients who were not suitable to undergo optimal cytoreductive surgery received chemotherapy for three to six cycles before operation, and then underwent cytoreductive surgery, followed with chemotherapy again for six cycles. The study included patient demographics, surgery procedures, surgery stage, pathologic findings, chemotherapy programs, and outcomes. *Results:* The mean age of the 29 patients was 58.5 years. One patient was at Stage IIIB, 23 at Stage IIIC, and five at Stage IV. The rate of optimal cytoreductive surgery was 79.3%. At the time of this review, three patients had stable disease - two with progressive disease, eight were partial responders, and 16 were complete responders; 16 patients were alive without evidence of disease, seven were alive with disease, and six had died from disease. The mean and median overall survival time was 46 and 48 months. *Conclusion:* Combination of neoadjuvant chemotherapy and cytoreductive surgery after laparoscopic diagnosis and evaluation is effective in the treatment of patients with PPC.

Key words: Laparoscopic diagnosis; Neoadjuvant chemotherapy; Cytoreductive surgery; Primary peritoneal carcinoma; Multi-center trial.

Introduction

Primary peritoneal carcinoma (PPC) is a malignancy that spreads widely inside the peritoneal cavity, involving mostly the omentum with minimal or no ovarian involvement [1, 2]. However histopathologic, immunohistochemical, and clinical similarities have been observed between PPC and serous epithelial ovarian cancer (EOC) [3-6]. Most of these patients were diagnosed with malignant ovarian carcinoma; optimal cytoreductive surgery is difficult to perform for patients with advanced stage of PPC, which is the main reason why those patients had a worse prognosis.

Therefore, we considered if tumors could be reduced before surgery, if there would be more chances to perform optimal cytoreductive surgery. All of the patients of our study were confirmed to be PPC first by laparoscopic biopsy. If they were not good candidates for optimal cytoreductive surgery, evaluated by laparoscopy, they received chemotherapy for three to six cycles first, and then underwent cytoreductive surgery, followed by chemotherapy for six cycles postoperatively. The aim of this study was to evaluate the clinical outcome and prognosis of patients with PPC treated with cytoreductive surgery combined with neoadjuvant chemotherapy after laparoscopic diagnosis and evaluation.

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Material and Methods

We reviewed the records of 29 patients with clinically and histologically confirmed PPC based on the Gynecologic Oncology Group criteria [3], who were treated between March 2001 and June 2009 at three hospitals all affiliated with Tongji University. Shanghai, China as follows:

1) Both ovaries had to be either physiologically normal in size or enlarged by a benign process (4.0 cm in the largest diameter).

2) Involvement at extraovarian sites had to be greater than that on the surface of either ovary.

3) Microscopically, the ovarian component had to be one of the following:

a) nonexistent;

b) confined to the ovarian surface epithelium with no evidence of cortical invasion;

c) involving the ovarian surface epithelium and underlying the cortical stroma but any given tumor size had to be less than 5 × 5 mm;

d) tumors less than 5 × 5 mm within the ovarian substance associated with or without surface disease.

4) Hstologic and cytologic characteristics of the tumor had to be predominantly of serous type, similar or identical to ovarian serous papillary adenocarcinoma of any grade.

The following clinical data were collected from the medical records of each patient: age at diagnosis, presenting symptoms, presence or absence of ascites, amount of ascites, preoperative CA125 values (U/ml), surgical stage, *modus operandi*, histopathology, type and cycle of chemotherapy, response to chemotherapy, follow-up time and survival status.

Fig. 1

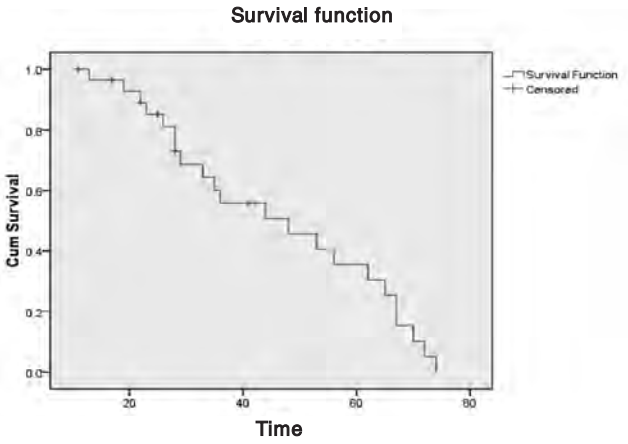

Fig. 2

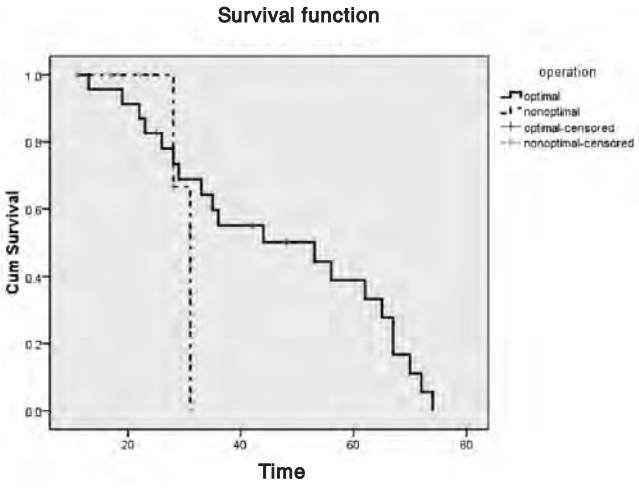

Fig. 3

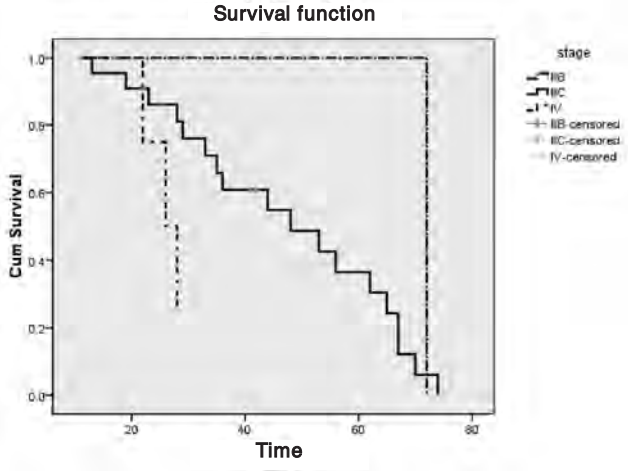

Figure 1. — Kaplan-Meier cumulative survival curve for overall survival.

Figure 2. — Kaplan-Meier cumulated survival curve for optimal and non-optimal surgery.

Figure 3. — Kaplan-Meier survival curve of women with PPC by stage.

All patients in our study were confirmed to have PPC by laparoscopic biopsy. After evaluation of laparoscopy, they received chemotherapy: 11 with paclitaxel (175 mg/m^2) and carboplatin (area under the curve 5); 18 patients received paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2) for three to six cycles, and then underwent cytoreductive surgery. Standard procedures for cytoreductive surgery consist of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and maximal debulking of metastatic tumors. Systematic pelvic and/or aortic lymphadenectomies are allowed. Then all patients receive treatment with the same chemotherapy program again as before for six cycles.

Each patient's clinical status was determined up to the last available date. Survival time was measured in months from the time of diagnosis to the date of last follow-up or death. Survival curves were generated using Kaplan-Meier survival analysis. Data were analyzed by SPSS 16.0 (SPSS Inc., Chicago, IL).

Results

Table 1 outlines the clinicopathologic characteristics of the patients. Cytoreductive surgeries followed by chemotherapy were performed by laparotomy in eight patients and in 21 by laparoscopy. At the end of the primary debulking operation, eight patients (20.7%) had documented macroscopic residual disease (> 1 cm), making the overall rate of optimal cytoreduction 79.3%.

The mean and median survival was 46 and 48 months. The survival curve for overall survival of all patients is shown in Figure 1. Patients who had optimal cytoreduction had a longer mean survival (46 months) than those who had suboptimal cytoreduction (41 months; Figure 2, $p = 0.042$). Also there was a difference in survival among stages of groups (Figure 3, $p = 0.032$).

At the time of this review, two patient had progressive disease, three patients had stable disease, eight were partial responders, and 16 were complete responders (Table 2); 16 patients were alive without evidence of disease, seven were alive with disease, and six had died from disease.

Discussion

PPC is a rare primary peritoneal tumor [7]. It is believed to arise from the secondary Müllerian system, which comprises the pelvic and lower abdominal mesothelial lining. The mesothelium of the peritoneum and the germinal epithelium of the ovary arise from the same embryologic origin, therefore the peritoneum may retain the multipotentiality of the Müllerian system and allow a primary carcinoma to develop. Thus, PPC shares many of the clinical and histologic features [7] of papil-

Table 1. — *Clinicopathologic characteristics of PPC patients*.

PPC (n = 29)	mean ± SD or n (%)
Mean age (years)	58.5 ± 9.4
Mean CA125 (U/ml)	2374.4 ± 1137.4
Mean volume of ascites (ml)	629.4 ± 315.6
Median survival (months)	43.0 ± 6.5
Mean survival (months)	46.3 ± 4.2
Main presenting symptom	
Abdominal distension	19 (65.5%)
Abdominal pain	11 (37.9%)
Gastrointestinal symptoms	14 (48.3%)
Weight loss	5 (17.4%)
Stage at diagnosis	
IIIB	1 (3.5%)
IIIC	23 (79.3%)
IV	5 (17.2%)
Surgery procedure	
Laparotomy	8 (27.6%)
Laparoscopy	21 (72.4%)
Optimal debulking	23 (79.3%)
Histologic type	
Serous	26 (89.7%)
Mucoid	2 (6.98%)
Clear cell	1 (3.5%)

Table 2. — *Response rate to adjuvant chemotherapy*.

	No. of patients	%
CR	16	55.2
PR	8	27.6
SD	3	10.3
PD	2	6.9
NE	0	0

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

lary serous ovarian carcinoma [8]. However, the etiology, pathogenesis, cells of origin, and clinical characteristics of PPC remain obscure. The differential diagnosis may include adenocarcinoma of unknown primary tissue, malignant mesothelioma, and peritoneal adenocarcinoma, as well as metastatic breast, gastrointestinal and ovarian malignancies [9].

Patients with PPC have been reported to have significantly worse [10-12] or similar [3, 13-15] survival rates compared to those with EOC. The outcome of PPC depends on age, surgery stage, size of focus, residual tumor, and physical state. Nam *et al*. [15] reported that the outcome of PPC is mainly decided by the degree of cytoreductive surgery. Most people go to doctors when there are significant symptoms which means at an advanced stage. The rate of optimal cytoreduction in PPC has been reported to vary from 33% to 70% [16, 17], which resulted in less than 1.0 cm residual tumor.

We use laparoscopy to explore PPC and evaluate the criteria for resectability, which is minimally invasive surgery. Because of the minimally invasive character of laparoscopy, patients can recover in a shorter time than with laparotomy [17], and thus chemotherapy is not postponed given their poor physical state. Moreover, the possibility of spread of malignant cells is much lower than with laparotomy. In our group of patients, we did not find metastasis from the puncture location in laparoscopy. Therefore, laparoscopy is a reliable method of exploring PPC in advanced-stage ovarian cancer and for selecting candidates for neoadjuvant chemotherapy in order to conduct complete cytoreduction surgery. It also contributes to a better quality of life for patients found to have unresectable disease [18].

The presence of residual disease after surgery is one of the most important adverse prognostic factors for survival [19]. Neoadjuvant chemotherapy has been proposed as an alternative approach to conventional surgery as the initial management of bulky ovarian cancer, with the goal of improving surgical quality. Primary surgical cytoreduction followed by chemotherapy usually is the preferred management of advanced (Stage III or IV) PPC and ovarian cancer. It helps in selecting patients for feasible and relative cytoreductive surgery. As the tumors can be reduced through chemotherapy before surgery, it is more likely that optimal surgery can be performed. In our group, 79.3% patients had optimal cytoreductive surgery after neoadjuvant chemotherapy, which is a higher rate of optimal cytoreductive surgery than previous reports [16, 17]. Also, in our study, the mean survival time in the optimal group was higher than non-optimal group.

Since 1979, cisplatin-based multi-agent chemotherapy has been regarded as the standard treatment for patients with epithelial ovarian cancer and, consequently, for patients with PPC [20]. In 1996, a randomized Gynecologic Oncology Group trial demonstrated a significant survival advantage for patients with advanced EOC whose residual disease was > 1.0 cm treated with paclitaxel plus cisplatin compared to similar patients who were treated with cisplatin plus cyclophosphamide [23]. As a result of this study, the combination of paclitaxel and cisplatin is considered the first-line chemotherapy for patients with serous epithelial cancer. Of 17 patients in our study, two patients had progressive disease, three patients had stable disease, eight were partial responders, and 16 were complete responders; 16 patients were alive without evidence of disease, seven were alive with disease, and six had died from disease. We had a higher rate of complete response than Nam *et al*. [15] reported.

The median survival time after cytoreductive surgery with combined neoadjuvant chemotherapy reported in our study (48 months) was comparable to that of an earlier study [16] (41 months) and far longer than the 11.3-17.8 months reported previously [13, 14, 20, 22]. This may be related to our combination treatment with neoadjuvant chemotherapy and cytoreductive surgery after laparoscopic diagnosis and evaluation. Although a larger sample is needed, we believe that the combination of neoadjuvant chemotherapy and cytoreductive surgery after laparoscopic diagnosis is effective in the treatment of patients with PPC, which prolongs patient survival time.

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