



Advanced primary peritoneal carcinoma: clinicopathological and prognostic factor analyses

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Abstract: Objective: To investigate the factors favoring a positive prognosis for advanced primary peritoneal carcinoma (PPC). Methods: Twenty-four cases meeting the criteria for PPC were analyzed retrospectively for the clinicopathologic profiles. Immunohistochemistry was used to determine the expressions of p53, Top2 α , Ki-67 and Her-2/neu. Then all these clinicopathological factors and molecular markers were correlated with the prognosis. Results: There were 15 cases of primary peritoneal serous papillary carcinoma (PPSPC), 6 cases of mixed epithelial carcinoma (MEC) and 3 cases of malignant mixed Mullerian tumor (MMMT). All patients underwent cytoreductive surgery with optimal debulking achieved in 3 cases. Among those receiving first-line chemotherapy, 13 patients received the TP regimen (paclitaxel-cisplatin or carboplatin) and 7 patients received the PAC regimen (cisplatin-doxorubicin-cyclophosphamide). The median overall survival of all patients was 42 months, while the breakdown for survival time for patients with PPSPC, MMT and MEC was 44, 13 and 19 months, respectively. The expressions of p53, Top2 α and Ki-67 were all demonstrated in 11 cases respectively. None showed the expression of Her-2/neu. There were significant differences in the median survival between patients with PPSPC and those with MMT (44 months vs 13 months, $P < 0.05$), also between patients receiving TP combination and those receiving the PAC regimen (75 months vs 28 months, $P < 0.05$). Another significant difference in the median progression-free survival (PFS) was identified between patients with positive p53 immunostaining and those with negative p53 immunostaining (15 months vs 47 months, $P < 0.05$), whereas age, menopausal status, residual tumor size and the other molecular factors did not significantly impact survival. Conclusion: Patients with PPC should be treated with a comprehensive management plan including appropriate cytoreductive surgery and responsive chemotherapy. Overestimating an optimal debulking surgery may not benefit survival. The pathologic subtype, chemotherapy regimen and p53 overexpression were significant prognostic factors.

Key words: Primary peritoneal carcinoma (PPC), Cytoreductive surgery, Chemotherapy, Immunohistochemistry, Prognosis

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INTRODUCTION

Female primary peritoneal carcinoma (PPC), first described by Swerdlow (1959), has the characteristic of diffuse involvement of the peritoneum by papillary carcinoma in the absence of an obvious primary site and grossly normal ovaries, or minimal involvement (Bloss *et al.*, 1993). Histologically identical to advanced epithelial ovarian cancer (EOC), PPCs account for 7%~13.8% of ovarian carcinomas

(Fromm *et al.*, 1990). Most reported PPC cases are primary peritoneal serous papillary carcinoma (PPSPC) (Chu *et al.*, 1999), while peritoneal mixed epithelial carcinoma (MEC) and malignant mixed Mullerian tumor (MMMT) are rarely reported. Despite growing interest in this entity, studies do not reach an agreement on its biological behavior and prognosis, especially when compared with EOC (Fromm *et al.*, 1990; Killackey and Davis, 1993; Bloss *et al.*, 2003). It is generally suggested that PPC should be managed following the treatment regimens established for EOC (Piver *et al.*, 1997; Eltabbakh *et al.*, 1998a). However, controversy exists concerning

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the ability to perform optimal surgical debulking and its clinical significance in PPC (Fromm *et al.*, 1990; Ben-Baruch *et al.*, 1996; Eltabbakh *et al.*, 1998a). So far only a few studies have examined the molecular changes associated with PPC and do not find a definite prognostic factor. The aim of this study was to develop an accurate analysis of PPC treatment by reviewing the long-term prognosis following comprehensive management of 24 patients with PPC and to investigate the correlation of some molecular markers with the prognosis.

MATERIALS AND METHODS

Twenty-four patients with PPC were treated at Peking University People's Hospital from May 1996 to April 2005. The diagnosis of PPC was confirmed after a review of the operative and pathological findings of each case, and was based on the Gynecologic Oncology Group (GOG) criteria described by Bloss *et al.* (1993): (1) The ovaries are normal in size or enlarged by a benign process; (2) The involvement in the extraovarian sites must be greater than the involvement on the surface of either ovary; (3) Microscopically, the ovaries are not involved with the tumor or exhibited only serosal or cortical implants less than 5 mm×5 mm; (4) The histopathological and cytological characteristics of the tumor are predominantly of the serous type. Since PPC cases with nonserous histology have been reported (Altaras *et al.*, 1990), we included cases with nonserous Mullerian histology that fulfilled other inclusion criteria. Surgical staging was performed according to the Federation International of Gynecology and Obstetrics (FIGO; 1985) staging criteria for ovarian cancer. Evaluation of the clinical response to first-line chemotherapy was based on the World Health Organization (WHO) criteria and the response was characterized as a complete response, a partial response, a stable disease or a progression. The toxicity effects of chemotherapy were evaluated according to the US National Cancer Institute Common Toxicity Criteria (CTC).

The following clinical data were collected from the charts of each patient: age at diagnosis, menopausal status, preoperative CA-125 (carcinoma antigen-125) values (U/ml), color Doppler ultrasonography findings, presence or absence of ascites and

ascitic cytology test, surgical stage, pathological subtype, whether primary cytoreductive surgery was optimal (largest residual tumor mass ≤ 2.0 cm) or suboptimal (largest residual tumor mass > 2.0 cm), first-line chemotherapy regimen, response to chemotherapy, second-look surgery, date of tumor recurrence or progression, second-line chemotherapy, and follow-up information for the patients.

Whenever available, tissue blocks were retrieved and immunohistochemistry was performed using a standard streptavidin-peroxidase method. The antibodies against Top2 α (clone Ki-Si), p53 (clone D07), Ki-67 (clone 7B11) and Her-2/neu (clone CB11) were used. Rabbit serum served as a negative control for the primary antibody. Sections from breast cancer known to exhibit the four molecular expressions were used as a positive control. Then the staining slides were scored blindly by the pathologist according to the percentage of stained cells out of 100 cells counted (0: $< 5\%$; 1: $5\% \sim 25\%$; 2: $26\% \sim 50\%$; 3: $> 50\%$).

Data analysis was performed using the SPSS software package (version 13.0). Estimated survival curves were calculated using the product-limit method of Kaplan and Meier, and comparisons of the survival distribution group among groups defined by a discrete parameter were made using the log rank test. *P* values of < 0.05 were considered to be statistically significant in all cases.

RESULTS

The mean age of the patients was 59.0 years (range 35~75 years). Eighteen patients were menopausal and 6 were premenopausal. Preoperative CA-125 values were elevated (> 35 U/ml) in 23 (95.8%) cases, and among them 9 cases had levels greater than 1000 U/ml. All patients underwent cytoreductive surgery, which essentially involved bilateral salpingo-oophorectomy and resection of massive tumor lesions. Subsequently, a hysterectomy, appendectomy, intestinal resection and anastomosis, and resection or biopsy of pelvic and para-abdominal aortal lymph nodes were performed according to the range of lesions. Upon exploratory laparotomy, ascites were present in all cases and the ascites cytology test was positive in 19 (79.2%) cases. After primary debulking surgeries, 3 patients achieved optimal cy-

toreduction, and 21 achieved suboptimal cytoreduction. The surgical stage was III_c in 21 (87.5%) and IV in 3 (12.5%) patients. Fifteen patients had PPSPC, 6 had MEC (including adenocarcinoma, squamous carcinoma, transitional cell carcinoma, and undifferentiated carcinoma) and 3 had MMMTs.

Twenty patients received a first-line combined chemotherapy with TP regimen (paclitaxel-cisplatin or carboplatin) or PAC regimen (cisplatin-doxorubicin-cyclophosphamide) postoperation. Two patients with MMMTs received a variation of the following regimen: one was administered single cisplatin, due to poor conditions; the other received a regimen of cisplatin/pirarubicin/etoposide. Another two patients could not tolerate chemotherapy because of hepatic dysfunction. After 3~4 courses of chemotherapy, 3 patients with suboptimal cytoreduction underwent an intermediate cytoreductive surgery. Of these 3 patients, 1 showed no residual carcinoma and 2 showed residuals with a diameter less than 1 cm. Furthermore, these 3 patients experienced a disease-free interval of 12, 15 and 49 months. Five patients (20.8%) received a second surgery due to recurrence or an intestinal obstruction. One patient underwent a second-look operation with no positive lesion found.

During the follow-up period (ranging from 1 to 112 months), 3 cases lost contact. The 20 patients treated with first-line chemotherapy were included in the clinical response analyses. Among these patients, 11 (55.0%) were in complete remission, 5 (25.0%) were in partial remission, and 4 (20.0%) exhibited tumor progression. The median overall survival was 42 months (95% confidence interval (CI): 22~62 months); the 2-year survival rate was 63.0%, and the 3-year survival rate was 50.0%.

The various clinical parameters and the median survival time of patients with PPC are listed in Table 1. The prognosis of patients with PPC was not correlated with age, menopause, or size of the residual tumor, but associated with the pathological subtype and the regimen of chemotherapy. There was a significant difference in the median survival between patients with PPSPC and MMTT (44 months vs 13 months, $P < 0.05$), as shown in Fig.1a. Among the 20 patients, 13 received the TP regimen and 7 received the PAC regimen. There were no significant differences in age, menopausal stage, ascitic cytology, residual tumor size, stage, pathologic subtype, chemotherapeutic

course or side effects between the two groups. The mean survival time of patients who received the TP regimen was 75 months and that of patients who received the PAC regimen was 28 months with a significant difference, as shown in Fig.1b.

Table 1 Effects of clinical and pathological factors on the median survival time

| Factor | N | Median survival (months) | P |
|---------------------------------|----|--------------------------|--------|
| Age (year) | | | |
| ≥60 | 13 | 30 | >0.05 |
| <60 | 11 | 58 | |
| Menopause | | | |
| Yes | 18 | 30 | >0.05 |
| No | 6 | 47 | |
| Residual tumor size (cm) | | | |
| ≥2 | 21 | 42 | >0.05 |
| <2 | 3 | 33 | |
| Pathological subtype | | | |
| PPSPC | 15 | 44 | <0.05* |
| MEC | 6 | 19 | |
| MMMT | 3 | 13 | |
| First-line chemotherapy regimen | | | |
| TP | 13 | 75** | <0.05 |
| PAC | 7 | 28** | |

* $P < 0.05$, PPSPC vs MMTT; ** Mean survival time, for median survival was not observed

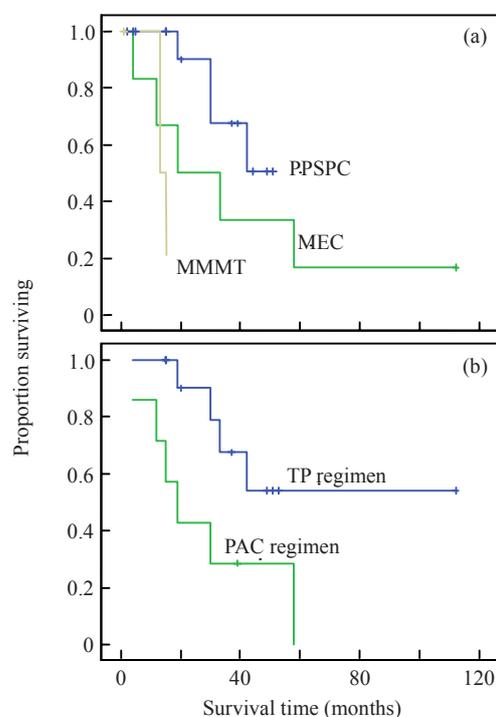


Fig.1 Survival curves by (a) pathological subtypes and (b) two kinds of chemotherapy regimens

Archival tissue blocks were available for immunohistochemistry study in 21 cases. The expressions of p53, Top2 α and Ki-67 were all demonstrated in 11 cases respectively. None showed the expression of Her-2/neu (demonstrated in Fig.2). The expression of the studied molecular markers, the median survival and progression-free survival (PFS) were listed in Table 2. As shown in Fig.3, a significant difference in the median PFS was identified between patients with positive p53 immunostaining and those with negative p53 immunostaining (15 months vs 47 months, $P < 0.05$).

DISCUSSION

To date, many studies have demonstrated the clinical and histopathological similarities between PPC and advanced EOC, as well as some differences in their biological characteristics and prognostic

factors. The mean age at the onset of PPC is generally thought to be 57~68 years, later than that of EOC (Eltabbakh et al., 1998b; Bloss et al., 2003). In the current study patients under 60 years of age had a longer survival time than did patients older than 60, but the differences were not statistically significant. This finding differs from a previous report indicating that age could significantly impact survival time (Eltabbakh et al., 1998a). The median survival time of PPC is generally 11~24 months (Fromm et al., 1990; Bloss et al., 1993; Killackey and Davis, 1993; Eltabbakh et al., 1998a), which is similar to that of EOC (Dubernard et al., 2004), although one report described that the median survival time of advanced EOC and PPC together was 45.8 months (Look et al., 2004). In the present study the median survival of all patients was 42 months.

Several studies have provided preliminary examination of the prognostic factors in patients with PPC. Eltabbakh et al.(1998a) demonstrated that age,

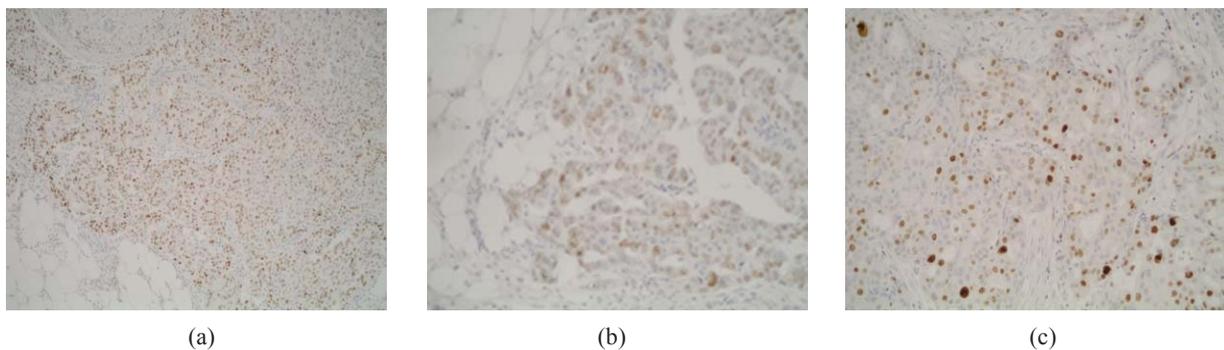


Fig.2 Immunohistochemical staining of PPC with (a) p53, (b) Top2 α and (c) Ki-67 antibodies
Original magnification: (a) 100 \times ; (b) 200 \times ; (c) 200 \times

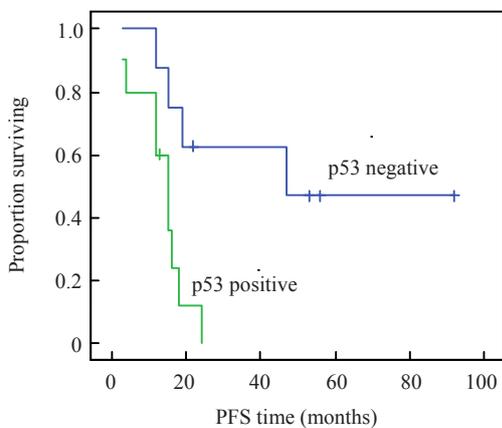


Fig.3 PFS curves by p53 immunostaining

Table 2 Effects of the expression of Top2 α , Ki-67 and p53 on the median survival and PFS

| | Median PFS (months) | P^a | Median survival (months) | P^b |
|---------------|---------------------|-------|--------------------------|-------|
| Top2 α | | | | |
| Positive | 16 | 0.24 | 68* | 0.21 |
| Negative | 15 | | 32* | |
| Ki-67 | | | | |
| Positive | 18 | 0.41 | 58 | 0.64 |
| Negative | 16 | | 42 | |
| p53 | | | | |
| Positive | 15 | 0.01 | 33* | 0.13 |
| Negative | 47 | | 71* | |

* Mean survival time, for median survival was not observed; ^a P for median PFS; ^b P for median survival

surgical stage, performance status, and the degree of cytoreductive surgery were significant prognostic factors for patients with PPC. Fromm *et al.* (1990) demonstrated that patients with PPC receiving multi-agent chemotherapy had a significantly longer survival time than those receiving single-agent chemotherapy. Look *et al.* (2004) reported that significant prognostic indicators included the prior surgery score, the completeness of the cytoreduction score and response to chemotherapy prior to surgery. Furthermore, extensive prior surgery without the protection of adjunctive intraperitoneal chemotherapy was associated with a poor prognosis. In the current study we reported that the pathological subtype and chemotherapy regimens had a statistically significant impact on survival time, whereas residual tumor size, age and menopausal status did not.

Since there are many similarities in the clinical profiles between PPC and EOC, many authors assert that optimal cytoreduction can significantly improve the prognosis of patients (Eltabbakh *et al.*, 1998a; Look *et al.*, 2004). However, PPC is of multifocal, multiclonal origin (Muto *et al.*, 1995), which is in contrast to primary EOC, and usually infiltrates the abdomino-pelvic peritoneum, diaphragm, liver, spleen, intestinal surface and roots of the mesenteries. Accordingly, cytoreductive surgery is not always optimal and it is necessary to evaluate whether the treatment of PPC should continue to be guided by the surgical procedures used to treat EOC. In the present study the median survival time was 33 months in patients who underwent optimal cytoreduction but was 42 months in those with suboptimal cytoreduction. The favorable survival reported in our study differed from previous reports that emphasized the importance of optimal cytoreduction (Eltabbakh *et al.*, 1998a; Look *et al.*, 2004). However, these findings were in agreement with previous reports indicating that residual tumor size did not influence survival time significantly (Fromm *et al.*, 1990; Mills *et al.*, 1988). According to the characteristics of PPC and our clinical experience, we believe that the surgical treatment for PPC should involve bilateral adnexectomy and resection of massive tumors to establish a firm diagnosis and reduce tumor load. However, if radical resection of tumors becomes very difficult and may result in severe injuries, the operative range should be limited so that postoperative combined chemotherapy could be administered as soon as possible. And intermediate cytoreduction can be an alternative.

Currently, according to the GOG criteria, the

first-line chemotherapeutic regimen of ovarian cancer, namely the TP regimen, is also recommended for PPC patients. Some authors believe that the TP regimen does not differ significantly from the PAC regimen with respect to the remission rate and survival time, although a thorough analysis of the relative effectiveness of the two regimens in PPC patients remains to be completed. Piver *et al.* (1997) compared 46 patients with PPC, among whom 25 received the PAC regimen and 21 received the TP regimen, and found no statistically significant differences in the overall survival and PFS time. Our findings demonstrated that the mean survival time was significantly longer in patients receiving the TP regimen than those receiving the PAC regimen, which was in agreement with Menzin *et al.* (1996)'s conclusions. Nevertheless, in light of the small sample size in the present study, large-scale, prospective, randomized and well-controlled studies are required to confirm the findings presented herein.

Most PPCs are serous papillary adenocarcinomas with relatively good prognoses (Killackey and Davis, 1993). Peritoneal MMMT is rare and is usually accompanied by a poor outcome. Garamvoelgyi *et al.* (1994) reviewed 15 cases of extragenital MMMTs and reported a median survival of 14 months. Shen *et al.* (2001) reported 5 patients with primary peritoneal MMMT, among whom 1 patient died within 1 month of diagnosis and 2 patients died within 1 year. In the present study the 3 cases with MMMT experienced a median survival of only 13 months after surgery, which was significantly different from the survival time of patients with PPSPC.

There is a lack of prognosis markers for patients with PPC. In this study we made an attempt at discovering some potential molecular markers that could help predict outcome. Gotlieb *et al.* (2001) found significant differences in Top2 α and Ki-67 expressions between the longer-survival EOC group and the shorter-survival one. Kowalski *et al.* (1997) described p53 overexpression in 48% of patients with PPC and Her-2/neu expression in 36%, although neither was predictive of prognosis. Halperin *et al.* (2001) reported that none of the expressions of Ki-67, p53 and Her-2/neu was significantly correlated with survival in PPC. In our relatively small study group we demonstrated that the overexpression of p53 was of prognostic value in terms of PFS, while Top2 α and Ki-67 expressions had no significant effect on survival.

In summary, the high survival rate reported here may be due to the comprehensive management plan in

which appropriate cytoreductive surgery generally involved bilateral adnexectomy and omentectomy. Some factors including pathological subtype, chemotherapy regimens and p53 overexpression had a statistically significant impact on survival time or PFS, whereas residual tumor size, age and menopausal status did not significantly impact the prognosis. The results of this small and heterogeneous study seem to indicate that optimal cytoreduction in primary surgery may not be a significant prognostic factor.

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