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Primary fallopian tube carcinoma - a retrospective analysis of 66 cases

L. Liu[1], X. Xu[2*], L. Jia[3*], M. Wei[4], B. Qian[4], Y. Wu[4], Y. Shen[4], X. Wang[4], H. Pei[4], X. Chen[4,5,6]

[1] Department of Obstetrics and Gynecology, Sihong People's Hospital, Sihong
[2] Department of Chemotherapy, Jiangsu Institute of Cancer Research, Nanjing, Jiangsu
[3] Department of Obstetrics and Gynecology, The Affiliated People's Hospital of Inner Mongolia Medical College, Inner Mongolia Autonomous Region
[4] Department of Gynecologic Oncology, Jiangsu Institute of Cancer Research, Nanjing, Jiangsu
[5] State Key Laboratory of Bioelectronics, Southeast University, Nanjing (China)
[6] Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX (USA)

Summary

Background: Primary fallopian tube carcinoma (PFTC) is a rare malignant gynecologic oncology. There was no consensus on the outcome related clinicopathological characteristics. Present study aims to determine the prognosis associate factors in PFTC. *Materials and Methods:* In this retrospective study, the authors identified 50 PFTC patients in Jiangsu Institute of Cancer Research and 16 cases in the Affiliated People's Hospital of Inner Mongolia Medical College between 1988 and 2013. Disease surveillance was conducted based on the follow-up protocol of MD Anderson Cancer Center. Cox proportional hazards model and log-rank test were used to assess the associations between potential clinicpathologic characteristics and the survival durations. *Results:* The median progression free survival (PFS) and overall survival (OS) of PFTC were 36.9 and 62.7 months, respectively. FIGO Stage ($p < 0.01$, 0.01), grade ($p = 0.02$, 0.03), tumor residual after initial debulking surgery ($p = 0.05$, 0.01), nadir CA-125 ($p = 0.01$, 0.01) were independently related with PFS and OS. The PFS and OS of patients with Stage II PFTC were similar as those with Stage III-IV (30.7 *vs* 28.3 and 61.9 *vs* 49.2 months, respectively) but poorer than those of Stage I cases (N/A). The PFS of patients with paclitaxel-based chemotherapy was longer than those with other regime (51.3 *vs* 33.1 months), but not OS (62.7 *vs* 42.6 months). The outcome of patients underwent optimal initial cytoreduction surgery was better than those of suboptimal ones (PFS 56.4 *vs* 21.2 months and OS 65.3 *vs* 47.9 months, respectively). *Conclusion:* PFTC patients with FIGO Stage II disease should be regarded as advanced disease. Paclitaxel based chemotherapy was associated with longer PFS but not OS in PFTC.

Key words: Fallopian tube carcinoma; Prognosis; Nadir CA-125.

Introduction

Primary fallopian tube carcinoma (PFTC) is an uncommon gynecologic cancer which constitutes about 0.14–1.8% of all malignant gynecological tumors [1]. The incidence of PFTC varies from 1.2 to 6.7 per million women in the Western populations. Presently, the most retrospectively studies in this disease involved small cohorts and there was no perspective study on the optimal initial therapy. Few studies are available regarding the influence of prognostic factors including well-defined therapy protocols for chemotherapy and surgery. Most controversies were reported due to heterogeneity of study design, the broad variety of definitions of patient's population, and the recruited standard.

There was a similarity of PFTC to epithelial ovarian cancer (EOC) in the molecular biological characteristics and clinical and pathological features. Evidences suggest that PFTC is associated with overexpression of p53 [2], HER2/neu [3], and c-myc [4]. BRCA 1/BRCA2 mutations were also reported to have a role in the tumorigenesis of PFTC [5-8]. The treatment line of PFTC is followed EOC. A new model deems that some human high-grade ovarian cancer may originate from secretory epithelial cells in the fallopian tube and epithelial-mesenchymal transition may play important role during this process [9]. However there are still several distinct characteristics to be emphasized. Different from EOC, PFTC is frequently found at early stage before tumor lesions spread to the extra-pelvic area or lymph nodes. The survival durations of PFTC is comparatively longer than those of EOC [10]. The authors have analyzed the relationship between the tumor markers, clinical and pathological features of EOC, PFTC, and primary peritoneal cancer and the prognosis in series studies [11-13].

To reveal the prognosis related factors including therapy selection, here the authors evaluated the clinical and pathological characteristics of PFTC from two Chinese centers and validated by another set of data from USA population (MD Anderson Cancer Center, MDACC).

**First co-authors contributed equally to the paper.*

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Table 1. — *The characteristic of PFTC.*

Characteristic	Percentage (%) / Median (range)
Age (years)	54.5 (25-82)
Baseline CA-125 level (U/ml)	595 (16-7840)
Nadir CA-125 level (U/ml)	10 (5-35)
Histology	
Serous	46 (69.7%)
Endometrioid	11 (16.7%)
Mixed	4 (6.1%)
Undifferentiated	3 (4.5%)
Unknown	2 (3.0%)
Grade	
1	14 (21.2%)
2	17 (25.8%)
3	35 (53.0%)
FIGO Stage	
I	18 (27.3%)
II	12 (15.2%)
III	25 (37.9%)
IV	11 (16.7%)
IHC	
P53(+)	44 (66.7%)
CA-125(+)	53 (80.3%)
Ki67(+)*	38 (57.6%)
EGFR(+)	21 (31.8%)

Ki67(+)*: the positive imminostaining cells >10% as cutoff point
FIGO: International Federation of Gynecology and Obstetrics
IHC: immunohistochemistry

Materials and Methods

Study population

This study was approved by the institutional review boards of Jiangsu Institute of Cancer Research (JICR) and Affiliated People's Hospital of Inner Mongolia Medical College (APHIMMC). The authors identified 50 PFTC patients in JICR and 16 cases in APHIMMC from clinical stations between January 1, 1988 and September 1, 2013. Those who did not undergo the standard first line treatment in the present centers were excluded. After primary therapy, the routine follow-up protocol was conducted according to the surveillance protocol of MDACC. The relevant clinic pathological data included: age, presenting symptoms, past medical history, family history, preoperative investigations (including tumor markers), the histological type and FIGO Stage and grade of the tumor, volume of ascites, details of the primary surgical procedure, management protocols of primary and recurrent disease, and follow-up information as shown in Table 1. All of the cases of PFTC were independently reviewed by L. Hou from JICR, who is a lead gynecological pathologist.

Diagnosis criteria and therapy principals

The pathological criteria of PFTC for differentiating it from ovarian and other gynecological malignancies were raised by Hu *et al.* (1950) and modified by Sedlis *et al.* (1978) [14]. This widely accepted proposal for diagnosis of PFTC includes these four essentials: the main tumor arises from the endosalpinx; the histological pattern reproduces the epithelium of tubal mucosa; transition from benign to malignant tubal epithelium is demonstrable; the ovaries or endometrium are either normal or contain tumor smaller than the tumor in the tube. System staging of PFTC was followed the International Federation for Obstetrics and Gynecology (FIGO) in 1991. Avidin-biotin peroxidase system was routinely performed for immunohistochemical staining. The primary antibodies were: p53 (1:100, DO-7), Ki67 (1:100, clone MIB-1), epidermal growth factor receptor (EGFR clone 3C6, $3mgml^{-1}$) and CA-125 (1:100, EPR1020(2).

The primary therapy mostly included cytoreductive surgery (CRS) and adjuvant chemotherapy. The predominant adjuvant chemotherapy protocols included: CAP (cyclophosphamide-500 mg/m^2, doxorubicin-30 mg/m^2, and cisplatin-75 mg/m^2), CP (carboplatin AUC-6 plus cyclophosphamide-500 mg/m^2) and TP (carboplatin AUC-6, paclitaxel 135-175 mg/m^2). The authors used the Response Evaluation Criteria in Solid Tumors (RECIST) criterion and adapted WHO standard to assess objective therapy response and tumor progression which took into account the measurement of the longest diameter for all target lesions [15-18]. Complete response (CR) was thought to be the disappearance of all target lesions; partial response (PR) was at least a 30% decrease in the sum of the longest diameter of target lesions, the baseline sum longest diameter as reference; progressive disease (PD) was at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded, since the treatment started or the appearance of one or more new lesions; stable disease (SD) was defined to be neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, the smallest sum longest diameter since the treatment started as reference. The criteria of complete clinical remission included: (1) no residual tumor on physical examination and imaging studies; (2) absence of tumor-associated clinical symptoms; and (3) serum CA-125 concentration of less than or equal to 35 U/ml. Pathological complete remission was judged by laparoscopy and/or laparotomy. Optimal CRS was defined as the threshold of $\leq$ 1 cm of the residual tumor, and suboptimal debulking was determined as having more than one cm of nodules left. Overall survival (OS) was defined as the time interval from diagnosis until death, or until last follow-up examination of patients who are still alive. Progression-free survival (PFS) was the length of time during and after primary treatment wherein the patient's condition did not worsen.

Statistical analysis

Cox proportional hazards model was used to assess the relationship between the clinical characteristics and the survival. Stepwise regression was conducted to build the univariate and multivariate analysis models. The log-rank test and Kaplan-Meier curve were used to assess this relationship. Logistic regression analysis was used to explore outcome related factors. The p values < 0.05 was considered statistically significant. All analyses were conducted using the SPSS statistical software program (version 18.0).

Results

Patient characteristics

There were 46 (69.7%) serous subtype of PFTC in present study. Median follow-up time was 65.0 months (interquartile range, 46.9 months to 88.4 months). Thirty patients (45.5%) reported experiencing vaginal bleeding and discharge , 25 (37.8%) abdominal colicky pain, 16 (24.2 %) abdominal mass, and four (6.1 %) gastrointestinal dysfunction. There were nine (13.6 %) cases experiencing typical Latzko's triad of symptoms which consisted of intermittent profuse serosanguinous vaginal discharge,

Table 2. — *Primary therapy of PFTC.*

Variable	Percentage (n, %)
Neochemotherapy	
Yes	6 (9.1%)
No	60 (90.9%)
Surgery	
Biopsy or BSO	6 (9.1%)
TAH & BSO	9 (18.2%)
TAH & BSO & omentectomy	14 (21.2%)
TAH & BSO & omentectomy & lymphadenectomy	34 (51.5%)
Tumor residual	
Optimal (≤ 1 cm)	41(62.1%)
Suboptimal (> 1 cm)	18 (27.2%)
Unknown	7 (10.6%)
Lymph node metastasis	
Positive 6 (17.6%)	
Negative 26 (76.5%)	
Unknown	2 (5.9%)
Front line chemotherapy	
Non-paclitaxel	24 (36.4%)
Including paclitaxel	40 (60.1%)
Unknown	2 (3.0%)
No. of front line chemotherapy cycles (course)	
< 6	5 (7.6%)
≥ 6	61 (92.4%)
Radiotherapy	2 (3.0%)

TAH & BSO: total abdominal hysterectomy with bilateral salphingo-oophorectomy.

colicky pain relieved by discharge, and abdominal or pelvic mass. There were 35 (53.0%) patients with pelvic or abdominal mass and only six (9.1%) cases with ascites in physical examination. A definite or suspected preoperative diagnosis of PFTC was made only in eight (12.1%) of all patients.

Objective tumor response of primary treatment

CRS as the definite treatment which involves total abdominal hysterectomy with bilateral salphingo-oophorectomy and omentectomy in 48 (72.7%) PFTCs. Lymphadenectomy was performed in 34 (51.5%) selection patients as shown in Table 2. There were 41 (62.1%) patients that met optimal outcome by initial CRS and 40 (60.6%) cases that underwent chemotherapy including paclitaxel. At the end of initial treatment, there were 45 (68.2%) PFTCs meet the criteria of CR, nine (13.6%) cases that met PR, five (7.6%) cases that met SD, and seven (10.6%) cases that were PD.

Survival related factors

The median PFS and OS of PFTC were 36.9 months (18.8 - 55.0) and 62.7 months (48.1 - 77.3), respectively. Univariate Cox proportional hazards model revealed that FIGO Stage, pathological grade, outcome of CRS, nadir CA-125 level, ascites, and chemotherapy protocol were associated with OS and PFS while lymph node metastatic was associated with PFS but not OS (Table 3). Multivariate analysis revealed that FIGO Stage, nadir CA-125 level, outcome of CRS, and chemotherapy protocol were independent OS and PFS predictors in PFTC (Table 4).

Table 3. — *Univariate analysis of survival-related characteristics in PFTC.*

Variable	OS		PFS	
	OR	95% CI	OR	95% CI
FIGO Stage				
I	1.000	Reference	1.00	Reference
II	5.5	1.6–24.2	4.3	1.4–14.1
III	7.8	1.8–25.9	6.8	1.2–35.4
IV	9.7	2.3–42.5	10.7	1.9–57.8
Grade				
1	1.000	Reference	1.00	Reference
2	3.7	1.5–14.1	2.2	0.9–21.3
3	5.1	2.1–33.9	4.5	1.4–22.7
Lymph node metastasis	2.1	0.9–6.9	1.7	0.8–5.3
Tumor residual	6.2	3.2–12.8	5.3	2.7–11.3
Non-paclitaxel	2.3	1.5–5.2	1.5	1.3–3.9
Ascites	1.8	1.1–13.7	1.3	0.9–15.1
Nadir CA-125	1.03	1.0–1.06	1.04	1.01–1.08

OS: overall survival; PFS: progression-free survival; OR: odds ratio; CI: confidential interval

Table 4. — *Multivariate analysis of survival-related characteristics in PFTC.*

Variable	OS		PFS	
	OR	95% CI	OR	95% CI
FIGO Stage				
I	1.000	Reference	1.00	Reference
II	2.8	1.2–16.0	4.4	1.0–17.1
III	5.1	1.4–24.9	7.8	1.3–21.7
IV	6.4	1.9–32.3	8.7	1.8–24.8
Tumor residual	4.1	2.8–7.1	3.9	1.3–9.4
Non-paclitaxel	1.9	1.2–6.2	1.4	0.9–3.7
Nadir CA-125	1.01	1.0–1.04	1.01	1.01–1.05

The OS and PFS of FIGO Stage II patients with were poorer than those who were Stage I, but not Stage III-IV in PFTC (30.7 *vs* 28.3 and 61.9 *vs* 49.2 months, respectively; Figures 1A and 1B). Unlike in EOC, Stage II cases indicated poorer outcome than those of Stage I. In patients underwent paclitaxel based chemotherapy, the PFS but not OS durations were longer than those of non-paclitaxel ones (75.2 *vs* 48.4 months and 91.8 *vs* 62.3 months, respectively; Figures 2A and 2B).

Validation sets

To validate the present results from JICR in China, the authors analyzed another set of data from MDACC. Thirty-four PFTC patients at MDACC were identified between January 1, 1990 and February 1, 2011 as shown

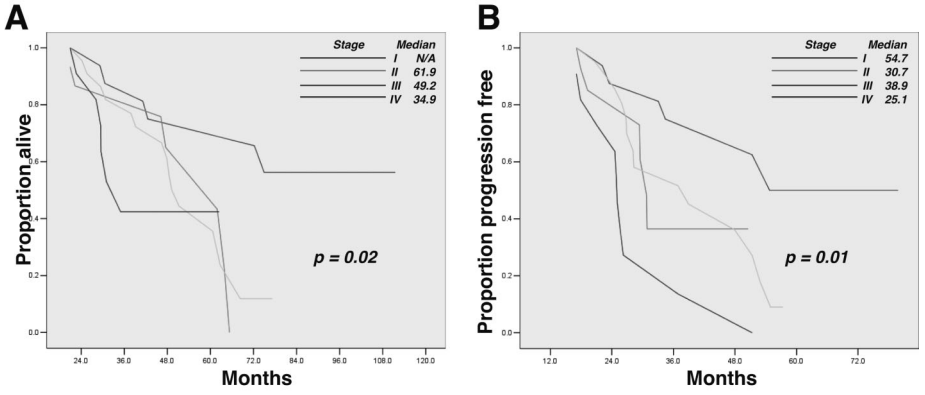

Figure 1. — PFTC patients with Stage II disease had poorer OS and PFS than those of Stage I but not Stage III-IV (1A, 1B).

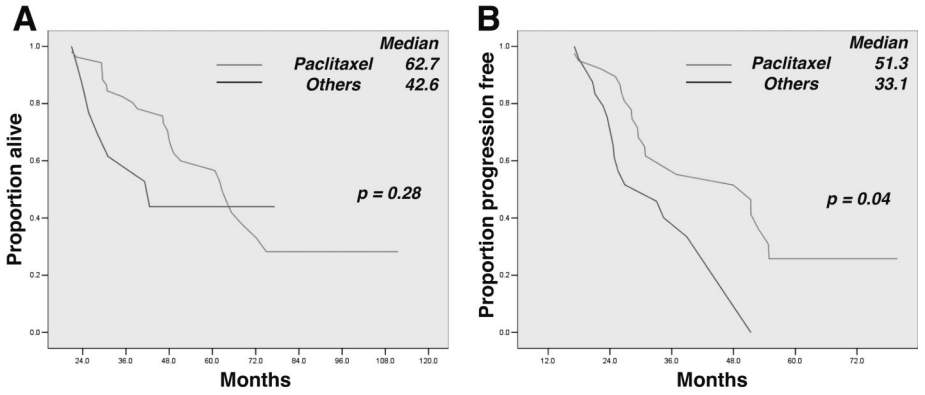

Figure 2. — PFTC patients who underwent paclitaxel based chemotherapy had longer PFS and but not OS than counterparts (2A, 2B).

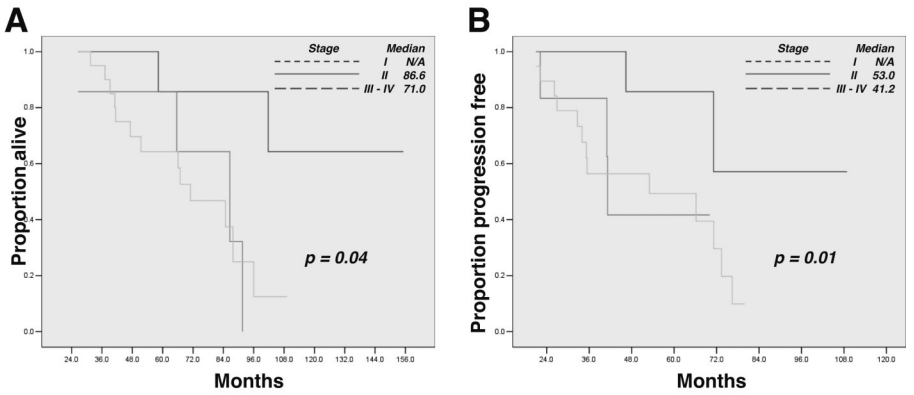

Figure 3. — PFTC patients from MDACC with Stage II disease had poorer OS and PFS than those of Stage I but not Stage III-IV (S1A, S1B).

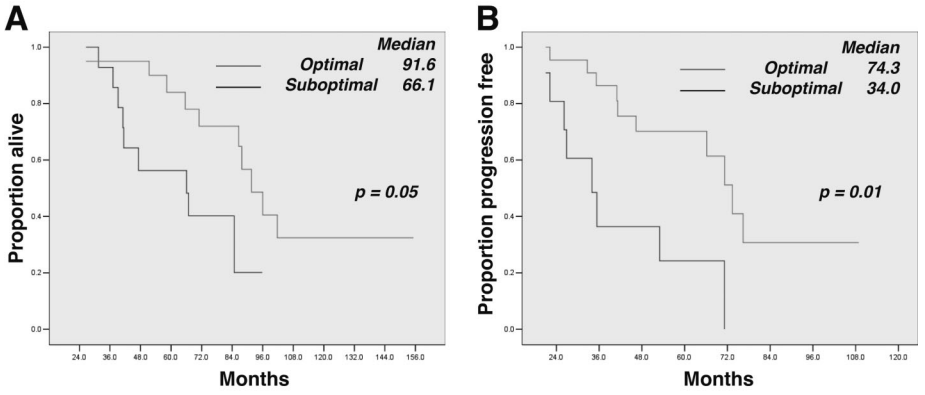

Figure 4. — PFTC patients who underwent optimal CRS had longer PFS and OS than counterparts (S2A, S2B).

Table 5. — *The characteristic of PFTC.*

Characteristic	Percentage (%) / Median (range)
Age (years)	53 (38-77)
Baseline CA-125 level (U/ml)	685 (7-5880)
Nadir CA-125 level (U/ml)	10 (4-35)
Ethnic group	
White	22 (64.7%)
Black	6 (17.6%)
Hispanic	3 (8.8%)
Eastern Asian	2 (5.9%)
Middle east	1 (2.9%)
Histology	
Serous	23 (67.6%)
Endometrioid	9 (26.5%)
Mixed	2 (5.9%)
Grade	
Low	4 (11.8%)
High	30 (88.2%)
FIGO Stage	
I	7 (20.6%)
II	6 (17.6%)
III	17 (50.0%)
IV	4 (11.8%)

FIGO: International Federation of Gynecology and Obstetrics.

Table 6. — *Univariate analysis of survival-related characteristics in PFTC.*

Variable	OS		PFS	
	OR	95% CI	OR	95% CI
FIGO Stage				
I	1.000	Reference	1.00	Reference
II	4.1	0.9–38.9	6.5	0.9–37.9
III	6.8	1.1–47.5	7.7	1.0–54.7
IV	9.7	1.3–57.1	11.5	1.2–97.2
Grade				
Low	1.000	Reference	1.00	Reference
High	2.3	0.9–25.1	3.2	0.9–35.7
Tumor residual	7.4	1.3–38.3	9.5	1.5–46.0
Ascites	1.4	1.1–28.1	1.5	1.2–38.5
Nadir CA-125	1.02	1.0–1.05	1.03	1.01–1.06

OS: overall survival; PFS: progression-free survival; OR: odds ratio; CI: confidential interval.

Table 7. — *Multivariate analysis of survival-related characteristics in PFTC.*

Variable	OS		PFS	
	OR	95% CI	OR	95% CI
FIGO Stage				
I	1.00	reference	1.00	reference
II	3.4	0.9–26.7	4.8	0.9–36.9
III	6.1	0.9–46.1	5.2	1.0–43.0
IV	9.7	1.3–70.3	8.8	1.1–63.9
Tumor residual	4.7	1.3–24.2	6.2	1.4–32.1
Nadir CA-125	1.01	1.0–1.03	1.02	1.01–1.03

in Table 5. Twenty-four patients (70.6%) were high-grade. Most of them (73.7%) were serous cancer. There were four (11.8%) patients who were reported to experience Latzko's triad of symptoms. Lymphadenectomy was performed in 20 (58.8%) selection patients. Cox proportional hazards model revealed that outcome of CRS and FIGO Stage were also associated to OS and PFS (Tables 6, 7). The PFS and OS durations of PFTC patients with Stage II disease were poorer than those of Stage I (p = 0.01 and p = 0.04, respectively; Figures 3A and 3B). The PFS and OS durations of PFTC patients who underwent optimal CRS were longer than those who did not undergo it (p = 0.01 and p = 0.05, respectively; Figures 4A and 4B).

Discussion

Primary fallopian tube carcinoma is infrequent and little information can be derived from a single institution. To the authors' knowledge, this is the first study from three institutions of PRC and USA to evaluate the survival associated clinical-pathological factors for this disease. The clinicopathologic features and biological behavior of PFTC is similar to EOC. Both tumors also show an increase among nulliparous women, are frequent of serous papillary histology, have advanced stage with a poor outcome, and mostly well respond to initially platinum-based chemotherapy [11, 19, 20]. Nevertheless, some differences appear between the two diseases: the median age of PFTC is younger than those of ovarian cancer in the present centers. PFTC is more often diagnosed in an earlier stage. There is also different regarding the need for routine lymphadenectomy and postoperative therapy of early stage disease.

The preoperative diagnosis ratio of PFTC is low and it was 12.1% in the present report [21]. The main clinical symptoms were abdominal pain (30-50%), vaginal bleeding and drainage (50-60%), and abdominal mass (12-61%) [22-23]. In this study, the patients that underwent typical Latzko's triad was 18.0%. Huang *et al.* argued that the so-called "triad" was inflammatory fallopian tube changes, but not specific symptoms of PFTC, and may cause unnecessary check [24]. Radiological study is helpful to find early stage PFTC. Neovascularization in fallopian tube cavity could be revealed by transvaginal Doppler ultrasound. MRI was more sensitive than CT and ultrasound for local invasion of this disease [25]. The positive rate of cervical/vaginal smears was only 0-23% and should not regarded as conventional measures [26]. The misdiagnosis of PFTC may reduce the actual prevalence rate of this disease. It is reported that serial sections of fallopian tube in EOC or primary peritoneal carcinoma will improve the detection rate for PFTC [27].

Due to the limited quantities, long time span and without unified treatment plan in most retrospective studies of PFTC, there was no consensus on outcome related factors. Presently, extent of disease is the only well-established prognosis indicator. FIGO Stage, pathological subtype, and grade were reported to be the main prognostic factors of PFTC from some single center studies [28, 29]. The present authors found that the survival duration of Stage II PFTC was poorer than that of Stage I, but similar to that of Stage III and IV cases. The present authors consider that PFTC confines to the fallopian tube for a comparatively long period before the breakthrough tubal and then relatively quickly spread to the ovarian, abdominal cavity or the distance. Considering that fallopian tube origin model of ovarian cancer, it may imply that part of the serous tubal intraepithelial carcinoma or locally invasive carcinoma spread to ovarian or pelvic was not thought to be Stage II PFTC, but ovarian or peritoneal carcinoma. Previous studies revealed that the prognosis of patients with Stage I and II PFTC was comparatively good, and should be regarded as the "early stage" [30], however there was controversy; the other study reported that the prognosis of Stage II PFTC was similar to those of advanced stage, like the present study [31]. The present authors further found that the nadir CA-125 level after primary therapy was independent prognostic indicator of this disease like that of EOC [32]. They did not find the relationship between immunoassaying results of p53, CA-125, EGFR, and Ki67 and the prognosis of PFTC [33].

There was no prospective trial on the most preferred surgical procedure and adjuvant chemotherapy. The management principal of this disease followed those of EOC. Today, initial CRS and adjuvant chemotherapy including carboplatin/paclitaxel were regarded as standard primary management of PFTC [34-35]. The objective response rate of carboplatin/paclitaxel as initial adjuvant chemotherapy in present research was similar to those of other studies (53-92%) [36-37]. There was no consensus on abdominal and pelvic lymph node dissection and the proportion of this procedure was 51.5%, higher than that of other reports [38]. The present authors found that tumor residual after initial CRS was independent prognosis factor.

There are limitations to the present study. Firstly, unavoidable selection biases inherent to its retrospective design. Age, initial CRS, chemotherapy protocols, and some additional salvage therapy may have reflected certain selected factors that may influence prognosis. Secondly, given the long term follow up and the heterogeneity of therapy strategies used throughout the 25 years study period, including the emergence of new protocols such as paclitaxel based chemotherapy and molecular targeted therapy and so on, it was impossible to unify the therapy strategy. Thirdly, the limited sample size may have also caused selection bias. Evaluating patients from China with validation set from America may have assisted in lessening this unfavorable effect.

In summary, in this study including patients from two centers with same recruited standard, the authors found that the prognosis of PFTC was associated with FIGO Stage, pathological grade, and surgical outcome. They also found that the prognosis of patients with Stage II disease was similar to those of Stage III and IV but not Stage I. Stage II of PFTC cannot be regarded as early stage.

Acknowledgements

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Address reprint requests to:
X. CHEN, M.D., Ph.D.,
Department of Gynecologic Oncology,
Jiangsu Cancer Hospital
42 Baiziting Road
Nanjing, Jiangsu 210009 (China)
e-mail: cxxxxcyd@gmail.com