



· 论 著 ·

# 101例原发性输卵管癌临床特点及预后影响因素分析

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**[摘要]** **背景与目的:** 原发性输卵管癌(primary fallopian tube carcinoma, PFTC)是女性罕见的恶性肿瘤,目前国内外报道较少。分析PFTC临床特点并探讨影响其预后的相关因素。**方法:** 回顾性分析2002年1月—2017年12月复旦大学附属妇产科医院收治的101例经手术后病理学确诊的PFTC患者的临床病理学资料并对预后进行随访,随访时间为5~141个月,平均随访时间为60.54个月,以年龄、绝经状态、生育史、输卵管结扎史、乳腺癌病史、临床症状、术前血清CA125水平、术前影像学表现、腹水细胞学检测、临床手术病理学分期、是否行盆腔淋巴结清扫术、是否为满意的瘤体减灭术(残余瘤直径 $\leq 1.0$  cm)、肿瘤组织病理学类型、肿瘤大小、免疫组织化学检测结果、术后化学治疗的疗程作为变量。应用Kaplan-Meier法计算并分析其总生存率及无进展生存率,应用Log-rank进行单因素分析检验,应用COX回归模型进行多因素分析,研究这些因素与患者总生存期(overall survival, OS)及无进展生存期(progression-free survival, PFS)之间的关联。**结果:** 101例PFTC患者的5年总生存率为79.3%,平均OS为91.89个月(95% CI: 81.90~101.88),中位OS为100个月(95% CI: 93.94~106.07)。5年无进展生存率为71.6%,平均PFS为89.47个月[95% CI: 78.80~100.14],中位PFS为98个月(95% CI: 77.69~118.31)。最常见的临床表现是附件肿块(36.6%),其次是阴道流血(14.9%),无特殊症状患者占10.9%。85例(84.2%)患者获得满意的瘤体减灭术(残余瘤直径 $\leq 1$  cm),16例(15.8%)患者获得次满意的瘤体减灭术。肿瘤组织学亚型主要为浆液型癌(91.1%)。术后诊断I/II期患者61例(60.4%),III/IV期患者40例(39.6%)。至末次随访日,全组患者复发率为43.6%。单因素变量分析及多因素变量分析显示,国际妇产科联盟(International Federation of Gynecology and Obstetrics, FIGO)分期( $P < 0.001$ ; HR=4.58; 95% CI: 2.361~8.882)、是否行盆腔淋巴结清扫( $P=0.002$ ; HR=0.338; 95% CI: 0.170~0.673)及残余肿瘤情况( $P < 0.001$ ; HR=4.655; 95% CI: 2.007~10.794)是显著的预后因素,而其他变量差异无统计学意义。**结论:** PFTC难以在术前得到明确诊断,其独特的生物学特征及发病机制仍处于研究当中,FIGO分期、是否行盆腔淋巴结清扫及残余肿瘤情况是影响PFTC患者预后的主要因素。

**[关键词]** 原发性输卵管癌;总生存期;无进展生存期;盆腔淋巴结清扫;残余肿瘤情况;预后分析

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**Retrospective analysis of clinical characteristics and prognostic factors in 101 patients with primary fallopian tube carcinoma** SUN Mingming<sup>1</sup>, BAO Lingjie<sup>1</sup>, YI Xiaofang<sup>1, 2</sup>, XU Congjian<sup>1, 2</sup>, JIANG Wei<sup>1, 2</sup> (1. Department of Gynecology, Obstetrics and Gynecology Hospital, Fudan University, Shanghai 200011, China; 2. Shanghai Key Laboratory of Female Reproductive Endocrine Related Diseases, Shanghai 200011, China)

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**[Abstract]** **Background and purpose:** Primary fallopian tube carcinoma (PFTC) is a rare female malignant tumor, and the diagnosis of PFTC is rarely considered preoperatively. It is an infrequent disease and hardly reported. In this study, we analyzed clinical characteristics in 101 PFTC patients and identified the prognostic factors for the disease. **Methods:** We reviewed medical records of patients with PFTC at the Obstetrics and Gynecology Hospital of Fudan University from January 2002 to December 2017.

The data included age, menopause status, childbearing history, tubal ligation history, breast cancer history, symptom, pretreatment CA125 level, imaging findings, ascitic cytology, debulking surgery or not, pelvic lymphadenectomy or not, surgical stage, pathologic subtype, tumor diameter, immunohistochemistry and chemotherapeutic course. The mean follow-up time was 60.54 months (ranging from 5 to 141 months). The Kaplan-Meier method was used to measure the overall survival and progression-free survival. A Log-rank univariate analysis was used to determine the prognostic factors related to the survival rate. The COX model multivariate analysis was used to identify independent prognostic factors. **Results:** A total of 101 patients with PFTC were identified. The 5-year overall survival was 79.3%, the mean overall survival was 91.89 months (95% CI: 81.90-101.88), and the median overall survival was 100 months (95% CI: 93.94-106.07). The 5-year progression-free survival was 71.6%, the mean progression-free survival was 89.47 months (95% CI: 78.80-100.14), and the median progression-free survival was 98 months (95% CI: 77.69-118.31). The most common clinical presentation was adnexal mass (36.6%), followed by vaginal bleeding (14.9%) and no specific symptom (10.9%). Residual disease was optimal in 85 (84.2%) patients and suboptimal in 16 (15.8%) patients. The histological subtype was predominantly the serous type (91.1%). Sixty-one patients (60.4%) were diagnosed at Stage I/II postoperatively. Forty (39.6%) patients were in Stage III/IV. Until the end of follow-up time, the recurrence rate of the group was 43.6%. Univariate analyses on overall survival revealed that the International Federation of Gynecology and Obstetrics (FIGO) stage ( $P<0.001$ ; HR=4.58; 95% CI: 2.361-8.882), with or without pelvic lymphadenectomy ( $P=0.002$ ; HR=0.338; 95% CI: 0.170-0.673) and residual tumor ( $P<0.001$ ; HR=4.655; 95% CI: 2.007-10.794) were significant prognostic factors. **Conclusion:** The diagnosis of PFTC is rarely considered preoperatively. Its unique biological features and pathogenesis are still under study. FIGO staging, pelvic lymphadenectomy and residual tumor are the main factors affecting the prognosis of patients with PFTC.

**[Key words]** Primary fallopian tube carcinoma; Overall survival; Progression-free survival; Pelvic lymphadenectomy; Residual tumor; Prognostic analysis

原发性输卵管癌 (primary fallopian tube carcinoma, PFTC) 由Rokitansky于1847年首次报道<sup>[1]</sup>, PFTC被认为是一种罕见的妇科恶性肿瘤, 占女性生殖道恶性肿瘤的0.14%~1.80%<sup>[2]</sup>。但最近的研究及数据显示, 作为上皮性卵巢癌最常见的亚型, 乳头状浆液性癌实际上起源于输卵管上皮, 因此我们可能低估了PFTC真正的发病率<sup>[1]</sup>, 此外, 在卵巢高级别浆液性腺癌患者中, 作为癌前病变的浆液性输卵管上皮内瘤变与卵巢高级别浆液性腺癌具有相同的TP53突变<sup>[3]</sup>。因此, 目前国际妇产科联盟 (International Federation of Gynecology and Obstetrics, FIGO) 认为PFTC的分期与卵巢癌分期一致, PFTC的诊治也按照卵巢癌诊治指南进行<sup>[4-5]</sup>。但随着临床研究的深入, 更多的临床数据表明, 早期和晚期的输卵管癌患者总生存率高于卵巢恶性肿瘤患者<sup>[6]</sup>, 且只有约4.0% (0.3%~15.0%) 的PFTC在术前确诊<sup>[7]</sup>。本研究通过回顾性分析复旦大学附属妇产科医院PFTC患者的临床资料, 对PFTC患者的生存预后因素进行探讨。

## 1 资料和方法

### 1.1 患者资料

收集2002年1月—2017年12月复旦大学附属妇产科医院在妇科手术中诊断为PFTC的101例患者的临床病理学资料, 所有患者的诊断均经复旦大学附属妇产科医院病理科术后病理学检查证实。所有病例的诊断均依照由Hu等建立、Sedlis等修改的PFTC诊断标准进行<sup>[8-10]</sup>, 该诊断标准至少应满足以下一项: ① 肿瘤主要来自输卵管, 起源于输卵管内壁; ② 组织学上, PFTC体现于再生输卵管黏膜上皮并常显示乳头状增生模式; ③ 若肿瘤累及输卵管壁, 良性上皮和恶性上皮之间的转化区是可证实的; ④ 卵巢与子宫内膜正常或包含比输卵管更少的肿瘤组织。手术病理分期信息来源于手术记录及病理学报告, 分期依据FIGO 2009诊断标准。本研究获得复旦大学附属妇产科医院伦理委员会的批准及对患者知情同意书的豁免。

收集内容包括患者诊断年龄、绝经状态、生育史、临床症状、术前血清CA125水平、术前影

像学表现、腹水细胞学检测、临床手术病理学分期、是否为满意的瘤体减灭术（残余瘤直径 $\leq 1.0$  cm）、肿瘤大小、手术方式、术后化疗治疗疗程及术后随访情况。

## 1.2 随访

患者在前2年内每3个月进行1次门诊随访评估，在接下来的3年内每6个月进行1次门诊随访评估，此后每年1次门诊随访。根据对病史的查阅及专人电话回访，随访信息更新至2018年12月23日，患者平均随访时间为60.54个月（5~141个月）。总生存期（overall survival, OS）定义为从首次诊断为PFTC至死亡或末次随访日的时间间隔，无进展生存期（progression-free survival, PFS）定义为从首次诊断为PFTC至患者首次发现复发之日的时间间隔，随访复发的指标包括血清学肿瘤标志物检测及影像学检查。

## 1.3 统计学处理

使用SPSS 19.0软件对数据进行处理， $P < 0.05$ 为差异有统计学意义。生存分析采用Kaplan-Meier法，对影响患者预后的因素的单因素分析采用Kaplan-Meier法计算，单因素分析采用Log-rank检验，对差异有统计学意义的因素再进行COX多因素回归分析。

## 2 结果

### 2.1 临床病理学资料特征

患者的临床病理学资料详见表1。

### 2.2 生存分析

至末次随访日期2018年12月23日，101例PFTC患者的5年总生存率为79.3%，平均OS为91.89个月（95% CI: 81.90~101.88），中位OS为100个月（95% CI: 93.94~106.07，图1）。5年无进展生存率为71.6%，平均PFS为89.47个月（95% CI: 78.80~100.14），中位PFS为98个月（95% CI: 77.69~118.31，图2）。根据随访情况，初次手术后复发的患者44例，其中接受再次手术联合化疗的患者5例，接受单纯继续化疗的患者30例，接受单纯中药治疗患者3例，接受免疫治疗患者1例，5例患者未行继续治疗。复发患者中有21例至末次随访日期尚存活，复发存活患

者中3例患者（14.3%）接受再次手术联合化疗，18例（85.7%）患者接收单纯继续化疗。

### 2.3 OS、PFS的单因素及多因素分析

对OS、PFS的单因素分析显示，只有FIGO分期（ $P < 0.001$ ；HR=4.58；95% CI: 2.361~8.882）、是否行盆腔淋巴结清扫（ $P = 0.002$ ；HR=0.338；95% CI: 0.170~0.673）及残余肿瘤情况（ $P < 0.001$ ；HR=4.655；95% CI: 2.007~10.794）是显著的预后因素（表1，图3~5）。为分析全组患者临床特征对OS的影响而进行的多因素变量分析结果见表2。根据Pectasides等<sup>[2]</sup>的研究，与上皮性卵巢癌的预后分析一致，PFTC的手术病理学分期及残余瘤直径是影响预后的重要变量，手术病理学分期越早以及尽量获得满意的瘤体减灭术（残余瘤直径 $\leq 1$  cm）能改善患者预后，与本研究结果一致。

## 3 讨论

根据Klein等<sup>[11]</sup>的研究，PFTC是一种罕见的、具有强侵袭力的恶性肿瘤，其5年生存率为35%。大多数PFTC患者在术前初步诊断为卵巢肿瘤或其他良性疾病，如输卵管积水、盆腔炎性疾病、输卵管结核、附件良性囊肿等。尽管准确的术前诊断是困难的，相比于卵巢癌，PFTC常在疾病早期被诊断<sup>[12]</sup>。PFTC起源于输卵管的腔，这是一个部分封闭的空间，可能延迟输卵管肿瘤经腹膜的播散。本研究结果也显示，原发性输卵管肿瘤多在早期得到确诊（I/II期占60.4%）。近期不同机构学者研究发现，预防性输卵管切除手术及良性疾病手术中意外发现微小、隐匿的输卵管上皮内瘤变可以解释输卵管癌患者更容易出现早期的肿瘤<sup>[6, 13-16]</sup>。

5%~20%的PFTC患者检测到包括腹痛、异常阴道出血或分泌物及可触及的盆腔包块的输卵管癌三联征，输卵管积液被认为是输卵管癌的病理学特征，但只有3%~14%的病例报告了这一现象<sup>[17]</sup>。临床工作中，宫颈癌筛查刮片病理学检查异常，而阴道镜检查、宫颈活检、子宫内膜诊刮阴性，结果之间的差异应考虑到PFTC可疑，且宫颈刮片中发现砂粒体也提示妇科恶性肿

表 1 101例PFTC患者的临床特征及预后因素的单因素分析

Tab. 1 Clinical characteristics in 101 PFTC women and univariate analyses of impact of various prognostic parameters

Characteristics	n (%)	Univariate analysis		
		P value	HR	95% CI
Age/year		0.434	0.761	0.384-1.509
≥60	42 (41.6)			
<60	59 (58.4)			
Menopause		0.745	1.133	0.535-2.397
Yes	76 (75.2)			
No	25 (24.8)			
Nulliparous		0.541	1.563	0.373-6.545
Yes	3 (3.0)			
No	98 (97.0)			
Tubal ligation history		0.480	1.536	0.466-5.064
Yes	8 (7.9)			
No	93 (92.1)			
Breast cancer history		0.784	0.757	0.103-5.550
Yes	3 (3)			
No	98 (97)			
Symptom		0.250	1.121	0.923-1.361
Vaginal bleeding	15 (14.9)			
Vaginal discharge	11 (10.9)			
Abdominal pain	13 (12.9)			
Palpable mass	37 (36.6)			
Combination	14 (13.9)			
None	11 (10.9)			
Pretreatment CA-125 $z_{95}$ /(U·mL <sup>-1</sup> )		0.299	1.505	0.696-3.257
<35	20 (19.8)			
≥35	58 (57.4)			
Unknown	23 (22.8)			
Imaging findings		0.714	1.124	0.602-2.100
Positive	40 (39.6)			
Negative	61 (60.4)			
Ascites		0.499	1.288	0.618-2.686
Presence	30 (29.7)			
Absence	71 (70.3)			
Ascitic cytology		0.152	0.558	0.252-1.239
Positive	17 (16.8)			
Negative	29 (28.7)			
Unknown	55 (54.5)			
Debulking Surgery		<0.001	4.655	2.007-10.794
Yes	83 (82.2)			
Residual mass ≤ 1 cm	85 (84.2)			
Residual mass > 1 cm	16 (15.8)			
No	18 (17.8)			
Pelvic lymphadenectomy		0.002	0.338	0.170-0.673
Yes	83 (82.2)			
No	18 (17.8)			
Surgical stage		<0.001	4.580	2.361-8.882
I / II	61 (60.4)			
III / IV	40 (39.6)			
Pathologic subtype		-	-	-
Serous	92 (91.1)			
Non-serous	8 (7.9)			
Unknown	1 (1.0)			
Chemotherapeutic course		0.145	0.617	0.323-1.180
≥6	63 (62.4)			
<6	38 (37.6)			
Tumor diameter D/mm		0.140	1.457	0.884-2.399
<50	51 (50.5)			
50-100	41 (40.6)			
≥100	9 (8.9)			
Operative type		0.224	0.661	0.340-1.288
Laparoscopic surgery	71 (70.3)			
Laparotomy	30 (29.7)			

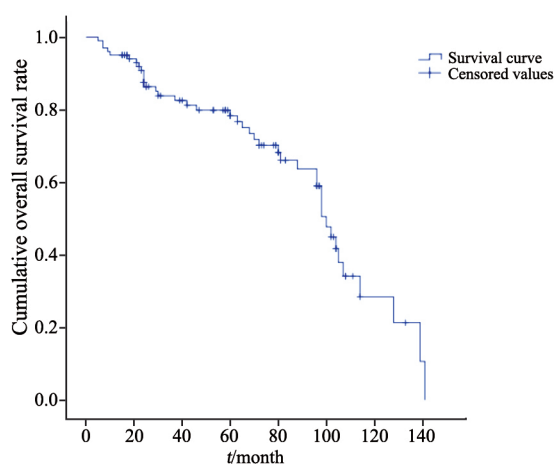


图 1 101例PFTC患者的OS生存曲线

Fig. 1 Survival curves of OS

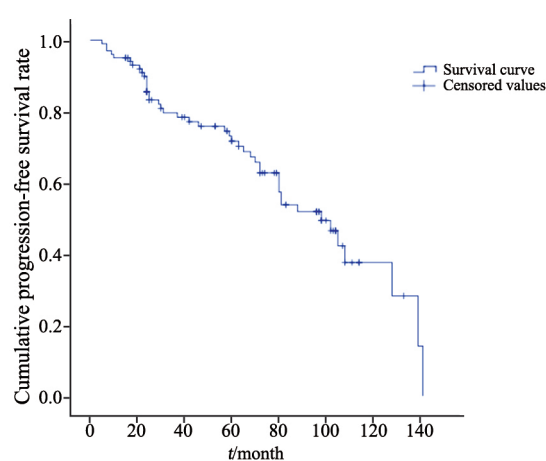


图 2 101例PFTC患者的PFS生存曲线

Fig. 2 Survival curves of PFS

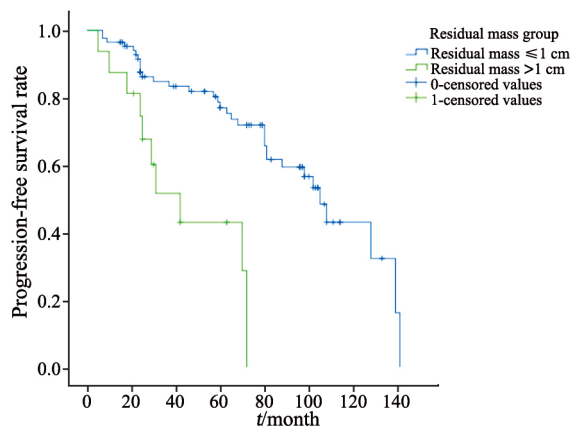
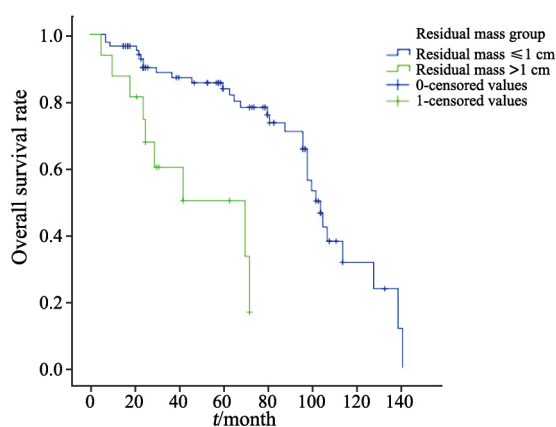


图 3 101例PFTC患者残余肿瘤的生存预后曲线

Fig. 3 Survival curves of prognostic factors for OS and PFS by residual tumor

表 2 PFTC患者总生存率重要预后参数的多因素COX回归分析

Tab. 2 Multivariate analyses of significant prognostic parameters on overall survival rate in patients with PFTC using COX regression

analysis				
Parameter	Wald	Risk ratio	P value	95% CI
Age	0.508	0.741	0.476	0.326-1.688
Menopause	0.542	0.711	0.462	0.287-1.763
Residual tumor mass	7.647	3.666	0.006	1.460-9.206
Pelvic lymphadenectomy	2.927	0.480	0.087	0.207-1.113
Surgical stage	14.807	4.096	<0.001	1.997-8.400
Chemotherapy courses	3.878	0.481	0.049	0.232-0.997

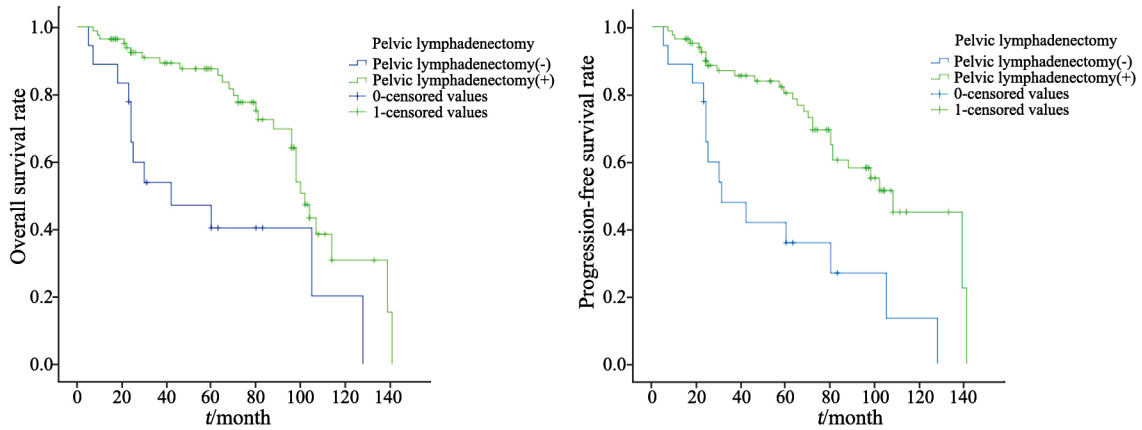


图4 101例PFTC患者是否行盆腔淋巴结清扫的生存预后曲线

Fig. 4 Survival curves of prognostic factors for OS and PFS by pelvic lymphadenectomy

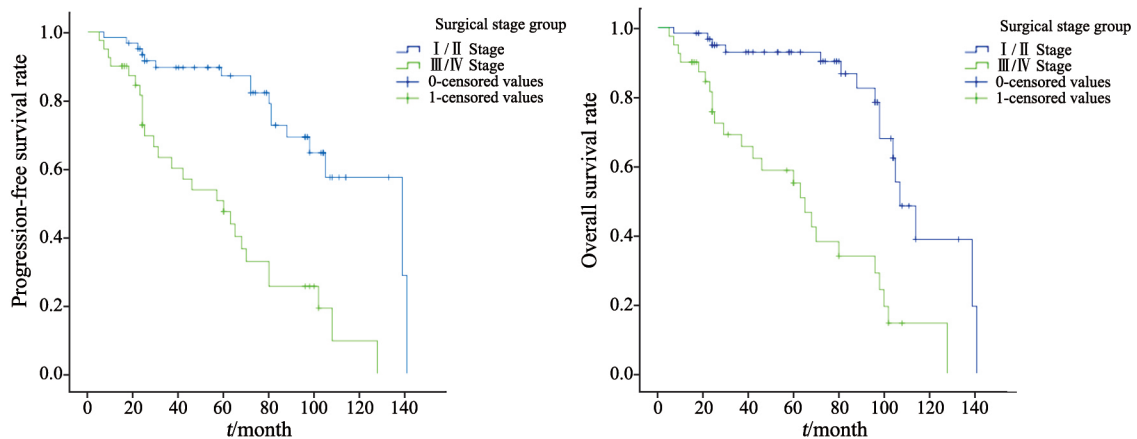


图5 101例PFTC患者FIGO分期的生存预后曲线

Fig. 5 Survival curves of prognostic factors for OS and PFS by FIGO stage

瘤, 此时需进一步详细检查<sup>[2]</sup>。PFTC最后的诊断仍然需要手术后的组织病理学确诊, 准确的术中评估及术中快速冰冻切片病理学检查结果都能为PFTC的确诊提供帮助。一旦发现输卵管恶性肿瘤, 全子宫切除、双侧附件切除、大网膜和阑尾切除、腹膜多点活检、留取腹水或腹腔冲洗液进行细胞学检查是首选治疗方法, 盆腔及腹主动脉旁淋巴结清扫目前存在争议<sup>[18]</sup>。输卵管恶性肿瘤最常见的组织学类型是浆液性癌, 其余较少的包括黏液性癌、子宫内膜样癌、透明细胞癌、肉瘤、移行细胞癌和未分化癌等, 就组织学分级而言, 大多数肿瘤分化较差<sup>[17]</sup>。化学药物治疗为主要的辅助治疗, 常用于术后杀灭残留癌灶, 控制复发, 也可用于复发病灶的治疗。通过大量研究观察, 化疗高应答率和生存数据的提高

表明以铂类药物联合紫杉醇为主的化疗药物作为PFTC的标准化疗方案<sup>[5, 12, 19-20]</sup>, 本研究中, 复发患者中有21例至末次随访日期尚存活, 复发存活患者中3例患者(14.3%)接受再次手术联合化疗, 18例(85.7%)患者接收单纯继续化疗, 也佐证了化疗的必要性。

意大利的一项多中心研究显示, PFTC与卵巢癌有着相似的生物学特征和临床特征, 患者年龄、肿瘤的手术分期、合并晚期疾病以及初次手术后残留肿瘤情况是生存率的重要预测变量<sup>[5, 17]</sup>。此外, 输卵管末端封闭、腹水细胞学阳性、输卵管内病变部位出现、HER-2/neu阳性表达、p53突变、术前CA125水平升高、淋巴脉管浸润、炎症反应过程出现均为PFTC重要的生存预后因素<sup>[1]</sup>。

本研究中,年龄、产次、输卵管结扎史、乳腺癌史、术前CA125水平、影像学表现、腹水细胞学、化疗疗程、肿瘤大小和手术方式与总生存率无显著相关,只有肿瘤分期( $P<0.001$ )、是否行盆腔淋巴结清扫( $P=0.002$ )和残余肿瘤大小( $P<0.001$ )与预后显著相关。对于妇科医师来说,应根据患者的各方面临床特征确定个体化诊疗方案,做到对PFTC的早期发现、规范的手术治疗及满意的瘤体减灭,尽量让患者从个体化的规范诊治中获益,这关系到输卵管癌患者的预后及疾病的整体生存率。

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