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Original Article

Unexpected primary fallopian tube carcinoma during gynecological operations: Clinicopathological and prognostic factors analyses of 67 cases

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ABSTRACT

Objective: The aim of the study was to analyze the clinicopathologic features, the survival rate, and the prognostic factors of women with unexpected primary fallopian tube carcinoma diagnosed during gynecological operations.

Materials and methods: We reviewed medical records of patients with unexpected primary fallopian tube carcinoma at the Obstetrics and Gynecology Hospital of Fudan University between January 2004 to December 2017. The survival analysis was based on the Kaplan–Meier method, and the results were compared using the log-rank test. Cox regression analysis was used to determine factors affecting survival.

Results: Sixty-seven patients with unexpected primary fallopian tube carcinoma were identified. The 5-year overall survival was 49.7%, the mean overall survival was 64 months [95% confidence interval (CI) 54–74], and the median overall survival was 59 months (95% CI 49–69). The mean follow-up time was 53.9 months (range 5–141 months). The most common clinical presentation was adnexal mass (38.8%), followed by vaginal bleeding (16.4%) and no specific symptom (13.4%). Cytoreductive surgery was performed initially in 57 (85.1%) patients. Residual disease was optimal in 56 (83.6%) patients and suboptimal in 11 (16.4%) patients. The histological subtype was predominantly the serous type (88.1%). 44 patients (65.7%) were diagnosed at Stage I/II postoperatively. 23 (34.3%) patients were in Stage III/IV. 51 patients (76.1%) had gone through laparoscopic surgery, 16 patients (23.9%) were performed laparotomy. Univariate analyses on overall survival revealed that only the International Federation of Gynecology and Obstetrics (FIGO) stage [$p < 0.001$; Hazard Ratio (HR), 6.433; 95% CI, 2.274–18.199], residual tumor ($p = 0.014$; HR, 4.957; 95% CI, 1.378–17.831) were significant prognostic factor. Pelvic lymphadenectomy did not show association with overall survival in our univariate or multivariate analyses. After an observation period of 70 months, we found an increased overall survival in the group of without lymphadenectomy.

Conclusions: The diagnosis of primary fallopian tube carcinoma is rarely considered preoperatively. The early stage and optimal debulking surgery with residual tumor ≤ 1 cm are important independent factors to improve patients' prognosis. However, there were no statistically significant correlations between lymphadenectomy and prognosis. The value of lymph node sampling or dissection needs to be reconsidered.

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Introduction

Primary fallopian tube carcinoma was described for the first time in 1847 by Rokitansky and in 1861 by Renaud. The youngest patient reported in the literature is 19 years old, the oldest 87 years old [1,2]. Primary fallopian tube carcinoma is recognized as a rare

gynecologic malignancy and accounts for approximately 0.14%–1.8% of female genital malignancies [3]. Recent data suggest that the true incidence of primary fallopian tube carcinoma has been substantially underestimated, this conclusion is based on compelling evidence that papillary serous carcinoma, the most common subtype of epithelial ovarian carcinoma, actually arises from the epithelial lining of fallopian tube [1]. C. Qiu et al. selected the highly differentially expressed gene (PAX8, CDH1, FOXA2, and ARX) as well as those corresponding proteins and examined their expression levels in tissue samples. Their study provided further evidence at a molecular level that the fallopian tube is likely the cellular source of ovarian low-grade serous carcinoma. And in the patients with high-grade serous cancer (HGSC), the precancerous lesions, serous tubal intraepithelial carcinomas (STICs), share identical TP53 mutations with high-grade serous cancer, indicating a clonal relationship between the two [4]. Therefore, nowadays, the FIGO also adapted the staging of ovarian cancer to primary fallopian tube carcinoma and suggested that it is surgically staged like ovarian cancer. The guidelines for ovarian cancers used for the management of primary fallopian tube carcinoma [5,6].

Although histologically and clinically, primary fallopian tube carcinoma resembles epithelial ovarian cancers, several distinct differences should be emphasized based on additional clinical data. Fallopian tube cancers present earlier and at advanced stage have a better overall survival than primary ovarian malignancies [7].

Because of the low incidence of primary fallopian tube carcinoma, only about 4% (0.3–15%) are diagnosed preoperatively [8]. The purpose of this study was to review the experience of managing primary fallopian tube carcinoma in our institution and to identify the possible prognostic factors.

Materials and methods

The data of sixty-seven patients with unexpected primary fallopian tube carcinoma diagnosed during gynecological operations at the Obstetrics and Gynecology Hospital of Fudan University between January 2004 to December 2017 was retrospectively analyzed. The final diagnosis was histopathologically determined by surgery. Cases were identified according to the primary fallopian tube carcinoma diagnostic criteria established by Hu et al. and modified by Sedlis [9,10]. We excluded the patients with discovery of primary fallopian tube carcinoma preoperatively, neoadjuvant chemotherapy, and primary debulking surgery performed at another hospital. All data obtained and research methodologies used in this study were approved by the Institutional Review Board of the Obstetrics and Gynecology Hospital of Fudan University and informed patient consent were obtained.

Staging information was derived from surgical notes and pathological reports. The information included the age at diagnosis, pre- or postmenopausal status, parity, presenting symptoms, pretreatment CA-125 values (U/ml), imaging findings, ascitic cytology, clinical surgical stage (based on the FIGO stage), whether cytoreductive surgery was optimal (i.e., ≤ 1.0 cm for the largest residual tumor mass) or not (i.e., > 1.0 cm for the largest residual tumor mass), immunohistochemistry expression, chemotherapeutic course, the patient condition and clinical outcomes at the last follow-up. Overall survival was defined as the time from the date of primary surgery to death or the latest observation.

Patients returned for a follow-up evaluation every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. The follow-up information was updated until December 23, 2018, based on a review of the medical record, and by direct contact with patients or their relatives. The survival analysis was based on the Kaplan–Meier method, and the results were

compared using the log-rank test. Cox regression analysis was used to determine factors affecting survival, and results are presented as HRs with 95% CIs. All statistical analyses were performed using Statistical Program for Social Sciences (SPSS) (version 19.0). A *p*-value of < 0.05 was considered significant.

Results

A detailed description of the clinical characters is shown in Table 1. The mean age at diagnosis was 60 years (range, 43–85 years). 50 patients were menopausal and 17 were premenopausal. 97% patients had history of delivery. There were only 8 (11.9%) patients had gone through tubal ligation. 3 patients had breast cancer history. The most common clinical presentation was adnexal mass (38.8%). Adnexal mass included any adnexal mass of unknown origin, nonspecific manifestation to know whether benign or malignant on imaging study. Followed by vaginal bleeding (16.4%), 9 (13.4%) patients had no specific symptom in the series. Preoperative CA-125 values elevated (≥ 35 U/ml) in 35 (52.2%) cases, and among them 10 cases had normal levels. The imaging results were indistinguishable in 62.7% cases. 32 patients with primary fallopian tube carcinoma undergone the surgery with the presumed diagnosis of ovarian cancer, 19 (59.4%) of them had gone through laparoscopic surgery. Preoperative diagnosis of adnexal benign cysts in 19 patients, and 16 (84.2%) of them were performed with laparoscopy. 6 patients had first diagnosis with hysteroscopy, 4 with endometrial carcinoma, 4 with pelvic inflammatory disease and 1 patient with cervical cancer, 1 with ascites of unknown origin in preliminary diagnosis. There were only 16 patients (23.9%) had laparotomy with the first diagnosis of ovarian cancer and adnexal cysts. Upon exploratory laparotomy, ascites was present in 25 cases and ascites cytology test was positive in 15 (22.4%) cases while 36 (53.7%) records were unavailable. Tumor diameter with < 50 mm took up 39 (58.2%) and ≥ 100 mm in 6 (9.0%) cases. Debulking surgery with residual tumor ≤ 1 cm was achieved in 83.6% of cases. The serous type was histologically predominant. The surgical stage was I/II in 44 (65.7%) and III/IV in 23 (34.3%) patients. 57 (85.1%) patients had gone through pelvic lymphadenectomy, however, after reviewing the pathologic records of these patients, 10 (10/57) patients had positive lymph node metastases. After primary surgery, 43 (64.2%) patients received a first-line combined chemotherapy with TP regimen (paclitaxel-cisplatin or carboplatin) no fewer than 6 courses, whereas 24 (35.8%) patients stopped earlier because of intolerance of side effects or uncomplaisance. None was underwent postoperative radiotherapy. The Ki-67 as a nuclear and nucleolar protein, which is tightly associated with somatic cell proliferation [11], was tested, with available records, 21 (31.3%) cases had high expression of Ki-67 ($\geq 60\%$).

The 5-year overall survival was 49.7%, the mean overall survival was 64 months (95% CI 54–74), and the median overall survival was 59 months (95% CI 49–69). The mean follow-up from the time of initial surgery was 53.9 months (range, 5–141 months) (Fig. 1). A detailed description of the clinical characters and results of univariate analyses on overall survival is shown in Table 1. At patient follow-up, a significant relationship between survival probability and FIGO stage at the time of diagnosis was found (Fig. 2). A significant correlation was found between residual tumor and life expectancy. Better results were obtained in patients treated with optimal surgery (residual tumor diameter ≤ 1 cm) (Fig. 2). Results of multivariate analyses carried out to determine the effect of demographic characteristics and clinical features on overall survival are provided in Table 2. Through our analyses, it revealed that overall survival first decreased when lymphadenectomy had not been performed, however, we found an increased overall survival in

Table 1

Clinical characteristics in 67 primary fallopian tube carcinoma women and Univariate analyses of impact of various prognostic parameters on overall survival.

Characteristics	Number of cases (%)	Univariate analysis		
		p	Hazard Ratio	95% confidence interval
Age (year)				
≥60	30 (44.8)	0.617	0.771	0.278–2.137
<60	37 (55.2)			
Menopause				
Yes	50 (74.6)	0.489	1.56	0.443–5.496
No	17 (25.4)			
Nulliparous				
Yes	2 (3.0)	0.412	2.376	0.301–18.788
No	65 (97.0)			
Tubal ligation history				
Yes	8 (11.9)	0.242	2.152	0.597–7.758
No	59 (88.1)			
Breast cancer history				
Yes	3 (4.5)	0.913	0.892	0.113–7.005
No	64 (95.5)			
Symptom				
Vaginal bleeding	11 (16.4)	0.699	1.061	0.785–1.434
Vaginal discharge	5 (7.5)			
Abdominal pain	8 (11.9)			
Palpable mass	26 (38.8)			
Combination	8 (11.9)			
None	9 (13.4)			
Pretreatment CA-125(U/mL)				
<35	10 (14.9)	0.521	1.379	0.517–3.680
≥35	35 (52.2)			
Unknown	22 (32.8)			
Imaging findings				
Positive	25 (37.3)	0.994	0.996	0.377–2.632
Negative	42 (62.7)			
Ascites				
Presence	25 (37.3)	0.223	1.847	0.689–4.955
Absence	42 (62.7)			
Ascitic cytology				
Positive	15 (22.4)	0.256	0.299	0.037–2.396
Negative	16 (23.9)			
Unknown	36 (53.7)			
Debulking Surgery				
Yes	57 (85.1)	0.014	4.957	1.378–17.831
Residual mass≤1 cm	56 (83.6)			
Residual mass>1 cm	11 (16.4)			
No	10 (14.9)			
Pelvic lymphadenectomy				
Yes	57 (85.1)	0.653	0.768	0.242–2.435
No	10 (14.9)			
Surgical stage				
I/II	44 (65.7)	<0.001	6.433	2.274–18.199
III/IV	23 (34.3)			
Pathologic subtype				
Serous	59 (88.1)			
Non-serous	7 (10.4)			
Unknown	1 (1.5)			
Chemotherapeutic course				
≥6 courses	43 (64.2)	0.07	0.322	0.094–1.098
<6 courses	24 (35.8)			
Tumor diameter				
<50 mm	39 (58.2)	0.671	0.831	0.354–1.950
50–100 mm	22 (32.8)			
≥100 mm	6 (9.0)			
Operative type				
Laparoscopic surgery	51 (76.1)	0.471	0.641	0.191–2.150
Laparotomy	16 (23.9)			

the group of without lymphadenectomy after 70 months follow up (Fig. 3). Both in univariate ($p = 0.653$) and multivariate ($p = 0.106$) analyses, there is no statistically significant correlation between pelvic lymphadenectomy and overall survival (Tables 1 and 2). According to Pectasides et al., as with epithelial ovarian cancers, stage and residual tumor are the most important prognostic variables in primary fallopian tube carcinoma [3], which is consistent with our study.

Discussion

Primary fallopian tube carcinoma is a rare, but extremely aggressive, malignant tumor. Its five-year survival rates are as low as 35% [12]. In our study, the 5-year overall survival was 49.7%, the mean overall survival was 64 months, and the median overall survival was 59 months. The survival is quite good due to the multidisciplinary diagnosis and standardized, individualized

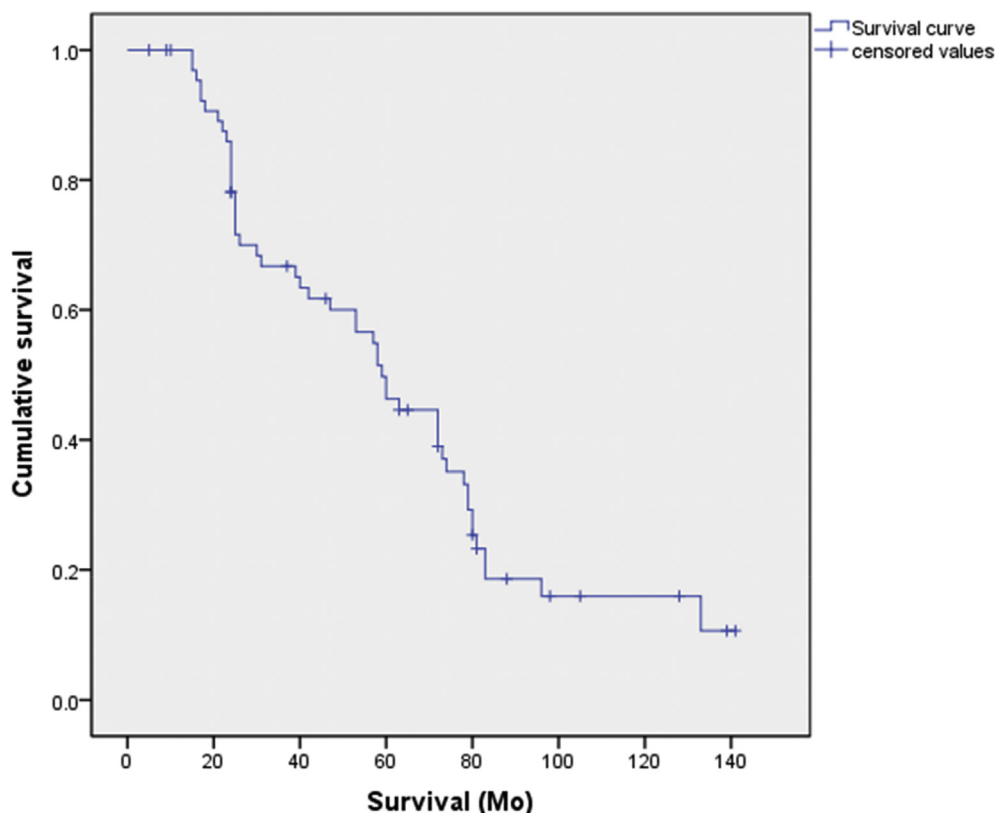


Fig. 1. Survival curves of overall survival.

treatment according to cancer treatment guideline. According to a multicenter retrospective Italian study, primary fallopian tube carcinoma shares several biological and clinical features with ovarian carcinoma. Stage, patient age, and, among patients with advanced disease, residual tumor after initial surgery represent important prognostic variables for survival [6,13]. According to a six gynecologic oncology centers' study in Turkey, advanced FIGO staged III and IV, suboptimal surgery, and pretreatment neutrophil to lymphocyte ratio (NLR) > 2.7 were adverse prognostic factors. The growing notion that the inflammatory process is linked to adverse outcomes in pelvic serous tumors [1]. Only the tumor stage ($p < 0.001$) and the residual tumor size ($p = 0.014$) were significantly related to overall survival in our studies.

In contrast to epithelial ovarian cancer is the importance of early lymphatic spread in this disease, the earlier diagnosis of PFTC leads to an apparent better survival [2,14]. Similar to previously published studies, although accurate preoperative diagnosis is difficult, primary fallopian tube carcinoma reportedly is most often diagnosed in an earlier stage of disease than its ovarian carcinoma counterpart [15]. Its origin within the tubal lumen, which is a partially enclosed space, might delay transperitoneal dissemination, therefore, in consistent with our study, the majority of primary fallopian tube carcinoma were diagnosed in stage I/II (65.7%). The identification of small, occult malignancies at the time of prophylactic surgery or surgery for benign disease could explain, at least in part, women with fallopian tube cancer are more likely to present with early stage tumors [7,16–19]. Moreover, fallopian tube carcinoma can be diagnosed at an earlier stage because of abdominal pain secondary to tubal distention.

The etiology of primary fallopian tube was widely studied in these years. Serous tubal intraepithelial carcinoma (STIC) is now

considered the precursor and the earliest morphologically recognizable form of tubal high-grade serous carcinoma, serous ovarian or peritoneal carcinoma. P53 signatures, as a precursor of STIC, containing a *TP53* mutation. Nearly all STIC overexpress p53 similar to high-grade serous carcinoma. For the development of fallopian tube carcinoma, a sequence of pathogenetic events has been proposed, beginning with genotoxic DNA damage, followed by *TP53* mutation and progressive loss of cell cycle control. According to numerous recent morphologic and molecular genetic studies, type II ovarian tumors mainly include high-grade serous carcinoma, which has a high level of genetic instability and is characterized by mutation of *TP53*. Gene expression profiles of tubal and ovarian serous carcinoma are similar and type II tumors appear to arise from a STIC in the fimbriated end of the fallopian tube that spreads to the ovary [20–22]. The diagnostic triad of abdominal pain, abnormal vaginal bleeding or discharge, and palpable pelvic mass has been detected in 5–20% of patients. Hydrops tubae profluens is considered to be pathognomonic of fallopian tube carcinoma, but it has been reported in only 3–14% of cases [13]. The discrepancy between an abnormal Pap smear and negative findings on colposcopy, cervical biopsy, and endometrial curettage should be considered suspicious for primary fallopian tube carcinoma, and psammoma bodies found in the Pap smear are suggestive of gynecologic malignancy, and more detailed examination is required [3]. In our studies, all of our primary fallopian tube carcinoma cases were diagnosed during operation and none of the case was suspected with primary fallopian tube carcinoma pre-operatively. Once fallopian tube malignancies appeared during operation, total abdominal hysterectomy with bilateral salpingo-oophorectomy and infracolic omentectomy, appendectomy, peritoneal washing, and peritoneal biopsy constitute the primary treatment of choice

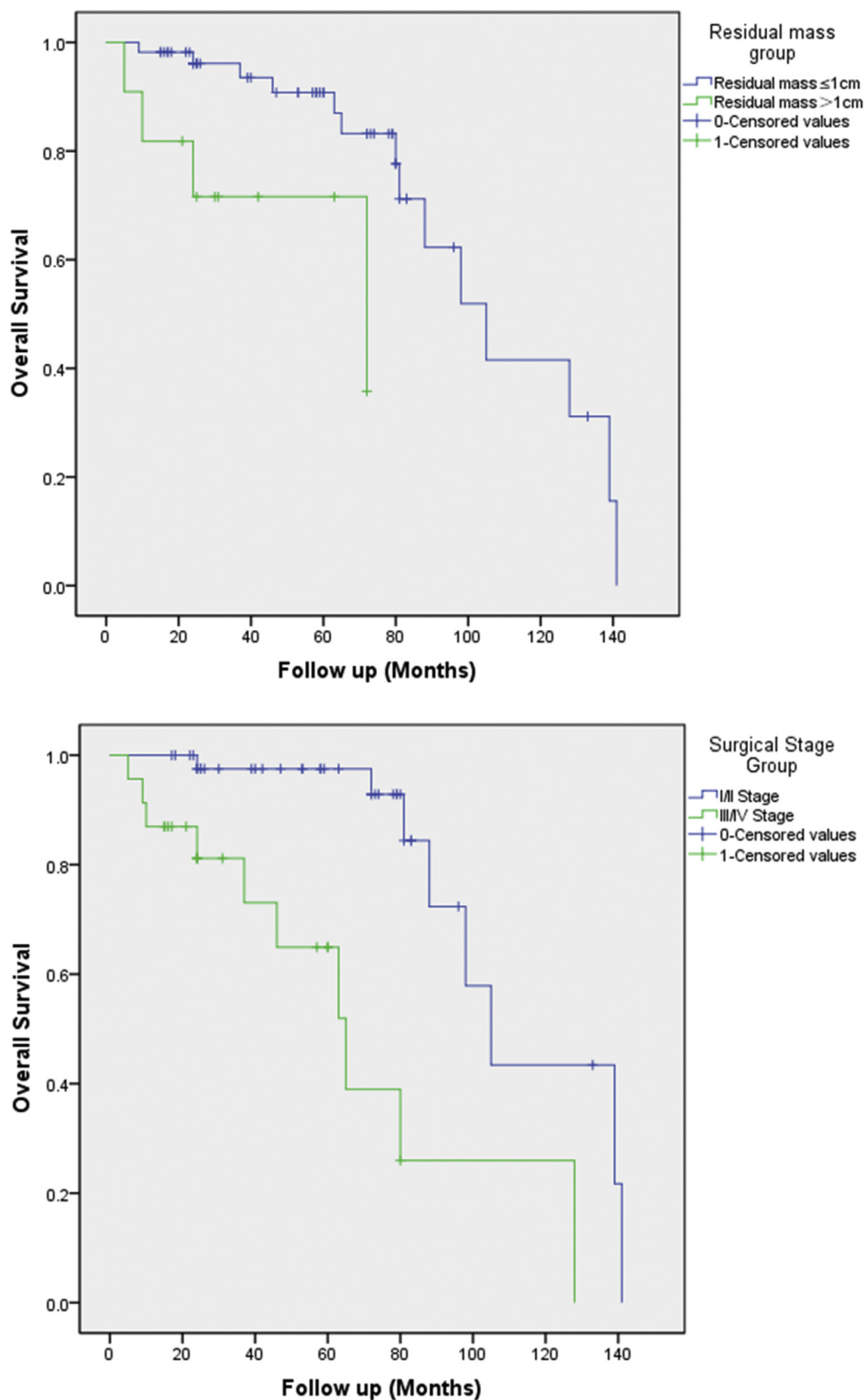


Fig. 2. Survival curves of prognostic factors for overall survival by FIGO stage and residual tumor.

for primary fallopian tube carcinoma; inclusion of pelvic and para-aortic lymphadenectomy has been controversial [6,15,23,24].

In case of primary fallopian tube carcinoma, few series have studied the frequency and precise distribution of nodal

involvement or role of systematic lymphadenectomy. It is still unclear whether lymphadenectomy aids in better staging of patients, or whether the procedure itself has therapeutic values by debulking gross and occult disease in primary fallopian tube

Table 2

Multivariate analyses of significant prognostic parameters on overall survival in patients with primary fallopian tube carcinoma Cox-regression analysis.

	Wald	Risk Ratio	P	95%CI
Age	0.427	0.656	0.513	0.185–2.322
Menopause	0.117	1.328	0.732	0.262–6.735
Pretreatment CA-125 level	0.271	1.343	0.603	0.442–4.078
Residual tumor mass	8.776	11.878	0.003	2.310–61.068
Pelvic lymphadenectomy	2.619	3.887	0.106	0.751–20.130
Surgical stage	13.387	15.473	<0.001	3.567–67.113
Chemotherapy courses	2.095	0.352	0.148	0.086–1.448

carcinoma [25]. In our study, positive result in retroperitoneal nodes metastases was 17.54% (10/57). The prognostic relevance of pelvic lymphadenectomy is still controversial. In M. Klein et al.'s study, although in univariate analysis, pelvic lymphadenectomy is not a significant prognostic factor, in multivariate analysis, it was a significant factor [12]. In patients affected by advanced epithelial ovarian cancers, systematic lymphadenectomy statistically significantly improves disease-free survival and reduces recurrence rates but improvement of overall survival is not statistically significant [25]. From the data of 189 consecutive patients with FIGO stage IIIC ovarian cancer between 2000 and 2011, S-J. Chang et al. reported that patients who underwent systematic lymphadenectomy had significant improved progression-free survival and overall survival [26]. According to X. Deffieux et al., in patients with primary tubal carcinoma, the left para-aortic chain above the level of the inferior mesenteric artery is the most frequently involved. In our present study, it revealed that overall survival first decreased when lymphadenectomy had not been performed, however, we found an increased overall survival in the group of without lymphadenectomy after 70 months follow up (Fig. 3). Both in univariate ($p = 0.653$) and multivariate ($p = 0.106$) analyses, there is no statistically significant correlation between pelvic lymphadenectomy and overall survival (Tables 1 and 2). Evaluations of lymphadenectomy as compared with no

lymphadenectomy in nonrandomized studies are prone to several bias, a prospectively randomized, adequately powered, international, multicenter trial add level 1 evidence to the long-standing discussion about the role of lymphadenectomy in advanced ovarian cancer. In their trial, they intraoperatively randomly assigned patients with newly diagnosed advanced ovarian cancer (FIGO stage IIB through IV) who had undergone macroscopically complete resection and had normal lymph nodes both before and during surgery to either undergo or not undergo lymphadenectomy. By analysis of overall survival (OS), progression-free survival (PFS) and postoperative complications, it revealed that the OS and PFS did not show a significant difference between the two groups. Postsurgical complications in favor of the no-lymphadenectomy group. They came to conclusions that lymphadenectomy is a procedure with a considerable treatment burden and the surgeon's decision as to whether to perform such a procedure may depend not only on disease characteristics such as stage or histology but also on the patient's age, performance status, or coexisting conditions [27].

In conclusion, the diagnosis of primary fallopian tube carcinoma is rarely considered preoperatively. The early stage and optimal debulking surgery with residual tumor ≤ 1 cm are important independent factors to improve patients' prognosis. However, the value of lymph node sampling or dissection needs to be reconsidered. For gynecologic surgeon, we should try to determine whether patients benefit from lymphadenectomy concerning overall survival. It must be noted that more extensive multicenter clinical research must be performed. 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.

Disclosure

This research received no specific grant from any funding agency in the public, commercial, or not-for profit sector.

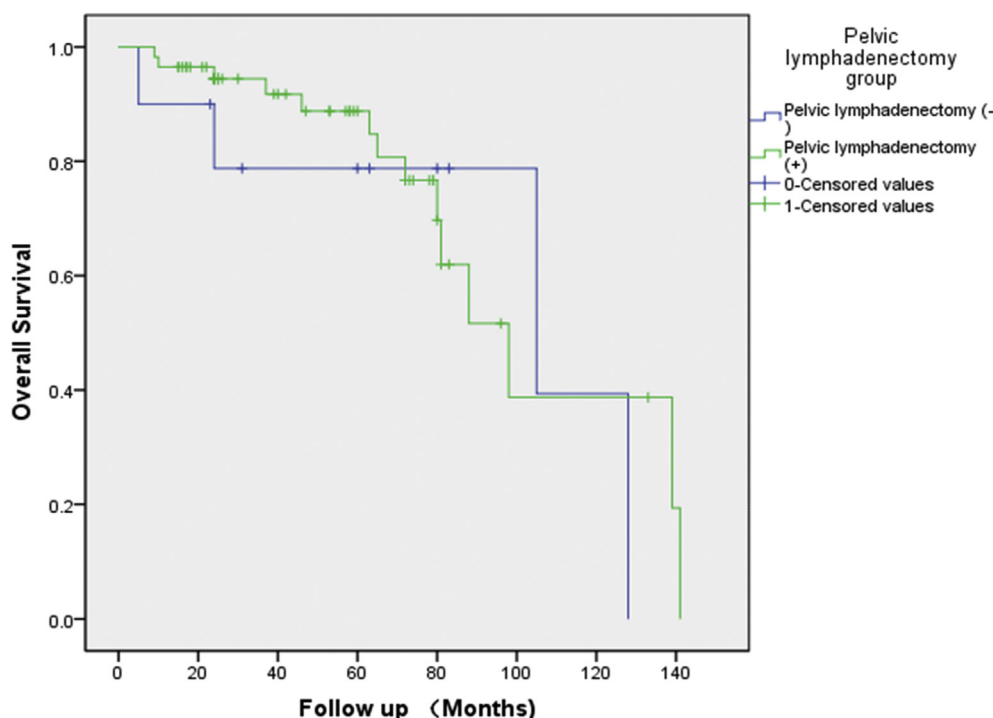


Fig. 3. Survival curves of prognostic factors for overall survival by pelvic lymphadenectomy.

Conflict of interest

None declare.

Author's contributions

All authors agreed to be accountable for all aspects of the work and ensuring accuracy and integrity and approved the final version of this manuscript.

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