Primary fallopian tube carcinoma: a single-institution retrospective study of 57 cases

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Research article

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Abstract

Background In order to identify the characteristics and factors affecting the treatment and prognosis of primary fallopian tube cancer(PFTC),we analyzed the clinical profile of PFTC in the past 10 years in our hospital, which is center in Western China.

Methods A retrospective analysis was performed on 57 patients diagnosed as PFTC at the Department of Obstetrics and Gynecology, the First Affiliated Hospital of Xi'an Jiaotong University from past ten years. The clinical index and a Cox proportional hazards model was used for univariate and multivariate survival analyses.

Results The mean age of PFTC at diagnosis was 57.35±9.01 years. Palpable pelvic and/or abdominal mass (68.4%) was the main clinical symptom. Preoperatively, 80.7% patients were misdiagnosed with ovarian cancer, and 43.8% of patients were at stage III. 26 patients were relapsed at the median of 18.5 (3-83) months. The 5-year overall survival (OS) rate was 15.4%, and the 5-year disease-free survival (DFS) was 11.5%. Additionally, univariate analysis showed that tumor stage and size of residual tumor were both related to 5-year OS and DFS. While level of serum carbohydrate antigen 125(CA125) pre-treatment was only related to DFS. The Cox proportional hazards model demonstrated that residual tumor size was the only independent factor related to both 5-year OS and DFS.

Conclusions PFTC is a more common malignancy at post-menopause stage in women. The symptoms are not typical in most case and often diagnose at late clinical stage. Tumor stage, level of CA125, and residual lesion size affected the disease-free survival or/ and overall survival.

Trial registration Not applicable.

Background

Primary fallopian tube carcinoma (PFTC) is a rare type of female genital tract malignant tumor that only accounts for 0.14–1.8% of all gynecological malignancies[1, 2]. Research has shown that the incidence of PFTC has been rising in the last decades[3]. Diagnosis of PFTC is frequently missed or delayed due to the fact that PFTC has the same intraoperative findings or pathological characteristics as serous-type epithelial ovarian carcinoma (EOC) or primary peritoneal serous carcinoma (PPSC)[4].

Now the management of PFTC is usually based on the same International Federation of Gynecology and Obstetrics (FIGO) guidelines which used for EOC, but debates referring to the optimal management of PFTC still exist due to differences of clinical characteristics between PFTC and EOC[4, 5]. For example, compare with EOC, PFTC is more apt to metastasis to the retroperitoneal lymph nodes and distant sites[6], and often found at the early stage because of showing the Latzko's triad of symptoms, which includes profuse sero-sanguinous vaginal discharge, an abdominal or pelvic mass, and colicky pain[7]. Furthermore, compared with macroscopic intraperitoneal metastasis of EOC, PFTC shows a high tendency of microscopic distant metastasis which results in a high risk of recurrence and poor outcome.

In the past 10 years, the worldwide incidence of PFTC tends to be increased year by year. In our hospital, the incidence of PFTC was increased from 0.98% in 2006, to 1.64% in 2010, and to 2.1% in 2016. Given the ascending of the incidence, lacking of the best treatment and poor prognosis, we performed this retrospective study to identify the factors affecting the prognosis of PFTC by using records of hospital-based patients in the First Affiliated Hospital of Xi'an Jiaotong University between 2006–2016. Medical records of 57 patients with PFTC were collected, and the clinical profiles were analyzed to improve the understanding of PFTC biological behavior and provide clinical evidence for the treatment guidelines.

Methods

Patients

A retrospective analysis was performed on the patients diagnosed with PFTC at the Department of Obstetrics and Gynecology, the First Affiliated Hospital of Xi'an Jiaotong University from May 2006 to May 2016. All patients were surgically staged and treated with chemotherapy. Patients with metastatic fallopian tube carcinoma, tumors of low malignant potential, neoadjuvant chemotherapy, and postoperative radiotherapy were excluded. Totally, 57 cases were included in the study.

Clinical and pathological characteristics

Information about demographic data, clinical symptoms, original diagnosis, treatment regimen and follow-up were extracted from medical records. The 2009 FIGO staging system was used to define tumor stage. Histologic evaluation and tumor grade was based on the World Health Organization (WHO) classification of malignant epithelial fallopian tube carcinoma and EOC. Specimens of each patient were subject to hematoxylin and eosin (H&E) staining and immunohistochemical staining. The pathological diagnosis, tumor grade and histologic type of PFTC were confirmed by two experienced gynecological pathologists, respectively.

Follow-up

Follow-up periods were begun from the month after the surgery and ended in February 2017. Five cases were drop-out because of loss of contact, accounting for 8.8% of all involved patients. This study, therefore, 52 patients were analyzed with a median follow-up of 24.5 months (range, 3–122 months).

Recurrence was determined by the elevation of serum carbohydrate antigen 125(CA125) and metastasis sites on image. Disease-free survival (DFS) is the interval between the time of last treatment and the time of recurrence or the end of the follow-up if no recurrent symbols detected.

Statistical analysis

The data were analyzed by SPSS 22.0. The clinical parameters were described by ratio or mean. The independent prognostic significance of parameters was estimated by using the Cox proportional hazards model. Survival rate was calculated using the Kaplan-Meier method. P-values < 0.05 were considered statistically significant.

Results

Clinical symptoms and pathological characteristics

A total of 57 patients with PFTC were enrolled in this retrospective study. As shown in Table 1, the mean age of PFTC at diagnosis was 57.35±9.01 years (range, 39–80 years). 42 patients (73.7%) were postmenopausal, only one (1.8%) patient was nulliparous, and the mean time of post-menopause was 8.18±8.12 years (range, 1–33 years).

The main clinical symptoms were palpable pelvic and/or abdominal mass (68.4%), abdominal pain (33.3%), abdominal distension (26.3%), abnormal vaginal bleeding (19.3%) and followed by discharge (10.5%). Only 4 patients (7%) experienced typical Latzko's triad symptoms including abdominal pain, vaginal bleeding or discharge, and a palpable pelvic mass. Furthermore, 6 cases (10.5%) were exhibited atypical clinical manifestation containing irregular menstruation (2 cases, 3.5%), urinary frequency and urgency (1 case, 1.75%), pantalgia (1 case, 1.75%), fever (1case, 1.75%), and severe edema of the lower limbs (1 case, 1.75%) (Table 1).

50 patients (87.7%) had unilateral fallopian tube tumor, while seven (12.3%) patients had bilateral fallopian tubes tumors. Preoperatively, only 6 patients (10.5%) were diagnosed as PFTC, 46 (80.7%) were misdiagnosed with ovarian cancer, and 5 (8.8%) were misdiagnosed as endometrial cancer. 44 patients (77.2%) had no preoperatively pathological results, only eight cases (14.0%) were shown adenocarcinoma cells in the ascites, and five cases (8.8%) were in the endometrial tissues (Table 1).

A primary tumor diameter greater than or equal to 5 cm were in 42 patients(73.7%), and majority of patients were at stage III (n = 25, 43.8%), 15 (26.3%) patients at stage I, 12 (21.1%) at stage II, and the rest at stage IV (n = 5, 8.8%). Consistently, serum carbohydrate antigen 125(CA125) was enhanced (≥35 U/mL) in 43 patients (75.4%) preoperatively in these 57 patients. The accuracy of intraoperative frozen pathological diagnosis was 70% (35/50), expelled 7 patients who without frozen results. The main common histologic subtype was serous adenocarcinoma (n = 54, 94.7%) with high-grade (n = 51, 89.5%) (Table 2).

Treatment Regimen

Surgery was the initial therapy for all patients, 30 (52.6%) patients were underwent complete tumor resection with residual lesion no larger than 1 cm. In these 57 patients, bilateral salpingo-oophorectomy was performed in all patients, accompanying with total hysterectomy (96.5%), omentectomy (77.2%),

pelvic lymphadenectomy (40.4%, with metastasis detected in two patients), para-aortic lymphadenectomy (10.5%, with metastasis detected in two patient), or appendectomy (29.8%, with metastasis detected in two patients), respectively.

In this cohort of 57 patients, 56 were received postoperative chemotherapy with intravenous paclitaxel plus platinum(TP) regimen. Among them, 30 (53.5%) were received ≥ six cycles of chemotherapy, and 36(64.3%) patients received ≥ two cycles of intraperitoneal chemotherapy, which contained cisplatinum 40 milligram(40mg) and recombinant human interleukin–2 500 international units (500 IU) for perfusion on the first and fifth days after surgery. Whereas the one case who had not received chemotherapy because of intolerance to the adverse effects.

Recurrence

Five patients were lost to follow-up. Among the remaining 52 patients, 26 patients (50%) were relapsed at the median of 18.5 (3–83) months. The recurrent sites involved the pelvis (n = 7, 26.9%), upper abdomen (n = 2, 7.7%), retroperitoneal lymph nodes (n = 3, 11.5%), and distant metastasis (n = 7; 1 in the lung, 3 in the liver, 1 in the bone, and 2 in the brain). Seven (26.9%) patients had elevated CA125 with no obvious image evidence for metastasis. At the time of data collection, 12 patients (46.2%) were still alive, and 14 (53.8%) were died from recurrence.

Survival analysis

The 5-year overall survival (OS) rate was 15.4%, and the 5-year Disease-free survival (DFS) was 11.5%. Additionally, univariate analysis showed that the 5-year OS was related to tumor stage (III/IV vs I/II, P = 0.013) and residual tumor size (≥1 vs <1 cm, P = 0.001) (Table 3). While DFS was significantly related to clinical tumor stage (III/IV vs I/II, P = 0.007), residual tumor size (≥1 vs <1 cm, P = 0.003), and pre-treatment CA125 level (<35 vs ≥35 U/mL, P = 0.047) (Table 4). Variables (including tumor stage, size of residual tumor, pelvic lymphadenectomy, and pre-treatment CA125 level) which shown significant difference in univariate analysis were entered into the multivariate analysis. The Cox proportional hazards model and curves of OS or DFS were demonstrated that residual tumor size was the only independent prognostic factor both related to 5-year OS and DFS (Table 5 & Fig. 1).

All other factors(such as age, postmenopausal period, histologic grade, primary tumor diameter, cycles for chemotherapy) did not have any significant influence on PFTC prognosis.

Discussion

Primary fallopian tube carcinoma (PFTC) is a rare gynecologic malignancy, and preoperatively accurate diagnosis of PFTC is still a dilemma in clinic. Higher misdiagnosis rate and the advanced stage when

identified lead to its poor outcome. To explore the clues for early diagnosis, we analyze the demographic and clinical characteristics of PFTC and identify variables affecting DFS and OS in patients in this study.

The median age of PFTC reported in literature is 55 years[8], and no childhood case was reported[9]. In our current series, the mean age was 57.35±9.01 years, and univariate analysis is failed to find a significant correlation between the age and survival results. Meanwhile, 42 (73.7%) are postmenopausal patients with a mean postmenopausal period of 8.18±8.12 years (1–33years) in our cohort study, which is similar to previous reports[10, 11]. All the evidence suggest postmenopausal women may be more prone to this malignancy.

In this study, the clinical symptoms of PFTC were diversified, and the most common symptoms are palpable pelvic and/or abdominal mass, followed by abdominal pain and abnormal vaginal bleeding or discharge, which are consistent with those described previously[12]. Furthermore, the percentage of patients with Latzko's triad of symptoms is very small (7%) and comparable with the earlier reported data (3–14%)[13, 14]. It is noteworthy that uncommon initial presentation including irregular menstruation, urinary frequency and urgency, pantalgia, fever and severe edema of the lower limbs may be also the indicators for PFTC. Because ascites may be a late manifestation of disseminated carcinomatosis with the entire abdominal peritoneal surface and omentum implanted with malignant nodules[15], or the mass might have been pressing might have been pressing on the bladder region[16]. In most cases, it is difficult to distinguish PFTC from ovarian cancer preoperatively or even intraoperatively. Previously research data reported that only 6.3–12.1% were diagnosed with PFTC preoperatively, and 50% were diagnosed intraoperatively[17, 18]. Consistently, 10.5% patients were diagnosed as PFTC preoperatively.

There are many factors that determine the prognosis of PFTC. In fact, findings about the relationship between CA125 and survival are controversial. Shamshirsaz reported that pretreatment serum CA125 value was a predictive factor both for DFS and OS[19]. However, Gungorduk reported that CA–125 had nothing to do with DFS or OS[8]. In this cohort, the level of CA–125 increased along with the ascending of clinical stage. Interestingly, CA125 had a significant correlation with DFS and a marginal correlation with OS by univariate analysis. Oppositely, multivariate analysis indicated that CA125 had no statistical significance in predicting OS or DFS. Advanced stage is an independent prognostic factor for OS and DFS. In this research, the proportion of PFTC patients at stage III was as high as 43.8%, indicating that a significant portion of cases were diagnosed at the late stage, which is consistent with the reported incidence (38.6%)[20]. Further univariate analysis showed that clinical stage had a significant association with DFS and OS, but multivariate analysis did not confirm this finding. Lowly differentiated tumors accounted for 89.5%(72.7–80.6% reported in the literature), and had no correlation with prognosis[14, 21]. In addition, residual tumor size was reported to be a predictive factor in previous studies. In our study, both univariate and multivariate analyses revealed that residual tumor size was the only independent prognostic variable for DFS and OS.

The optimal treatment for PFTC has not been well defined due to its rarity, and often managed in accordance with the principles of ovarian cancer. At present, whether PFTC patients need to undergo

lymph node sampling or dissection is still controversial. A high tendency of PFTC to spread lymphatically is explained by abundant lymphatic network in the fallopian tubes. The overall incidence of lymph nodes(LN) metastasis was 40%, with metastases to the pelvic lymph nodes in 2.4–23% of cases and to the para-aortic lymph nodes in 22–32%. Extensive lymphadenectomy has been demonstrated as an independent indicator for OS. Given that the lymphatic flow from the oviduct drains to the pelvic lymph nodes through lymphatic channels situated nearby the proximal part of the uterus, and the distal part of the tubes and fimbria have lymphatic channels joined to the para-aortic lymph nodes, some scholars advocate extensive lymphadenectomy and prefer to remove the systematic pelvic and para-aortic lymph nodes[22]. Koo reported that para-aortic lymphadenectomy was an important measure and speculated that the para-aortic lymph nodes were the sentinel lymph nodes in PFTC patients[23]. While some clinicians performed pelvic lymphadenectomy only, or favored lymph node sampling or did not perform lymphadenectomy. In our current series, pelvic lymphadenectomy was performed in 23 cases, two patients were accompanied with metastasis. Para-aortic lymphadenectomy was performed in 6 cases, only one patient detected metastasis. However, lymphadenectomy had no significant influence on OS or DFS by univariate analysis. There have been very few studies assessing the importance of appendectomy and omentectomy in PFTC patients[24]. Previous reports described that appendectomy or omentectomy have no relationship with survival or postoperative complications[25]. Consistent with this, we also revealed that appendectomy or omentectomy was not an independent risk factor for prognosis by univariate analysis.

Because of the propensity for microscopic distant spread and the relatively high risk of recurrence, chemotherapy after surgery seems to have a strong rationale as adjuvant treatment for PFTC patients, and the response rate to cisplatin-based chemotherapy was 53–92%. Gemignani suggested a marked survival advantage of paclitaxel-based chemotherapy in PFTC patients with minimal residual disease[26]. Tresukosol reported that dose of 200 mg/m^2 paclitaxel could achieve a complete clinical response in a patient with recurrent platinum-resistant disease[27]. However, our data showed that the platinum-taxane combination was not an independent prognostic factor for DFS or OS.

Conclusions

In conclusion, preoperative diagnosis of PFTC is difficult because of the untypical symptoms and silent course of the neoplasm. It is more common in post-menopausal women. For PFTC patients at late clinical stage, lymph node sampling or dissection may be under consideration. Tumor stage, level of CA125, and residual lesion size affected the disease-free survival and overall survival.

Abbreviations

PFTC: primary fallopian tube cancer; OS: overall survival; DFS: disease-free survival; CA125: serum carbohydrate antigen 125; EOC: epithelial ovarian carcinoma; PPSC: primary peritoneal serous carcinoma; FIGO: International Federation of Gynecology and Obstetrics; WHO: World Health Organization; H&E: hematoxylin and eosin; TP: paclitaxel plus platinum; LN: lymph nodes.

Declarations

Ethics approval and consent to participate This article is a retrospective study. Retrospective research was conducted on already available data. Before the first submission, no ethical approval was required by the regulations of the host institutions. However, all the procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

Consent for publication Not applicable.

Availability of data and materials The dataset analysed in this study was extracted from the Gynecological CancerDatabase of the First Affiliated Hospital of Xi'an Jiaotong University.

Competing interests The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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Authors' contributions ZM: data collection, project development and manuscript editing. LG: data collection and analysis. HL: data collection and analysis. YX: project development, manuscript editing and supervision.

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Tables

Table 1 Clinical characteristics of 57 patients diagnosed with PFTC

Characteristics	No. Patients	%
Age(years)	57.35±9.01	
Menopause at diagnosis	42	73.7
Postmenopausal years	8.18±8.12	
Nulliparous	1	1.8
Main clinical manifestation		
Latzko triad symptom	4	7.0
Vaginal bleeding	11	19.3
Vaginal discharge	6	10.5
Abdominal pain	19	33.3
Pelvic mass	39	68.4
Abdominal distension	15	26.3
Atypical symptoms	6	10.5
Involved fallopian tube		
Right	29	50.9
Left	21	36.8
Bilateral	7	12.3
Preoperativediagnosis		
Primary fallopian tube carcinoma	6	10.5
Ovarian cancer	46	80.7
Endometrial cancer	5	8.8
Preoperative pathological results		
Adenocarcinoma	8	14.0
Endometrial carcinoma	5	8.8
No	44	77.2

Atypical symptoms：irregular menstruation in 2(3.5%) patients, urinary frequency and urgency in 1(1.75%), pantalgia in 1(1.75%), fever in 1(1.75%), and severe edema of lower limbs in 1(1.75%) cases.

Characteristics	No. Patients	%
Interoperative frozen results		
Primary fallopian tube carcinoma	35	52.6
Ovarian cancer	6	10.5
Adnexal malignant tumor	8	14.0
Abdominal tuberculosis	1	1.8
No	7	12.3
Histologic subtype		
Serous	54	94.7
Endometrial	1	1.8
Transitional cell	1	1.8
Malignant mixed mullerian tumor	1	1.8
Grade		
1	1	1.8
2	5	8.8
3	51	89.5
FIGO stage		
I	15	26.3
II	12	21.1
III	25	43.8
IV	5	8.8
Preoperative serum CA125(U/ml)		
≥35	43	75.4
35	14	24.6

Table 2 Pathological characteristics of 57 patients diagnosed with PFTC

Table 3 Impact of prognostic factors on OS by univariate analysis in PFTC

Factors	No.	HR	95%CI	P
Age group(years)		0.951	0.375-2.413	0.916
<60	32			
≥60	25			
Postmenopausal period(years)		1.167	0.451-3.023	0.750
<10	33			
≥10	24			
Pre-treatment CA125 level(U/ml)		0.237	0.053-1.056	0.059
<35	14			
≥35	43			
FIGO stage		0.264	0.093-0.751	0.013
I/II	27			
III/IV	30			
Grade		1.462	0.328-6.509	0.618
≤2	6			
>2	51			
Residual tumor(cm)		0.174	0.060-0.503	0.001
≤1	30			
<1	27			
Pelvic lymphadenectomy		0.546	0.203-1.468	0.231
Yes	23			
No	34			
Appendectomy		0.910	0.338-2.448	0.852
Yes	17			
No	40			
Omentectomy		0.701	0.227-2.171	0.539
Yes	44			
No	13			
Primary IP chemotherapy		0.927	0.365-2.354	0.873
Yes	36			
No	21			
TP chemotherapy(courses)		1.181	0.454-3.072	0.733
≥6	30			
<6	27			
Tumor diameter(mm)		0.617	0.178-2.137	0.446
<50	15			
≥50	42			

Table 4 Impact of prognostic factors on DFS by univariate analysis in PFTC

Factors	No.	HR	95%CI	P
Age group(years)		1.047	0.413-2.656	0.922
<60	32			
≥60	25			
Postmenopausal period(years)		1.254	0.482-3.260	0.643
<10	33			
≥10	24			
Pre-treatment CA125 level(U/ml)		0.217	0.048-0.982	0.047
<35	14			
≥35	43			
FIGO stage		0.238	0.084-0.678	0.007
I/II	27			
III/IV	30			
Grade		1.019	0.231-4.495	0.981
≤2	6			
>2	51			
Residual tumor(cm)		0.207	0.073-0.590	0.003
≤1	30			
<1	27			
Pelvic lymphadenectomy		0.468	0.173-1.265	0.135
Yes	23			
No	34			
Appendectomy		1.017	0.379-2.731	0.973
Yes	17			
No	40			
Omentectomy		0.925	0.303-2.831	0.892
Yes	44			
No	13			
Primary IP chemotherapy		0.706	0.278-1.795	0.465
Yes	36			
No	21			
TP chemotherapy(courses)		1.115	0.428-2.902	0.824
≥6	30			
<6	27			
Tumor diameter(mm)		0.487	0.141-1.685	0.256
<50	15			
≥50	42			

Table 5 Variables predictive of survival by Cox proportional hazards model in PFTC

		Wald c^2	Risk ratio	95% CI	P
OS	FIGO stage				0.668
	Residual tumor	10.429	0.174	0.06-0.503	0.001
	Pelvic lymphadenectomy				0.759
	Pre-treatment CA125 level				0.645
DFS	FIGO stage				0.782
	Residual tumor	8.69	0.207	0.073-0.590	0.003
	Pelvic lymphadenectomy				0.902
	Pre-treatment CA125 level				0.515

Figures

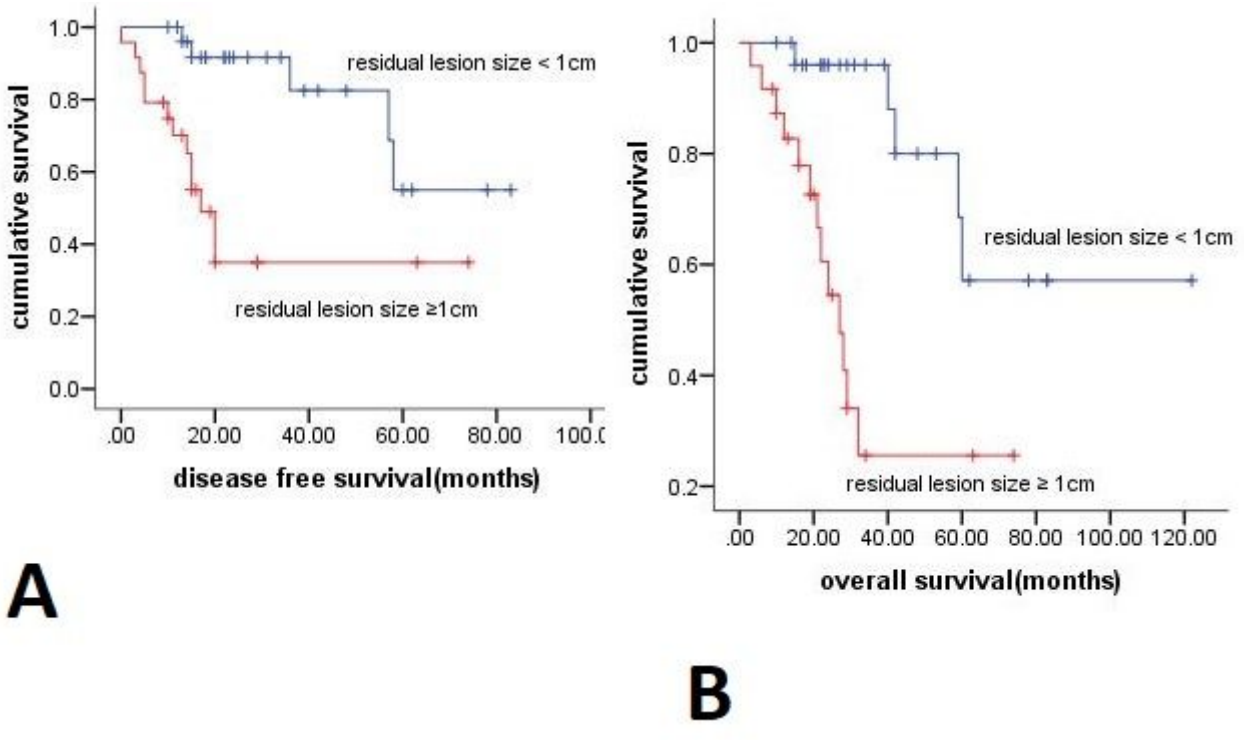

Figure 1

a The disease free survival(DFS) was significant longer in patients with residual tumor was no larger than 1 cm. b The overall survival(OS) was significant longer in patients with residual tumor was no larger than 1 cm.