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Original Article

Preferred method of therapy for patients with early-stage high-grade neuroendocrine carcinoma of the cervix

Yuanyuan Zhang[1*], Lin Li[2*], Ziyi Wang[3*], Yi Huang[4], Suiyu Luo[5], Yongmei Peng[6], Ning Li[1], Yang He[4], Chunmei Li[5], Keqiang Zhang[3], Hongying Yang[6], Qi Zhou[2], Lingying Wu[1]

[1]Department of Gynecologic Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 17 Panjiayuan, Chaoyang District, Beijing 100021, China; [2]Chongqing Key Laboratory of Translational Research for Cancer Metastasis and Individualized Treatment, Chongqing University Cancer Hospital, Chongqing 400030, China; [3]Department of Gynecologic Oncology, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, 283 Tongzipo Road, Yuelu District, Changsha 410013, Hunan Province, China; [4]Department of Gynecologic Oncology, Hubei Province Cancer Center/Hubei Cancer Hospital, The Affiliated Cancer Hospital of Tongji Medical Colleague of Huazhong University of Science and Technology, 116 Western Zuodaoquan Road, Hongshan District, Wuhan 430079, Hubei Province, China; [5]Department of Gynecology and Obstetrics, Henan Provincial People's Hospital/Zhengzhou University People's Hospital, The Affiliated People's Hospital of Henan University, Weiwu and Jingsan Road, Jinshui District, Zhengzhou 450003, Henan Province, China; [6]Department of Gynecologic Oncology, Yunnan Province Cancer Center/Yunnan Cancer Hospital, The Third Affiliated Hospital of Kunming Medical University, 519 Kunzhou Road, Xishan District, Kunming 650100, Yunnan Province, China. [*]Equal contributors.

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Abstract: High-grade neuroendocrine carcinoma of the uterine cervix (HGNECC) is a rare and overly aggressive malignancy. Due to its rarity, there is no standard treatment. A majority of early-stage patients receive radical hysterectomy and lymph node dissection (RH+LND), followed by adjuvant chemotherapy. To explore the most suitable methods of therapy, a multicenter retrospective review of HGNECC patients was conducted. A total of 133 patients (I-IIA, FIGO 2009) treated from March 2003 to September 2018 were enrolled in this study. The 5-year DFS and OS rates for stages IB and IIA were 44.8% and 39.5%, and 53.8% and 39.6%, respectively. The median DFS and OS for stages IB and IIA were 41 months and 12 months, and 63 months and 45 months, respectively. The RH+LND surgery procedure was associated with a significantly better DFS (P=0.015) and OS (P=0.006), while the bilateral salpingo-oophorectomy (BSOE) was also associated with a better OS (P=0.023). The efficacy of paclitaxel-platinum (TP/C) adjuvant chemotherapy regimens need to be confirmed using clinical trials, especially for tumors with a diameter of >4 cm (P=0.0005). Therefore, the RH+LND+BSOE procedure was recommended for HGNECC patients at stages IB-IIA. TP/C is an alternative chemotherapy regimen that results in optimal survival. Moreover, a tumor diameter of >4 cm, LNM, DSI, and LVSI were confirmed as high-risk factors for worse DFS and OS. Patients without risk factor, 1 or 2 or 3 risk factors, and 4 risk factors had significantly different DFS and OS values.

Keywords: Neuroendocrine cervical carcinoma, radical hysterectomy surgery, ovary dissection, radiation, chemotherapy, risk factors

Introduction

Neuroendocrine cervical carcinoma (NECC) accounts for 0.9-2% of all cervical cancers [1-3]. NECC is considered to be an exceedingly aggressive malignant lesion compared with other types of cervical cancers, such as squamous cell cancer of the cervix [1, 2, 4, 5]. Neuroendocrine tumors encompass several histological subtypes, including low and high-grade, and carcinoid tumors. High-grade neuroendocrine carcinomas can be categorized as small cell and large cell neuroendocrine carcinomas that show poor prognosis even at stages I-IIA (International Federation of Gynecology and Obstetrics stage, FIGO, 2009) [6, 7]. Cer-

tain high-grade neuroendocrine cervical carcinoma (HGNECC) cohorts have developed distant metastases and lymph node metastasis (LNM) even during these early stages [1, 3, 5, 8-12]. Thus, patients with HGNECC require a therapeutic strategy that is different to that which is used on other common histological types. However, treatment choices available for these patients are limited, and a standard therapeutic protocol is not available, while certain opinions are controversial [3]. Treatment methods for these patients overlap with that of other common histological types of cervical cancer [3, 5]. It can be difficult to conduct randomized prospective clinical trials to determine the most effective management strategies due to its rarity. Therefore, retrospective studies are necessary. We conducted a retrospective study based on real-world evidence obtained from 6 Gynecological Oncology Centers to determine the appropriate therapeutic methods and analyze the clinicopathological prognostic factors for patients with HGNECC.

Materials and methods

Gynecological Oncology Centers at the 6 hospitals, the National Cancer Center of China, Henan Provincial People Hospital, Hunan, Hubei, Chongqing, and Yunnan Cancer Hospital, contributed to the design and review of this study. After approval was obtained from the Ethics Committees of all Institutions involved, a total of 133 patients treated from March 2003 to September 2018 were enrolled in this study. Only medical records and follow-up data were reviewed. This study did not infringe on patient privacy or interfere with any clinical decisions. Histological features and immune profiles were used to confirm the pathological characteristics. Patient demographics, preoperative and postoperative imaging, surgical procedure details, and outcomes were thoroughly reviewed.

The FIGO 2009 staging system was used to define the stage of patients at diagnosis. In general, the most commonly recommended methods of treatment for patients with HGNECC at stages I-IIA in China are: 1) radical hysterectomy (RH), system lymph node dissection (LND, at least including the pelvic region) with or without bilateral-salpingo-oophorectomy (BSOE) followed by 2) chemotherapy with or without 3) radiotherapy/concurrent chemoradiotherapy (CCRT). The outcomes at the last follow-up were recorded as disease-free progression, disease recurrence, or death. The metastatic status of each patient was determined by increasing the secretion of neuron-specific enolase (NES) and physical imaging. The imaging methods used were computed tomography, magnetic resonance imaging (MRI), and positron emission tomography (PET). Clinical variables, including age, pathological subtype, stage, surgical procedures, chemotherapy regimens, chemotherapy course, recurrence and survival status, progression-free survival time (PFS), and overall survival time (OS), were recorded. After initial treatment, patients without tumor relapse were confirmed through physical examination and imaging, and their disease-free survival (DFS) and OS values, which were calculated from the time of diagnosis to last follow-up or death, were recorded.

Descriptive statistics for continuous covariates are described as mean ± standard deviation (mean ± SD), and the Mann-Whitney test was used to analyze differences. Categorical variables were recorded as frequencies and were compared using χ^2 and Fisher's exact tests. The Kaplan-Meier method was used for time to event analyses, and data were compared using the log-rank test. A Cox proportional hazards model was adopted to estimate the effect of predictors using univariate and multivariate settings on survival time. The categorical covariates associated with progression or death were recorded by calculating the odds ratios (OR) and 95% confidence intervals (CI). Multivariate Cox regression analysis was used to identify independent prognostic factors. Data were analyzed using Statistical Package for Social Sciences (SPSS) 22.0 software. The survival curve was plotted using Graphpad Prism 5.1 software. A P value of <0.05 was considered to indicate a significant difference.

Results

Data on a total of 178 patients with HGNECC were reviewed, and 74.1% of patients (133/178) were found to have been diagnosed at an early stage and were enrolled in this study. Most cases (81.2%) were diagnosed as small cell neuroendocrine carcinoma. The demographic characteristics of the entire cohort are presented in Table S1. The age of patients with

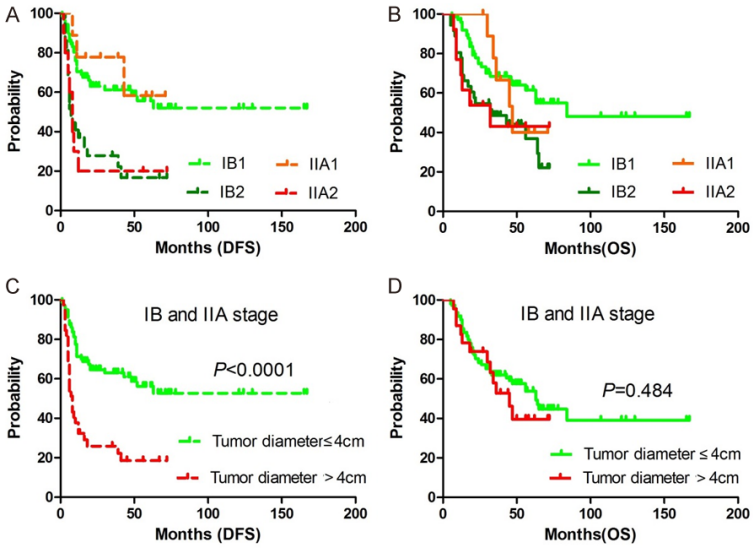

Figure 1. Survival curves. Probability of DFS (A) and OS (B) for HGNECC patients at I-IIA stages. IB1 and IIA1, IB2 and IIA2 had a similar survival cures respectively, the survival cures were re-examined by tumor diameter: Probability of DFS (C) and OS (D) for patients with tumor diameter ≤4 cm and >4 cm of IB-IIA stages. The X-axis denotes survival period (months) after the initial treatment, and the Y-axis denotes survival rate.

early-stage HGNECC was 42.22±9.37 years at diagnosis, while aged individuals (48.65±9.57 years) were more often diagnosed at the late-stage (IIB-IV).

An overview of the therapeutic techniques used is presented in Figure S1. Most patients (125/133, 93.9%) with early-stage HGNECC underwent surgery as the primary method of treatment. In contrast, six patients (6/133, 4.5%) underwent definitive chemotherapy either with or without radiation at diagnosis, whereas 2 patients (1.5%) did not receive any therapy. Most patients (114/125, 91.2%) who received surgery had also undergone adjuvant chemotherapy. Among patients who received surgery, 121 patients (121/125, 96.8%) underwent RH and LND, while three patients (3/125, 2.4%) underwent simple hysterectomy (Table S1 and Figure S1). Chemotherapy with or without radiotherapy was the second most common therapeutic method. A combination of cisplatin with etoposide (EP) was the most commonly used (n=63), while paclitaxel with cisplatin (TP, n=24) and carboplatin (TC, n=11) were used for certain patients. As for radiotherapy, 72 patients received radiotherapy, while one patient received definitive radiation as monotherapy, and four patients received CCRT, while 66 patients received adjuvant radiotherapy.

The survival curves for stages I-IIA patients are presented in **Figure 1** (survival curves of stages I-IV patients are shown in Figure S2). Among patients with early-stage HGNECC, the estimated 3-year disease-free survival (DFS) and overall survival (OS) rates for patients at stages IB and IIA were 51.9% and 47.4%, and 61.9% and 52.8%, respectively. The estimated 5-year DFS and OS rates for patients at stages IB and IIA were 44.8% and 39.5%, and 53.8% and 39.6%, respectively. The median DFS and OS durations for patients at stages IB and IIA were 41 months and 12 months, and 63 months and 45 months, respectively. Due to the trend of the survival curves shown in **Figure 1A** and **1B**, the patients were divided into two groups: IB1-IIA1 (tumor diameter ≤4 cm) and IB2-IIA2 (tumor diameter >4 cm). Tumors with a diameter of ≤4 cm showed better DFS (P<0.0001), but this difference was not significant in OS (P=0.484) (**Figure 1C** and **1D**).

The univariate analysis showed that a tumor diameter of >4 cm, deep stromal invasion (DSI), LNM, LVSI, and NAC were prognostic factors for poor DFS, while a tumor diameter of >4 cm, LNM, LVSI, NAC, and pre-operative radiation were prognostic factors for poor OS. A P-value of <0.05 was used for the univariate analysis, and the relative categorical covariates were set in the multivariate analysis (**Table 1**). Overall, large tumor size and LVSI were identified as independent prognostic factors for poor DFS. In contrast, large tumors, LNM, and pre-operative radiation were identified as independent prognostic factors for poor OS using multivariate analyses. The survival curves of groups with high-risk, as identified through pathology, are shown in **Figure 2**. The survival curves revealed that tumor diameter (>4 cm), LNM, LVSI, and DSI indicated worse DFS, while LVSI and LNM were strongly associated with poorer OS.

Table 1. Univariate and multivariate analyses of DFS and OS based on clinic-pathological factors in patients with HGNECC at early-stage

	DFS				OS				
	N	Univariate analysis		Multivariate analysis		N	Univariate analysis		Multivariate analysis	
		HR (95%)	P	HR (95%)	P		HR (95%)	P	HR (95%)	P
Stage										
IB	87	0.863 (0.447-1.663)	0.659			91	0.89 (0.619-1.280)	0.530		
IIA	18	Reference				18	Reference			
Age										
<40	42	0.979 (0.577-1.658)	0.936			43	1.013 (0.757-1.356)	0.929		
≥.9	63	Reference				66	Reference			
Tumor size										
≤ umo	69	0.308 (0.183-0.518)	*0.000*	0.350 (0.206-0.594)	*0.000*	70	0.421 (0.237-0.750)	*0.003*	0.413 (0.227-0.751)	*0.004*
>4 cm	36	Reference		Reference		39	Reference		Reference	
Histological heterogeneity										
Pure	85	1.000 (0.518-1.928)	1.000			89	0.896 (0.632-1.271)	0.539		
Mix	20	Reference				20	Reference			
Parametrium invasion										
No	98	0.777 (0.310-1.944)	0.589			102	1.253 (0.617-2.547)	0.532		
Yes	7	Reference				7	Reference			
Deep cervical stromal invasion										
No	30	0.490 (0.254-0.946)	*0.034*	0.864 (0.418-1.785)	0.692	32	0.535 (0.259-1.108)	*0.092*	0.629 (0.299-1.321)	0.221
Yes	75	Reference		Reference		77	Reference		Reference	
LVSI										
No	39	0.367 (0.197-0.683)	*0.002*	0.434 (0.231-0.816)	*0.009*	41	0.431 (0.223-0.833)	*0.012*	0.750 (0.346-1.625)	0.466
Yes	66	Reference		Reference		68	Reference		Reference	
LNM										
No	66	0.544 (0.324-0.912)	*0.021*	0.794 (0.456-1.382)	0.415	68	0.456 (0.257-0.809)	*0.007*	0.538 (0.297-0.978)	*0.042*
Yes	39	Reference		Reference		41	Reference		Reference	
Ovary preserved										
No	75	0.855 (0.494-1.482)	0.577			78	0.762 (0.569-1.020)	*0.068*	0.769 (0.568-1.042)	0.090
Yes	30	Reference				31	Reference		Reference	
NAC										
No	83	0.491 (0.281-0.859)	*0.013*	0.837 (0.455-1.540)	0.567	86	0.426 (0.229-0.792)	*0.007*	0.733 (0.357-1.506)	0.398
Yes	22	Reference		Reference		23	Reference		Reference	
CT cycle										
<5	63	0.967 (0.745-1.254)	0.799			65	1.021 (0.763-1.366)	0.890		
≥5	42	Reference				44	Reference			

CT reagements			0.451			0.813		
EP	59	0.772 (0.274-2.172)	0.524	63	0.772 (0.235-2.542)	0.671		
TP	24	0.577 (0.185-1.797)	0.343	24	0.759 (0.212-2.722)	0.672		
TC	11	0.382 (0.095-1.534)	0.175	11	0.621 (0.139-2.781)	0.533		
EC	5	0.349 (0.064-1.910)	0.225	5	0.255 (0.026-2.455)	0.237		
others	6	Reference		6	Reference			
Pre-operative RT								
No	103	0.307 (0.074-1.267)	0.102	107	0.418 (0.203-0.859)	*0.018*	0.412 (0.198-0.859)	*0.018*
yes	2	Reference		2	Reference		Reference	
Post-operative RT								
No	48	0.798 (0.471-1.351)	0.401	48	1.096 (0.822-1.462)	0.531		
Yes	58	Reference		61	Reference			

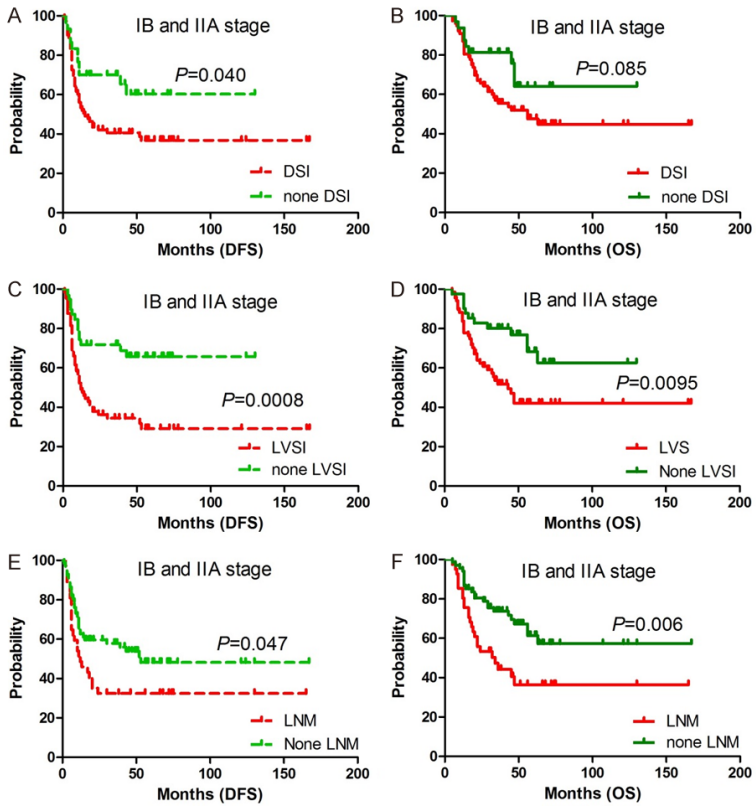

Figure 2. Survival curves. Probability of DFS (A) and OS (B) in groups with/without the high risk factor of deep stromal invasion (DSI), Probability of DFS (C) and OS (D) in groups with/without the high risk factor of lymphovascular space invasion (LVSI), Probability of DFS (E) and OS (F) in groups with/without the high risk factor of lymph node metastasis (LNM). The X-axis denotes survival period (months) after the initial treatment, and the Y-axis denotes survival rate.

Comparisons between the survival outcomes of the multimodalities of treatment are presented in **Figure 3**. **Figure 3A** and **3B** show that RH+LND surgery showed a significant differences in OS (P=0.015) and DFS (P=0.006) from that of Hystoectomy (S) +LND and other therapies. Moreover, the BSOE surgical procedure may improve DFS (**Figure 3C**, P=0.235) and OS (**Figure 3D**, P=0.023). To determine whether the addition of postoperative radiotherapy (including CCRT) to RH+LND and chemotherapy could improve survival, the median survival time and estimated survival rate were calculated. The adjuvant chemotherapy group and the chemotherapy with radiotherapy (including CCRT) group showed a median DFS of 9.5 months and 7 months, respectively, while the estimated 3-year DFS rates were 30% and 23.5%, respectively, and the estimated 5-year DFS rate was 30% and 15.7%. However, in the adjuvant chemotherapy group and the chemotherapy with radiotherapy (including CCRT) group, the median OS was 13 months and 43 months, respectively, while the estimated 3-year OS rates were 48.2% and 51.7%, respectively, and the estimated 5-year OS rates were 36.2% and 38.8%, respectively. The lower DFS rate in patients with radiotherapy combined with chemotherapy may indicate that this group may have a larger tumor burden or be of a poor condition after surgery. However, these OS results suggest that radiotherapy may be a potential optimal treatment option for selected patients (for instance, patients with a large tumor diameter) (**Figure 3E** and **3F**).

Considering significant differences in the survival rates of patients with different high-risk pathological factors, we attempted to define an appropriate combination of high-risk factors (Figure S3) to predict survival. Patients with no risk factors showed promising DFS and OS rates, while patients with one, two, or three high-risk factors showed similar DFS and OS rates (Figure S3), and these results were merged into a single survival curve (**Figure 4A** and **4B**, blue line). Obviously, patients with four risk factors showed worse DFS and OS. Therefore, patients without any risk factors, 1-3 risk factors, and four risk factors were analyzed separately for each method of treatment. For the group with 1-3 risk factors, patients who had received ≥5 cycles of chemotherapy did not show significantly better survival (**Figure 4C** and **4D**). In contrast, those who had received CCRT or chemotherapy with radiotherapy showed only a slightly better DFS rate (P= 0.397), without a significant difference in OS (P=0.855) (**Figure 4E** and **4F**). Nevertheless, patients who had received <5 cycles of chemotherapy had a median survival time of 63 months, whereas those who had received ≥5

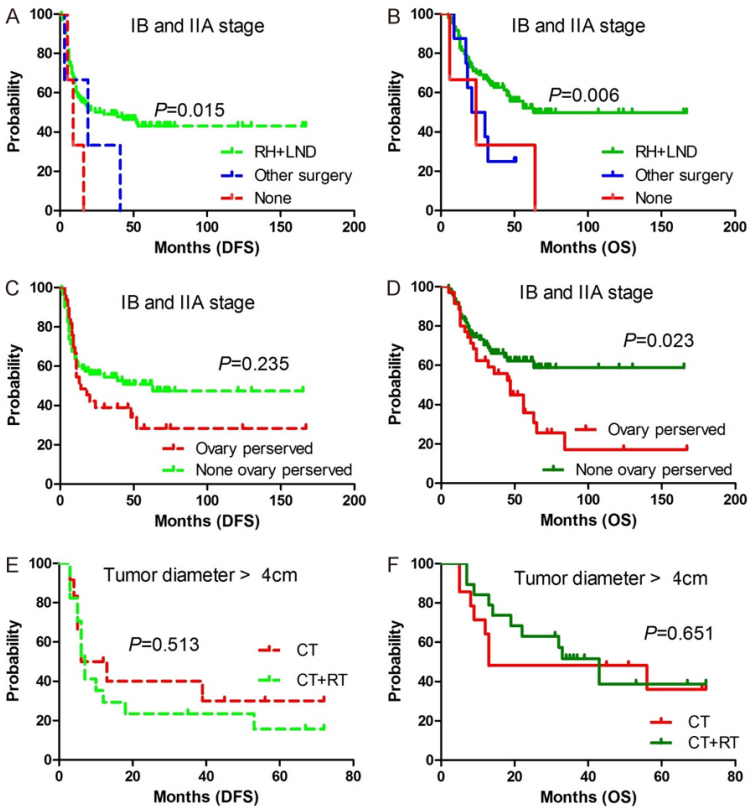

Figure 3. Survival curves. Probability of DFS (A) and OS (B) curves for patients underwent surgery. The other surgery included simple hysterectomy with lymph node ectomy and unspecific surgery. Probability of DFS (C) and OS (D) curves for patients having underwent RH+LND and bilateral salpingo-oopharectomy procedure. Probability of DFS (E) and OS (F) curves for patients with big tumor diameter (>4 cm) having underwent RH+LND surgery followed by chemotherapy and with/without radiotherapy groups. The X-axis denotes survival period (months) after the initial treatment, and the Y-axis denotes survival rate.

cycles did not reach the median survival time. For the 0 risk and 4 risk factors groups, neither ≥5 cycles of chemotherapy nor the addition of radiotherapy to surgery and chemotherapy (including CCRT) produced a significantly better survival rate (Figure S4). For the 0 risk factors group, the estimated 5-year DFS was 81.8% (<5 cycles) vs. 85.7% (≥5 cycles), and 87.5% (chemotherapy+RT) vs. 80% (Chemotherapy only), while the estimated 5-year OS was 81.8% (<5 cycles) vs. 100% (≥5 cycles) and 100% (chemotherapy+RT) vs. 80% (Chemotherapy only). Neither of the groups achieved the median DFS and OS scores. For the 4 risk factors group, the estimated 5-year DFS was 11% (<5 cycles) vs. 0% (≥5 cycles), and 0% (chemotherapy+RT) vs. 14.3% (Chemotherapy only), while the estimated 5-year OS rates were 33.3% (<5 cycles) vs. 14.8% (≥5 cycles) and 20.5% (chemotherapy+RT) vs. 12% (Chemotherapy only). The median DFS was 6 months (chemotherapy+RT) vs. 6 months (Chemotherapy only), and median OS was 10 months (chemotherapy+RT) vs. 6 months (Chemotherapy only). The median DFS was 10 months (≥5 cycles) vs. 6 months (<5 cycles), and median OS was 19 months (≥5 cycles) vs. 13 months (<5 cycles).

The efficacy of the chemotherapy regimens was evaluated in patients with at least one risk factor. The survival probability of various regimens was recorded (Figure S5). The results demonstrated that TP/TC showed better efficacy than EP based on DFS (**Figure 5**; *P*=0.099) but was not significantly different based on OS (*P*=0.932). The 5-year DFS rates were 38.5% (EP) and 52% (TP), while the 5-year OS rates were 52.8% (EP) and 52.6% (TP).

Furthermore, our data indicated that patients with large tumors (>4 cm) who received TP regimens showed statistical significance based on DFS, but not on OS (Figure S6A and S6B). For patients who had received TP/EP chemotherapy cycles, the 3-year estimated DFS rates were 22.2% (<5 cycles) and 25.6% (≥5 cycles), while the median DFS was 5.5 months vs. 11 months (<5 cycles vs. ≥5 cycles) and the estimated 3-year OS rates were 50% (<5 cycles) and 53.8% (≥5 cycles) (Figure S6C and S6D).

Data on recurrence are presented in Table S2. The most involved organs were the liver and the lung. The rate of lymph node metastasis was higher in tumors with a larger diameter at initial diagnosis: 42.9% and 70% for stage IB2 and stage IIA2, respectively, compared with that of stage IB1 (28.8%) and stage IIA1 (22.2%).

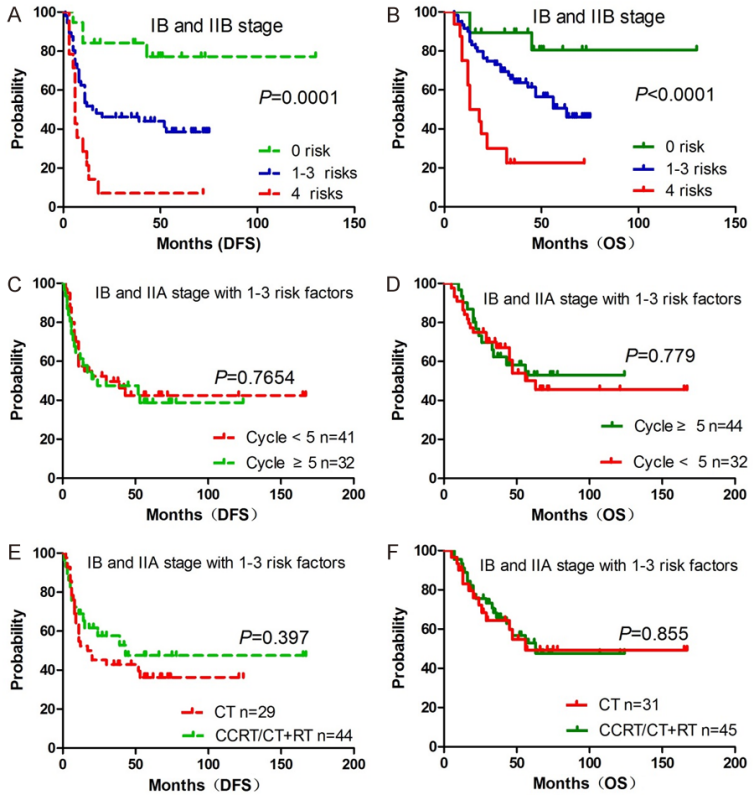

Figure 4. Survival curves. Probability of DFS (A) and OS (B) curves for patient's groups with/without risks after surgery. Probability of DFS (C) and OS (D) curves for patients with 1-3 risks in <5 or ≥5 chemotherapy cycles groups. Probability of DFS (E) and OS (F) curves for patients with 1-3 risks in adjuvant chemotherapy (CT) with/without radiotherapy (RT, including CCRT) groups. The X-axis denotes survival period (months) after the initial treatment, and the Y-axis denotes survival rate.

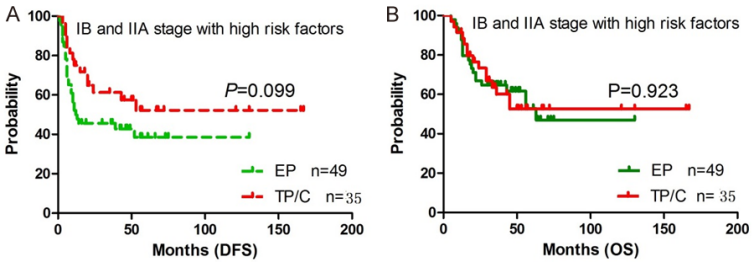

Figure 5. Survival curves. Probability of DFS (A) and OS (B) curves for patients with at least one risk having received chemotherapy regimens of EP or TP/TC groups (after surgery). The X-axis denotes survival period (months) after the initial treatment, and the Y-axis denotes survival rate.

Discussion

The first description of small cell endocrine carcinoma of the cervix was made in 1957 [13]. Since then, the high metastatic potential of this type of HGNECC has been a concern [1, 2, 14]. This disease continues to have a higher disease failing survival rate than other common types of cervical cancer. Similarly, therapeutic strategies used on other histological subtypes have been applied [1, 3-5, 15, 16]. Previous literature has reported that the 5-year survival rate was only 32-38.6% [17-19] for all I-IIA HGNECC patients, while median survival was 31-40.7 months [11, 17, 20]. Our study showed that the estimated 5-year DFS rates for stages IB and IIA were 44.8% and 39.5%, respectively, and that the estimated 5-year OS rates were 53.8% and 39.6%, respectively, while the median DFS for stages IB and IIA were 41 months and 12 months, respectively, and the OS values were 63 months and 45 months, respectively.

In general, most patients at the early-stage in China receive surgery, followed by chemotherapy. Ninety-four percent of (125/133, 94%) patients in our study underwent surgery, and RH+LND was used on most of these patients. These patients achieved promising DFS and OS rates. These procedures have also been recommended by multiple studies [12, 18, 21]. Chan et al. indicated that only patients with small tumors could undergo surgery for long-term survival [17]. However, a beneficial survival trend was obtained in our cohorts, including for those with tumors with a diameter of >4 cm. Moreover, BSOE should be recommended for these patients because this procedure is associated with a significantly promising OS. To our knowledge, this is the first study to suggest that the ovary-sparing procedure should not be performed on HGNECC populations.

DSI, LVSI, LNM, and a tumor diameter of >4 cm were identified as pathological prognostic fac-

tors associated with a worse DFS. The multivariate analyses identified tumor size and LNM as independent prognostic factors for OS. These results are consistent with the results of other studies [2, 18-20, 22-24]. These prognostic risk factors were designated as high-risk factors. We found that patients with no, 1-3, and 4 risk factors showed significantly different survival trends. The treatment schemes were analyzed in multiple combined high-risk groups, such as no risk, tumor diameter of >4 cm, at least one high-risk, and four risk factors groups, to determine the potential benefits of each procedure. Since adjuvant chemotherapy has been shown to provide benefits for early-stage patients, most patients in our cohort received chemotherapy. The benefits of chemotherapy are not presented in this study. The course of chemotherapy administered was analyzed in each group. Although it has been reported that ≥5 cycles of EP chemotherapy could significantly improve survival, this was not reported in our study. Additionally, various chemotherapy schemes were analyzed to determine their survival outcomes. The most commonly used chemotherapy regimen was EP, for which results obtained from the counterpart of small cell disease in the lung were extrapolated [25]. Paclitaxel is another chemotherapy regime used for the treatment of various types of cervical cancer, such as squamous cell carcinoma, whereas it is rarely used for small cell lung cancer [18, 19]. Xie et al. demonstrated that the use of paclitaxel and platinum-derived agents could achieve a favorable OS for HGNECC patients with large tumor size [26]. Significantly favorable DFS rates were also achieved in our cohorts, but a similar trend was not achieved for OS. The benefit of TP/C on DFS was determined for patients with at least one risk, although the result was not statistically significant.

The application of RH+LND, followed by adjuvant chemotherapy, has been used as an informal treatment method [24, 27]. There is much controversy surrounding the use of radiation, in which it is not known whether adjuvant radiation therapy/CCRT could improve survival compared with adjuvant chemotherapy alone. Chen et al. demonstrated that better survival rates were not obtained using adjuvant chemoradiation, compared with adjuvant chemotherapy alone, for patients at the early stages of the disease [28]. Hoskins et al. showed that the 3-year failure-free survival rate of stages I-II patients with small cell NECC was 80% for patients who had received RT and platinum-based combination chemotherapy as primary therapy [29]. Xie et al. suggested that radiation should be reserved for selected patients with mixed histology [26]. Hou et al. reviewed Surveillance Epidemiology and End Results database (SEER) data and reported that RH or RT yielded an almost equally low 5-year OS in stage I and stage II patients (61% vs. 53%, P=0.27; 48% vs. 28%, P=0.308) [23]. Another study found that nonsurgical management techniques, such as chemotherapy and radiotherapy alone when used as primary treatment, may be of benefit to early-stage patients [30]. In our study, we did not find that radiation could significantly improve survival. Thus, a better DFS was observed in the 0 and 1-3 risk groups, and the 0 risk group also presented better OS, while a more prolonged median OS was also obtained for patients with a tumor diameter of >4 cm and 4 risk factors.

In summary, we confirmed that a higher incidence of hematogenous distant metastasis occurred at initial diagnosis and recurrence. The most metastatic sites were lymph nodes with a rate of 33.9% at initial diagnosis, which was higher than that of other common histological types [16]. Among patients with recurrence, the liver, lung, and lymph nodes were the most frequent metastatic sites. In contrast, recurrence in the local area, pancreas, bone, brain, and adrenal was also observed and has been previously reported [22, 31, 32]. Therefore, these organs should be routinely examined after initial treatment.

Given the exceedingly poor prognosis of the disease, the propensity of spreading and the lack of effective therapeutic methods, our study suggested that patients with HGNECC at stages I-IIA should be treated with systematic multimodalities, and the surgical procedure of RH+LND and BSOE can be recommended. A tumor diameter of >4 cm, DIS, LVSI, and LNM are associated with a significantly worse DFS. Moreover, adjuvant radiation/CCRT can be considered based on its benefits in selected patients. Adjuvant chemotherapy regimens of TP/C as an optimal chemotherapy regimen appeared to present a better DFS, especially in the tumor diameter of >4 cm group. However,

further studies are necessary to warrant these findings.

Strengths and limitations

We recognize the limitations of this retrospective study that have been caused by the nature of this research study. Additionally, novel treatment methods, such as targeted therapies and immune-checkpoint inhibitors, were not included because very little data are available. For example, TP53, KRAS, MSH2 mutations were not measured for their potential use for the administration of individual treatment strategies [33-35]. However, the potential efficacy of targeted therapies and immune-checkpoint inhibitors are presented in a series of patients with recurrent metastasis.

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Disclosure of conflict of interest

None.

Abbreviations

BSOE, Bilateral salpingo-oophorectomy; CCRT, Chemoradiotherapy; CI, Confidence intervals; DFS, Disease-free survival; DSI, Deep stromal invasive; EP, Etoposide; FIGO, International Federation of Gynecology and Obstetrics stage; HGNECC, High-grade neuroendocrine carcinoma of the uterine cervix; LND, Lymph node dissection; LNM, lymph node metastasis; LVSI, lymph-vascular space invasive; MRI, Magnetic resonance imaging; NAC, Neoadjuvant chemotherapy; NECC, Neuroendocrine cervical carcinoma; NES, Neuron-specific enolase; OR, Odds ratios; OS, Overall survival; PET, Positron emission tomography; RH, Radical hysterectomy; SD, Standard deviation; SPSS, Statistical Package for Social Sciences; TC, Paclitaxel with carboplatin; TP, Paclitaxel with cisplatin.

Address correspondence to: Hongying Yang, Department of Gynecologic Oncology, Yunnan Province Cancer Center/Yunnan Cancer Hospital, The Third Affiliated Hospital of Kunming Medical University, 519 Kunzhou Road, Xishan District, Kunming 650100, Yunnan Province, China. Tel: +86-13888087358; E-mail: jyahy@tom.com; Qi Zhou, Chongqing Key Laboratory of Translational Research for Cancer Metastasis and Individualized Treatment, Chongqing University Cancer Hospital, Chongqing 400030, China. Tel: +86-189083845-29; E-mail: qizhou9128@163.com; Lingying Wu, Department of Gynecologic Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 17 Panjiayuan, Chaoyang District, Beijing 100021, China. Tel: +86-13910865483; E-mail: wulingying@csco.org.cn

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Table S1. Demographic characteristic of patients with uterus cervical neuroendocrine tumor

Group	FIGO Stage				
	N (%)	IB1	IB2	IIA1	IIA2
Total	133	74	36	10	13
Age					
<40	53 (39.8)	33 (44.6)	14 (38.9)	3 (30)	3 (23.1)
≥40	80 (60.2)	41 (55.4)	22 (61.1)	7 (70)	10 (76.9)
Histology (% =N/total)					
High	133 (100)	74 (55.6)	36 (27.1)	10 (7.5)	13 (9.8)
Small cell	108 (81.2)	61 (82.4)	28 (77.8)	7 (70)	12 (92.3)
Large cell	1 (0.8)	0 (0)	1 (2.8)	0 (0)	0 (0)
mix	24 (18.0)	13 (17.6)	7 (19.4)	3 (30)	1 (7.7)
Primary treatment (% =N/total)					
Surgery	125 (100)	73 (58.4)	33 (26.4)	9 (7.2)	10 (8.0)
SH+LND	3 (2.4)	2 (2.3)	1 (3.0)	0 (0)	0 (0)
RH+LND	121 (96.8)	71 (97.2)	31 (93.9)	9 (100)	10 (100)
others	1 (0.8)	0 (0)	1 (3.0)	0 (0)	0 (0)
Ovary reserved (% =N/surgery)					
Yes	33 (26.4)	22 (30.1)	7 (21.2)	3 (33.3)	1 (10)
No	91 (72.8)	50 (68.5)	26 (78.8)	6 (66.7)	9 (90)
unknown	1 (0.8)	1 (1.4)	0 (0)	0 (0)	0 (0)
Post-Operation Pathology					
DSI (% =N/surgery)					
<1/2	36 (28.8)	26 (35.6)	5 (15.2)	3 (33.3)	2 (20)
≥1/2	88 (70.4)	47 (64.4)	27 (81.8)	6 (66.7)	8 (80)
unknown	1 (0.8)	0 (0)	1 (3.0)	0 (0)	0 (0)
LVSI (% =N/surgery)					
Yes	76 (60.8)	38 (52.1)	24 (72.7)	5 (55.6)	9 (90)
No	49 (39.2)	35 (47.9)	9 (27.3)	4 (44.4)	1 (10)
LNM (% =N/surgery)					
Yes	46 (36.8)	21 (28.8)	13 (39.4)	4 (44.4)	8 (80)
No	78 (62.4)	52 (71.2)	19 (57.6)	5 (55.6)	2 (20)
Unknown	1 (0.8)	0 (0)	1 (3)	0 (0)	0 (0)
NAC (% =N/surgery)					
Yes	26 (20.8)	6 (8.2)	14 (42.4)	1 (11.1)	5 (50)
No	99 (79.2)	67 (91.8)	19 (57.6)	8 (88.9)	5 (50)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chemotherapy Post-operation (% =N/surgery)					
Yes	114 (91.2)	65 (89. 0)	31 (93.9)	9 (100)	9 (90)
No	11 (8.8)	8 (11.0)	2 (6.1)	0 (0)	1 (10)
Preoperation Radiation (% =N/surgery)					
Yes	2 (1.6)	1 (1.4)	0 (0)	0 (0)	1 (10)
No	123 (98.4)	72 (98.6)	33 (100)	9 (100)	9 (90)
Adjuvant Radiation (% =N/surgery)					
Yes	66 (52.8)	38 (52.1)	21 (63.7)	4 (44.4)	3 (30)
No	58 (46.4)	35 (47.9)	11 (33.3)	5 (55.6)	7 (70)
unknown	1 (0.8)	0 (0)	1 (3.0)	0 (0)	0 (0)
Without operation (% =N/none-surgery)					
None operation	8	1	3	1	3

Chemotherapy only	1 (12.5)	0 (0)	0 (0)	0 (0)	1 (33.3)
Radiation only	1 (12.5)	0 (0)	1 (33.3)	0 (0)	0 (0)
C and R	4 (50)	0 (0)	2 (66.7)	0 (0)	2 (66.7)
none therapy	2 (25)	1 (100)	0 (0)	1 (100)	0 (0)

SH: Simple hystoectomy; RH: radical hystoectomy; LND: Lymph node dissection; SI: Stromal invasion; LVSI: Lymph vascular space invasion; LNM: lymph node metastasis.

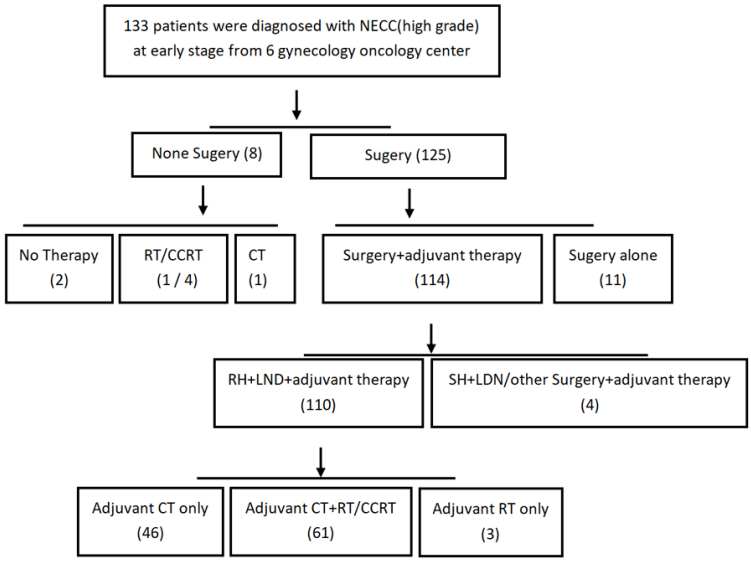

Figure S1. Overview chart of involved patients.

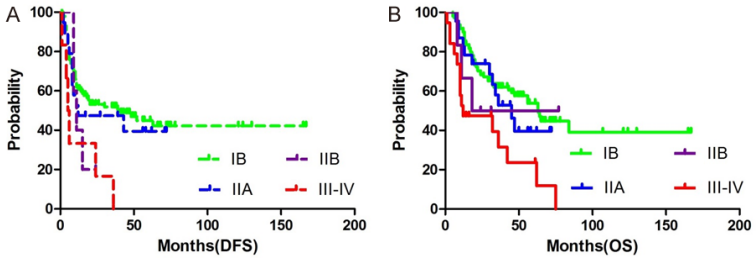

Figure S2. Survival curves. DFS (A) and OS (B) curves for patients HGNECC at I-IV stages. The x-axis denotes survival period (months) after the initial treatment, and the y-axis denotes survival rate.

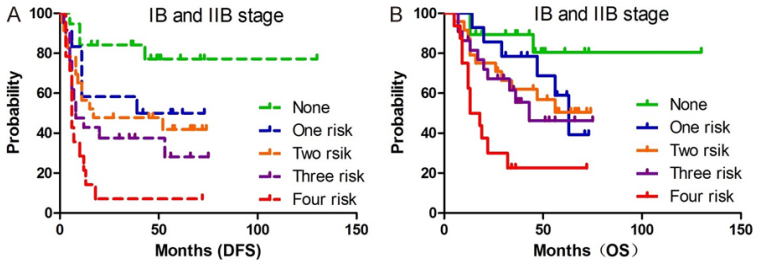

Figure S3. Survival curves. In patients who received surgery with high risk pathological factors including DSI, LVSI, LNM and tumor diameter >4 cm. these factors were combined and divided into five groups as none risk, one risk, two risks, three risks and four risks, survival probability of DFS (A) and OS (B) was plotted. The x-axis denotes survival period (months) after the initial treatment, and the y-axis denotes survival rate.

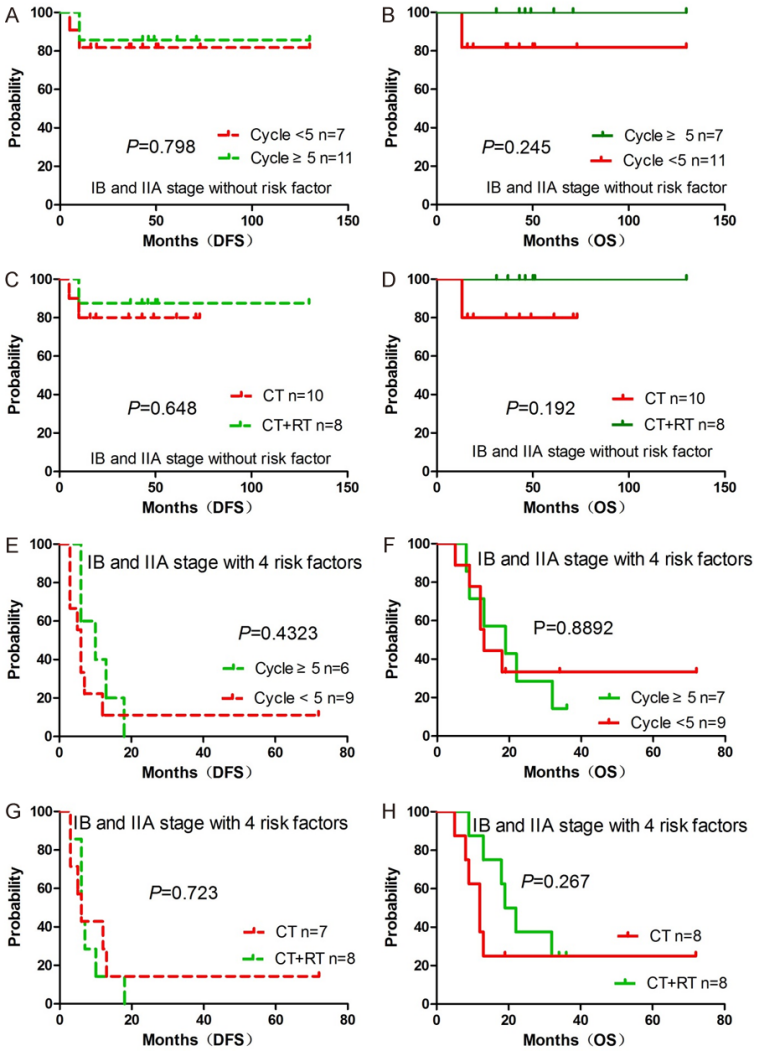

Figure S4. Survival curves. DFS (A) and OS (B) curves for patients without any risk having received <5 or ≥5 chemotherapy cycles group (adjuvant chemotherapy after surgery). DFS (C) and OS (D) curves for patients without any risk having received adjuvant chemotherapy (CT) with/without radiotherapy group (RT including CCRT). DFS (E) and OS (F) curves for patients with 4 risks having received <5 or ≥5 chemotherapy cycles group (adjuvant chemotherapy after surgery). DFS (G) and OS (H) curves for patients with 4 risks having received adjuvant chemotherapy (CT) with/without radiotherapy groups (RT including CCRT). The x-axis denotes survival period after initial treatment, and the y-axis denotes survival rate.

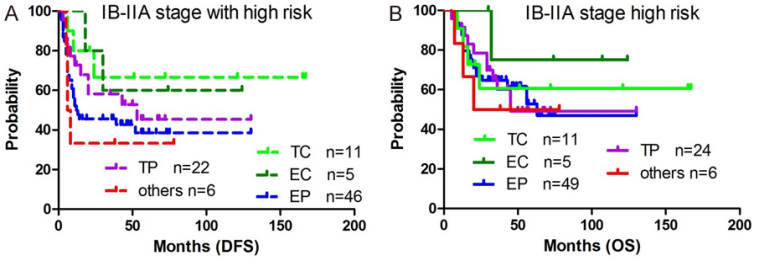

Figure S5. Survival curves. DFS (A) and OS (B) for patients with at least one risk having received different adjuvant chemotherapy regimes groups. The x-axis denotes survival period after initial treatment, and the y-axis denotes survival rate.

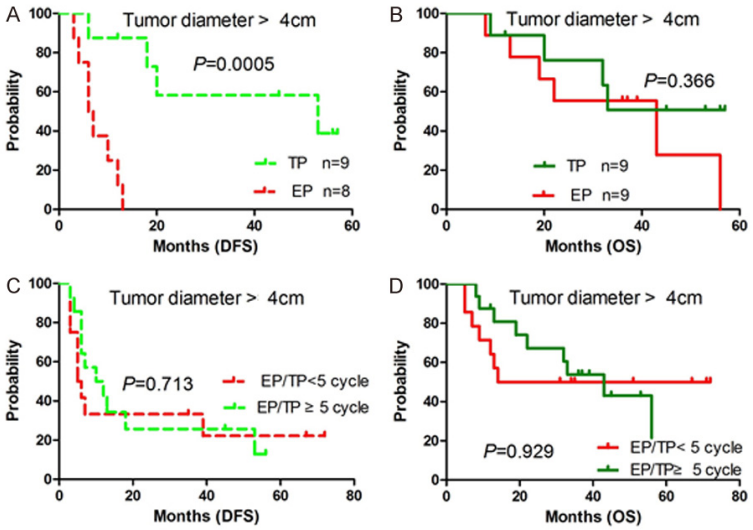

Figure S6. Survival curves. DFS (A) and OS (B) curves for patients with big tumor diameter >4 cm having received different adjuvant chemotherapy regimes of EP or TP groups (after surgery). DFS (C) and OS (D) curves for patients with big tumor diameter >4 cm having received chemotherapy of EP/TP in <5 or ≥5 cycles group (after surgery). The x-axis denotes survival period (months) after the initial treatment, and the y-axis denotes survival rate.

Table S2. Metastasis status at diagnosis and recurrence

FIGO Stage	Total/surgery N (n)	Metastasis at diagnosis (n/N= %)				Recurrence site (n, n/recurrence= %)								
		Copus	Ovary	LN	Other	n (/N= %)	Local	LN	Liver	adrenal	lung	brian	bone	Other
IB1	74 (20)	0 (0)	1 (1.4)	21 (28.4)	/	28 (37.9)	5 (18.5)	4 (14.8)	20 (70.4)	1 (3.7)	8 (3.0)	0 (0)	3 (11.1)	1 (3.7)
IB2	36 (15)	4 (11.1)	1 (2.8)	15 (41.7)	/	20 (55.6)	2 (10)	4 (20)	12 (60)	1 (5)	4 (20)	2 (10)	2 (10)	0 (0)
IIA1	10 (3)	0 (0)	0 (0)	2 (20.0)	1 (10)	1 (10)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Unk (1)
IIA2	13 (8)	0 (0)	0 (0)	7 (53.8)	3 (23.1)	8 (61.5)	0 (0)	4 (50)	5 (62.5)	1 (12.5)	2 (25)	0 (0)	2 (25)	0 (0)
Total	133 (46)	4 (30.1)	2 (1.5)	45 (33.9)	4 (3.0)	57 (42.8)	7 (12.3)	13 (22.8)	37 (64.9)	3 (5.3)	14 (24.6)	2 (3.5)	7 (12.3)	2 (3.5)

/: cannot evaluation, a serie patients with multiple sites of metastasis; N, total patients.