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Original Article

Postoperative prognosis and risk factors in patients with early cervical cancer

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Abstract: Objective: The goal of this study was to evaluate the postoperative prognosis and associated risk factors of early cervical cancer. Methods: The study included 90 early cervical cancer patients who had received radical surgery from January 2008 to June 2011 at Gansu Provincial Hospital. After surgery, the patients were followed up, and survival analysis was conducted by using Cox regression to identify risk factors associated with prognosis of early cervical cancer. Results: All the patients were followed up at a median period of 51 months. During the period, there were 21 deaths and 8 recurrences. The OS was (83.53±2.7) months, and the DFS was (74.18±3.5) months. The clinical stage (DFS: P=0.009; OS: P=0.008), tumor size (DFS: P=0.036; OS: P=0.041), lymph node metastasis (DFS: P=0.003; OS: P=0.006), depth of tumor invasion (DFS: P=0.019; OS: P=0.005), and vascular invasion (DFS: P=0.006; OS: P=0.001) were associated with the prognosis in early cervical cancer patients postoperatively. Furthermore, the clinical stage (DFS: HR=0.121, P=0.006; OS: HR=0.209, P=0.031), lymph node metastasis (DFS: HR=0.179, P=0.010; OS: HR=0.198, P=0.009), depth of tumor invasion (DFS: HR=0.203, P=0.012; OS: HR=0.118, P=0.003), and vascular invasion (DFS: HR=0.134, P=0.009; OS: HR=0.193, P=0.003) were independent risk factors of the prognosis in early cervical cancer postoperatively. Conclusion: Clinical stage, tumor size, lymph node metastasis, depth of tumor invasion, and vascular invasion were risk factors of the prognosis in early cervical cancer patients postoperatively.

Keywords: Cervical cancer, surgical treatment, prognosis, risk factor

Introduction

Cervical cancer is the third most common malignant tumor worldwide in women population [1, 2]. Annually, there are about 510,000 new cases globally, of whom, about 150,000 in China represent ~30% of all new cases. Each year, around 200,000 women die of cervical cancer, among whom, about 53,000 patients were from China, accounting for ~40% of the overall mortality [3]. Statistically, the mean age of onset was 45 years with a peak age under 30 in China [4, 5]. In recent years, the epidemic areas in China have been spreading gradually from impoverished mountainous areas to coastal economic regions, maybe because of the increased incidence of human papilloma virus (HPV) infection. Over the past several decades, a great many of patients have died of cancer metastasis and recurrence, yielding a 5-year survival ranged from 50% to 90%, although several progresses have been achieved on diagnosis and treatment for cervical cancer [6-9].

Several risk factors associated with the prognosis of cervical cancer have been identified, including tumor size, lymph node metastasis, clinical stage, depth of tumor invasion and vascular invasion, etc. Some studies showed tumor size was associated with the prognosis of cervical cancer. Such a study was conducted in 366 patients, where all the patients were followed up for 94 months, and showed that 2 cm in tumor size is of prognostic value in stage IB cervical cancer [10]. Another study showed that tumor size and lymph node status were closely associated with prognosis of advanced cervical cancer [11]. However, most of studies were conducted in western countries. Furthermore, the results from these studies have been inconsistent. Some studies identified that tumor size

was associated with the prognosis of cervical cancer independently, while, other studies indicated tumor size was not associated with the prognosis of cervical cancer [11-14]. The different genetic background, surgical technique, and follow-up period may cause the different analysis results. Therefore, there is a necessity to re-conduct analysis and evaluation on the risk factors associated with the prognosis of early cervical cancer after surgery in Chinese women, which will favor the development of individualized and comprehensive prevention and control measures in China.

In the current study, a long-term follow-up in 90 early cervical cancer patients was performed on patients that underwent radical surgery at Gansu Provincial Hospital from January 2008 to June 2011. This study was done in order to identify the potential the risk factors with the postoperative prognosis of early cervical cancer.

Materials and methods

Patients

A total of 90 early cervical cancer patients were enrolled in this study from January 2008 to June 2011 at Gansu Provincial Hospital. All the patients received a complete diagnostic evaluation, including chest X-rays, liver ultrasonography, and whole body bone scan to exclude the presence of distant metastasis. All patients were pathologically diagnosed with early cervical cancer and at the clinical stage of Ia-IIa [12]. All the patients received no treatment before the enrollment. In this study, clinical and pathological information was collected, including age, tumor size, pathologic type, pelvic lymph node metastasis, clinical stage, depth of invasion, vascular invasion, concomitant diseases, and intraoperative blood loss. The clinical stage was in accordance with the International Federation of Gynecology and Obstetrics criteria. This study was approved by the Ethical Committee and Institutional Review Board. Written informed consent was obtained from each patient.

Therapeutic strategy

All patients enrolled in this study were scheduled for a radical surgery. Patients in clinical stage Ia underwent a sub-radical hysterectomy; patients in clinical stage Ib-II with tumor size ≤4 cm received radical hysterectomy plus pelvic lymph node dissection; patients in clinical stage Ib-II with tumor size >4 cm received conventional radiotherapy (total dose: 20 Gy, once a week with 10 Gy for each time) and neoadjuvant chemotherapy (cisplatin and bleomycin) prior to surgery [7, 8]. Then, 2 weeks after the treatment, patients received radical hysterectomy combined with pelvic lymph node dissection.

Patients with one of followings received postoperative radiotherapy and chemotherapy: 1) postoperative pathological examination showed that infiltration depth of tumor ≥1/2 of cervical muscular layer; 2) tumor involving the vasculature; 3) pelvic lymph node metastasis; 4) tumor involving the operation margin [7, 8]. Radiotherapy: Total dose 40~45 Gy with a period of 4 to 6 weeks. Chemotherapy: Cisplatin and bleomycin with a total of 2-4 periods (14 days as a period), there was a 4-week intermittent between two consecutive periods.

Follow-up

The follow-up was conducted until June 2016. A physical examination was conducted every 3 months for the first 2 years after the surgery, then every 6 months thereafter. Overall survival (OS) is defined as the period from the surgery date to the death date from any cause. Disease-free survival (DFS) is defined as the period from the surgery date to the date of the first evidence of disease progression (tumor recurrence, metastasis, or the presence of a new tumor) or tumor associated death.

Statistical analysis

SPSS (version 19.0, IBM Company, Chicago, IL) was used for l analysis. Survival curves were conducted by using Kaplan-Meier method. The potential factors associated with the prognosis were screened using the univariate Cox regression, then the factors with $P<0.1$ were included in the multivariate Cox regression to identify the independent prognostic factors. A P value <0.05 was considered statistically significant.

Results

Patient characteristics

The clinicopathological data of the patients are shown in **Table 1**.

Table 1. Clinic pathological characteristics of patients with early cervical cancer

Main age (year)	43.1±15.1
Age range (n/%)	
<30 years	21/23.3
≥30 years	69/76.7
Pelvic lymph node metastasis (n/%)	
Yes	39/43.3
No	51/56.7
Tumor size (n/%)	
≤4 cm	61/67.8
>4 cm	29/32.2
Depth of invasion (n/%)	
>1/2 muscular layer	34/37.8
<1/2 muscular layer	56/62.2
Vascular invasion (n/%)	
Yes	29/32.2
No	61/67.8
Pathologic type (n/%)	
Squamous cell carcinoma	78/86.7
Adenocarcinoma	12/13.3
Clinical stage (n/%)	
Ia	6/6.7
Ib	54/60.0
IIa	30/33.3
Concomitant disease	
Hypertension (n/%)	21/23.3
Diabetes (n/%)	16/17.8
Hysteromyoma (n/%)	33/36.7
Intraoperative blood loss (n/%)	
<266 mL	61/67.8
≥266 mL	29/32.2

Survival analysis

All patients were followed up for a median period of 51 months. During the follow-up period, a total of 21 deaths and 8 recurrences were reported. The OS was (83.53±2.7) months, and the DFS was (74.18±3.5) months, the survival curves are shown in **Figures 1**, **2**.

Risk factors associated with the clinical prognosis

To screen the risk factors with the survival, a univariate Cox regression was firstly performed with several potential factors, including age, tumor size, pathologic type, pelvic lymph node metastasis, clinical stage, depth of invasion, vascular invasion, concomitant diseases, and intraoperative blood loss. The results show that clinical stage, tumor size, depth of invasion, vascular invasion, and lymph node metastasis are negatively associated with OS and DFS, while other factors, including age, pathological types, concomitant diseases and intraoperative blood loss fail to show any correlation with the survival (**Table 2**). Furthermore, multivariate Cox regression showed that clinical stage, tumor invasion depth, vascular invasion and lymph node metastasis were found to be inde-

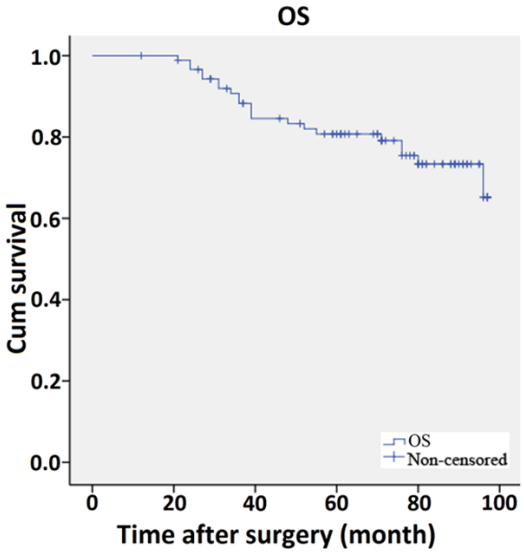

Figure 1. Overall survival in patients with early cervical cancer. OS, overall survival.

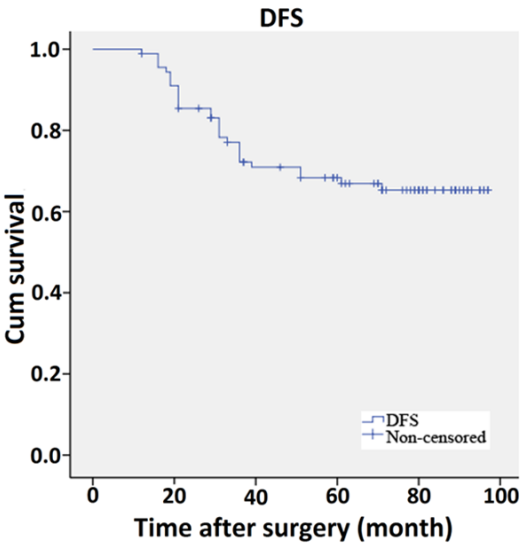

Figure 2. Disease-free survival in patients with early cervical cancer. DFS, disease-free survival.

Table 2. Univariate Cox regression analysis of the risk factors associated with the prognosis in patients with early cervical cancer

Variables	DFS		OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (≥30 vs. <30)	0.796 (0.290~2.810)	0.891	0.806 (0.199~2.369)	0.761
Clinical stage (I vs. II)	0.193 (0.088~0.981)	0.009	0.197 (0.066~0.471)	0.008
Tumor size (>4 vs. ≤4)	0.230 (0.119~0.606)	0.036	0.222 (0.081~1.661)	0.041
Pathologic type (squamous vs. adeno)	1.305 (0.668~3.103)	0.679	1.691 (0.451~5.709)	0.519
Depth of invasion (deep vs. shallow)	0.343 (0.091~2.107)	0.019	0.319 (0.097~0.829)	0.005
Vascular invasion (Yes vs. No)	0.344 (0.149~1.328)	0.006	0.493 (0.159~1.218)	0.001
Lymph node metastasis (Yes vs. No)	0.102 (0.060~0.611)	0.003	0.314 (0.121~0.981)	0.006
Hypertension (Yes vs. No)	0.519 (0.180~2.311)	0.669	0.710 (0.209~2.120)	0.586
Diabetes (Yes vs. No)	0.881 (0.306~3.610)	0.399	0.811 (0.109~2.930)	0.301
Hysteromyoma (Yes vs. No)	0.619 (0.221~2.609)	0.571	0.610 (0.216~2.316)	0.511
Intraoperative blood loss (≥266 vs. <266)	0.710 (0.319~3.361)	0.706	0.663 (0.261~3.091)	0.639

Note: DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Table 3. Multivariate Cox regression analysis of the risk factors associated with the prognosis in patients with early cervical cancer

Variables	DFS		OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Clinical stage (I vs. II)	0.121 (0.038~0.319)	0.006	0.209 (0.061~0.933)	0.031
Depth of invasion (deep vs. shallow)	0.203 (0.081~0.610)	0.012	0.118 (0.063~0.519)	0.003
Vascular invasion (Yes vs. No)	0.134 (0.091~0.691)	0.009	0.193 (0.066~0.819)	0.003
Lymph node metastasis (Yes vs. No)	0.179 (0.050~0.313)	0.010	0.198 (0.088~0.871)	0.009

Note: DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

pendent risk factors associated with the clinical prognosis (DFS and OS) of early cervical cancer (**Table 3**).

Discussion

There has been marked progress in the detection and diagnosis of early cervical cancer in recent years, which make makes it possible for most patients to have a radical surgery at early stage, but a part of patients died of tumor recurrence and metastasis after radical surgery [15]. Thus far, the exact mechanism underlying these malignances, and the risk factors of the postoperative prognosis have not been well elucidated [16]. Even though, some previous studies have identified several risk factors associated with the prognosis of cervical cancer, but most of them were conducted in western countries, and were not all conducted in the early cervical cancer [10, 11]. Therefore, a preliminary study in Chinese women was conducting on patients who were diagnosed with early cervical cancer.

In this study, 90 early cervical cancer patients were followed up from 12 months to 97 months with a median period of 51 months after the radical surgery. During the follow-up period, there were 21 deaths and 8 recurrences. The OS of this group was (83.53±2.7) months, and the DFS was (74.18±3.5) months. The result showed the clinical stage, tumor size, depth of invasion, vascular invasion and lymph node metastasis were risk factors of the prognosis in early cervical cancer. Furthermore, the clinical stage, depth of invasion, vascular invasion, and lymph node metastasis were independently associated with the prognosis of early cervical cancer.

Tumor size was found to be an independent risk factor associated with the prognosis in a group of stage Ib cervical cancer patients, and tumor size of 4 cm can be used as a threshold of poor prognosis after surgery [17]. The results of this study indicate that tumor size is a risk factor associated with the prognosis, but is not an independent risk factor, which is inconsistent

with previous studies. The different clinical stage of the studies may be attributed to the controversial results. Furthermore, patients in this study were treated with an individualized comprehensive therapy, which can also cause the different results. In addition, previous studies have showed that clinical stage, depth of invasion, vascular invasion were risk factors associated with the prognosis of patients with cervical cancer [13, 14]. The findings were basically consistent with the previous studies, indicating that tumor size (>4 cm), deep invasion (>1/2 muscular layer) and vascular invasion predicted a poor prognosis. Therefore, in clinical practice, patients at high risk should be monitored and followed up closely, in order to improve the clinical prognosis. Additionally, this study also showed that lymph node metastasis was an independent risk factor in early cervical cancer. At present, lymph node metastasis is widely recognized as a major risk factor in cervical cancer. Fang et al. reported that the incidence of pelvic lymph node metastasis in early cervical cancer was 23.35%, which was associated with the prognosis of the patients [18]. Cheng and his colleagues' study showed that the 5-year OS was 31.96% in patients with 2 or more lymph node metastasis, which was significantly lower than those without lymph node metastasis, the 5-year OS was 79.33% [19]. A retrospective study by Zhu et al. showed a negative correlation between the number of lymph node metastasis and the survival rate of patients [20]. Therefore, after radical surgery, attention should be paid on patients with lymph node metastasis, and postoperative radiotherapy and chemotherapy was an effective strategy to reduce the recurrence and metastasis of cervical cancer and improve the long-term survival.

This present study has some limitations. First, the small size of patients were included in this study. Second, only clinicopathological variables were included in the analysis model to identify the potential risk factor, while, biomarkers as novel prognosis predictors were gaining more and more attention in recent years, such as EphA2, nm23-H1, MMPs and E-cadherin [21, 22]. In future studies, an expanded number of samples and further screening of potential biomarkers will be included.

To conclude, clinical stage, tumor size, depth of invasion, vascular invasion, and lymph node metastasis can be used to predict the prognosis of early cervical cancer after surgery. Monitoring and follow-up should be strengthened, and perioperative adjuvant therapy should be conducted to reduce the local recurrence and distant metastasis in patients at high-risk, which will further improve the survival of early cervical cancer patients after surgery.

Disclosure of conflict of interest

None.

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