RESEARCH ARTICLE

Clinical and Pathological Factors Related to the Prognosis of Chinese Patients with Stage Ib To IIb Cervical Cancer

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Abstract

Objective: The aim of this retrospective study is to analyze the clinical and pathological factors related to the prognosis of Chinese patients with stage Ib to IIb cervical cancer. Methods and Results: 13 clinical pathological factors in 255 patients with stage Ib to IIb cervical cancer undergoing radical hysterectomy and systematic lymphadenectomy were analyzed to screen for factors related to prognosis. The cumulative 5-year survival of the 255 patients was 75.7%. The result of the univariate analysis suggested that clinical stage, cell differentiation, depth of cervical stromal invasion, parametrial tissue involvement, and lymph node metastasis were prognostic factors for patients with stage Ib to IIb cervical cancer (P <0.05). Compared with cases with involvement of iliac nodes, obturator nodes, or inguinal lymph nodes, cases with metastasis to the common iliac lymph nodes had a poorer prognosis (P <0.05). Cases with involvement of four or more lymph nodes had a poorer prognosis than those with involvement of three or fewer lymph nodes (P <0.05). Using multivariate Cox proportional hazards model regression analysis, non-squamous histological type, poor differentiation, parametrial tissue involvement, and outer 1/3 stromal invasion were found to be independently related to patients poor prognosis (P <0.05). Conclusion: Non-squamous histological type, poor cell differentiation, parametrial tissue involvement, and outer 1/3 stromal invasion are the independent poor prognostic factors for patients with stage Ib to IIb cervical cancer.

Keywords: Uterine cervical neoplasms - pathology - prognosis - Cox proportional hazards regression model

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Introduction

Cervical cancer is a major global public health problem and the third worldwide leading cause of cancer death in women (Pointreau et al., 2010). Annually, it is estimated that 493,000 women worldwide will be diagnosed with cervical cancer and that 273,000 will die from the disease (Wright et al., 2007). In China, there will be about 130,000 new cases of cervical cancer diagnosed and about 30,000 women who will die from the disease every year. In Lao PDR, the cervical cancer mortality rate was 9.2 per 100,000 in 2007-2008 (Nguyen et al., 2011). To reduce mortality and improve prognosis, it is necessary to identify all factors related to the prognosis of patients with cervical cancer, so that patients can receive targeted and individualized treatment based on the presence of risk factors or not, consequently, the treatment effect can be optimized, the survival time can be extended, and the quality of life can be improved.

At present the conclusions of the studies about the prognostic factors of cervical cancer in different research institutions are not entirely consistent. After reviewing of 25 articles using Medline and known literature,Greasman et al. found that only three (12%) identified LVSI as an independent risk factor while 88% and 61% of those evaluated, noted lymph node metastasis and tumor size/ depth of invasion to be significant risk factors for survival (Greasman et al., 2004). Srisomboon et al. found that significant prognostic factors for stage Ib cervical cancer included tumor histology, nodal status, and the presence of lymph-vascular space invasion (Srisomboon et al., 2011). Sakuragi found that there was a significant relationship between the number of lymph nodes removed and disease-free survival in node-positive patients, the bigger the number of lymph nodes removed was,the longer disease-free survival would be (Sakuragi, 2007), but there were no more studies to confirm the above argument. Other factors such as clinical stage, cell differentiation, histological type, parametrial tissue involvement were thought to be relevant to the prognosis of cervical cancer in many studies,but whether those factors are the independent prognostic factors needs more studies.There were few studies about the influence of uterine body involvement on prognosis of cervical cancer.

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The aim of this retrospective analysis on 255 patients with Ib-II b cervical cancer was to explore the influence of age, clinical stage, cell differentiation, histological type, depth of invasion, parametrial tissue involvement, uterine body involvement, lymphovascular space invasion (LVSI), lymph node metastasis (LNM), adjuvant therapy, preoperative leukopenia, and preoperative anemia on prognosis.

Materials and Methods

A total of 255 patients with stage Ib-II b cervical cancer, who were treated with radical hysterectomy and systematic lymphadenectomy in the Department of Obstetrics and Gynecology, Qilu Hospital, Shandong University, China between 2005 March and 2010 July and had complete follow-up data were analyzed. Of these, 218 had squamous cell carcinoma, 32 adenocarcinoma, 4 adenosquamous carcinoma, and 1 small cell neuroendocrine carcinoma. The subjects' age range was from 24 to 84 years old, and the average age was 45.25 ± 10.63 years old.

Of the 255 cases studied, the patients with one or more poor prognostic factors, such as positive lymph nodes, positive margins, LVSI(+), non-squamous histopathological type, poor cell differentiation, parametrial tissue involvement, were treated with surgery and adjuvant therapy as follows: 91 with surgery and postoperative radiotherapy, 33 with surgery and postoperative chemotherapy, 41 with surgery and postoperative chemoradiotherapy.

The clinical and pathological information and follow-up survival information of patients were recorded in an excel table based on the classification. The survival time was from the time of surgery to the time of death or last follow-up, the deadline of follow-up was August 1, 2010, and the median follow-up time was 2.083 years.

The data in the original information table were classified and quantified, and the statistical table was completed to prepare for statistical analysis.

Note: 1). the quantitative indicators of the position of lymph node metastasis: 1, the obturator and/or iliac lymph nodes were involved (Group A); 2, the inguinal nodes were involved, no matter iliac and/or obturator lymph nodes were or were not involved (Group B); 3, the common iliac lymph nodes were involved, regardless of whether iliac and/or obturator lymph nodes were involved (Group C); and there was no case in which both common iliac lymph nodes and inguinal lymph nodes were involved in the patients studied. 2) Positive surgery margin appeared in only one patient; therefore, it was not included in the factors studied.

Univariate analysis was performed using the Kaplan-Meier method, and multivariate analysis was performed with Cox proportional hazards regression model. χ^2 analysis was used to compare the incidence of lymph node metastasis in patients with different clinical stages, the proportions of histological type in different age groups, and the relationship between tumor size and other risk factors. Statistical analysis was completed using the SPSS19.0 Software.

Results

Descriptive Results

With the FIGO stage increasing, the incidence of lymph node metastasis tended to increase (Ib, 18.4%; IIa, 24.2%; IIb, 33.3%), however, there was no statistically significant difference ($\chi^2 = 4.634$, $P = 0.099 > 0.05$) . Increase in age led to decrease in the proportion of non-squamous cell histological type (<40 years old, 21.95%; 40-60 years old, 11.49%; >60 years old, 4%), and there was a statistically significant difference ($\chi^2 = 7.106$, $P = 0.029 < 0.05$). Increase in tumor diameter resulted in gradual increase in incidence of outer 1/3 stromal invasion

Table 1. Result of Univariate Analysis on Clinical and Pathological Factors Related to the Prognosis of 255 Patients Studied

Factors	Grouping	Cases	Mortality Cases	Mean Survival Time(year)		3-yearSurvival(%)	χ^2 value	P value
				Estimate	Std.Error			
Parametrial tissue	Negative	231	29	4.59	0.13	80.9	8.05	0.01
involvement	Positive	24	8	2.8	0.29	60.5		
LNM	Negative	197	22	4.66	0.13	82.7	6.42	0.01
	Positive	58	12	3.61	0.26	70.3		
Number of LNM	1	13	1	3.7	0.2	85.7	0.14[1)]	0.71[1)]
	2 or 3	23	2	4.2	0.31	86.2	5.75[2)]	0.02[2)]
	≥4	22	9	2.55	0.46	43.1	7.01[3)]	0.01[3)]
Number of Lymph Nodes	≥20	21	4	3.06	0.38	72.7	0.01	0.94
Resected for LNM	≤19	37	8	3.04	0.3	67.6		
Position of LNM	Group A	47	9	3.72	0.27	72.6	0.10[4)]	0.75[4)]
	Group B	7	1	3.75	0.53	83.3	21.16[5)]	0.000[5)]
	Group C	4	2	0.88	0.25		4.21[6)]	0.04[6)]
HGB	≥110g/l	198	26	4.57	0.14	81.1	2.28	0.32
	90-<110g/l	36	7	3.31	0.25	73.4		
	<90g/l	21	4	3.38	0.48	64.9		

Note: 1) comparison between group with one positive lymph node and group with two or three positive lymph nodes; 2) comparison between group with one positive lymph node and group with four or more positive lymph nodes; 3) comparison between group with two or three positive lymph nodes and group with four or more positive lymph nodes; 4) comparison between group A and group B; 5) comparison between group A and group C; 6) comparison between group B and group C. The 3-year cumulative survival of group C could not be calculated due to small number of cases, high mortality

Table 2. Result of Univariate Analysis on Clinical and Pathological Factors Related to the Prognosis of 255 Patients Studied

Factors	Grouping	Cases	Mortality Cases	Mean Survival Time(year)		5-yearSurvival(%)	χ^2 value	P value
				Estimate	Std.Error			
Age(Years Old)	<40	82	10	4.62	0.21	80.9	0.82	0.66
	40-60	148	22	4.43	0.17	73.7		
	>60	25	5	3.98	0.39	70.9		
FIGO Stage	Ib	141	14	4.58	0.15	82.6	1.05[4)]	0.31[4)]
	IIa	66	9	4.49	0.25	78.5	6.43[5)]	0.01[5)]
	IIb	48	14	3.74	0.27	60.5	1.19[6)]	0.28[6)]
Cell	Well-moderate Differentiation	136	13	4.8	0.14	85.8	8.1	0.004
Differentiation	Poor Differentiation	119	24	4.04	0.22	62.5		
Histological Type	squamous	219	31	4.51	0.13	76.3	1.23	0.27
	Non-squamous	36	6	3.99	0.39	70.3		
Stromal Invasion	<1/3	69	8	4.74	0.19	83.7	0.07[1)]	0.79[1)]
	1/3-2/3	55	5	4.66	0.21	82.9	3.72[2)]	0.05[2)]
	>2/3	131	24	4.15	0.21	67.6	4.03[3)]	0.05[3)]
Uterine Body	Negative	246	34	4.5	0.13	76.4	2.42	0.12
Involvement	Positive	9	3	3.37	0.71	54.7		
Tumor Size	<2cm	46	8	4.24	0.29	71.4	1.5	0.47
	2-4cm	146	18	4.63	0.15	81.7		
	>4cm	63	11	4.19	0.29	65.5		
LVSI	Negative	226	32	4.51	0.13	76.6	1.54	0.22
	Positive	29	5	3.95	0.48	67.3		
WBC	Normal	236	34	4.45	0.14	74.9	0.09	0.77
	$<4.0\times10^9$/L	19	3	4.45	0.37	81.2		
Treatment	Surgery	90	13	4.58	0.19	77.8	2.81	0.42
	Surgery Plus Radiotherapy	91	16	4.42	0.2	74.6		
	Surgery Plus Chemotherapy	33	3	4.57	0.28	86		
	Surgery Plus chemoradiotherapy	41	5	3.82	0.45	67.6		

Note: 1) comparison between <1/3 group and 1/3-2/3 group; 2) comparison between <1/3 group and >2/3 group; 3) comparison between 1/3 -2/3 group and >2/3 group; 4) comparison between Ia group and IIa group; 5) comparison between Ia group and IIb group; 6) comparison between IIb group and IIa group

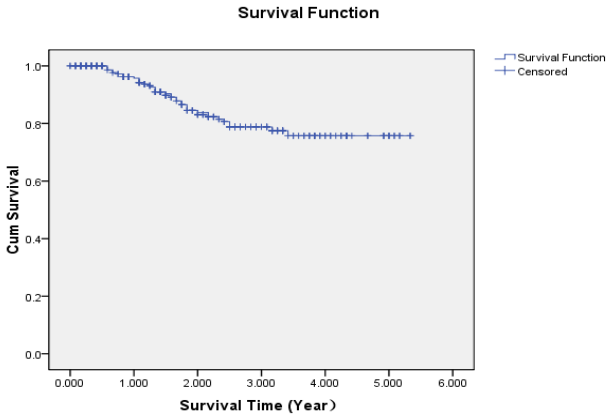

Figure 1. The Survival Curves of 255 Patients with Stage I b-II b Cervical Cancer

(<2cm, 23.9%; 2-4cm, 40.8%; >4-6cm, 53.4%; >6cm, 85.7%; $\chi^2 = 21.395$, $P = 0.000 < 0.05$) and lymph node metastasis (<2cm, 10.9%; 2-4cm, 17.8%; >4-6cm, 40.8%; >6cm, 50%; $\chi^2 = 20.742$, $P = 0.000 < 0.05$), and there was a statistically significant difference .

Results of univariate analysis

The 5-year cumulative survival of 255 patients was 75.7%, and the survival rate gradually declined in the 3 years after surgery. However, when the follow-up time was more than 3 years, the survival rate did not continue to decline and instead stabilized (Figure 1).

Survival analysis with the Kaplan-Meier method suggested that clinical stage, cell differentiation, parametrial invasion, depth of stromal invasion, and lymph node metastasis were related to the prognosis of patients with stage Ib-II b cervical cancer ($P < 0.05$), while age, histological type, uterine body involvement, tumor size, LVSI, preoperative leukopenia, and preoperative anemia were not related to that. Patients with ≥ 4 positive lymph nodes had a poorer prognosis than those with ≤ 3 positive lymph nodes ($P < 0.05$), and patients with positive common iliac lymph nodes had a poorer prognosis than those with positive iliac, obturator, or inguinal lymph nodes ($P < 0.05$) (Table 1, Table 2).

Results of multivariate Cox proportional hazards regression analysis

To explore the influence of the above listed 13 non-repetitive factors on prognosis of patients simultaneously, multivariate analysis was performed with the Cox proportional hazards regression model. To facilitate the analysis and interpretation of the results, based on the results of univariate analysis, the group of the inner 1/3 stroma invasion and the group of the 1/3-2/3 stroma invasion were merged into a group of inner 2/3 stroma invasion, and the groups treated with surgery and radiotherapy, surgery and chemotherapy, and surgery and radiotherapy and chemotherapy were merged into a group with adjuvant treatment .

Table 3 indicated that non-squamous cell histological type, poor tumor cell differentiation, outer 1/3 stromal

Table 3. Result of Multivariate Analysis on Clinical and Pathological Factors Related to the Prognosis of 255 Patients Studied

Factors	B	SE	Wald	df	P	Exp(B)	95.0% CI for Exp(B)	
							Low bound	Up bound
Degree of Cell Differentiation	1.29	0.41	9.85	1	0.002	3.63	1.62	8.14
Histological Type	1.33	0.54	6.19	1	0.013	3.79	1.33	10.8
Depth of Stromal Invasion	0.83	0.35	5.69	1	0.017	2.29	1.16	4.51
Parametrial Tissue Involvement	1.02	0.4	6.46	1	0.011	2.78	1.26	6.13

invasion, and parametrial invasion were independent risk factors for the prognosis of patients with stage Ib to II b cervical cancer, and non-squamous cell histological type was the first independent risk factor, the mortality risk of patients with non-squamous cell carcinoma was 3.787 times as high as that of patients with squamous cell carcinoma.

Discussion

The factors, which affect the prognosis of patients with cervical cancer, are very complex and interactive, and they jointly affect the prognosis of patients. Because of different condition, which leads to different data and different status distribution of factors, the results regarding prognostic factors for cervical cancer are inconsistent in different research organization. The results of the univariate analysis in this study suggested that clinical stage, cell differentiation, depth of cervical stromal invasion, parametrial invasion, and lymph node metastasis were related to the prognosis of patients with stage Ib to II b cervical cancer. The multivariate Cox proportional hazards model regression analysis suggested that non-squamous histopathological type, poor cell differentiation, parametrial tissue involvement, and outer 1/3 stromal invasion were the independent poor prognostic factors for patients with stage Ib to IIb cervical cancer when all relevant factors were taken into account.

The univariate analysis of this study indicated that there was no significant difference between the 5-year cumulative survival of patients with squamous cell carcinoma and that of patients with non-squamous cell carcinoma. The reason may be that patients with non-squamous cell carcinoma received adjuvant treatment. Then, the multivariate analysis testified that non-squamous cell histological type was the first independent risk factor for the prognosis of patients with stage Ib to II b cervical cancer. It is in accordance with results of recent studies.

There were 32 cases of adenocarcinoma, 4 cases of adenosquamous carcinoma, and 1 case of neuroendocrine small cell carcinoma in this study. Park et al. found that the DFS and OS of patients with adenocarcinoma were significantly shorter than that of patients with squamous cell carcinoma (Park et al., 2010). Farley et al. reported that the 5-year survival of patients with stage II - IV adenosquamous carcinoma was significantly lower than that of patients with adenocarcinoma of the same stage (Farley et al., 2003). Chen et al. reported that the 5-year survival of patients with small cell carcinoma was significantly lower than that of patients with squamous cell carcinoma or adenocarcinoma (Chen et al., 2008). According to the above-mentioned results, patients with adenocarcinoma, patients with adenosquamous carcinoma, and patients with small cell neuroendocrine carcinoma were merged into a group with non-squamous cell carcinoma, this grouping is reasonable and can guarantee the accuracy of the results.

Following surgery, adenocarcinoma, adenosquamous carcinoma and small cell carcinoma need multimodality treatment with radiotherapy and chemotherapy (Farley et al., 2003; Chen et al., 2008; Park et al., 2010). It is believed that patients with stage Ib-IIb non-squamous cell cervical cancer should be given comprehensive postoperative adjuvant therapy including radiotherapy and chemotherapy.

In this paper, the result of univariate analysis suggested that lymph node metastasis was relevant to the prognosis of patients with stage Ib-II b cervical cancer, while the result of multivariate analysis suggested that lymph node metastasis was not relevant to the prognosis of patients with stage Ib-II b cervical cancer. It differed from many other research results. The reason may be that the weights of the various prognostic factors in the objects and research methods were different in different research units.

Wright et al. suggested that parametrial tissue infiltration could increase the risk of tumor recurrence and shorten DFS and OS (Wright et al., 2007). Munagala et al. found that the number of parametrial invasion was the sole factor that affected OS and DFS, and the 5-year survival of patients with bilateral parametrial invasion was significantly lower than that of patients with unilateral parametrial infiltration (Munagala et al., 2010). Regarding the relation between the pattern of parametrial invasion and prognosis, Van et al. pointed out that regardless of whether the lesion of parametrial infiltrate was separated from the primary tumor, the prognosis was not optimistic (Van et al., 2011). This study only confirmed that the parametrial infiltration was an independent prognostic factor of Ib-II b cervical cancer because of the limit of sample size. The relation between the number and pattern of parametrial invasion and prognosis requires a study with a larger sample size.

Hellebrekers et al. reported that the depth of invasion > 10 mm was an independent factor of prognostic significance for DFS (Hellebrekers et al., 2000). Ho et al. reported that the outer 1/3 invasion was identified as an independent poor prognostic factor (Ho et al., 2004). In this study, patients were divided into three groups according to the depth of stromal invasion, and outer 1/3 invasion was confirmed to be an independent poor prognostic factor. Therefore, patients with 1/3 outer stromaI invasion should be highly considered for adjuvant therapy.

At present, there are various reports about whether

LVSI is an independent prognostic factor for cervical cancer. Creasman et al. reviewed 25 articles using Medline and the known literature and found only 3 articles (12%), which identified LVSI as an independent prognostic factor for cervical cancer (Creasman et al., 2004). Therefore, they thought that regarding LVSI as an independent determinant whether adjuvant therapy should be used after radical hysterectomy was questionable. Results of this study suggested that LVSI was not a prognostic factor for stage Ib-II b cervical cancer. The reason may be that the weight of LVSI may be relatively lighter compared to other factors such as parametrial invasion and stromal infiltration for stage Ib-II b cervical cancer.

Ruiz et al. pointed out that the spread of cervical cancer to the endometrium or myometrium was rare, but indicated a poor prognosis (Ruiz et al., 1995). Gungor et al. found that squamous cell carcinoma could also metastasize to the ovaries by endometrial and transtubal spread in the absence of lymph node involvement (Gungor et al., 2011). Especially in young patients for whom preservation of the ovaries is important, gross intraoperative inspection of the radical hysterectomy specimen and endometrium should be performed and ovaries should be evaluated carefully. In this study, the 5-year cumulative survival of patients with uterine body involvement and that of patients without uterine body involvement were 54.7%,76.4%, respectively, although uterine body involvement was not relevant to the prognosis of patients with stage I b-II b cervical cancer; however, patients with uterine body involvement had relatively poor prognosis. The relationship between uterine body involvement and the prognosis of patients with cervical cancer requires a study with a larger sample size.

In this study, FIGO stage was relevant to the prognosis in the univariate analysis, but it was not relevant to the prognosis in the multivariate analysis. This may be because of the limitations of FIGO clinical stage. FIGO stage of cervical cancer ignores the results of imaging, such as MRI or CT, and surgical pathology, such as parametrial invasion, LVSI, lymph node metastasis, and so on., which may affect the accuracy of FIGO stage (Kodaira et al., 2003).

Horn et al. reported that the lesion diameter >4 cm indicated a poor prognosis, and Plante et al. reported that the lesion diameter >2 cm had a high risk of recurrence (Horn et al., 2007; Plante et al., 2011). In this study, subjects were divided into three groups based on the maximum diameter of tumors: <2 cm, 2-4 cm, 4 cm. There was no significant difference in the 5-year survival of the three groups in the univariate analysis, and the multivariate analysis suggested that tumor size was not an independent prognostic risk factor for Ib to IIb cervical cancer. The reasons may be as follows: there is no uniform standard in the measure of tumor size, and because tumor shape is irregular, the tumor size described by the maximum tumor diameter may be less accurate. Some scholars suggested that tumor size based on the tumor volume measured by preoperative MRI examination may be more accurate.

The results of this study indicated that leukopenia might have nothing to do with the prognosis of patients with I b to II b cervical cancer. Fyles et al. found that hemoglobin levels prior to and during treatment were strongly correlated with tumor size (Fyles et al., 2000). Marchal et al. suggested that anemia was correlated with patient survival, and it appeared to be one of the most powerful prognostic factors after clinical stage and tumor size, but it has not been proven to be an independent factor (Marchal et al., 2005). Anemia was not relevant to the prognosis for stage I b-II b cervical cancer in this study. The reasons may be as follows: anemia may not be a prognostic factor for cervical cancer, and hemoglobin levels represented preoperative levels and anemia might be corrected during the treatments in this study, thus the adverse effects of anemia on the prognosis of patients could be eliminated.

The results of this study suggested that age was not relevant to the prognosis of patients with stage Ib-II b cervical cancer, although the proportion of non-squamous cell decreased with the increase of age, but the prognosis of young patients was not poorer than that of old patients. It is in accordance with the research of Póká et al. (1994).

In this study, all patients who had any prognostic risk factor received adjuvant therapy, and the group treated with surgery alone was composed of patients with no prognostic risk factors. In the univariate analysis, the 5-year survival of groups treated with surgery and adjuvant therapy was not significantly different from the 5-year survival of the group treated with surgery alone. These statistical results illustrate the following: after patients with prognostic risk factors received surgery plus adjuvant therapy, their survival would not be significantly different from that of patients without prognostic risk factors, and it is necessary for patients with prognostic risk factors to receive adjuvant therapy, as adjuvant therapy can improve their prognosis. In this study, there were no significant differences among the 5-year survival of patients treated with surgery and adjuvant radiotherapy, or adjuvant chemotherapy, and adjvant chemoradiotherapy. The above results may be different from other studies, which may be due to the differences in indication for adjuvant therapy and sample size in different research organizations.

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