RESEARCH ARTICLE

A retrospective survey of influencing factors on patient survival without local recurrence and total survival in patients with early cervical cancer

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Abstract

Objective: The article is based on the results of a retrospective review to observe the survival without local recurrence and the influencing factors of overall survival in patients with early cervical cancer.

Methods: Retrospective analysis was performed on clinical and pathological data of 247 cases of early cervical cancer treated by radical resection in the period January 2011 to January 2018. Univariate and multivariate Logistic Regression Models were used to evaluate the survival without local recurrence and independent factors affecting overall survival.

Results: All patients were classified by the FIGO(Federation International of Gynecology and Obstetrics) stage. The difference between adjuvant chemotherapy and brachytherapy was statistically significant ($p<0.05$). The median local relapse-free survival time of 247 patients was 45.0 months, and the postoperative follow-up for 2 years, 5 years and 10 years was 4.45% (11/247), 6.88% (17/247) and 8.50% (21/247), respectively. Influencing factors were, presence or absence of lymphatic vascular space infiltration, tumour diameter, whether treated with external pelvic irradiation, adjuvant chemotherapy and proximal treatment were related to local recurrence and survival of patients with early cervical cancer ($p<0.05$).

Conclusion: Patients with a smaller tumour size, no lymph node metastasis and external pelvic irradiation had a better overall survival.

Patients with early cervical cancer should be treated with a combination of extracavitatry irradiation and brachytherapy to reduce the risk of local recurrence.

Keywords: Cervical cancer, Radical operation, Local recurrence free survival, Total survival, Influencing factors.
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Introduction

Cervical cancer is one of the common malignant tumours of the female reproductive system. It has been recently observed that younger patients are developing cervical cancer. It has been speculated that there will be an increase of 100000 patients with cervical cancer annually, with a death toll of nearly 35000. The disease has a huge burden on the families and the society.[1,2] Currently, radical operation and radiotherapy are mostly applied clinically for the patients with early-stage cervical cancer. But postoperative recurrence is still encountered in over 30% of patients. The clinical prognosis for such relapsing patients is poor, and the 5-year survival rate is low.[3,4] The clinicopathologic data of 247 patients with cervical cancer who were received and treated by radical operation in our hospital from January 2011 to January 2018 were retrospectively analyzed. Among them, 21 patients relapsed at the residual end after the operation. Single-factor and multi-factor Logistic regression models were used to analyze the influencing factors of survival and overall survival of the early cervical cancer patients without postoperative local relapse so as to provide more reference for selection of follow-up treatment schemes.

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Patients and Methods

The clinicopathologic data of 247 patients with cervical cancer who were received and treated by radical operation in our hospital from January 2011 to January 2018 were retrospectively analyzed. Inclusion criteria: definite diagnosis of cervical cancer diagnosed by postoperative histopathologic examination; Federation International of Gynecology and Obstetrics (FIGO) staging: Phase I-IIA2;[5] These patients had undergone radical hysterectomy and received radiotherapy before the operation. Excluded were patients with distant metastasis; combined with other types of malignant tumours. High risk cases for anaesthesia and surgery, patients with severe organic diseases or those with incomplete clinical data were also excluded. The research scheme was approved by the Ethics Committee, and patients and their family members signed the informed consent form for

anonymously publishing their case history.

All patients selected for the analysis had undergone radical hysterectomy with pelvic lymphadenectomy or para-aortic lymph node sampling.

All patients were subjected to Varian 2300C/D medical linear accelerator for external irradiation of the pelvic cavity, along with 6MVX linear intensity modulated radiation therapy, The frequency of radiotherapy was 25-30, 1.8Gy/time, 5 times/week. HM-HDR 192Ir after-loading radiotherapy machine of Jiangsu Hai Ming Medical Devices Co., Ltd. was used for the brachytherapy, and the total number of applications were 4-6, 3Gy/time, once weekly.

Chemotherapy: Cis-platinum 40mg/m^2 intravenous infusion was chosen as the synchronous chemotherapy regimen, once a week, 3-6 times. paclitaxel + cis-platinum was selected as the neoadjuvant chemotherapy scheme, in which 135-175 mg/m^2 intravenous infusion was used for paclitaxel and 60-80 mg/m^2 intravenous infusion for cis-platinum. One course of treatment lasted for 3 weeks with a total of 2-3 courses, Postoperative adjuvant chemotherapy scheme was paclitaxel + cis-platinum or paraplatin, in which 135-175 mg/m^2 intravenous infusion was used for paclitaxel, 60-80 mg/m^2 cis-platinum, and AUC 5 mg/ml/min with paraplatin intravenously. One course of treatment lasted 3 weeks, with a total of 1-2 course.

The Follow-up visits for this study were taken till December 30, 2018. The patients were re-examined once every 3 months within 24 months after the end of the treatment. Later, the patients were checked once every 6 months. After 3 years, the patients were re-examined once every 12 months. The follow-up examination included physical examination, colposcopy, pelvic cavity MRI or CT and abdominal ultrasound, etc. If the residual end relapse after the operation was suspected, histopathologic biopsy was conducted. Postoperative local relapse refers to vaginal residual end recurrence. i.e. pure vaginal residual end recurrence which may involve bladder or rectum but no distant metastasis in other regions of the pelvic cavity. Distant metastasis refers to lymphatic metastasis and organ metastasis in the non-pelvic cavity. Overall survival refers to from the beginning of operation completion to death, loss of follow-up visit or the end of follow-up visit. The survival without local relapse refers to the period of operation completion to the first time of postoperative vaginal residual end recurrence.[5]

Statistical method: SPSS 20.0 software was chosen to analyze the data. Enumeration data comparison was conducted by χ^2 test or exact probability, expressed with %. Kaplan-Meier method was used for survival analysis, and inter-group comparision was performed by Log-rank test. Multiple-factor analysis was carried out by Cox regression model. The inspection level was α=0.05.

Results

A total of 284 patients were included in this study of whom 9 were lost to follow-up. Finally, 275 completed the study, including 226 cases without relapse and metastasis and 21 cases with vaginal residual end recurrence. For the 247 patients, the age ranged from 27 to 76 years old, with the median age of 46.0(35.0-56.0). For the patients included

Table-1: Clinicopathologic data analysis (n,%).

Index		Patients included (n=247,%)	Patients with vaginal residual end recurrence (n=21,%)	p
Age (years)	≤45	133(53.85)	11(52.38)	0.41
	>45	114(46.15)	10(47.62)	
FIGO staging	IA1	4(1.62)	1(4.76)	0.01
	IA2	4(1.62)	1(4.76)	
	IB1	103(41.70)	8(38.10)	
	IB2	33(13.36)	5(23.81)	
	IIA1	66(26.72)	2(9.52)	
	IIA2	37(14.98)	4(19.05)	
Histopathological type	Squamous carcinoma	218(88.26)	18(85.71)	0.38
	Miscellaneous	29(11.74)	3(14.29)	
Vaginal cut edge	Negative	239(96.76)	20(95.24)	0.62
	Positive	8(3.24)	1(4.76)	
Lymphatic metastasis	No	171(69.23)	17(80.95)	0.07
	Yes	76(30.77)	4(19.05)	
Parametrial infiltration	No	231(93.52)	20(95.24)	0.54
	Yes	16(6.48)	1(4.76)	
Lymphatic vascular space infiltration	No	155(62.75)	18(85.71)	0.00
	Yes	92(37.25)	3(14.29)	
Depth of interstitial infiltration	≤ 1/2 layer	62(25.10)	3(14.29)	0.08
	>1/2 layer	185(74.90)	18(85.71)	
Maximum diameter of tumour	<4 cm	173(70.04)	11(52.38)	0.00
	≥4 cm	74(29.96)	10(47.62)	
Neurotropic invasion	No	210(85.02)	20(95.24)	0.04
	Yes	37(14.98)	1(4.76)	
External irradiation of pelvic cavity	No	29(11.74)	16(76.19)	0.00
	Yes	218(88.26)	5(23.81)	
Adjuvant chemotherapy	No	33(13.36)	10(47.62)	0.00
	Yes	214(86.64)	11(52.38)	
Brachytherapy	No	37(14.98)	16(76.19)	0.00
	Yes	210(85.02)	5(23.81)	

Federation International of Gynecology and Obstetrics(FIGO).

Table-2: Single-factor analysis on influencing factors of survival without local relapse and overall survival after the operation.

Index		Survival without local relapse (%)		P	Overall survival (%)		P
		5 years	10 years		5 years	10 years	
Age (years)	≤45	87.95	55.27	0.69	88.62	87.41	0.90
	>45	91.86	77.42		89.31	72.08	
FIGO staging	IA1	83.37	66.74	0.02	100.00	100.00	0.06
	IA2	70.00	70.00		88.24	70.00	
	IB1	94.06	86.24		92.83	92.83	
	IB2	80.23	-		87.73	-	
	IIA1	95.77	95.77		90.25	86.44	
	IIA2	89.49	68.34		72.59	58.90	
Histopathological type	Squamous carcinoma	93.71	84.26	0.58	89.32	80.75	0.66
	Miscellaneous	86.93	79.44		85.09	84.64	
Vaginal cut edge	Negative	92.04	83.55	0.84	89.24	81.65	0.76
	Positive	94.62	-		91.74	-	
Lymphatic metastasis	No	91.23	81.06	0.18	91.47	80.58	0.04
	Yes	93.58	93.58		83.97	83.97	
Parametrial infiltration	No	91.84	83.26	0.69	89.46	81.70	0.00
	Yes	89.26	89.26		77.31	68.82	
Lymphatic vascular space infiltration	No	89.42	81.73	0.01	89.72	81.44	0.73
	Yes	97.86	92.51		89.12	89.12	
Depth of interstitial infiltration	≤ 1/2 layer	94.31	92.00	0.12	92.16	88.44	0.28
	> 1/2 layer	92.00	83.57		87.65	80.90	
Maximum diameter of tumour	< 4 cm	94.26	88.09	0.00	91.47	90.15	0.00
	≥ 4 cm	84.94	73.00		82.61	69.54	
Neurotropic invasion	No	91.45	84.00	0.38	90.26	82.55	0.69
	Yes	86.22	-		75.00	-	
External irradiation of pelvic cavity	No	51.84	25.10	0.00	69.32	61.04	0.00
	Yes	97.62	94.68		93.11	86.79	
Adjuvant chemotherapy	No	74.25	62.00	0.00	81.94	75.80	0.04
	Yes	95.84	89.51		90.67	79.63	
Brachytherapy	No	60.41	46.89	0.00	72.07	66.85	0.00
	Yes	98.24	92.00		94.61	82.35	

and the patients with vaginal residual end recurrence, the comparison differences in FIGO staging, lymphatic vascular space infiltration, neurotropic invasion, maximum diameter of tumour, external irradiation of pelvic cavity, adjuvant chemotherapy and brachytherapy had statistical significance ($p<0.05$), as shown in Table-1.

Among the 247 patients, the median survival time without local relapse was 45.0(31.0-55.0) months. The vaginal residual end recurrence rates were 4.45% (11/247), 6.88% (17/247) and 8.50% (21/247) respectively after 2 years, 5 years and 2- years of postoperative follow-up visit. Twenty-two patients died, and 12 of them had vaginal residual end recurrence. One expired due to pulmonary infection one due to infectious shock, one due to thrombus and 7 patients died due to unclear reasons.

The Single-factor analysis for determining survival without local relapse and overall survival after the operation showed that, FIGO staging, lymphatic vascular space infiltration, maximum diameter of tumour, external irradiation of pelvic cavity, adjuvant chemotherapy and brachytherapy were relayed to the survival of early cervical cancer patients without local relapse after the operation ($p<0.05$). Lymphatic metastasis, parametrial infiltration, maximum diameter of tumour, external irradiation of pelvic cavity, adjuvant chemotherapy and brachytherapy were relayed to the overall survival of early cervical cancer patients after the operation ($p<0.05$), as shown in Table-2.

The Multi-factor analysis on the influencing factors of survival without local relapse and overall survival after the operation with the results of Cox regression model showed that, external irradiation of the pelvic cavity and brachytherapy were independent influencing factors for patients' survival without local relapse after the operation ($p<0.05$), while maximum diameter of the tumour, lymphatic metastasis and external irradiation of pelvic cavity were independent influencing factors of patients' overall survival after the operation ($p<0.05$), as shown in

Table-3: Cox model analysis of independent influencing factors of survival without local relapse after the operation.

Index	β	SE	Exp (β)	95%CI	P
External irradiation of pelvic cavity	2.31	0.44	0.83	4.21-23.55	0.00
Brachytherapy	-1.68	0.46	0.19	0.07-0.49	0.00

Table-4: Multiple-factor analysis of influencing factors of overall survivalafter the operation.

Index	β	SE	Exp (β)	95%CI	P
Maximum diameter of tumour	-0.63	0.38	0.60	0.34-0.96	0.04
Lymphatic metastasis	-0.78	-0.31	0.47	0.30-0.90	0.02
External irradiation of pelvic cavity	1.54	0.35	4.89	4.17-8.69	0.00

Table-3 and Table-4.

Discussion

Postoperative recurrence of early cervical cancer is a clinical hot issue, with rare reports on the influencing factors of postoperative vaginal residual end recurrence.[6] Studies have indicated that,[7] about 70%-75% of cervical cancer patients relapse within 2 years after the first therapy. The recurrence rate of invasive cervical cancer after the treatment is as high as 30%-35%, while 1/3 relapses are limited to the pelvic cavity. In this study, on 247 patients, the median survival time without local relapse was 45.0 months. The vaginal residual end recurrence rate was 4.45% after postoperative follow-up visit of 2 years (11/247), indicating that the patients with early cervical cancer undergoing radical surgery should be followed-up for 2 years at an interval of 3 months.

Preoperative FIGO staging is considered to be one of important reference index for cervical cancer patients to select the treatment method and evaluate the prognosis. Parametrial infiltration can be used to decide whether the patients should choose operation or chemoradiotherapy.[8] Existing study shows that,[9] the later the preoperative FIGO staging is done, the higher is the risk of postoperative pathological complications. The above indices can generate the obvious influence on the long-term prognosis of cervical cancer patients after the operation. In this study, the single-factor analysis result showed that, FIGO staging was related to the survival of cervical cancer patients without local relapse after the operation ($p<0.05$), indicating that the earlier FIGO staging for the patients in Phase I-IIA2, the lower the recurrence risk of postoperative vaginal residual end tumour.

The report of some scholars indicates that,[10] the risk of vaginal residual end recurrence for the patients with positive postoperative vaginal incision is about 2-3 times higher than that of the patients with negative postoperative vaginal incisal edge. Meanwhile, positive incisal edge is independently correlated with vaginal residual end recurrence after radical hysterectomy. But in this study, the multiple-factor analysis result did not verify this view. The author considered that the small sample size and neoadjuvant chemotherapy for some patients may be the important reasons for this phenomenon. In this study, 32 patients received neoadjuvant chemotherapy before the operation (12.96%), which can effectively control the tumour volume, promote tumour extinction, lower the risk of lymphatic metastasis and may cause some high-risk pathological factors present "false negative", thus affecting disease state and formulation of postoperative adjuvant therapy scheme.[11,12] The multiple-factor analysis result verified that maximum diameter of tumour and lymphatic metastasis are independent influencing factors of postoperative overall survival of early cervical cancer patients ($p<0.05$). Thus, for the early cervical cancer patients who receive pre-operative neoadjuvant chemotherapy, the condition of the patient is assessed to decide whether adjuvant chemo radiotherapy would further improve clinical prognosis.

Radiotherapy is one of important components of postoperative adjuvant therapy scheme for cervical cancer patients, while postoperative adjuvant radiotherapy has been proven to reduce 40%-50% of local relapse risk.[13,14] In this study, the adjuvant chemo radiotherapy was given for the high-risk patients of lymphatic metastasis, positive vaginal incisal edge, and parametrial infiltration and medium-risk patients according to Sedlis standards,[15] and postoperative local relapse risk was lower than that in the previous reports. In the opinion of the author, this may be because only external irradiation of pelvic cavity was conducted without after-loading therapy in the previous reports. In addition, as the time of follow-up visit extends, the radiotherapy gradually improves local control rate of cervical cancer patients after the operation, and this is finally reflected in the improvement of overall survival.[16] The multi-factor analysis result showed that external irradiation of pelvic cavity was an independent influencing

factor of survival without local relapse and overall survival of early cervical cancer patients after the operation ($p<0.05$). A clinical report also holds that,[17-19] although postoperative radiotherapy can reduce the recurrence risk and increase local control rate, it cannot improve overall survival benefit.[20,21] As this is a retrospective study and the chemotherapy scheme and cycle count have certain differences, hence, the above conclusions still need to be verified by large-scale prospective clinical study.

Conclusion

In conclusion, early cervical cancer patients should be treated with a combination of external irradiation of pelvic cavity and brachytherapy to reduce local relapse risk after surgery. Patients with small maximum diameter of tumour and without lymphatic metastasis benefit more by external irradiation of pelvic cavity. This study also has some limitations as the small sample size and monocentric factors can bias the conclusion. Also the retrospective design can have numerous uncontrollable confounding factors and lastly some incomplete data was also included which may have caused a statistical bias.

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