Original Article
An analysis on postoperative recurrence and prognostic factors of patients with cervical carcinoma

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Abstract: Objective: To investigate postoperative recurrence and prognostic factors of patients with cervical carcinoma in order to provide a basis for improving the therapeutic level of cervical carcinoma. Methods: The clinical characteristics and follow-up data of patients with cervical carcinoma treated with surgery in our hospital between January 2007 and December 2011 were retrospectively analyzed. The recurrences among patients with different features were investigated. Cox model was used to investigate factors associated with recurrences. Results: Among 167 patients with cervical carcinoma, 33 cases relapsed during postoperative follow-up period (19.8%). The time to recurrence ranged from 4.0 to 39.0 months after surgery and the median time to recurrence was 12 months after surgery. The 1-, 2- and 3-year recurrence rates were 10.2%, 15.6% and 18.6%, respectively. The main site of recurrence was pelvis. Multivariate cox regression analysis showed that risk factors affecting recurrence for these patients included advanced clinical stage (IIb and III) (RR = 1.61, 95% CI: 1.05-2.49), poor differentiation (RR = 1.48, 95% CI: 1.03-2.11), non-squamous cell carcinoma (RR = 2.25, 95% CI: 1.30-3.90), accompanied by lymph node metastasis (RR = 3.06, 95% CI: 1.57-5.99) and no postoperative adjuvant therapy (RR = 2.15, 95% CI: 1.21-3.84). 34 patients died during postoperative follow-up period. The survival time ranged from 4 to 60 months and the median survival time was 36 months. The 1-, 2- and 3-year survival rates were 95.8%, 89.2% and 79.6%, respectively. The survival rate of patients in recurrence group was statistically significantly different from that of patients in non-recurrence group (χ^2 = 56.102, P < 0.001). Conclusion: There is still risk of recurrence after surgery for patients with cervical cancer and the prognosis of relapsed patients is poor. Patients with advanced clinical stage, poor differentiation, non-squamous cell carcinoma or without postoperative adjuvant therapy or accompanied by lymph node metastasis are more likely to relapse after surgery. Thus, these patients should be treated in a comprehensive manner to prevent recurrence and improve survival time.

Keywords: Cervical carcinoma, recurrence, prognosis, relevant factors

Introduction

Cervical carcinoma is currently one of the most common gynecologic malignant tumors in the world. Each year, about 530 000 new cases are diagnosed with and 260 000 cases die of cervical carcinoma in the globe. In China, cervical carcinoma is the second most common gynecologic malignant tumor, only second to breast cancer with its annual incidence of 9.84/100 000 and annual mortality rate of 6.12/100 000 [1, 2]. In recent years, with popularized screening and the development of diagnosis and treatment technologies, most patients with cervical carcinoma become able to be treated

timely in the early stage. Nevertheless, some of these patients are still facing the risk of recurrence after surgery. Previous statistics shows that the recurrence/uncontrolled rate after treatment reaches up to 29%~38% [3, 4] in patients with cervical carcinoma. The prognosis of these patients after recurrence will deteriorate. Most of them will die within the following 2 years and only about 10% of them can survive for more than 5 years [5, 6]. Therefore, it becomes a research hotspot to reduce the postoperative recurrence rate of patients with cervical carcinoma for prolonging their survival time. Through a retrospective analysis on the clinical features and follow-up data of patients

with cervical carcinoma receiving surgery in our hospital, this study is intended to investigate factors affecting the postoperative recurrence and prognosis of these patients so as to provide a basis for improving the therapeutic level of cervical carcinoma and prolonging patients' survival time.

Materials and methods

Object of study

The study objects were patients with cervical carcinoma who received surgery in our hospital from January 2007 to December 2011. Inclusion criteria were as follows: a. Patients who had underwent surgery; b. Pathologically diagnosed cervical carcinoma; c. Available clinical and follow-up data in detail. Exclusion criteria were as follows: a. Complicated by tumors at other sites; b. Severe dysfunction of major organs like the heart, liver, brain or kidney; c. Preoperative distant metastasis of cervical carcinoma. A total of 167 patients with cervical carcinoma were enrolled into this study. Their age ranged from 26 to 71 years with a median age of 50 years, averaging (49.3±9.1) years. Findings of FIGO staging were as follows: 45 cases in stage Ib (26.9%), 68 cases in stage IIa (40.7%), 34 cases in IIb (20.4%) and 20 cases in stage III (12.0%). 89 cases had tumor diameter < 4 cm at primary lesion (53.3%) and 78 cases tumor diameter ≥ 4 cm (46.7%). Pathological findings included 133 cases of squamous carcinoma (79.6%), 21 cases of adenocarcinoma (12.6%), 6 cases of adenosquamous carcinoma (3.6%), 4 cases of clear cell carcinoma (2.4%) and 3 cases of small cell carcinoma (1.8%). The degree of differentiation was as follows: 71 highly differentiated cases (50.3%), 35 moderately differentiated cases (3.6%) and 61 poorly differentiated cases (36.5%).

Research methods

Clinical features and follow-up data of enrolled patients were collected by consulting hospitalization records, auxiliary checklists, follow-up records and other medical records. Associated information was excerpted using a unified questionnaire, mainly including age, clinical staging of cervical carcinoma, pathological pattern, tumor size, relevant test results, treatment characteristics, recurrences, the last follow-up time and survival time etc. Clinical staging was conducted strictly according to 2009 Inter-

national Federation of Gynecology and Obstetrics (FIGO) staging system. Differentiation of pathological tissues was detected according to World Health Organization (WHO) grading system.

Treatment methods

All patients received radical trachelectomy of radical hysterectomy + pelvic lymphadenectomy. Further, age, personal willingness and the condition of ovary (during operation) of patients were considered comprehensively to determine whether patients should be spayed or not. 30 patients directly received radical trachelectomy and 137 patients received adjuvant chemotherapy at first and then received radical trachelectomy within 1-3 weeks. 123 patients received adjuvant chemotherapy and/or radiotherapy after operation. Chemotherapy regimen included oxaliplatin for injection + vincristine + bleomycin (PVB) and paclitaxel + oxaliplatin (TP). Radiotherapy regimen included external irradiation DT5200cGy and intracavitary after loading brachytherapy at the site 0.5 cm below mucosa (24.0 Gy/thrice).

Follow-up methods

All patients were followed by such methods as telephone follow-up or out-patient reexamination to collect their data. The follow-up cycle was once every three months within 1 year after operation, once every six months with 5 years after operation and once every year thereafter. Patients were followed till death or February 1, 2015. The follow-up rate of enrolled patients was 100%. Time to recurrence referred to the period from the day of operation to the time of recurrence. Survival time referred to the period from the day of operation to death or the cut-off day of follow-up.

1.5 Statistical analysis Statistical analysis was made by using SPSS20.0 software. Measurement data was described by using mean ± SD and t test was used for statistical inference. Enumeration data was described by using relative numbers like rate and constituent ratio and χ^2 test was used for statistical inference. Kaplan-Meier method was used to estimate the recurrence rate of patients with different features and Log-rank test was used for comparison. Cox proportional hazard regressive model ($\alpha_{admission}$ = 0.05, $\alpha_{discharge}$ = 0.10) was used to study factors affecting the recurrence

Table 1. Results of univariate analysis on postoperative recurrences in patients with cervical carcinoma (n = 167)

Factors	Total cases	Postoperative recurrences		X^2	P
		Number of cases	Recurrence rate (%)		
Total	167	33	19.8		
Age (year [s])					
< 45	72	16	22.2	0.484	0.487
≥ 45	95	17	17.9		
Clinical staging					
Ib-IIa	113	15	15.0	7.623	0.006*
IIb-III	54	18	29.6		
Diameter of tumor(cm)					
< 4	89	12	13.5	4.736	0.030*
≥ 4	78	21	26.9		
Degree of differentiation					
Highly/moderately differentiated	106	13	12.3	7.091	0.008*
Poorly differentiated	61	20	32.8		
Pathological pattern					
Squamous carcinoma	133	18	13.5	15. 794	< 0.001*
Non-squamous carcinoma	34	15	44.1		
Depth of myometrial invasion					
< 2/3	110	20	18.2	0.507	0.477
≥ 2/3	57	13	22.8		
Lymphatic metastasis					
None	104	14	13.5	6.899	0.009*
Yes	63	19	30.2		
Blood vessel invasion					
None	121	18	14.9	6.610	0.010*
Yes	46	15	32.6		
Preoperative adjuvant chemotherapy					
None	30	8	26.7	1.100	0.294
Yes	137	25	18.2		
Surgical margin					
Negative	159	29	18.2	4.846	0.028*
Positive	8	4	50.0		
Postoperative adjuvant chemotherapy					
None	44	16	36.4	11.530	0.001*
Yes	123	17	13.8		

Note: $^*P < 0.05$.

of patients with cervical carcinoma after surgery. The significance level was α = 0.05 and P < 0.05 meant that there was statistically significant difference.

Results

Recurrence

During follow-up, a total of 33 patients had recurrences with a total recurrence rate of 19.8% (33/167). The earliest one occurred 4.0 months after operation and the latest one 39.0 months after operation. The median time to recurrence was 12.0 months. The 1-, 2- and 3-year recurrence rates were 10.2% (17/167), 15.6% (26/167) and 18.6% (31/167), respectively. Among these recurrences, there were 24 cases of pelvic (vaginal and parametrial) recurrence (72.7%), 2 cases of para-aortic lymph node metastasis (6.1%), 4 cases of distant (lung and bone) metastasis (12.1%) and 3

Table 2. Results of multivariate cox stepwise regressive analysis on postoperative recurrences in patients with cervical carcinoma (n = 167)

Independent variable	Coefficient of regression	Standard error (SE)	Wald χ^2	P	RR (95% CI)
Clinical staging (control group = Ib-IIa)	0.478	0.221	5.757	0.016	1.61 (1.05-2.49)
Degree of differentiation (control group = highly/moderately differentiated)	0.391	0.183	6.015	0.014	1.48 (1.03-2.11)
Pathological pattern (control group = squamous carcinoma)	0.811	0.281	19.784	< 0.001	2.25 (1.30-3.90)
Lymphatic metastasis (control group = none)	1.121	0.342	18.547	< 0.001	3.06 (1.57-5.99)
Postoperative adjuvant therapy (control group = yes)	0.767	0.295	9.221	0.002	2.15 (1.21-3.84)

Note: Adjusted factors including diameter of tumor, negative/positive surgical margins and blood vessel invasion.
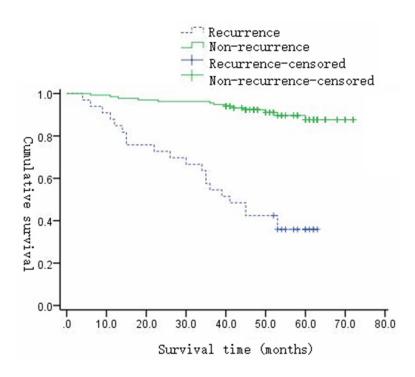

Figure 1. Comparison of survival curves of patients with cervical carcinoma between recurrence group and non-recurrence group.

cases of concurrent pelvic recurrence and distant metastasis (9.1%).

Univariate analysis on recurrence

Log-rank test showed that follow-up recurrence rates had no statistically significant difference among patients from different age group, with different depth of myometrial invasion and with or without preoperative adjuvant therapy (P > 0.05). However, follow-up recurrence rates had statistically significant difference among patients with different clinical staging, diameter of tumor, degree of differentiation, pathological pattern, negative/positive surgical margins or with or without lymphatic metastasis, blood vessel invasion and postoperative adju-

vant chemotherapy (P < 0.05) (**Table 1**).

Multivariate analysis on recurrence

Variables which had been proved to be of significance for recurrence in univariate analysis were included to perform multivariate cox proportional hazard stepwise regressive analysis. Results showed that there was statistically significant overall difference among regressive equations (χ^2 = 47.847, P < 0.001). Five factors, including advanced clinical staging (stage IIb and III), poor differentiation, non-squamous cell carcinoma, accompanied by lymphatic metastasis and no postoperative adjuvant therapy, were independent risk factors for the recurrences of patients with cervical carcinoma (P < 0.05) (**Table 2**).

Survival situation

Among 167 patients with cervical carcinoma, 34 cases died during postoperative follow-up. Their survival time was 4-60 months with a median survival time of 36 months. Their 1-, 3- and 5-year survival rates were 95.8% (160/167), 89.2% (149/167) and 79.6% (133/167), respectively. The survival situation of patients in recurrence group and non-recurrence group was as follows: a. 33 patients with cervical carcinoma in recurrence group survived for 4-60 months during follow-up with a median survival time of 36 months and their 1-, 3- and 5-year

survival rates were 84.8%, 63.6% and 36.4%, respectively; b. 134 patients with cervical carcinoma in non-recurrence group survived for 6-72 months during follow-up with a median survival time of 14 months and their 1-, 3- and 5-year survival rates were 98.5%, 95.5% and 90.3%, respectively. There was statistically significant difference between these two groups (χ^2 = 56.102, *P* < 0.001) (**Figure 1**).

Discussions

As one of the most common gynecologic malignant tumors, cervical carcinoma has caused great damage to the physical and mental health of woman. Currently, its treatment regimen is mainly based on a comprehensive consideration of the overall condition of tumor staging, patients' age and reproduction requirement [7, 8]. Although surgical and chemoradiotherapy technologies have been improved continuously, the problem of patients' high recurrence rate after radical trachelectomy hasn't been solved yet [9]. Therefore, it is of great significance to investigate risk factors affecting patients' postoperative recurrence and then establish a proper comprehensive treatment regimen accordingly for preventing the recurrence of cervical carcinoma after operation and improving therapeutic effect and patients' quality of life.

Among 167 cases receiving radical trachelectomy in this study, 33 cases had recurrence (19.8%) during follow-up and the time to recurrence mainly concentrated on within 2 years after operation (26/33). Pelvic cavity was the major site of recurrence (vaginal and parametrial). This is consistent with previous relevant researches [10, 11], indicating that after radical trachelectomy, patients are still facing risk of recurrence, especially within 2 years after operation. Hence, follow-up monitoring should still be used after operation for these patients. In the early days after operation, follow-up should be conducted relatively frequently. Meanwhile, much attention should be paid to the recurrence of pelvic cavity.

In addition, it is also found that five factors, including advanced clinical staging (stage IIb and III), poor differentiation, non-squamous cell carcinoma, accompanied by lymphatic metastasis and no postoperative adjuvant therapy, were independent risk factors for the recurrences of patients with cervical carcino-

ma. This is also consistent with conclusions of previous studies [12, 13]. There are three possible reasons [14-16]. Firstly, since the differentiation of cancer cells of poorly differentiated cervical carcinoma is poor, cells are mostly immature. With vigorous cells lacking in inhibition which proliferate constantly and invade tissues and cells around, patients are subject to recurrence. Secondly, non-squamous cell carcinoma is dominated by adenocarcinoma, which is less sensitive to radiotherapy and with high lymphatic metastasis compared with squamous cell carcinoma. Thus, patients are subject to recurrence. Thirdly, the main purpose of postoperative adjuvant radiotherapy and chemotherapy is to make up for the deficiency of surgery, improve local control rate and thus reduce postoperative recurrence. These findings suggest that for patients with abovementioned features, much attention should be paid to possible recurrences after operation. Besides, before operation, measures should be taken to decrease the risk of recurrence as much as possible (such as eliminating metastasized lymph nodes thoroughly and conducting adjuvant postoperative chemoradiotherapy whenever possible). After operation, follow-up reexamination should performed more frequently and purposefully to take measures for recurrences as early as possible.

So far, no effective treatment is available for recurrent cervical carcinoma yet. Patients are mainly treated by radiotherapy, chemotherapy combined with surgery comprehensively based on factors such as their features of recurrence, previous treatment and physical condition. However, the prognosis is poor in general [17, 18]. Moreover, it is also found that after radical trachelectomy, the overall survival situation of patients is good (5-year survival rate reaches up to 79.6%). But the prognosis of patients who had recurrence is poor-most of them die within 1-2 weeks after recurrence. This is consistent with similar previous studies [19]. It suggests that the key to prolong postoperative survival time of patients with cervical carcinoma is to prevent postoperative recurrence.

In conclusion, patients with cervical carcinoma still have the risk of recurrence after surgical treatment. Patients with advanced clinical staging, poor differentiation, non-squamous cell carcinoma, accompanied by lymphatic metastasis and no postoperative adjuvant therapy have higher risk of recurrence. Once recurrence

occurs, the prognosis of patients will be poor. Therefore, in clinical practice, patients with above features should be treated under comprehensive consideration, thus preventing postoperative recurrence and prolonging patients' survival time.

Disclosure of conflict of interest

None.

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