·Clinical Research·

Risk factors and prognosis of IB-IIB cervical carcinoma with common iliac lymph node metastasis

Long Huang[1,2], Min Zheng[1,2], Ji-Hong Liu[1,2], Ying Xiong[1,2], Hui Ding[1,2], Li Tang[1,2], Hui-Yun Wang[1,2]

[1] State Key Laboratory of Oncology in Southern China, Guangzhou, Guangdong 510060, P.R. China; [2] Department of gynecology, Cancer Center, Sun Yat-sen University, Guangzhou, Guangdong 510060, P.R. China

[**Abstract**] **Background and Objective:** Pelvic lymph node metastasis is an important prognostic factor of cervical cancer. The prognosis of cervical cancer patients with common iliac lymph node metastasis is poor, but few systematic studies have been reported . This study was to investigate the characteristics, risk, treatment and prognosis of stage IB–IIB cervical carcinoma patients with common iliac lymph node metastasis. **Methods:** A total of 960 patients with cervical cancer receiving radical hysterectomy and bilateral pelvic lymphadenectomy were selected from the hospitalized patients in the Cancer Center of Sun Yat-sen University between January 1995 and December 2005, and analyzed retrospectively. **Results:** Of the 960 patients, 288 (30.0%) had pelvic lymph node metastasis, and 45 (4.7%) had positive common iliac lymph node. The 5-year overall survival rate (OS) of patients with common iliac lymph node metastasis was 46.1%, and 67.5% in patients with other pelvic lymph node metastasis ($P < 0.05$). Univariate analysis showed that clinical stage, serum level of squamous cell carcinoma antigen (SCC-Ag) > 4 μg/L before treatment, depth of cervical invasion ⩾2/3 and positive parametrial margin were associated with common iliac lymph node metastasis ($P < 0.05$). Patients with ⩾3 pelvic lymph node metastasis (excluding common iliac lymph node) or recurrence had poor prognosis ($P < 0.05$). Factors predictive of common iliac lymph node metastasis on Logistic forward regression were SCC-Ag > 4 μg/L ($P = 0.026$, OR = 2.303) before treatment and positive parametrial margin ($P = 0.045$, OR = 2.634). **Conclusions:** Cervical cancer patients with common iliac lymph node metastasis had poorer prognosis compared with patients with other pelvic lymph node metastasis. SCC-Ag >4 μg/L before treatment and positive parametrial margin were the independent predictive factors for common iliac lymph node metastasis of cervical carcinoma. Pelvic lymph node metastasis (excluding common iliac lymph node) ⩾ 3 or recurrence was prognostic factors for patients with common iliac lymph node metastasis.

Key words: Common iliac lymph node, metastasis, cervical cancer, risk factors, prognosis

Cervical cancer is the second major malignant tumor in women[1], half a million women are diagnosed as having cervical cancer each year in the world, leading to 9% of the deaths in women[2]. Pelvic lymph node metastasis is the major risk factor which affects the prognosis of cervical cancer patients. The pelvic lymph node metastasis rate in stage IB-IIB cervical cancer is reported to be 15%–31%[3-5]. Once pelvic lymph node metastasis occurs, the 5-year overall survival rate reaches approximately 30%–60%[6]. The probability of common iliac lymph node metastasis is relatively low in pelvic lymph node metastasis, but once it happened, the survival rate of the patients would decrease significantly[5,6]. However, few systematic studies on characteristics, risk factors, treatment and prognosis of common iliac lymph node metastasis have been reported. Here, through retrospective study, we systematically analyzed clinical and pathological data of 960 patients with IB-IIB cervical cancer receiving radical hysterectomy and explored the characteristics, related risk factors, treatment and prognosis of patients with common iliac lymph node metastasis.

Materials and Methods

Objects of study

A total of 960 patients with IB-IIB stage cervical cancer who received radical treatment in gynecologic surgery from January 1995 to December 2005 in the Cancer Center of Sun Yet-sen University were studied. Forty-five cases were recruited with the following conditions: (1) IB-IIB stage according to international federation of gynecologists & obstetricians (FIGO) stage; (2)

Correspondence to: Min Zheng; Tel: +86-20-87343100;
Email: zheng_min_2006@yahoo.com.cn

This paper was translated from Chinese into English by *CJC* Medical Translation and edited by Jing-Yun Ma on 2010-03-14.

The Chinese version of this paper is avaiable at http://www.cjcsysu.cn/cn/article.asp?id=16328.

Received: 2009-07-14; Accepted: 2010-02-01

Grant: Guangdong Provincial Scientific Research (No. 2004B30301007).

underwent a wide range hysterectomy and pelvic lymph node dissection; (3) diagnosed as cervical invasive carcinoma with common iliac lymph node metastasis; and (4) with complete postoperative follow-up information.

Clinical data

The average age of the 45 patients was 45 years, with a median age of 44 years (25-56 years). According to FIGO diagnostic criteria in 1995, 16 cases had stage IB (35.6%) cervical cancer, 10 cases IIA (22.2%), 19 cases IIB (42.2%), 39 (86.7%) cases had squamous cell carcinoma and 6 (13.3%) cases had adenocarcinoma. The metastasis rate was 4.7% (45/960), accounting for 15.6% (45/288) of pelvic lymph node metastasis.

Methods

Clinicopathological parameters High risk factors related to common iliac lymph node metastasis of cervical cancer were selected for analysis, such as age, serum SCC-Ag level before treatment, clinical stage, histological grade, tumor size, histological type, depth of cervical invasion, cervical canals invasion, parametrial margin, vaginal margin, the group number of positive pelvic lymph nodes metastasis (excluding iliac lymph node metastasis) and postoperative adjuvant treatment.

Treatment In 45 patients with common iliac lymph node metastasis, 8 (17.8%) refused postoperative adjuvant treatment and 37 (82.2%) underwent postoperative adjuvant treatment. Among these 37 patients, 13 received radiotherapy, 7 received chemotherapy and 17 received combined radiotherapy and chemotherapy. CBP adjuvant chemotherapy program was used (CTX (cyclophosphamide) + BLM (bleomycin) + Carbo). Seven cases received radical surgery and bilateral pelvic arterial chemotherapy through Carbo simultaneously, and additional BLM and CTX after radical surgery.

Follow-up

Out-patient clinic review, telephone calls and letter correspondence were used for follow-up. The follow-up was started from the day of pathological diagnosis. The overall survival (OS) time was calculated from surgery to death. The progression free survival (PFS) time was calculated from surgery to recurrence or death. The deadline of follow-up was November 15, 2009 and the follow-up rate was 93.4% (897/960) with a median follow-up time of 62 months (1–140 months).

Statistical methods

Statistical analysis was performed using SPSS. χ^2 test was used for univariate analysis of classification variables; Logistic regression was used for multivariate analysis; Kaplan-Meier method was used for statistics of 5-year overall survival rate and comparison of survival curve; and Log-rank test was used for survival rate comparison.

Results

Common iliac lymph node metastasis rate of cervical cancer and metastatic characteristics

Among 960 IB–IIB stage cervical carcinoma patients with common iliac lymph node metastasis, 288 patients (30.0%) had pelvic lymph node metastasis. Forty-five (4.7%) patients had common iliac lymph node metastasis. The general distribution characteristics of lymph node metastasis were as follows: 196 cases (20.4%, 196/960) had obturator lymph node metastasis, 63 (6.6%, 63/960) had internal iliac lymph node metastasis, 68 (7.1%, 68/960) had external iliac lymph node metastasis, 45 (4.7%, 45/960) had common iliac lymph node metastasis, 17 (1.8%, 17/960) had inguinal lymph node metastasis and 18 (1.9%, 18/960) had peritoneal paraaortic lymph node metastasis (Table 1, Figure 1).

The pelvic lymph node metastasis distribution of the 45 patients complicated with common iliac lymph node metastasis was as follows: 8 cases (17.8%) had solitary iliac lymph node metastasis and 37 (82.2%) had multiple lymph node metastasis, including 21 (46.7%) of obturator lymph node—internal iliac lymph node/external iliac lymph node—common iliac lymph node metastasis, 6 cases (13.3%) of internal iliac lymph node/external iliac lymph node—common iliac lymph node metastasis and 10 cases (22.2%) of obturator lymph node—common iliac lymph node metastasis. Complicated obturator lymph node metastasis occurred in 21 patients, internal iliac lymph node metastasis in 18 patients, external iliac lymph node metastasis in 22 patients, inguinal lymph node metastasis in 5 patients and peritoneal para—aortic lymph node metastasis in 4 patients. Twenty-one cases had continuous metastasis through lymphatic drainage pattern (obturator lymph node—internal iliac lymph node/external lymph node—common iliac lymph node), 24 cases had jumping lymph node metastasis (6 cases of internal/external iliac lymph node—common iliac lymph node metastasis, 10 cases of obturator lymph node—common iliac lymph node metastasis and 8 cases of solitary metastasis in common iliac lymph node).

High risk factor analysis of common iliac lymph node metastasis of cervical cancer

Univariate analysis of the clinical and pathological characteristics of 45 patients with common iliac lymph node metastasis showed that clinical stage, serum level of squamous cell carcinoma antigen (SCC-Ag) > 4 μg/L before treatment, depth of cervical invasion ⩾ 2/3 and positive margin in parametrium were associated with common iliac lymph node metastasis ($P < 0.05$), other factors such as age, pathological grade, tumor size, pathologic histology types, cervical canals invasion and vaginal margin showed no statistical significance ($P > 0.05$) between the two groups as shown in Table 1. Multivariate analysis was performed by Logistic regression model, and the results showed that only SCC-Ag > 4 μg/L before treatment ($P = 0.026$, OR = 2.303) and positive margin in parametrium ($P = 0.045$, OR = 2.634) were the independent risk factors of common iliac lymph node metastasis (Table 2).

Prognosis of cervical carcinoma patients with common lymph node metastasis

As displayed by Kaplan-Meier method, the 5-year overall survival rates of groups of non-pelvic lymph node metastasis, pelvic lymph node metastasis (excluding iliac lymph node metastasis) and common iliac lymph node metastasis were 91.5%, 67.5% and 46.1%, respectively (Figure 2). There was

Table 1 Clinicopathological factors associated with common iliac lymph node metastasis and 5-year overall survival (OS) in univariate analysis

	Common iliac lymph node					Common iliac lymph node positive patients		
	Positive	Negative	Metastasis rate (%)	χ^2	*P* value	5-year OS	χ^2	*P* value
Age (years)				0.796	NS		0.000	NS
⩽ 40	15	366	3.9			43.1		
> 40	30	549	5.2			37.3		
Histology				0.011	NS		0.006	NS
Squamous	39	798	4.7			33.1		
Adencarcinoma	6	117	4.9			50.0		
Clinical stage							0.774	NS
Ib	16	448	3.4	7.546	0.023	45.0		
IIa	10	246	3.9			50.0		
IIb	19	221	7.9			32.6		
Histological grade							1.501	NS
G1	5	108	4.4	0.075	NS	50.0		
G2	27	510	5.0			38.9		
G3	13	247	5.0			27.6		
SCC-Ag (μg/L)				17.218	< 0.001		0.768	NS
⩽ 4	27	678	3.8			30.4		
> 4	18	129	12.2			51.0		
Tumor diameter (cm)				2.083	NS		0.313	NS
⩽ 4	31	684	4.3			48.7		
> 4	14	192	6.8			41.7		
Depth of cervical invasion				9.104	0.003		0.005	NS
< 2/3	10	331	2.9			42.9		
⩾ 2/3	35	401	8.0			29.4		
Parametrial margin				23.859	< 0.001		0.051	NS
Negative	35	855	2.9			41.6		
Positive	10	44	18.5			36.0		
Uterine corpus invasion				1.647	NS		1.443	NS
Negative	15	341	4.2			38.7		
Positive	30	451	6.2			43.6		
Vagina margin				0.421	NS		0.181	NS
Negative	41	843	4.6			38.3		
Positive	4	58	6.5			50.0		
No.of group metastasis				–	–		4.372	0.037
< 3	19	–	–			67.7		
⩾ 3	26	–	–			37.0		
Recurrence				–	–		8.127	0.004
No	32	–	–			59.7		
Yes	13	–	–			16.4		
Adjuvant therapy				–	–		1.134	NS
NA	8	–	–			37.5		
RT	13	–	–			38.9		
CT	7	–	–			42.9		
RT + CT	17	–	–			39.2		

NS, no significance; NA, no adjuvant therapy; RT, adjuvant radiotherapy, CT, adjuvant chemotherapy; RT+CT, adjuvant radio-chemotherapy.

statistical significance in the 5-year overall survival rates between groups with no lymph node metastasis group and common iliac lymph node metastasis ($P < 0.001$) while there were significant differences in the 5-year overall survival rates of patients with pelvic lymph node metastasis (excluding common iliac lymph node metastasis) and common iliac lymph node metastasis ($P = 0.029$).

The difference was significant between pelvic lymph node metastasis (excluding common iliac lymph node metastasis) < 3 groups and pelvic lymph node metastasis (excluding common iliac lymph node metastasis) ⩾ 3 groups ($P < 0.001$) in 45 cervical carcinoma patients with common iliac lymph node metastasis (Figure 3). Non-recurrence group and recurrence group also had significant differences ($P = 0.004$), as shown in Figure 4. Thirty-seven (82.2%) of 45 patients received postoperative adjuvant treatment (13 cases of radiotherapy, 7

Table 2 Risk factors of 45 patients with common iliac lymph node metastasis

	B	SE	Wald	Sig.	Hazard	95% CI	
						Lower	Upper
SCC-Ag >4 μg/L	0.834	0.374	4.964	0.026	2.303	1.106	4.797
Positive parametrial margin	0.969	0.484	4.002	0.045	2.634	1.020	6.805
Clinical stage	0.265	0.216	1.506	0.220	1.303	0.854	1.990
Depth of cervical invasion > 2/3	0.655	0.428	2.342	0.126	1.924	0.832	4.450

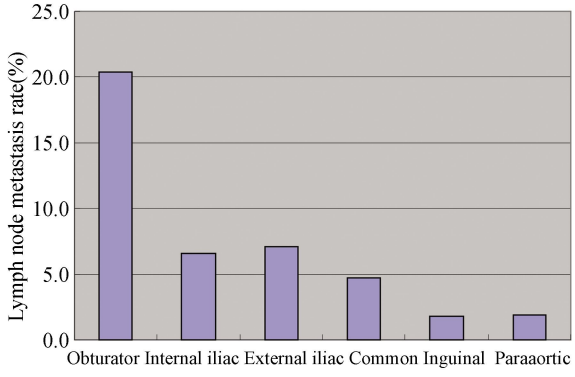

Figure 1 Lymph node metastasis rates

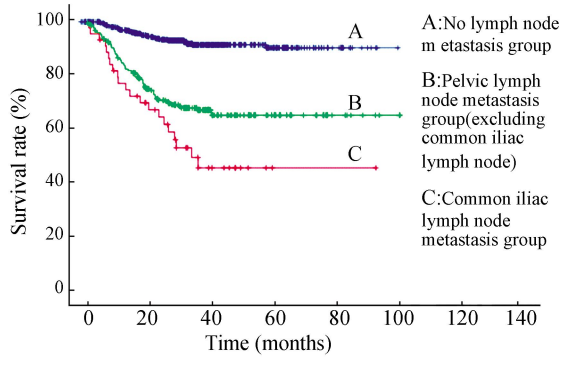

Figure 2 Overall survival of cervical cancer patients with pelvic lymph node metastasis (excluding common iliac), common iliac lymph node metastasis or without lymph node metastasis

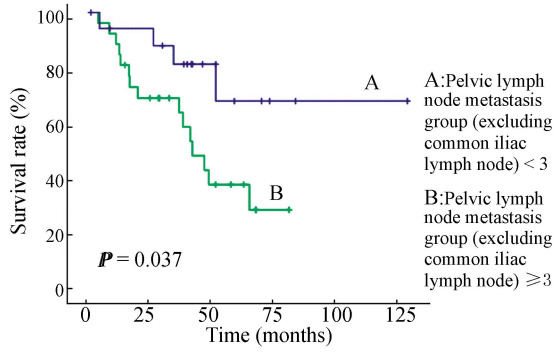

Figure 3 Overall survival of cervical cancer patients with pelvic lymph node metastasis < 3 or ≥ 3 groups (excluding common iliac)

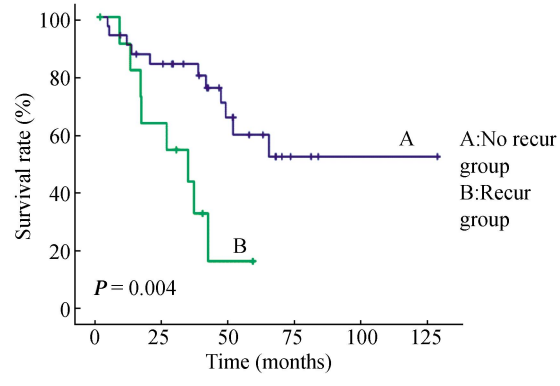

Figure 4 Overall survival of cervical cancer patients with or without recurrence

cases of chemotherapy and 17 cases of combined radiotherapy and chemotherapy), and 8 (17.8%) patients refused adjuvant treatment. The 5-year overall survival rates of radiotherapy group after surgery, chemotherapy group, combined radiotherapy and chemotherapy group and non-treatment group were 38.9%, 42.9%, 39.2% and 37.5%, respectively, without significant difference ($P > 0.05$).

Discussion

Lymph node metastasis is the main factor affecting the prognosis of cervical carcinoma, and the patients with pelvic lymph node metastasis have a poor prognosis. Monk *et al.* [3] reported that the 5-year overall survival rate of patients with non-lymph node metastasis was 85%–90%, and ours was 91.2%. Patients with solitary lymph node metastasis had longer survival period than with multiple lymph node metastasis. In stage I–II cervical carcinoma, the 5-year overall survival rate of lymph node positive patients was reported to be 52.0%–62% [5] compared with 57.4% of our data, the common iliac lymph node metastasis rate was 2.0%–9.1% in stage I–II cervical carcinoma [1,2], and was 4.7% in our data. The 5-year overall survival rate of patients with common iliac lymph node metastasis was 25%–47.8% [5,7], and ours was 46.1%. These results indicated that all our results were identical to previous studies. The prognosis of cervical carcinoma patients with common pelvic lymph node metastasis became poorer significantly. Therefore, before treating patients with common iliac lymph node, it is necessary to judge the status of the patients and evaluate the metastasis risk with comprehensive consideration of the tumor markers, clinical and pathological

characteristics for the best selection of treatment strategy and improvement of the 5-year overall survival rate. Due to the low common iliac lymph node metastasis rate of cervical carcinoma, few studies about the related high risk factors of the common iliac lymph node metastasis have been reported. We found that clinical stage, SCC-Ag > 4 μg/L before treatment, depth of cervical invasion > 2/3 and positive margin in parametrium were associated with common iliac lymph node metastasis through univariate analysis, while through multiple analysis, we found that only SCC-Ag >4 μg/L before treatment, depth of cervical invasion > 2/3 and positive margin in parametrium were the independent risk factors in the common iliac lymph node metastasis. SCC-Ag is one of the most thoroughly studied indicators of lymph node metastasis related tumor markers. Takeshima *et al.*[8] have indicated that the value of SCC-Ag was defined as 4 μg/L, the sensitivity and the specificity of lymph node metastasis judgment were 59.1% and 93.9%, and the positive and negative prediction values were 65.0% and 92.2%, respectively. Once SCC-Ag was higher than 4 μg/L, the risk of lymph node metastasis increased by 8.4 folds. Feng *et al*.[9] found that the risk increased by 4.2 folds. Our data showed that common iliac lymph node metastasis rate of cervical carcinoma patients with serum SCC-Ag > 4 μg/L before treatment was 12.2%, which was much higher than the metastasis rate of patients with serum SCC-Ag ⩽ 4 μg/L before treatment (3.8%). The common iliac lymph node metastasis risk of patients with SCC-Ag > 4 μg/L before treatment was 2.3 times that of patients with SCC-Ag ⩽ 4 g/L, suggesting that 4 μg/L is of great significance in evaluating the risk of common iliac lymph node metastasis. Thus, rapid pathological section should be performed for the suspected metastatic lymph node of patients with SCC-Ag > 4 μg/L, if the results were positive, biopsy taking or peritoneal para-aortic lymph node removal is necessary, which avoided unnecessary removal of lymph node and misdiagnosis of lymph node metastasis, and improved the prognosis of patients. In addition, we found that positive margin in parametrium was also an independent risk factor of common iliac lymph node metastasis. The rate of common iliac lymph node metastasis in cervical carcinoma patients with negative or positive margin in parametrium was 2.9% and 18.5%, respectively, and the risk of positive patients was 2.6 times higher than negative patients. Therefore, patients with positive margin in parametrium shown by frozen biopsy, pelvic lymph node and high peritoneal aortic lymph node should be removed, and radical laparotomy of cervical cancer type III, but not type II or other extended hysterectomy should be performed.

The patients with a pelvic lymph node metastasis ⩾ 3 and recurring common iliac lymph node metastasis showed poor prognosis in univariate analysis. The 5-year overall survival rates of common iliac lymph node metastasis patients with a pelvic lymph node metastasis (excluding common iliac lymph node metastasis) < 3, common iliac lymph node metastasis patients with a pelvic lymph node metastasis (excluding common iliac lymph node metastasis) ⩾ 3, and the common iliac lymph node metastasis in the non-recurrent group, and recurrent group were 67.7%, 37.0%, 59.7% and 16.4%, respectively. Therefore, for common iliac lymph node metastasis patients with a pelvic lymph node metastasis (excluding common iliac lymph node metastasis) ⩾ 3, we suggested that more appropriate treatment strategy should be selected in order to improve the survival rate. Chen *et al.* reported that postoperative adjuvant treatment raised the 5-year overall survival rate of cervical carcinoma patients with pelvic lymph node metastasis[10]. However, in our 45 cases of cervical carcinoma with common iliac lymph node metastasis, postoperative adjuvant treatments did not significantly increasethe 5-year overall survival rate of patients. The 5-year overall survival rates of post-operational radiotherapy group, chemotherapy group, the combined radiotherapy and chemotherapy group and non-treatment group were 38.9%, 42.9%, 39.2% and 37.5%, respectively, no significant differences were found among these four groups (P > 0.05). Thus, the postoperative adjuvant treatment strategy for the cervical carcinoma patients with common iliac lymph node metastasis needed to be further studied. Perspective studies for searching more appropriate treatment strategy are also necessary to improve the prognosis of these patients. The small number of patients in our study may lead to bias in data analysis, therefore, sample size needed to be enlarged for further studies so as to draw a more accurate conclusion.

References

[1] Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002 [J]. CA Cancer J Clin, 2005, 55(2):74-108.

[2] Schiffman M, Castle PE, Jeronimo J,et al. Human papillomavi-rus and cervical cancer[J]. Lancet, 2007, 370:890-907.

[3] Monk B J, Cha D S, Walker J L, et al. Extent of disease as an indiation for pelvic radiation following radical hysterectomy and bilateral pelvic lymph node dissection in the treatment of stage IB and IA cervical carcinoma[J]. Gynecol Oncol, 1994, 54(1):4-9.

[4] Sakuragi N, Satoh C, Takeda N et al. Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with stages IB, II A and II B cervical carcinoma treated with radical hysterectomy[J]. Cancer,1999,85(7):1547-1554.

[5] Aoki Y, Sasaki M, Watanabe M, et al. High-risk group in node-positive patients with stage IB, II A, and II B cervical carcinoma after radical hysterectomy and postoperative pelvic irradiation [J]. Gynecol Oncol, 2000, 77:305-309.

[6] Yeh SA, Leung SW, Wang CJ, et al. Postoperative radiotherapy in early stage carcinoma of the uterine cervix: treatment results and prognostic factors [J]. Gynecol Oncol, 1999, 72(1):10-15.

[7] Kodaira T, Fuwa N, Nakanishi T, et a1. Long-term clinical outcomes of postoperative pelvic radiotherapy with or without prophylactic paraaortic irradiation for stage I - II cervical carcinoma with positive lymph nodes [J]. Am J Clin Oncol, 2004, 27 (2):140-148.

[8] Takeshima N, Hirai Y, Katase K, et a1. The value of squamous cell carcinoma antigen as a predictor of nodal metastasis in cervical cancer [J]. Gynecol Oncol, 1998, 68 (3):263 -266.

[9] Feng SY, Zhang YN, Liu JG, et al. Risk factors and prognosis of node-positive cervical carcinoma [J]. Chinese Journal of Cancer, 2005, 24(10): 1261-1266.

[10] Cheng X, Cai SM, Li ZT, et al. Prognosis of patients with stage IB-IIB node positvie cervical carcinoma [J]. Chinese Journal of Cancer, 2003, 22(11): 1219-1223.