

# The Prognosis of Patients with Stage Ib–IIb Node–Positive Cervical Carcinoma after Radical Surgery

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**OBJECTIVE** To investigate the influence of positive lymph nodes on the prognosis for patients with stage Ib–IIb cervical carcinoma.

**METHODS** Sixty–six patients with stage Ib~IIb cervical carcinoma who underwent a radical hysterectomy and pelvic lymphadenectomy were analyzed retrospectively. The potential prognostic factors were calculated by the Cox proportional hazard model.

**RESULTS** The 5–year survival of the patients with pelvic lymph node metastasis was 40.7%. The Cox proportional hazard model analysis showed that cellular differentiation, the number of positive nodes and adjuvant therapy were independent prognostic factors ( $P < 0.05$ ). The 5–year survival of patients with 1 positive node was higher than that of those with 2 or more positive nodes (56.5% vs 36.4%,  $P < 0.05$ ). The distant metastasis rate in the former group (5.9%) was lower than the latter's (32.7%) ( $P = 0.05$ ). However, there was no significant difference of pelvic recurrence between the 2 groups ( $P > 0.05$ ). The 5–year survival of the patients who had no adjuvant therapy (12.6%) was much lower than that (53.7%) of those with adjuvant therapy ( $P < 0.05$ ). However, there no obvious differences among the effect of adjuvant radiotherapy, chemotherapy and chemoradiotherapy ( $P > 0.05$ ).

**CONCLUSION** The prognosis of patients with stage Ib–IIb node–positive cervical carcinoma who underwent radical surgery was poor. Adjuvant therapy can increase the survival rate, decrease the pelvic recurrence and distant metastasis.

**KEYWORDS:** cervical carcinoma, lymph node metastasis, adjuvant therapy, prognosis.

**R**adical hysterectomy with bilateral pelvic lymphadenectomy produces an expected 85%–90% 5-year survival rate in women without lymphatic spread with stage Ib and IIa cervical carcinoma. However, once tumors involve regional lymph nodes, 5-year survival has been reported to be only 30%–60%.<sup>[1]</sup> It has been confirmed that pelvic lymph node metastases are an important factor that influences the prognosis. However, many questions such as the relationship between the number, the site of positive nodes, the modality of postoperative adjuvant therapy and the prognosis have not as yet been clarified. This study investigated the factors that could influence the prognosis of patients with stage Ib–IIb node–positive cervical carcinoma.

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## MATERIALS AND METHODS

### Clinical materials

From January 1992 to December 1997, 398 women with stage Ib-IIb cervical carcinoma as staged by the International Federation of Gynecology and Obstetrics (FIGO) received radical surgery in the Department of Gynecologic Oncology at the Cancer Hospital of Fudan University. Only 66 patients who undertook Wertheims-Meigs' surgery (radical hysterectomy and pelvic lymphadenectomy) were histologically confirmed to have positive pelvic lymph nodes. Follow-up information available was included in our study. The patients' median age at diagnosis was 49 years (21~71years). Among them, 8 patients were in stage Ib (12.1%), 37 patients (56.1%) in stage IIa and 21 patients (31.8%) in stage IIb. There were 41 women (62.1%) with squamous carcinoma, 20 cases (30.3%) with adenocarcinoma, 4 (6.1%) with adenosquamous carcinoma and 1 patient (1.5%) with small cell carcinoma. Histologically, the carcinomas in 4 patients (6.1%) were well differentiated, 46 cases (69.7%) moderately differentiated and 16 (24.2%) poorly differentiated. The average lymph nodes resected were 14.8 per patient. The average positive lymph nodes resected were 3.7 (1~28) per patient. The average diameter of the cervical tumors was 3.6 cm (1~7cm). The patients' clinico-pathologic characteristics are listed in Table 1.

### Methods of treatment

Preoperative brachytherapy was given to 64 patients who had a huge tumor or vaginal vault involvement (3-4 fractions, with a total dose of 15-20 Gy at point A). Eleven patients received intraarterial chemotherapy before operation because of a bulky tumor or parametrial extension. The chemotherapy regimen was cisplatin (DDP) + 5-Fluorouracil (5FU) with 2~3 cycles at 3-weeks intervals.

The Wertheims-Meigs' procedure included radical hysterectomy and bilateral pelvic lymphadenectomy. Three patients underwent para-aortic lymph-node (PALN) resection because of suspicious metastasis.

Table 1. Clinico-pathologic characteristics of patients with node-positive cervical carcinoma after radical surgery

Factor	n	Percentage (%)
Age(years)		
< 40	15	22.7
≥ 40	51	77.3
Stage		
IB	8	12.1
IIA	37	56.1
IIb	21	31.8
Tumor size(cm)		
< 4	31	47.0
≥ 4	35	53.0
Histology		
Squamous	41	62.1
Adenocarcinoma	20	30.3
Adenosquamous	4	6.1
Others	1	1.5
Differentiation		
Poor	16	24.2
Moderate	46	69.7
Well	4	6.1
Pelvic lymph node metastases		
1	17	25.8
≥ 2	49	74.2
Parametrial extension		
Negative	58	87.9
Positive	8	12.1
Vaginal margin involved		
Negative	64	97.0
Positive	2	3.0
Depth of stromal invasion		
≤ 2/3	19	28.8
> 2/3	47	71.2
Lymphovascular invasion		
Negative	47	71.2
Positive	19	28.8

Postoperative external beam irradiation was administered to 18 patients (27.3%) with 6 MV X-ray routine anterior and posterior. The dose was 35~45 Gy at point B with a 1.8 Gy daily fraction. Two patients with a positive vaginal margin were given extra brachytherapy with a dosage of 15 Gy at 0.5 cm under the vaginal mucosa. Twelve cases with positive common iliac nodes and 3 with para-aortic

lymph node (PALN) metastasis received an additional 40 Gy to the PALN chain area. Ten patients (15.2%) were given postoperative chemotherapy. The regimen consisted of (DDP) + (5FU) + Cyclophosphamide (CTX) for squamous carcinoma, and (DDP) + (5FU) + Mitomycin (MMC) for adenocarcinoma with 2~6 cycles at 3~4-week intervals. Nineteen patients (28.8%) received adjuvant radiotherapy and chemotherapy as mentioned above.

**Follow-up**

All the patients were followed-up after the treatment. The median follow-up time was 32 months (2~108 months).

**Statistical analysis**

Disease-free survival time (DFS) was defined as the time from the surgery date to recurrence or metastasis. Overall survival time (OS) was defined as the time from the surgery date to those patients lost or to death. Data analysis was performed with a SPSS10.0 statistical package. The survival curves were constructed by the Kaplan-Meier method. The differences in survival were compared using the Log-rank test. Multivariate analyses were performed with the Cox proportional hazard model. The correlation analysis was performed by Kendall's method. Pearson's chi-square or Fisher's exact test was used to compare the difference of proportions. A probability value of  $P < 0.05$  was considered significant.

**RESULTS**

**Survival rate**

The 5-year overall survival rate of the patients with pelvic lymph node metastasis was 40.7% with a mean survival time of 54.9 months.

**The relationship between the number of positive nodes and prognosis**

The 5-year survival rate of patients with 1 positive node (56.5%) was higher than that (36.4%) of those with 2 or more positive nodes ( $P < 0.05$ ). The former's distant metastasis rate (5.9%) was lower than the latter's (32.7%) ( $P = 0.05$ ). However, there was no difference of pelvic recurrence between them ( $P > 0.05$ ). See Table 2, Fig.1.

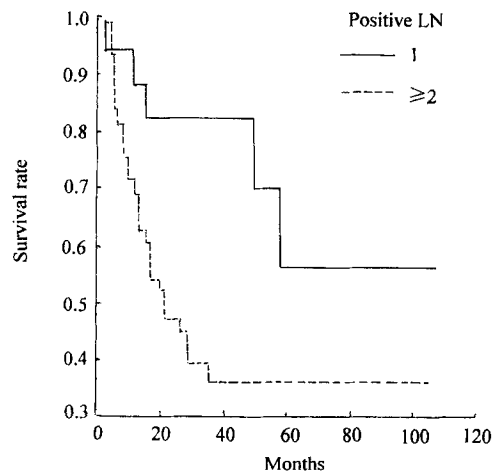


Fig.1. Overall survival according to 1 vs. 2 or more positive lymph nodes.

Table 2. Relationship between the number of positive nodes and prognosis

Number of positive nodes	n	5-Year survival (%)	P	Recurrence rate (%)	P	Metastasis rate (%)	P
1	17	56.5	0.033	23.5	0.807	5.9	0.050
≥ 2	49	36.4		26.5		32.7	

Table 3. Relationship between the site of positive nodes and prognosis

Site	n	5-Year survival (%)	P	Recurrence rate (%)	P	Metastasis rate (%)	P
Common iliac or above	15	33.3	0.086	13.3	0.318	53.3	0.005
Lower than common iliac	51	43.1		29.4		17.6	

**The relationship between the site of positive nodes and prognosis**

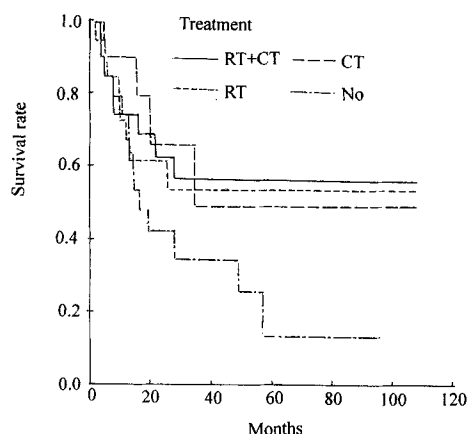
The 5-year survival (33.3%) of the patients with positive common iliac nodes and PALN was less than that (43.1%) of patients with external common iliac node involvement, but there was no significant difference ( $P>0.05$ ). The former's pelvic recurrence rate (13.3%) was less than the latter's (29.4%), but there was no significant difference ( $P>0.05$ ). However, the former's distant metastasis (53.3%) were much greater than that (17.6%) of the latter's ( $P<0.01$ ). The number of positive lymph nodes was closely correlated with the site of lymph node metastasis. The relative coefficient was 0.557 ( $P<0.01$ ). See Table 3.

**The relationship between adjuvant therapy and prognosis**

The 5-year survival rate of the patients who had no adjuvant therapy was 12.6%, much lower than that of those with adjuvant therapy (53.7%) ( $P<0.05$ ). The 5-year survival rates of the adjuvant radiotherapy, adjuvant chemotherapy, and adjuvant chemo-radiotherapy groups were 53.5%, 49.2%, and 56.1%, respectively ( $P>0.05$ ). The pelvic recurrence (42.1%) and distant metastasis (31.6%) of patients treated with surgery alone were higher than those with adjuvant-treated groups. However, the differences were not significant ( $P>0.05$ ). See Table 4, Fig. 2.

**Table 4. Relationship between adjuvant therapy and prognosis (%)**

Group	n	5-Year survival	Recurrence rate	Metastasis rate
No adjuvant therapy	19	12.6	42.1	31.6
Radiotherapy	18	53.5	22.2	22.2
Chemotherapy	10	49.2	20.0	10.0
Radiochemotherapy	19	56.1	15.8	21.1



**Fig.2.** Overall survival according to adjuvant therapy (radiotherapy [RT], chemotherapy [CT], radiochemotherapy [RT+CT], no adjuvant therapy [No]).

**Multivariate analysis of prognostic factors**

The Cox proportional hazard model analysis showed that cellular differentiation, number of positive nodes and adjuvant therapy were independent prognostic factors ( $P<0.05$ ). See Table 5.

**Table 5. Cox proportional hazard model analysis of variables in predicting overall survival**

Factor	Coefficient	RR	95% CI	P
Age	-0.031	0.970	0.932-1.010	0.136
Stage	0.283	1.327	0.379-4.644	0.658
Tumor size	0.332	1.394	0.984-1.975	0.061
Histology	-0.035	0.966	0.563-1.659	0.900
Differentiation	0.787	2.196	1.104-4.370	0.025*
Number of positive nodes	0.076	1.079	1.006-1.158	0.034*
Parametrial extension	0.484	1.623	0.584-4.508	0.353
Vaginal margin involved	-1.007	0.365	0.029-4.655	0.438
Depth of stromal invasion	0.423	1.526	0.856-2.722	0.152
Lymphovascular permeation	0.270	1.311	0.500-3.437	0.582
Nerve invasion	0.101	1.106	0.092-13.337	0.937
Adjuvant therapy	-1.684	0.186	0.075-0.459	0.000*

\* $P<0.05$

## DISCUSSION

Radical surgery has been confirmed to be an efficacious treatment in most patients with early stage (Ib-IIa) cervical carcinoma, and the 5-year survival rate has been between 50% -90% over the past 20 years. The reported risk factors for recurrence of cervical carcinoma included the clinical stage, tumor size, histological types, cellular differentiation, the depth of stromal invasion, parametrial extension, vaginal margin involvement, lymphovascular tumor embolism, lymph node metastasis, race, and age.<sup>[2-6]</sup> In most studies the presence of pelvic lymph node metastases has been associated with increased pelvic recurrence and distant metastases, and a decrease in overall survival. Our Cox proportional hazard model analysis showed cellular differentiation, number of positive nodes and adjuvant therapy were independent prognostic factors ( $P < 0.05$ ). The 5-year survival rate of patients with 1 positive node (56.5%) was higher than that (36.4%) of those with 2 or more positive nodes ( $P < 0.05$ ). There were no differences in pelvic recurrence between them. However, the former's distant metastases rate (5.9%) was lower than the latter's (32.7%) ( $P = 0.05$ ). In the analysis of lymph node metastases sites, the 5-year survival (33.3%) of the patients with positive common iliac node and para-aortic lymph nodes (PALN) was lower than that (43.1%) of patients with external common iliac node involvement. but there was no significant difference, which conforms to the report by Tsai et al.<sup>[7]</sup> The number of positive nodes was positively correlated with the site of positive nodes ( $P < 0.01$ ). The result showed that the more positive pelvic nodes there were, the higher incidence of high level node metastases, which supported external irradiation of the PALN chain area for multiple pelvic node involvement. The distant metastasis rate was 32.7% in patients with multiple positive lymph nodes, which showed the limitation of adjuvant radiotherapy and theoretically supported the postoperative combined chemotherapy.

The prognosis of patients with positive lymph nodes was poor because of local recurrence and distant metastasis. How to improve the prognosis of these

patients has been the focus in gynecological cancer. Stock et al.<sup>[8]</sup> compared postoperative whole pelvic irradiation with those treated with radical hysterectomy alone, and the former treatment improved the pelvic control rate, 5-year disease-free survival (DFS) and overall survival (OS) (78% vs 45%, 65% vs 41%, 58% vs 46%, respectively).

Peters' study<sup>[9]</sup> demonstrated that postoperative radiochemotherapy could greatly improve the 4-year DFS and OS compared to the adjuvant radiotherapy alone. In our study, adjuvant therapy improved the 5-year survival over that of the surgery alone (53.7% vs 12.6%) and decreased the pelvic recurrence and distant metastasis, which emphasizes the clinical importance of adjuvant therapy in patients with positive nodes. In our study the 5-year survival of the adjuvant radiochemotherapy group was higher than adjuvant radiotherapy alone or chemotherapy alone. The pelvic recurrence (42.1%) and distant metastasis (31.6%) of the surgery-alone group were higher than the other 3 therapeutic groups. However, the differences were not significant which may be due to the limited cases studied. The results should be verified in prospective clinical trials with more data.

The therapy of patients with stage IIb cervical carcinoma is still an controversial problem.<sup>[10]</sup> Although radical radiotherapy (RT) is the proper choice for patients with stage IIb cervical cancer in general, the therapeutic effect was not as good as we expected if the tumor was too bulky or histologically an adenocarcinoma. So some gynecologists try to use brachytherapy and/or neoadjuvant chemotherapy to decrease the lesion first and then perform radical surgery for some stage IIb patients with a bulky tumor or slight (less than 1/2) parametrial extension. Postoperative adjuvant therapy would then be recommended according to risk factors. In our study, the 5-year survival of the patients with stage IIb cervical carcinoma was only 54.3%, which was not at all satisfying. So we advocate that radical surgery should be taken cautiously for this group of patients. Any attempt to improve the prognosis by means of adjuvant therapy is inadequate if the parametrium can not be thoroughly dissected from the pelvic wall.

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