ORIGINAL ARTICLE

Survival and prognosticators of node-positive cervical cancer patients treated with radical hysterectomy and systematic lymphadenectomy

Masayoshi Hosaka · Hidemichi Watari · Takashi Mitamura · Yousuke Konno · Tetsuji Odagiri · Tatsuya Kato · Mahito Takeda · Noriaki Sakuragi

Abstract

Objective Lymph node metastasis (LNM) is known to be the most important prognostic factor in cervical cancer. We analyzed the number of positive lymph nodes and other clinicopathological factors as prognostic factors for survival in node-positive patients with cervical cancer.

Methods Node-positive cervical cancer patients ($n = 108$) who underwent radical hysterectomy and systematic lymphadenectomy in Hokkaido University Hospital from 1982 to 2002 were enrolled. Clinicopathological data including age, stage, histologic subtype, and the number of LNM sites were collected. The main outcome was the overall survival (OS) rate for Stage Ib–IIb patients treated with surgery and postoperative radiotherapy.

Results The 5-year OS rate of patients with 1 positive node was 93.3%, that for 2 nodes was 77.3%, for 3 nodes it was 33.3%, and for 4 or more it was 13.8%. The OS rate of patients with 1 or 2 LNM sites was significantly better than that for patients with more than 2 LNM sites. The OS rate of patients with adenocarcinoma (Ad) (28.6%) was significantly lower than that for patients with other histologic subtypes (squamous cell carcinoma; 66.7%, adenosquamous carcinoma; 75.0%, $p = 0.0003$). Multivariate analysis revealed that >2 LNM sites and Ad were independent prognostic factors for survival. The 5-year OS rate of patients with 1 or 2 LNM sites was 86.8%, a more favorable prognosis than the OS rates in other reports.

Conclusion More than two LNM sites and adenocarcinoma were independent prognostic factors for node-positive patients with cervical cancer.

Keywords Cervical cancer · Prognostic factor · Number of pelvic lymph node metastasis sites

Introduction

Many studies have reported that pathological type, bulky tumor, deep stromal invasion, lymph vascular space involvement and lymph node metastasis (LNM) are prognostic factors for recurrence in Stage Ib–IIb cervical cancer patients [1–3]. In particular, LNM is reported to be the most important prognostic factor for invasive cervical cancer. Node-positive patients usually receive adjuvant radiotherapy (RT) after surgery [4]. However, there is no clear evidence that RT contributes to improving the overall survival of node-positive patients [5, 6]. The aim of this study was to identify clinicopathological risk factors (including the number of LNM sites) for recurrence, and to stratify survival according to these risk factors for node-positive patients.

Patients and methods

Patients

We enrolled 108 node-positive cervical cancer patients among 425 total cervical cancer patients who underwent radical hysterectomy and systematic pelvic lymphadenectomy in our institution from 1982 to 2002. The patients' characteristics are shown in Table 1. The median age was

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Table 1 Clinicopathologic variables and 5-year overall survival in node-positive 108 patients

Variable	Number of patients	5-year OS	p value
Clinical stage			
Ib	19	78.9	
IIa	6	66.7	
IIIb	83	57.8	NS
Histologic type			
Squamous	90	66.7	
Adenosquamous	4	75.0	Squamous/adenosquamous versus adeno: 0.0003
Adeno	14	28.6	
Deep stromal invasion			
−	45	74.0	
+	63	53.3	0.01
Parametrial invasion			
−	45	76.4	
+	63	50.7	0.005
Bulky tumor			
−	58	74.6	
+	50	47.5	0.001
Corpus invasion			
−	65	66.7	
+	43	53.2	NS
Vaginal invasion			
−	83	65.6	
+	25	50.0	NS
Number of lymph node metastasis sites			
1	45	93.3	
2	22	77.3	
3	12	33.3	1, 2 sites versus 3, ≥4 sites: <0.0001
≥4	29	13.8	

Table 2 Prognostic factors for node-positive patients with cervical cancer

Univariate analysis		Multivariate analysis			HR
Factor	p value	SE	95% CI	p value	
Pure adeno + −	0.0006	0.40	0.11–0.55	0.0005	4.0
Stage Ib, IIa/IIIb	0.16				
Parametrial invasion + −	0.01	0.40	0.33–1.59	0.42	
Vaginal invasion + −	0.10				
Corpus invasion + −	0.22				
Deep stromal invasion + −	0.047	0.41	0.51–2.6	0.73	
Bulky tumor + −	0.006	0.38	0.35–1.5	0.39	
Over 3 sites LNM + −	<0.0001	0.43	0.04–0.22	<0.0001	10.6

Multivariate analysis showed that Ad and >2 LNM sites were independent prognostic factors for survival

*SE* standard error, *CI* confidence interval, *HR* hazard ratio

Statistical analysis

Categorical variables were analyzed using the chi-square test or Fisher's exact test. We used the Kaplan–Meier method, the log-rank test for survival analysis, and the Cox hazard method for prognostic analysis. A result was considered significant when the *p* value was <0.05.

Results

The median number of pelvic lymph nodes removed was 65 (range 23–117). The 5-year OS of node-positive patients was 62.0%, which was significantly worse than that of 310 node-negative patients (94.8%) ($p < 0.0001$, Fig. 1). The survival rate differed according to the number of positive lymph node sites: 1 site, 93.3%; 2 sites, 77.3%; 3 sites, 33.3%; ≥4 sites, 13.8%. The survival of patients with >2 sites was significantly worse than the survival of patients with 1 or 2 sites ($p < 0.0001$, Fig. 2). There was no significant difference among the survivals for each clinical stage (78.9% for Stage Ib, 66.7% for IIa, and 57.8% for IIb) (Ib vs. IIa, $p = 0.59$; Ib vs. IIb, $p = 0.14$; IIa vs. IIb, $p = 0.73$). We grouped Stage Ib and IIa into one group for univariate analysis because the number of patients for Stage IIa was small.

Survivals according to histologic subtype were 66.7% for SCC, 75.0% for Ad-Sq, and 28.6% for Ad. The survival of patients with Ad was significantly worse than that for patients with other histologic types ($p = 0.0003$). Univariate analysis revealed that a histologic subtype of Ad ($p = 0.0006$), PI ($p = 0.01$), BT ($p = 0.006$), and DSI ($p = 0.047$), and having >2 LNM sites ($p < 0.0001$) were statistically significant. Multivariate analysis showed that

50 years (range 28–71). Among these patients, 19 had clinical Stage Ib, 6 had Stage IIa, and 83 had Stage IIb. The numbers of patients with squamous cell carcinoma (SCC), adenocarcinoma (Ad), and adenosquamous carcinoma (Ad-Sq) were 90, 14 and 4, respectively. All patients received whole-pelvic irradiation (50 Gy/25 fr) as post-surgical adjuvant therapy. The median follow-up period was 54 months (range 4–171).

LNM and pathological factors

We counted the number of pelvic lymph nodes positive for metastasis separately on the left and right sides. We also analyzed pathological factors, including deep (≥2/3) stromal invasion (DSI, $n = 63$), parametrial invasion (PI, $n = 63$), bulky tumor (BT, $n = 50$), corpus invasion ($n = 43$), and vaginal invasion ($n = 25$) (Table 2).

Fig. 1 Five-year overall survival of cervical cancer patients. The 5-year overall survival in patients with LNM was significantly worse than that in patients with LNM (with LNM: 62.0% vs. without LNM: 94.8%, $p < 0.0001$)
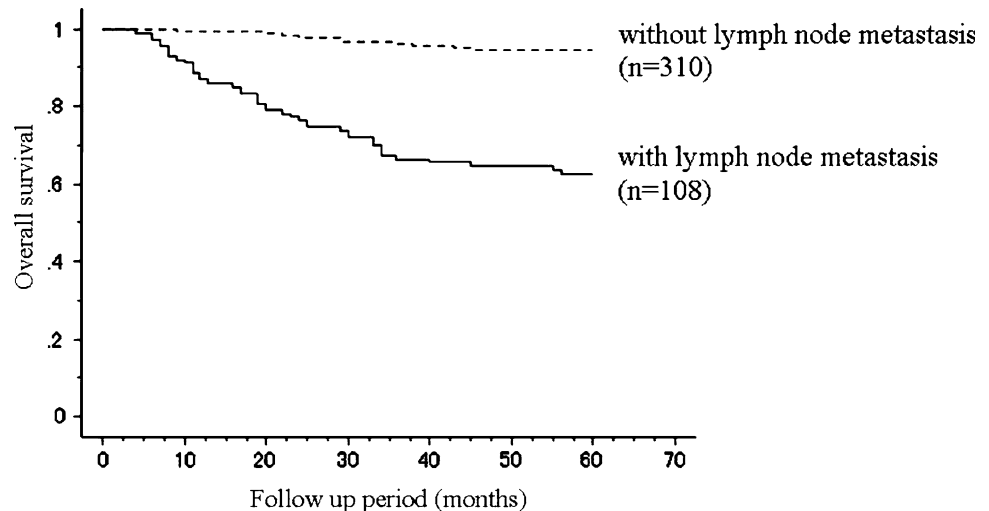
Fig. 2 Five-year overall survival of patients with lymph node metastasis according to the number of lymph node metastasis sites (1 site, 93.3%; 2 sites, 77.3%; 3 sites, 33.3%; ≥ 4 sites: 13.8%). The survival of patients with >2 sites was significantly worse than the survival of patients with 1 or 2 sites ($p < 0.0001$) (1 site vs. 2 sites, $p = 0.06$; 2 sites vs. 3 sites, $p = 0.008$; 3 sites vs. ≥ 4 sites, $p = 0.24$; 1 site vs. 3 sites, $p < 0.0001$; 1 site vs. ≥ 4 sites, $p < 0.0001$; 2 site vs. ≥ 4 sites, $p < 0.0001$; <2 sites vs. >3 sites, $p < 0.0001$)
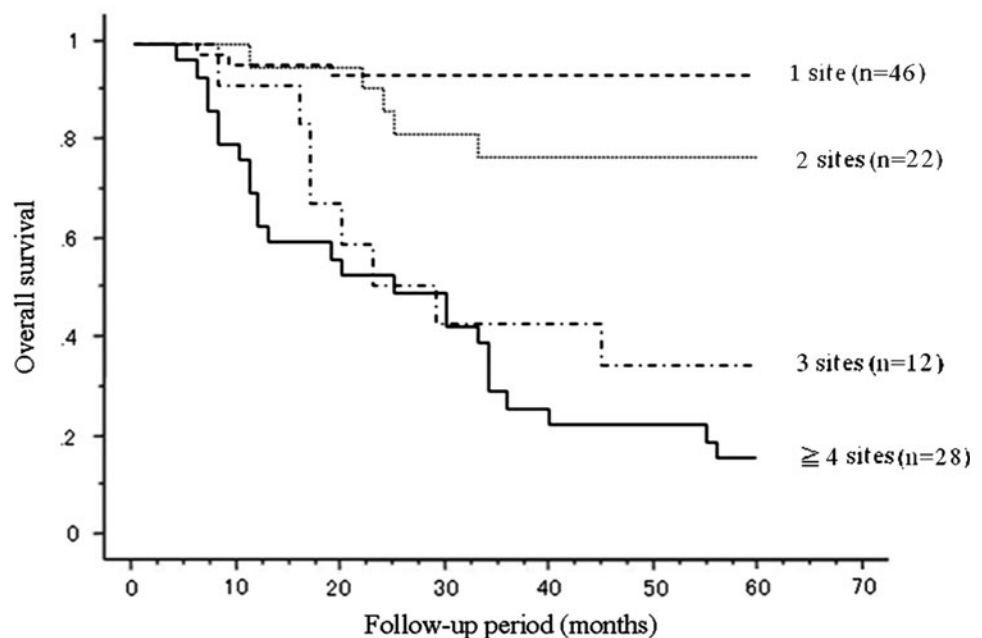
Ad ($p = 0.0005$) and >2 LNM sites ($p < 0.0001$) were independent prognostic factors for survival (Table 2).
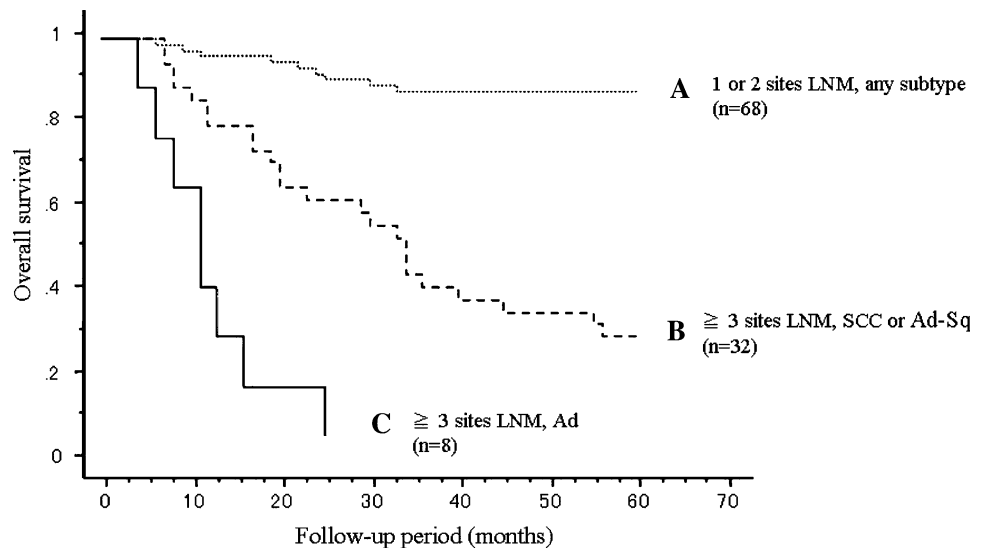
The survival of node-positive patients was stratified by combining these independent prognostic factors into three groups (Fig. 3): group A, 1 or 2 LNM sites irrespective of histologic subtype ($n = 68$); group B, >2 LNM sites with SCC or Ad-Sq ($n = 32$); and group C, >2 LNM sites with Ad ($n = 8$). The survivals of each group were 86.8, 25.0, and 0% for groups A, B, and C, respectively (A vs. B, $p < 0.0001$; B vs. C, $p < 0.0001$; A vs. C, $p < 0.0001$).

Discussion

The 5-year survival of patients with 1 or 2 LNM sites was significantly better than that of patients with >2 LNM sites.

There have been some reports that the 5-year OS reduces by as much as 50–60% depending on the number of LNM sites in cervical cancer; >1 site has a significantly poorer prognosis than 1 site [2, 7]. Tsai et al. reported that the 5-year OS rate of patients with 1 positive node site (84%) was statistically different from that of patients with >1 site (61%) [8]. The survival of patients with 1 or 2 LNM sites (86.8%) in our institution seems favorable compared with previous reports in the literature, and we speculate that the reason is at least in part due to the radicality of our surgery. We have performed type IV radical hysterectomy (Piver classification)—a more radical method than type II or III radical surgery [9, 10]. In addition, we removed more lymph nodes than in other reports [11] (Table 3). A therapeutic effect of lymphadenectomy was not clear for cervical cancer, but several reports have shown that extensive

Fig. 3 Stratification according to the number of lymph node metastasis (LNM) sites and histologic subtype. The survival of patients with 1 or 2 LNM sites of any histologic subtype was significantly better than that of other groups. (A vs. B, $p < 0.0001$; B vs. C, $p < 0.0001$; A vs. C, $p < 0.0001$)

Table 3 Number of lymph nodes removed in systematic lymphadenectomy and survival for Stage Ib–IIb cervical cancer patients

References	Pelvic average (range)	Clinical stage	5-year OS of node-positive patients (%)
Kim et al. [22]	21 (6–43)	Ib–IIb	50.0
Cheng et al. [23]	NA	Ib–IIb	53.5
Hosaka et al.	65[a] (23–117)	Ib–IIb	62.0

NA not assessed

[a] Reported as the median

lymphadenectomy increases survival. Pieterse et al. [12] reported that the 5-year disease-free survival of node-positive patients with ≥18 removed lymph nodes was about 20% higher than that of patients with <18 removed lymph nodes. Kenter et al. [13] reported that in 63 patients with positive nodes, those with complete lymphadenectomy had significantly fewer recurrences (25%) than those with incomplete lymphadenectomy (56%). Recently, sentinel lymph node biopsy has become common, and when these lymph nodes are negative for metastasis, many gynecologists omit the systematic lymphadenectomy. There are many benefits of this method, including low invasiveness and a low rate of complications [14, 15], but Marchiole et al. [16] reported that the sentinel lymph node biopsy method resulted in 14.3% false negatives, and Lentz et al. [17] described that 15% of the negative sentinel nodes had micrometastasis. Therefore, a complete lymphadenectomy may be able to elevate the detection rate of LNM and may improve the prognosis in cases with 1 or 2 LNM sites.

We administered whole pelvic irradiation as the adjuvant therapy to node-positive patients postoperation. Unfortunately, RT did not contribute to improving the survival of patients with >2 LNM sites (Fig. 2). Some reports indicate that adjuvant concurrent chemoradiotherapy (CCRT) with

cisplatin is superior to RT alone for both OS and progression-free survival of node-positive patients [18, 19]. We need to further investigate the effectiveness of adjuvant CCRT for patients with multiple LNM sites in the future.

Adenocarcinoma was an independent prognostic factor for node-positive cervical cancer. However, there was no significant difference between the survivals of patients with Ad and those with SCC but without LNM in our study. Ad cases with bulky tumors seemed to tend to have many LNM sites, but no statistically significant difference between these two sets of patients was found (Table 4). Berek et al. [20] and Irie et al. [21] reported that the 5-year survival for node-positive patients with Stage Ib–IIb cervical adenocarcinoma was 10–48%. This was probably caused by the biological aggressiveness and resistance to adjuvant therapy of Ad compared to SCC [1]. However, the 5-year survival for Ad patients with 1 or 2 LNM sites was 100% in our institution— apparently not inferior to the survival for SCC/Ad-Sq patients. Unfortunately, the survival of patients with both Ad and >2 LNM sites was quite poor. Peters et al. [19] reported the effect of GOG109 on CCRT using cisplatin and 5-fluorouracil versus RT alone as an adjuvant therapy after radical surgery for Stage Ia–IIa.

Table 4 Clinicopathological data for adenocarcinoma cases with lymph node metastasis

No.	Number of LNM sites	Bulky	PI	DSI	Vaginal invasion	Corpus invasion	Subtype	Follow-up periods (months)	Outcome
1	5	+	+	+	−	−	M	13	DOD
2	2	−	+	−	−	−	M	60	NED
3	3	−	+	−	−	−	M	24	DOD
4	4	+	+	+	−	−	E	25	DOD
5	8	+	+	+	−	−	M	6	DOD
6	2	−	−	−	−	−	M	60	NED
7	9	+	+	+	+	+	M	4	DOD
8	2	−	+	−	−	+	M	60	NED
9	3	+	+	+	−	+	M	8	DOD
10	7	−	+	+	−	+	C	9	DOD
11	2	+	−	−	−	+	E	60	NED
12	1	+	−	+	+	+	M	60	AWD
13	4	+	−	−	+	−	M	11	DOD
14	2	+	−	+	−	−	M	60	NED

PI parametrial invasion, *DSI* deep stromal invasion, *M* mucinous adenocarcinoma, *E* endometrioid adenocarcinoma, *C* clear cell adenocarcinoma, *DOD* dead of disease, *NED* no evidence of disease, *AWD* alive with disease

The 5-year OS of the group undergoing CCRT for Ad was 80%, significantly higher than that of the group undergoing RT alone for Ad (40%). Some reports have described the responses of advanced or relapsed patients to CT; the response of Ad to paclitaxel was 31%, that of non-SCC to topotecan and cisplatin was 27%, and that of non-SCC to docetaxel and carboplatin was 86% [22, 23]. We therefore need to compare the survival effect of adjuvant CT to those of RT alone or CCRT for Ad cases in a clinical trial setting. Furthermore, we should investigate the synergistic effects of molecular targeting drugs. To find good target molecules for cervical cancer, we need to perform basic and/or clinical research on Ad to improve survival. Watari et al. [24] recently reported that positive clusterin expression with multiple positive nodes gave a significantly poorer prognosis than negative expression, and suggested a potential combination of clusterin-targeting drugs to improve survival in such cases. Since this report targeted a small number of patients, further data evaluation for a large population is needed to establish optimal therapies for Ad and multiple LNM.

Conflict of interest No author has any conflict of interest.

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