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Prevalence and Predicting Factors for Pelvic Lymph Node Metastasis in Stage IB1 Cervical Carcinoma

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ABSTRACT

Objective To determine the prevalence of pelvic nodal metastasis and predicting factors in women with stage IB1 carcinoma of the cervix who underwent radical hysterectomy and pelvic lymphadenectomy.

Design Cross sectional analytic study.

Setting Department of Obstetrics & Gynecology, Faculty of Medicine, Chiang Mai University.

Subjects Patients with stage IB1 carcinoma of the cervix who underwent radical hysterectomy and pelvic lymphadenectomy at Chiang Mai University Hospital between January 2000 and December 2002.

Results Of 251 evaluable patients, radical hysterectomy was performed in 232 patients (92%) and was abandoned in 19 patients (8%). The prevalence of lymph node metastasis was 24%. Patient's age, gross tumor description, and preoperative treatment were no statistic significantly associated with pelvic lymph node metastasis. Histologic grade, depth of invasion, lymphvascular space invasion, parametrial invasion, and uterine invasion were significantly correlated with pelvic lymph node metastasis. From logistic regression analysis, the independent predicting factors for pelvic nodal metastasis were lymphvascular space invasion ($p < 0.0001$) and parametrial invasion ($p = 0.02$).

Conclusion The prevalence of pelvic lymph node metastasis in stage IB1 carcinoma of the cervix is 24%. The strongest predicting factors of node metastasis are lymphvascular space invasion and parametrial invasion.

Key words: cervical carcinoma, radical hysterectomy, pelvic lymph node metastasis

Cervical cancer is the most common female cancer in Thailand.[1] Optimal management for both the primary lesion and potential sites of metastatic disease is mandatory in definitive treatment of cervical cancer.[2] For stage IB and IIA carcinoma of the cervix, both pelvic radiation and radical surgery are accepted

treatments with comparable outcome.[3,4] Prevalence and distribution of nodal and parametrial metastasis have a significant impact on the design of appropriate treatment as well as on prognosis.

The main objective of this study is to determine the prevalence of pelvic nodal metastasis as well as its predicting factors in women with stage IB1 carcinoma of the cervix undergoing radical hysterectomy and pelvic lymphadenectomy at our institution.

Materials and Methods

The medical records of patients with FIGO stage IB1 carcinoma of the cervix who underwent radical hysterectomy and pelvic lymphadenectomy at Chiang Mai University Hospital between January 2000 and December 2002 were retrospectively reviewed with special emphasis on the clinicohistopathologic findings at the time of initial operation.

During the study period, 251 patients with stage IB1 carcinoma of the cervix were assessed and planned for radical hysterectomy and pelvic lymphadenectomy with or without bilateral salpingo-oophorectomy. Some patients received a cycle of preoperative cisplatin (75 mg/m^2) because of a prolonged waiting period for the available operating room (more than 3 weeks after diagnosis) in an attempt to minimize the chance of tumor progression and dissemination in the interim. Patients with metastasis to pelvic and/or paraaortic lymphatics identified intraoperatively, had either radical hysterectomy abandoned and received only bilateral pelvic/paraaortic lymphadenectomy or radical hysterectomy and bilateral pelvic lymphadenectomy done as planned depending on preference of responsible surgeons. In the same period, 49 patients with stage IB1 carcinoma of the cervix underwent pelvic radiation therapy as a primary treatment.

Clinical data including patient age, gross tumor description at first clinic visit, and preoperative treatment were collected and analyzed for their association with pelvic nodal metastasis.

All of the pathology materials were evaluated and reviewed by either one of the 2 gynecologic pathologists (S.S. and S.K.). The tumors were classified histologically as squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, neuroendocrine carcinoma, and others. Squamous cell carcinomas were graded as well differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3) by using a modified Broders's method. A grade of well, moderately, or poorly differentiated was assigned to each of the adenocarcinomas based on the architectural features. For adenosquamous carcinomas, the grade were assigned according to their adenocarcinoma components. All neuroendocrine carcinomas in this study were classified as poorly differentiated tumors (grade 3).[5] The depth of tumor invasion was categorized by the proportion of the cervical wall invaded as inner third, middle third, and outer third. Lymphvascular space involvement was defined as the presence of neoplastic cells within endothelium-lined spaces and was classified as none, few (less than 10 involved spaces), and many (10 or more involved spaces). Tumor invasion to the uterine cavity, adnexae, parametrium, vaginal margin, and pelvic nodes was also determined.

The Chi-squared test or Fisher's exact test were used for an analysis of association with pelvic nodal metastasis of all categorical variables. Student's t test was used for a continuous variable. The logistic model was applied in a multivariate analysis to determine the independent predicting factors for pelvic nodal metastasis. Statistical significance was defined by the p-value of less than 0.05.[6] This study was carried out under ethical approval of the Research Ethical Committee of Chiang Mai University Hospital.

Results

There were 251 patients with stage IB1 carcinoma of the cervix who underwent radical hysterectomy and pelvic lymphadenectomy during the study period. The mean age at diagnosis of the patients was 43.8 years(17-75). Clinical and histopathologic characteristics of the study group are presented in Table 1. The majority of patients (80%)

had gross cervical lesions identified on clinical examination. Approximately 30% of the patients received preoperative chemotherapy. The predominant histologic type was squamous cell carcinoma (68%) followed by adenocarcinoma (26%) and adenosquamous carcinoma (6%). Nearly half of the tumors (53%) were moderately differentiated (grade 2). Forty-two percents of the patients had disease invaded to the outer third of cervical wall whereas one-third of the patients had a tumor with invasion to the inner third of cervical wall. Twenty two percents of the patients had extensive lymphvascular space invasion. Parametrial invasion was identified in 12% of the patients. Of 251patients, 232 patients (92%) had radical hysterectomy performed whereas 19 patients (8%) had radical hysterectomy abandoned. In the patients who actually underwent radical hysterectomy and had uterine specimens evaluated histologically, 10% were found to have tumor invasion to the uterus. There were 161 patients who had adnexae removed at the time of surgery, and 13% of them had tumor involvement to the adnexae. Following hysterectomy, 10% of the patients had positive vaginal margin for preinvasive or invasive diseases.

All of the patients in this study had pelvic lymphadenectomy performed. Twenty-four percents of the patients were found histologically to have metastatic diseases to the pelvic lymph nodes. The mean age of the patients was 44.29 ± 7.97 years in pelvic lymph node metastasis group, and 42.42 ± 8.43 years in nonmetastasis group (p-value = 0.117). Patient's age, gross tumor description at first clinic visit, and preoperative treatment in this study were found to be no statistic significantly associated with pelvic lymph node metastasis. Histologic grade, depth of invasion, lymphvascular space invasion, parametrial invasion, and uterine invasion were significantly correlated with pelvic lymph node metastasis (Table 2).

Logistic regression analysis was performed to assess the independent association of clinical and histopathological factors with pelvic nodal metastasis. All factors found to be statistically significant in the univariate analysis were included. The independent predicting factors for pelvic nodal metastasis were lymphvascular space invasion ($p < 0.0001$) and parametrial invasion ($p = 0.02$).

Table 1. Clinical and histopathological characteristics

Characteristics	Number	Percent
Primary tumor description(n = 251)		
Gross	202	80.48
Occult	49	19.52
Preoperative chemotherapy(n = 251)		
No	176	70.12
Yes	75	29.88
Histologic type(n=251)		
Squamous cell carcinoma	170	67.73
Adenocarcinoma	64	25.50
Adenosquamous carcinoma	15	5.98
Neuroendocrine carcinoma	1	0.40
Others	1	0.40
Histologic grade(n = 251)		
1	74	29.48
2	132	52.59
3	45	17.93

Characteristics	Number	Percent
Depth of invasion(n = 232)		
Inner third	78	33.6
Middle third	57	24.6
Outer third	97	41.8
Lymphvascular space invasion(n = 232)		
None	134	57.8
Few	46	19.8
Many	52	22.4
Parametrial invasion(n = 231)		
No	203	87.9
Yes	28	12.1
Uterine invasion(n = 232)		
No	209	90.1
Yes	23	9.9
Adnexal invasion(n = 161)		
No	140	86.96
Yes	21	13.04
Vaginal margin(n = 232)		
Negative	209	90.1
Positive for preinvasive lesion	12	5.2
Positive for invasive lesion	11	4.7

Table 2. Frequency of pelvic nodal metastasis by clinical and histologic characteristics

Characteristics	Number (Percent)	p-value
Gross primary tumor		
Gross	48/202 (23.8)	0.9
Occult	12/49 (24.5)	
Preoperative chemotherapy		
No	40/176 (22.7)	0.5
Yes	20/75 (26.7)	
Histologic type		
Squamous cell carcinoma	44/170 (25.9)	0.485
Adenocarcinoma	11/64 (17.2)	
Adenosquamous carcinoma	5/15 (33.3)	
Neuroendocrine carcinoma	0/1 (0.0)	
Others	0/1 (0.0)	
Histologic grade		
1	10/74 (13.5)	0.014
2	41/132 (31.1)	
3	9/45 (20.0)	

Characteristics	Number (Percent)	p-value
Depth of invasion		
Inner third	7/78 (9.0)	0.008
Middle third	9/57 (15.8)	
Outer third	26/97 (26.8)	
Lymphvascular space invasion		
None	5/134 (3.7)	<0.001
Few	12/46 (26.1)	
Many	25/52 (48.1)	
Parametrial invasion		
No	26/203 (12.8)	<0.001
Yes	15/28 (53.6)	
Uterine invasion		
No	34/209 (16.3)	0.029
Yes	8/23 (34.8)	
Adnexal invasion		
No	34/140 (24.3)	0.767
Yes	3/21 (14.3)	
Vaginal margin		
Negative	36/209 (17.2)	0.450
Positive for preinvasive lesion	3/12 (25.0)	
Positive for invasive lesion	3/11 (27.3)	

Discussion

The prevalence of pelvic lymph node metastasis for stage IB1 carcinoma of the cervix in our study population is 24% which is in upper margin of the previously reported which range from 12.7-27% for stage IB.[7, 8] The prevalence would be even higher if data from stage IB2 carcinoma patients were taken into account and a combined stage IB1 and IB2 prevalence was considered. This could not be simply explained by bias on patient selection for surgery because our selection criteria for surgery was exactly the same as what had been accepted as a standard treatment guideline for stage IB carcinoma of the cervix in the literature.[2,7-9] Patients with stage IB1 carcinoma have been universally considered as being ideal candidates for radical hysterectomy and pelvic lymphadenectomy with alternative option of radiation treatment. In our institution where both surgical and radiotherapeutic facilities were available, radiation therapy was usually reserved for the patient who was surgically unfit.

Delayed surgery because of a prolonged waiting period for the available operating room, might play a role in a high prevalence of pelvic nodal metastasis in our study. However, preoperative chemotherapy were given to the patients with prolonged surgical waiting period in an attempt to reduce that chance and more importantly, all of the patients who underwent surgery were reevaluated clinically just before surgery and they were all confirmed to remain in the initially diagnosed stage. In our opinion, the high prevalence of pelvic nodal metastasis in our study has raised an issue of biolcgical/immunological difference as a possible explanation. In addition, the prevalence of pelvic nodal metastasis and parametrial invasion of 24% and 12% respectively in our study have confirmed that removal of parametria and pelvic lymph nodes are essential components of surgical management of stage IB1 carcinoma of the cervix. We did not routinely perform

paraaortic lymphadenectomy in this patient population so our data regarding prevalence of paraaortic nodal metastasis and its predicting factors are insufficient to draw any meaningful conclusions on this topic issue.

Lymphvascular space invasion and parametrial invasion were shown to be independent predicting factors for pelvic lymph node metastasis from the logistic regression analysis in this study. This is consistent with findings from a previously published study.[10] However, patient's age, depth of invasion, and histologic grade were also found to be independent predicting factors in that study. In our study, depth of invasion, histologic grade, as well as uterine invasion were associated with pelvic nodal metastasis in the univariate analysis but did not reach statistical significance in the multivariate analysis.

Regarding patient's age, it has been shown in the literature that generally there is not much difference in prognosis between younger and older patients with stage I or IIA cancers.[11,12] We did not find a significant association of patient's age with pelvic nodal metastasis in our study. Tumor size was shown to be one of the most significant pathologic prognostic factors in patients with surgically treated stage IB and IIA squamous cell carcinoma in many studies.[13,14] However, we did not include tumor size into our analysis because of the fact that in this study we only considered patients with stage IB1 so the tumor size was automatically limited to that of equal to or less than 4 centimeters. In addition, we personally feel that in clinical practice, clinical tumor size is a very subjective parameter with a wide range of interobserver variability especially when it is used to distinguish the size of 2 small tumors. Therefore, we only differentiated gross from occult tumor and examined their association with pelvic nodal metastasis. Occult primary tumors have been demonstrated to have a potential for pelvic nodal metastasis(24%). However, primary tumor description did not exhibit any correlation with pelvic nodal metastasis.

Preoperative chemotherapy did not have a significant impact on risk of pelvic nodal metastasis in our study. This finding has put in doubt the value of preoperative chemotherapy in preventing tumor progression or dissemination. Further specific, controlled studies are needed to address more clearly the role of preoperative chemotherapy in this particular setting.

There have been several published reports that confirmed similar prognosis of squamous cell carcinoma and adenocarcinoma for comparable stages.[15,16] There was no significant correlation between histologic type and pelvic nodal metastasis in our study. However, the number of the patients who had what seemed to be a high-risk cell type; such as adenosquamous and neuroendocrine carcinoma were too small to make a conclusion regarding an impact of these high-risk cell type on pelvic lymph node metastasis.

Vaginal margin was another factors that showed no significant association with pelvic nodal metastasis. One could assume from this finding that extension of the tumor to the vagina represents a different mechanism of tumor spread from dissemination of the tumor to the pelvic lymph node.

In summary, we have demonstrated the prevalence of pelvic lymph node metastasis and its predicting factors in the patients with stage IB1 carcinoma of the cervix. However, the number of the patients in this study was too small and follow-up information was still lacking. We realize that additional data on recurrence and survival from a follow-up study with greater number of the patients will provide more definite information about prognostic factors and more clinically applicable treatment guideline for this patient population.

References

1. Deerasamee S, Srivatanakul P. Cervix Uteri. In: Deerasamee S, Martin N, Sontipong S, Sriamporn S, Sriplung H, Srivatanakul P, editors. Cancer in Thailand, 1992-1994. Lyon: International Agency for Research on Cancer; 1999. p. 56-9.
2. Hacker NF. Cervical Cancer. In: Berek JS, Hacker NF, editors. Practical gynecologic oncology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2003. p. 345-406.