Extent of Lymphovascular Space Invasion and Risk of Pelvic Lymph Node Metastases in Stage IB1 Cervical Cancer

Anchalee Chandacham MD*, Kittipat Charoenkwan MD*,
Sumalee Siriaunkgul MD**, Jatupol Srisomboon MD*,
Prapaporn Suprasert MD*, Chailert Phongnarisorn MD*,
Chalong Cheewakraingkrai MD*, Sitthicha Siriaree MD*,
Charuwan Tantipalakorn MD*, Chumnan Kietpeerakool MD*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai*
*** Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai*

Objective: *To evaluate whether the extent of lymphovascular space invasion (LVSI) is a risk factor for pelvic lymph node metastases in stage IB1 cervical cancer.*
Material and Method: *The clinicopathological data of 397 patients with stage IB1 cervical cancer undergoing radical hysterectomy and pelvic lymphadenectomy (RHPL) at Chiang Mai University Hospital between January 1998 and December 2002 were analyzed. The histology, tumor grade, depth of stromal invasion, uterine corpus involvement, parametrial invasion and LVSI were analyzed for their association with pelvic node metastases. The extent of LVSI was classified as negative, minimal (< 10 LVSI / cervical specimen), and extensive (≥ 10 LVSI / cervical specimen).*
Results: *Of the 397 patients, 146 (36.8%) had tumors containing LVSI, 82 (20.7%) and 64 (16.1%) had minimal and extensive LVSI, respectively. Fifty nine (14.9%) patients had pelvic node metastases. Using multivariable analysis, LVSI ($p < 0.001$), depth of stromal invasion ($p < 0.001$), tumor grade ($p < 0.001$), and parametrial invasion ($p < 0.001$) were significant predictors of pelvic node metastases. The extent of LVSI either minimal or extensive degree significantly influenced pelvic node metastases.*
Conclusion: *The presence of LVSI especially extensive involvement was significantly associated with the risk of pelvic node metastases in stage IB1 cervical cancer.*

Keywords: *Lymphovascular space invasion, Pelvic node metastases, Cervical cancer*
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Patients with stage IB cervical cancer can be treated with either radical hysterectomy and pelvic lymphadenectomy (RHPL) or radiation therapy with equivalent survival outcome[1]. Pelvic node metastases appear to be the most important prognostic factor that affect recurrence and survival[2-4]. Various pathologic factors have been reported as being associated with a high risk of lymph node metastases in women undergoing RHPL for early stage cervical cancer, including tumor size, depth of cervical stromal invasion, parametrial involvement and presence of lymphovascular space invasion (LVSI)[3,5-7].

LVSI has been shown to be one of the independent predicting factors for pelvic node metastases in several studies[3,8-10]. In addition, the quantity or the extent rather than only the presence of LVSI has been reported to correlate significantly with a risk of lymph node metastases in women with early stage squamous carcinoma of the cervix[8]. The aim of this study was to evaluate the association between the presence and the extent of LVSI and the risk of lymph node metastases in stage IB1 cervical cancer patients who were treated with RHPL.

Correspondence to : Chandacham A, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. Phone: 0-1992-0845, E-mail: achainual@yahoo.com

Material and Method

The clinicopathological data of 418 patients with stage IB1 cervical cancer undergoing RHPL at Chiang Mai University Hospital between January 1998 and December 2002 were retrospectively reviewed after approval of the Research Ethics Committee. The patients' age, histological cell type, grade of carcinoma, depth of cervical stromal invasion, parametrial invasion, uterine corpus involvement, surgical margin status and LVSI were analyzed for association with lymph node metastases. Some patients received a cycle of preoperative cisplatin chemotherapy (75 mg/m^2) because a prolonged waiting period (more than 3 weeks) for available operating room in an attempt to minimize the risk of tumor progression and dissemination in the interim.

All the pathology materials were reviewed by our gynecologic pathologist (S.S.).The tumors were classified histologically as squamous cell carcinoma, mucinous adenocarcinoma, adenosquamous carcinoma, and others including neuroendocrine carcinoma, clear cell adenocarcinoma, mixed adenocarcinoma, and adenosarcoma. The depth of cervical stromal invasion was categorized by the proportion of cervical wall invaded as inner third, middle third and outer third. LVSI was defined as the presence of neoplastic cells inside an endothelium-lined space in the cervical stroma. Tumor invasion to the uterine corpus, adnexa, parametrium, vaginal margin and pelvic nodes were also determined.

Pathologic evaluation of LVSI was specially reviewed for its presence and extent in the total uterine cervix specimens. The extent of LVSI was classified into 3 categories based on the total number of LVSI identified in the cervical specimen. The 3 categories were: negative (no LVSI), minimal (< 10 LVSI), and extensive ($\leq$ 10 LVSI).

The Chi-square test was used for analysis of association between lymph node metastases and all categorical variables. The Fisher's exact test was used instead of the Chi-square test if more than 25% of the cells on the 2x2 table except histology, tumor grade and depth of invasion. For vaginal margin we included HSIL into the group of margin negative for cancer. The logistic model was applied in a multivariable analysis to determine the independent predicting factors for lymph node metastases. p value < 0.05 was considered statistically significant.

Results

During the study period, 418 women with stage IB1 cervical cancer underwent RHPL at Chiang Mai University Hospital. Twenty one patients were excluded from the study because of incomplete pathologic data due to some histologic slides were not available. The remaining 397 patients were eligible for analysis. The mean age of the 397 patients was 43.6 years with a range of 17 – 75 years. The clinicopathological data of these patients are shown in Table 1. There were 146 (36.8%) women whose tumors contained LVSI, 82 (20.7%) had minimal amount of LVSI and 64 (16.1%) had extensive LVSI. Thirty five (8.8%) patients had parametrial invasion identified in the hysterectomy specimens. Pelvic node metastases were detected in 59 (14.9%) patients. Involved vaginal margins were found in 25 (6.3%) patient, 13 (3.3%) were positive for high grade squamous intraepithelial lesions but we included them into the group of negative margin for cancer , and 12 (3.0%) had positive margin for invasive cancer. In 233 patients who had salpingo-oophorectomy performed, none had ovarian metastases. However the HSIL was found on a fallopian tube of 1 patient.

Tumor grade, depth of stromal invasion, uterine corpus involvement, parametrial invasion and the presence of LVSI were all significantly correlated with pelvic node metastases on univariable analysis as shown in Table 1. Multivariable (Table 2) analysis demonstrated that LVSI ($p < 0.001$), depth of stromal invasion ($p < 0.001$), and parametrial involvement ($p < 0.001$) were significant predictors of pelvic node metastases. Further evaluation of the association between the extent of LVSI and pelvic node metastases showed that patients whose tumors contained minimal amount of LVSI had significantly higher incidence of nodal metastases when compared with those whose tumors had no LVSI ($p < 0.001$). Among the tumors with LVSI, extensive involvement was significantly associated with pelvic node metastases compared with minimal LVSI ($p = 0.015$).

Discussion

This study showed that the presence of tumor emboli in the lymphovascular space was highly associated with pelvic node metastases. Patients with stage IB1 cervical cancer whose tumor contained extensive LVSI had up to 40% incidence of pelvic node metastases compared with the overall 15% of such incidence in these study subjects. These findings were in accordance with the study of Roman et.al, which evaluated the influence of quantity of LVSI on the risk of pelvic node metastases in women with early-stage cervical cancer. LVSI correlated significantly with the

Table 1. Frequency of pelvic nodal metastases by clinical and histologic characteristics: Univariable analyses (N = 397)

Characteristics	Number (%)	Pelvic lymph node metastases (%)		p-value	OR	95%CI
		Negative	Positive			
Age (years)						
≤ 50	324 (81.6)	275 (84.9)	49 (15.1)	0.757	0.89	0.42-1.85
> 50	73 (18.4)	63 (86.3)	10 (13.7)			
Preoperative Cisplatin						
No	327 (82.4)	278 (85.0)	49 (15.0)	0.874	0.94	0.45-1.96
Yes	70 (17.6)	60 (85.7)	10 (14.3)			
Histology						
Squamous CA	257 (64.7)	210 (81.7)	47 (18.3)	0.066		
Mucinous adeno CA	105 (26.5)	97 (92.4)	8 (7.6)			
Adenosquamous CA	23 (5.8)	20 (87.0)	3 (13.0)			
Others	12 (3.0)	11 (91.7)	1 (8.3)			
Tumor grade						
1	110 (27.7)	107 (97.3)	3 (2.7)	<0.001		
2	215 (54.2)	168 (78.1)	47 (21.9)			
3	72 (18.1)	63 (87.5)	9 (12.5)			
Depth of invasion						
Inner third	127 (32.0)	121 (95.3)	6 (4.7)	<0.001		
Middle third	114 (28.7)	104 (91.2)	10 (8.8)			
Outer third	156 (39.3)	113 (72.4)	43 (27.6)			
Parametrial involvement						
Negative	362 (91.2)	321 (88.7)	41 (11.3)	<0.001	8.29	3.73-18.49
Positive	35 (8.8)	17 (48.6)	18 (51.4)			
Corpus involvement						
Negative	367 (92.4)	319 (86.9)	48 (13.1)	0.002	3.85	1.60-9.16
Positive	30 (7.6)	19 (63.3)	11 (36.7)			
LVSI						
Negative	251 (63.2)	236 (94.0)	15 (6.0)	<0.001	6.97	3.48-13.41
Positive	146 (36.8)	102 (69.9)	44 (30.1)			
Minimal	82 (20.7)	64 (78.0)	18 (22.0)	<0.001	2.43	1.11-5.35
Extensive	64 (16.1)	38 (59.4)	26 (40.6)			
Vaginal margin						
Negative	372 (93.7)	320 (86.0)	52 (14.0)	0.86	3.00	0.73-11.49
Positive	12 (3.0)	8 (66.7)	4 (33.3)			
HSIL	13 (3.3)	10 (76.9)	3 (23.1)			

CA : carcinoma ; LVSI : lymphovascular space invasion , HSIL : High grade squamous intraepithelial lesion

Table 2. Multivariable analyses of predicting factors for pelvic lymph node metastases

Factors	OR	95% CI	p - value
Tumor grade	1.59	0.96-2.65	0.071
Depth of invasion	2.01	1.26-3.22	0.003
Parametrial involvement	3.09	1.36-7.06	0.007
Corpus involvement	1.91	0.77-4.76	0.165
LVSI	4.15	2.12-8.12	<0.001

OR ; Odd ratio, 95% CI ; 95% confidence interval

risk of nodal metastases[8]. The other significant predictors of nodal metastases in the report of Roman et al were depth of stromal invasion and parametrial involvement which were similar to the findings in our study. LVSI, depth of stromal invasion, and parametrial involvement were significant predictors of pelvic node metastases in both univariable and multivariable analyses in our study. Tumor size was also significantly associated with nodal metastases on univariable analyses in the report of Roman et al which included patients with stage IA2, IB1, IB2, and IIA squamous carcinoma of the cervix, while only patients with stage IB1 cervical cancer were analyzed for nodal metastases in the present study. A large surgicopathologic study of stage I squamous carcinoma of the cervix conducted by the GOG also noted that LVSI, depth of stromal invasion and tumor size were independent predictors of pelvic node metastases[5].

The frequency of LVSI in our study (36.8%) is lower than that reported in the literature which ranged from 55-77%[8,11,12]. This discrepancy may result from different stages of cervical cancer included in those studies because LVSI is highly correlated with the stage or size of tumor, the number of invasive foci and the depth of cervical stromal invasion. In addition, definite diagnosis of LVSI is still problematic. There are considerable interobserver variation in diagnosis of LVSI. Retraction artifacts is a well-known phenomenon that may be mistaken for LVSI. Implantation of surface epithelium due to surgical manipulation has also been found to cause confusion[13]. In our study, all the pathology slides were reviewed by one of our authors who is gynecologic pathologist. Specific and strict criteria were used to make a diagnosis of LVSI. However, the cut-off point between minimal (< 10 LVSI per cervical specimen) and extensive (≥ 10 LVSI per cervical specimen) was arbitrary. Notably, we have demonstrated that the mere presence of LVSI significantly increased the risk of pelvic node metastases regardless of the extent. As expected, the risk of pelvic node metastases appeared considerably higher in patients with extensive LVSI. Various criteria are used to evaluate the extent, density, or degree of LVSI, i.e. the maximum number of foci of LVSI present per 10 high-power fields [8] and the number of LVSI per high-power field in the worst affected slide[11].

Although LVSI correlates significantly with the risk of node metastases in women with early-stage cervical cancer, its influence on recurrence and survival remains inconclusive. Atasii et al reported 200 patients with early-stage cervical cancer undergoing radical hysterectomy and pelvic lymphadenectomy. LVSI was detected in 83% of all tumors, and in 77% of those with stage IB. Of the stages IB cancers, 21% had pelvic node metastases. The authors concluded that lymph node metastases and LVSI were the only significant factors on multivariate analysis for disease-free interval and overall survival[12].

In a GOG study, after multivariable analysis, the relative risk of recurrence was 1.7 ($p = 0.006$) in the presence of the LVSI[3]. In a retrospective case-control surgicopathological study of the clinical significant of LVSI and lymph node micrometastases in early-stage cervical cancer, the relative risk of recurrence was estimated to be 2.64 ($p < 0.01$)[14]. After univariable and multivariable analysis, two studies showed that LVSI was a significant risk factor of death in patients with early-stage cervical cancer[15,16]. In contrast, there seems to be from a literature review that only 3 in 25 articles identified LVSI as an independent risk factor for overall survival of patients with early-stage cervical cancer[9].

The limitation of this study is the retrospective by nature which makes the results more susceptible to recall bias especially on preoperative treatment detail. Also the data on tumor size not uniformly recorded. This makes the effect of tumor size uninterpretable in term of its significance as a predictor for nodal metastases. In addition, longer follow-up in needed to be able to determine the recurrence, survival outcome and prognostic factors of this study population. However, with the large number of patients in this study along with the extensive histopathologic review and interpretation, the information obtained will be valuable as a basic description of the behavior of early-stage cervical cancer and could be used preoperatively to determine from initial cervical biopsy data the chance of receiving adjuvant treatment such as post operative chemoradiation in patients undergoing primary radical surgery.

In conclusion, LVSI was a significant predictor of pelvic node metastases in patients with stage IB1 cervical cancer undergoing radical hysterectomy and pelvic lymphadenectomy.

References

1. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997; 350: 535-40.
2. Lee Y, Wang KL, Lin MH, Lin C, Wang K, Lan C, et al. Radical hysterectomy with pelvic lymph node dissection for treatment of cervical cancer : a clini-

cal review of 954 cases. Gynecol Oncol 1989; 32: 135-42.
3. Delgado G, Bundy B, Zaino R, Sevin B, Creasman WT, Major F. Prospective surgical-pathologic study of disease-free interval in patients with stage Ib squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. Gynecol Oncol 1990; 38: 352-7.
4. Monk BJ, Tewari K, Gamboa-Vijicic G, Burger RA, Manetta A, Berman ML. Does perioperative blood transfusion affect survival in patients with cervical cancer treated with radical hysterectomy? Obstet Gynecol 1995; 85: 343-8.
5. Delgado G, Bundy BN, Fowler WC, Stehman FB, SevinB-U, Creasman WT, et al. A prospective surgical pathologic study of stage I squamous carcinoma of cervix : a Gynecologic Oncology Group study. Gynecol Oncol 1989; 35: 314-20.
6. Zreik TG, Chambers JT, Chambers SK. Parametrial involvement, regardless of nodal status: a poor prognostic factor for cervical cancer. Obstet Gynecol 1996; 87: 741-6.
7. Barber H, Sommers S, Rotterdam H, Kwon T. Vascular invasion as a prognostic factor in stage IB cancer of the cervix. Obstet Gynecol 1978; 52: 343-8.
8. Roman LD, Felix JC, Mudersphch LI, Varkey T, Burnett AF, Qian D, et al. Influence of quantity of lymph-vascular space invasion on the risk of nodal metastases in women with early-stage squamous cancer of the cervix. Gynecol Oncol 1998; 68: 220-5.
9. Creasman WT, Kohler MF. Is lymph vascular space involvement an independent prognostic factor in early cervical cancer? Gynecol Oncol 2004; 92: 525-9.
10. Ho CM, Chien TY, Huong SH, Wu CJ, Shih By, Chang SC. Multivariate analysis of the prognostic factors and outcomes in early cervical cancer patients undergoing radical hysterectomy. Gynecol Oncol 2004; 93: 458-64.
11. Sykes P, Allen D, Cohen C, Scurry J, Yeo D. Does the density of lymphatic vascular space invasion affect the prognosis of stage IB and IIA node negative carcinoma of the cervix ? Int J Gynecol Cancer 2003; 13: 313-6.
12. Atasii T, Asku MF, Cetinkaya MP. Prognostic factors that affect survival after the treatment of the early stage cervical carcinoma. Int Surg 2000; 85: 147-51.
13. Ostor AG. Studies on 200 cases of early squamous cell carcinoma of the cervix. Int J Gynecol Pathol 1993; 12: 193-207.
14. Marchiole P, Buenerd A, Benchaib M, Nezhat K, Dargent D, Mathevet P. Clinical significance of lymphovascular space involvement and lymph node micrometastasese in early-stage cervical cancer: a retrospective case-control surgicopathological study. Gynecol Oncol 2005; 97: 727-32.
15. Morice P, Piovesan P, Rey A, Atallah D, Haie-Meder C, Pautier P, et al. Prognostic value of lymphovascular space invasion determined with hematoxylin-eosin staining in early stage cervical carcinoma: results of a multivariate analysis. Ann Oncol 2003; 14: 1511-7.
16. Hertel H, Kohler C, Michels W, Possover M, Tozzi R, Schneider A. Laparoscopic-assisted radical vaginal hysterectomy (LARVH): prospective evaluation of 200 patients with cervical cancer. Gynecol Oncol 2003; 90: 505-11.

ปริมาณการลุกลามหลอดเลือดหลอดน้ำเหลืองของปากมดลูกกับความเสี่ยงต่อมะเร็งแพร่กระจายไปที่ ต่อมน้ำเหลืองอุ้งเชิงกรานในมะเร็งปากมดลูกระยะ 1 บี 1

อัญชลี จันทร์แจ่ม, กิตติภัต เจริญขวัญ, สุมาลี ศิริอังกุล, จตุพล ศรีสมบูรณ์, ประภาพร สู่ประเสริฐ, ชัยเลิศ พงษ์นริศร, ฉลอง ชีวเกรียงไกร, สิทธิชา สิริอารีย์, จารุวรรณ ตันติพลากร, ชำนาญ เกียรติพีรกุล

จุดประสงค์: *เพื่อประเมินความสัมพันธ์ระหว่างปริมาณการลุกลามหลอดเลือดหลอดน้ำเหลืองกับการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองเชิงกรานในมะเร็งปากมดลูกระยะ 1 บี 1*

วัสดุและวิธีการ: *วิเคราะห์ข้อมูลทางคลินิกและทางพยาธิวิทยาของผู้ป่วยมะเร็งปากมดลูกระยะ 1 บี 1 จำนวน 397 ราย ที่มารับการผ่าตัดมดลูกออกแบบถอนรากถอนโคนและเลาะต่อมน้ำเหลืองเชิงกรานที่โรงพยาบาลมหาราชนครเชียงใหม่ในช่วง เดือนมกราคม 2541 ถึงเดือนธันวาคม 2545 วิเคราะห์ความสัมพันธ์ระหว่างชนิดและระดับของเซลล์มะเร็ง การลุกลามสโตรมา การลุกลามตัวมดลูก การลุกลามพารามีเทรียม และการลุกลามหลอดเลือดหลอดน้ำเหลืองกับการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองเชิงกราน ปริมาณการลุกลามหลอดเลือดหลอดน้ำเหลืองแบ่งออกเป็น 3 ระดับ คือ ผลลบ ผลบวกปริมาณเล็กน้อย (< 10 ต่อชิ้นเนื้อปากมดลูก) และปริมาณมาก (≥ 10 ต่อชิ้นเนื้อปากมดลูก)*

ผลการศึกษา: *ในผู้ป่วย 397 ราย ตรวจพบการลุกลามหลอดเลือดหลอดน้ำเหลืองในก้อนมะเร็งของผู้ป่วย 146 ราย (ร้อยละ 36.8) โดยมีปริมาณเล็กน้อย 82 ราย (ร้อยละ 20.7) และปริมาณมาก 64 ราย (ร้อยละ 16.1) มีมะเร็งแพร่กระจายไปที่ต่อมน้ำเหลืองเชิงกราน 59 ราย (ร้อยละ 14.9) จากการวิเคราะห์พหุตัวแปรพบว่า การลุกลามหลอดเลือดหลอดน้ำเหลือง (ค่าพี < 0.001) การลุกลามสโตรมา (ค่าพี < 0.001) ระดับเซลล์มะเร็ง (ค่าพี < 0.001) และการลุกลามพารามีเทรียม (ค่าพี < 0.001) เป็นปัจจัยสำคัญของมะเร็งแพร่กระจายไปที่ต่อมน้ำเหลืองเชิงกราน ปริมาณของการลุกลามหลอดเลือดหลอดน้ำเหลืองมีผลสำคัญต่อมะเร็งแพร่กระจายไปที่ต่อมน้ำเหลืองเชิงกราน*

สรุป*: การลุกลามของเซลล์มะเร็งเข้าไปในหลอดเลือดหลอดน้ำเหลืองโดยเฉพาะถ้ามีปริมาณมากมีความสัมพันธ์อย่างมีนัยสำคัญกับการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองเชิงกรานในมะเร็งปากมดลูกระยะ 1 บี 1*