RESEARCH COMMUNICATION

Lymphovascular Space Invasion as a Prognostic Determinant in Uterine Cancer

Chalong Cheewakriangkrai[1]*, Kannika Panggid[1], Sumalee Siriaungkul[2], Surapan Khunamornpong[2], Prapaporn Suprasert[1], Jatupol Srisomboon[1]

Abstract

The objective of this study was to evaluate the clinical significance of lymphovascular space invasion (LVSI) in patients with uterine cancer in terms of lymph node metastasis, recurrence and survival rate. A total of 190 patients with newly diagnosed uterine cancer who underwent total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy, peritoneal washing or ascitic fluid collection, and pelvic/paraaortic lymph node sampling at Chiang Mai University Hospital between January 1999 and December 2004 were evaluated. All medical records and histopathologic slides were retrospectively reviewed to determine the relationship between LVSI and clinicopathological characteristics. LVSI was present in 79 patients (42%) and significantly correlated with lymph node metastasis (p<0.001), BMI < 25 kg/m2 (p<0.001), advanced FIGO stage (p< 0.001), poor histologic grade (p<0.001), and deep uterine invasion (p<0.001). Patients with LVSI, when stratified by FIGO stage, also had a significant lower 5-year survival rate. For those who had disease recurrence, LVSI and histologic grade were found to be independent prognostic factors in a multivariate analysis. LVSI was one of the prognostic determinants for disease recurrence and associated with poor survival in patients with uterine cancer.

Key Words: Uterine cancer - lymphovascular space invasion - prognostic factor

Asian Pacific J Cancer Prev, **8**, 363-366

Introduction

In developed countries, uterine cancer is the most common female genital tract malignancy. It is one of the significant cancer-related causes of death in women worldwide (Jemal et al., 2006). A number of surgical and pathological parameters, including histological type, histological grade, stage, depth of myometrial invasion, vascular invasion, and cervical involvement have been found to have prognostic value in endometrial cancer (Prat, 2004). At present, surgery is the cornerstone of treatment for uterine cancer. The adjuvant radiotherapy is indicated to the patients who have high risk for local relapse of disease. However, approximately 10-20% of early-staged patients still have disease recurrence and finally die of endometrial cancer (Creutzberg et al., 2000). Therefore, other prognostic determinants need to be identified to provide more accurate information for patients who are at risk of disease recurrence or progression. Recent studies have shown that lymphovascular space involvement (LVSI) is one of the pathologic variables that influence the rate of pelvic lymph node metastases and prognosis of the patients with uterine cancer who had positive para-aortic node (Cohn et al., 2002; Watari et al., 2005).

The purpose of this study was to evaluate the clinical significance of LVSI on lymph node metastasis, recurrence and survival in patients with uterine cancer.

Materials and Methods

A total of 190 patients with newly diagnosed uterine cancer were treated at Chiang Mai University Hospital between January 1999 and December 2004. All patients underwent surgical staging procedures including total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy, peritoneal washing or ascitic fluid collection, and pelvic/paraaortic lymph node sampling. After approval of the Research Ethics Committee, the medical records were retrospectively reviewed for clinical data including age, surgicopathological stage according to 1988 FIGO classification, and disease status of recurrence or metastases. All histopathologic slides were reviewed by two gynecologic pathologists (S.S., S.K.) of our institution for tumor grade, histological type, presence or absence of LVSI without knowledge of the clinical outcome. Histological subtypes were based on WHO classification. On Haematoxylin and Eosin (H&E)-stained sections, the

[1]Department of Obstetrics and Gynecology, [2]Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. For Correspondence: E mail: ccheewak@mail.med.cmu.ac.th Fax: +66 53 946112

presence of LVSI was considered positive when tumor emboli were noted within a space obviously lined by endothelial cells.

Statistical analysis

The correlation between the clinicopathological variables and the presence of LVSI were made with χ^2 or Fisher's exact test when appropriate. Multivariate analysis was performed using a logistic regression model. Cox regression analysis was used for time to event analyses. The Kaplan-Meier method was used for survival analyses. The significance of the survival difference was examined by the log-rank test. Data were analysed using the SPSS for Windows (version 11.5) software package.

Results

The median age of the patients was 55 years (22-75 years). The median body mass index (BMI) was 23.6 kg/m2 (14.2-45.5 kg/m^2). The clinicopathological characteristics and the presence of LVSI were described in Table 1. Tumor cell type was endometrioid in 170 (89.5%) cases, clear cell in 4 (2%), papillary serous in 3 (2%), sarcoma in 4 (2%), endometrial stromal sarcoma (ESS) in 2 (1%), carcinosarcoma in 5 (3%), and mucinous in 1 (0.5%). The tumor was limited to endometrium in 17 (8.9%) cases, inner half of the myometrium in 77 (40.5%), and outer half of the myometrium in 90 (47.3%). The FIGO (1988) stages of the patients were as follows: 20 (10.5%) Ia, 46 (24.2%) Ib, 30 (15.8%) Ic, 6 (3.2%) IIa, 14 (7.4%) IIb, 19 (10%) IIIa, 3 (1.6%) IIIb, 41 (21.6%) IIIc, and 11 (5.8%) IVb. LVSI was identified in 79 of 188 cases (42%). Lymph node metastasis was found in 33 (43.4%) patients who had LVSI compared to 9 (8.7%) of those without LVSI ($p<0.001$). Seventy-nine percent of patients with positive nodes also had LVSI. The clinicopathological variables that significantly correlated with LVSI were as follows: lymph node metastasis ($p<0.001$), BMI < 25 kg/m^2 ($p<0.001$), FIGO stage III-IV ($p< 0.001$), high histologic grade ($p<0.001$), and myometrial invasion greater than half ($p<0.001$). In multivariate analysis, only BMI ($p=0.012$) and depth of myometrial invasion ($p=0.005$) were independently and significantly correlated with LVSI (Table 2). The median follow-up was 35.3 months (range 1.9-89.5 months) and 40 patients died at analysis time. Histologic grade and LVSI were found to be independent prognostic variables for prediction of disease recurrence by multivariate analysis ($p=0.002$ and $p=0.019$, respectively), as described in Table 3. The recurrence of disease was found in 5 (5%) cases of the patients without LVSI compare with 19 (30%) of those with LVSI ($p<0.001$). Seventy-nine percent of the patients who had disease recurrence were positive for LVSI. The estimated 5-year survival rates of the patients with and without LVSI were 62.6% (95%CI= 48 to 77%) and 80.2% (95%CI = 69 to 91%), respectively ($p=0.0014$)(Fig.1). For FIGO stage I-II, the estimated 5-year survival rates of patients with and without LVSI were 72.5% (95%CI= 52 to 93%) and 79.5% (95%CI = 67 to 92%), respectively, compared with 57% (95%CI= 39 to 76%) and 88% (95%CI = 72 to 104%) of those who had FIGO stage III-IV with and without LVSI, respectively ($p=0.0116$)(Fig.2 and Fig.3).

Table 1. Correlation of Clinicopathologic Characteristics of 190 Patients with Surgically Staged Uterine Cancer and the Presence of LVSI

		No. of pts	No. with LVSI (%)	P value
Age	≤ 50	56	24 (43)	0.880
	> 50	134	55 (41)	
BMI (kg/m2)	< 25	70	40 (57)	< 0.0001
	≥ 25	55	14 (25)	
	Not available	65		
FIGO stage	I-II	116	32 (28)	< 0.0001
	III-IV	74	47 (64)	
Histologic grade	1	86	22(26)	< 0.0001
	2	49	26(53)	
	3	36	23(64)	
	Not available	19		
Depth of myometrial invasion	≤ 1/2	94	22(23)	< 0.0001
	> 1/2	88	56(64)	
	Not available	8		
Cell type	Endometrioid	170	69(41)	0.334
	Others	19	10(53)	
	Not available	1		
Peritoneal cytology	Negative	151	55(36)	0.132
	Positive	12	7(58)	
	Not available	27		
Lymph node involvement	Negative	137	44(32)	< 0.0001
	Positive	42	33(79)	
	Not available	11		

Table 2. Logistic Regression Analysis to Determine the Independent Factors Associated with the Presence of LVSI

Factors	Odds ratio	95% CI	P value
BMI (kg/m2)	3.68	(1.34-10.10)	0.012
FIGO stage	1.55	(0.42-5.69)	0.511
Histologic grade	2.97	(0.89-9.94)	0.077
Depth of myometrial invasion	4.39	(1.56-12.32)	0.005
Lymph node involvement	0.39	(0.08-1.95)	0.249

Table 3. Univariate and Multivariate Logistic Regression Analysis of All Prognostic Variables for Prediction of Disease Recurrence in Uterine Cancer Patients

Prognostic variables	Univariate P value	Multivariate Odds ratio	95%CI	P value
BMI (kg/m2)	0.122	-	-	
FIGO stage	0.002	2.31	(0.42-12.7)	0.337
Histologic grade	< 0.0001	9.32	(2.22-39.2)	0.002
LVSI	< 0.0001	0.15	(0.03-0.73)	0.019
Depth of myometrial invasion	0.048	0.50	(0.10-2.51)	0.395
Cell type	0.010	1.84	(0.18-19.0)	0.607
Cervical involvement	0.005	2.39	(0.61-9.46)	0.214
Lymph node involvement	0.048	1.80	(0.29-11.2)	0.529
Peritoneal cytology	0.088	-	-	

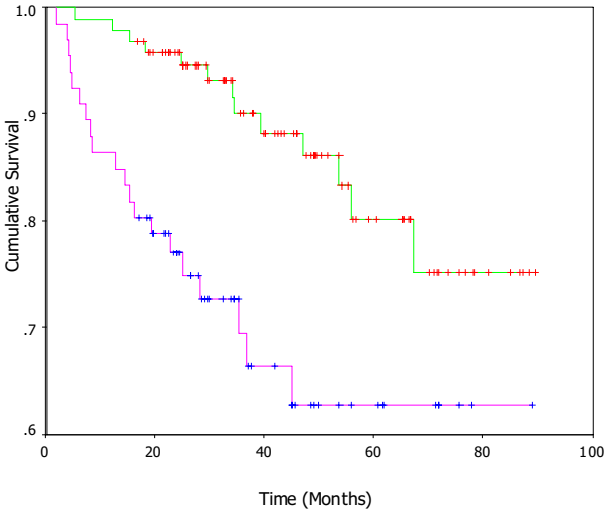

Figure1. Comparison of Kaplan-Meier Survival Curves of Patients with (lower bar) and without (upper bar) LVSI (log rank test, P= 0.0014)

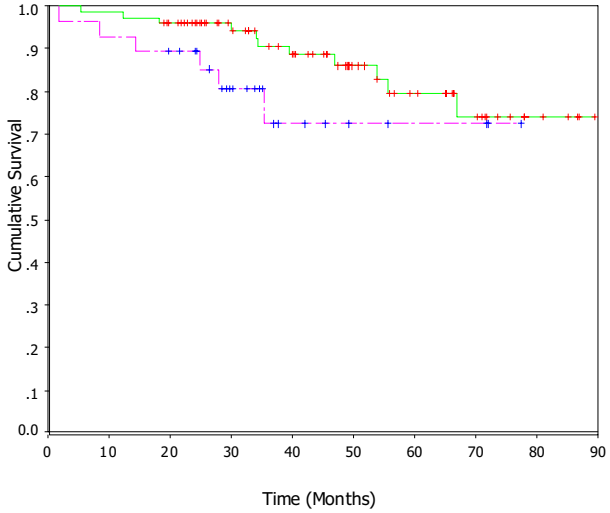

Figure2. Comparison of Kaplan-Meier Survival Curves in FIGO stage I-II between Patients with (lower bar) and without (upper bar) LVSI (log rank test, P= 0.0116)

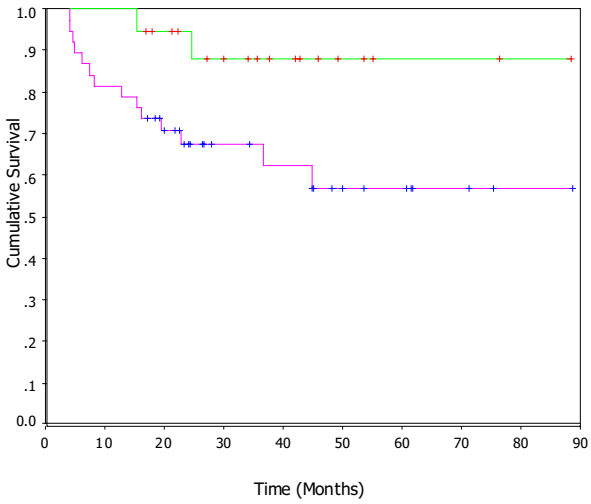

Figure 3. Comparison of Kaplan-Meier Survival Curves in FIGO Stage III-IV between Patients with (lower bar) and without (upper bar) LVSI (log-rank test, P= 0.0116)

Discussion

In this study we found that LVSI was present in 42% of uterine cancer patients compared to 25.6% in the report of Briet et al (2005). The estimated 5-year survival rates of the patients with and without LVSI were 62.6% and 80.2%, respectively. This findings closely resembled to the report of Abeler et al (1992) which revealed an 64.5% 5-year survival rate for endometrial carcinoma patients with demonstrable vascular invasion compared with 83.5% for those in whom vascular invasion was absent.

In our study, the prognostic significance of LVSI was more obvious when stratified by FIGO stage. The patients who had advanced disease (FIGO stage III-IV) with LVSI positive tumor had a poorer estimated 5-year survival rate (57% vs.88%). Lymph node metastasis was found in 43.4% of cases with LVSI positive compared to only 8.7% of those without LVSI ($p<0.001$). Watari et al.(2005) found that LVSI and number of positive para-aortic nodes were independent prognostic factors for survival for stage IIIc endometrial cancer patients.

In multivariate analysis, we found that BMI less than 25 kg/m^2 and deep myometrial invasion were independently and significantly correlated with LVSI. This could reflect the aggressiveness of biologic behavior of tumor. As for type II endometrial cancer, the lesion is noted in a woman who is often older and thinner characterized by the absence of estrogen-related risk factors, nonendometrioid histologies, no concurrent hyperplasia, high grade, and poor prognosis. Such tumor is aggressive and has worse prognosis than type I which is estrogen dependent (Kurman et al.,1994; Carter et al., 2006). LVSI has been found to be an important predictive factor of recurrent disease (Briet et al.,2005; Alexander-Sefre et al.,2004).

In our study, we found that LVSI and histologic grade were significant prognostic variables for prediction of disease recurrence in multivariate analysis. Although the extents of lymph node dissection in surgically staged endometrial cancer patients seem to vary between institutions, LVSI could be one of a good predictors for disease recurrence. LVSI was significantly associated with pelvic lymph node metastasis in several studies (Cohn et al., 2002; Mariani et al., 2002; Tsuruchi et al.,1995; Hachisuga et al.,1999). Our data support the idea that pelvic lymph node metastasis by itself is a strong indication for treatment with adjuvant pelvic radiation therapy giving no additional contribution in clinical decision making by the presence of LVSI. Contrary to the group with negative nodes, LVSI was an independent indicator for relapse of disease. Therefore, LVSI might be considered a clinically important risk factor in surgically staged patients with negative nodes (Briet et al., 2005).

In conclusion, the presence of LVSI remains one of the prognostic determinants for disease recurrence and associates with poor survival in patients with uterine cancer. Although it has not been included in the FIGO staging criteria, patients with LVSI positive tumors should be followed up closely due to their clinical significance.

References

Abeler VM, Kjorstad KE, Berle E (1992). Carcinoma of the endometrium in Norway: a histopathological and prognostic survey of a total population. *Int J Gynecol Cancer*, **2**, 9-22.

Alexander-Sefre F, Singh N, Ayhan A, et al (2004). Clinical value of immunohistochemically detected lymphovascular invasion in endometrioid endometrial cancer. *Gynecol Oncol*, **92**, 653-9.

Briet JM, Hollema H, Reesink N, et al (2005). Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. *Gynecol Oncol*, **96**, 799-804.

Carter J, Pather S (2006). An overview of uterine cancer and its management. *Expert Rev Anticancer Ther*, **6**, 33-42.

Cohn DE, Horowitz NS, Mutch DG, et al (2002). Should the presence of lymphvascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? *Gynecol Oncol*, **87**, 243-6.

Creutzberg CL, van Putten WL, Koper PC, et al (2000). Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet*, **355**, 1404-11.

Hachisuga T, Kaku T, Fukuda K, et al (1999). The grading of lymphovascular space invasion in endometrial carcinoma. *Cancer*, **86**, 2090-7.

Jemal A, Siegel R, Ward E, et al (2006). Cancer statistics, 2006. *CA Cancer J Clin*, **56**, 106-30.

Kurman RJ, Zaino RJ, Norris HJ (1994). Endometrial carcinoma. In: Kurman RJ, ed: Blaustein's Pathology of the Female Genital Tract. 4th ed. New York: Springer- Verlag, pp 439-86.

Mariani A, Webb MJ, Keeney GL,et al (2002). Assessment of prognostic factors in stage IIIA endometrial cancer. *Gynecol Oncol*, **86**, 38-44.

Mariani A, Webb MJ, Keeney GL, et al (2002). Predictors of lymphatic failure in endometrial cancer. *Gynecol Oncol*, **84**, 437-42.

Prat J (2004). Prognostic parameters of endometrial carcinoma. *Hum Pathol*, **35**, 649-62.

Tsuruchi N, Kaku T, Kamura T, et al (1995). The prognostic significance of lymphovascular space invasion in endometrial cancer when conventional hemotoxylin and eosin staining is compared to immunohistochemical staining. *Gynecol Oncol*, **57**, 307-12.

Watari H, Todo Y, Takeda M, et al (2005). Lymph-vascular space invasion and number of positive para-aortic node groups predict survival in node-positive patients with endometrial cancer. *Gynecol Oncol*, **96**, 651-7.