THE PROGNOSTIC SIGNIFICANCE OF LYMPHOVASCULAR SPACE INVOLVEMENT IN PATIENTS WITH UTERINE-CONFINED ENDOMETRIOID ENDOMETRIAL CANCER

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Objective

We evaluated whether or not lymphovascular space involvement (LVSI) is a risk factor for the relapse of disease in patients with uterine-confined endometrioid endometrial cancer.

Methods

A retrospective chart review was carried out of 165 patients with uterine confined endometrioid-type endometrial cancer after initial treatments including total abdominal or laparoscopic hysterectomy, and bilateral salpingo-oophorectomy, with or without lymphadenectomy, peritoneal washing between 1998 and 2010. The patients with positive peritoneal cytology were not excluded.

Results

The median age was 52 years (range, 26 to 81 years) with a median follow-up of 46 months (range, 1 to 144 months). One hundred twenty-four patients (75.2%) received no adjuvant treatment, 41 patients (24.8%) received adjuvant treatment including platinum-based chemotherapy, radiation therapy, and chemoradiation. LVSI was present in 29 patients (17.6%). Eight patients (4.8%) developed recurrences. Using univariate analysis, age > 50 years, the tumor grade, and LVSI were found to relate to recurrence-free survival ($P < 0.05$). LVSI was associated with other prognostic factors such as old age, a higher tumor grade, and deeper myometrial invasion. But multivariate analysis showed no significance. LVSI was not an independent factor to predict recurrence ($P = 0.093$).

Conclusion

LVSI was associated with an increased likelihood of recurrence via univariate analysis in patients with uterine-confined endometrioid endometrial cancer. Multivariate analysis showed no statistical significance. The presence of LVSI seems to have no effect, in and of itself, to alter the treatment plan or to predict the prognosis.

Keywords: Endometrial cancer; lymphatic vessels; Recurrence

Endometrial cancer is the most common gynecological malignancy in the Western world. For patients with a uterine-confined early-stage endometrial carcinoma, the influence of prognostic factors such as patient age, the tumor grade, and the depth of invasion are well-recognized [1]. The presence of lymphovascular space involvement (LVSI) has also been shown to be an independent prognostic factor in several studies, yet its association with recurrence was not shown on the multivariate analysis in other studies [2]. LVSI was associated with compromised survival in patients who are at clinical stages I and II, but not in patients at surgical stages I or II [3].

LVSI has been described as a predictor for nodal metastases or

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poor survival for several types of gynecologic cancers [4-7]. Once LVSI has occurred, the tumor cells theoretically have the potential to metastasize to regional lymph nodes or further. Thus, LVSI has been noted as an important prognostic factor that is significantly correlated with nodal metastases, tumor recurrence, and patient survival [1,2,8]. The findings of previous studies have been contradictory with respect to the significance of LVSI as an independent prognostic factor. In this study, we focused on patients with uterine-confined endometrioid endometrial cancer. The objective of our study was to evaluate the prognostic significance of lymphovascular space involvement in patients with uterine-confined endometrioid endometrial cancer.

Materials and Methods

We retrospectively reviewed the pathologic and clinical data on all the patients who were diagnosed with endometrial cancer between January 1998 and June 2010 at the Department of Obstetrics and Gynecology, Gil Hospital, Gachon University of Medicine and Science. All the subjects underwent a total abdominal hysterectomy or laparoscopic hysterectomy, bilateral salpingo-oophorectomy (BSO), peritoneal washing cytology, and with/without lymphadenectomy. The patients with uterine-confined endometrial cancer were included. The histology of all the patients was the endometrioid type and all other histologic subtypes were excluded. The patients with positive peritoneal cytology were not excluded. Clinic-pathologic data such as age, tumor grade, myometrial invasion depth, presence of LVSI, presence of hormone receptor, cervical involvement, and peritoneal cytology were reviewed. LVSI was defined as the presence of viable tumor cells in the endothelial-lined channels, that is, either lymphatics or capillaries, outside the tumor mass. The follow-up consisted of three months for first three years, six months for next two years, and then yearly reviews. The patients were routinely followed for at least 5 years.

Statistical analysis of the data was performed using chi-square test and Fisher's exact test in univariate analysis. Cox proportional hazard model was used in multivariate analysis. The odds ratios and 95% confidence intervals were calculated. *P*-values less than 0.05 were considered significant. Statistics were analyzed using SPSS ver. 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

One hundred sixty-five patients fulfilled the study criteria. All the

Table 1. Clinical characteristics of patients (n = 165)

Variables	
Median age, years (range)	52 (26–81)
Hysterectomy BSO	46 (27.9)
Hysterectomy BSO PLND	95 (57.6)
Hysterectomy BSO PLND PALND	24 (14.5)
Adjuvant treatment	
None	124 (75.2)
Radiation therapy	23 (13.9)
Chemotherapy	12 (7.3)
Platinum-based chemoradiation	6 (3.6)
Mean retrieved pelvic lymph nodes (range)	19.9 ± 16.6 (4–73)
Mean retrieved paraaortic lymph nodes (range)	1.4 ± 4.7 (2–32)

Values are presented as number (%).

BSO, bilateral salpingo-oophorectomy; PLND, pelvic lymph node dissection; PALND, para-aortic lymph node dissection.

patients underwent a hysterectomy with BSO surgical treatment. Pelvic lymph node dissection was performed on ninety-five patients and both pelvic and para-aortic lymph node dissection was performed on twenty-four patients. The mean number of removed pelvic lymph nodes was 19.9 ± 16.6 (range, 4 to 73) and the mean number of removed para-aortic lymph nodes was 1.4 ± 4.7 (range, 2 to 32) (Table 1). Twenty-nine (17.6%) patients were found to have LVSI. All the cases were negative for lymph node involvement. Adjuvant treatment was administered to the patients: 23 patients received radiation therapy, six received chemoradiotherapy, and 12 received chemotherapy. Eight patients (4.8%) developed recurrences. The median time to recurrence was 27 months. LVSI was significantly correlated with an increasing depth of myometrial invasion, a higher tumor grade, and age > 50 years ($P < 0.05$) (Table 2). Five-year progression-free survival was significantly associated with age, a higher tumor grade, and LVSI by univariate analysis (Table 3, Fig. 1). But the pathologic factors were not significant in multivariate analysis (Table 4). The median follow-up of the overall patients was 46 months (range, 1 to 144 months). The five-year progression free-survival rate of all patients was 78%. Recurrence occurred in five patients who have LVSI and in three patients who did not have LVSI (Table 5) and there was no death of disease in our patients.

Discussion

LVSI is associated with lymph node metastasis and is evaluated ac-

Table 2. Clinicopathologic factors associated with LVSI (n=165)

Variables	LVSI		P-value
	Negative	Positive	
Age (yr)			
≤50	69 (41.8)	5 (3.0)	0.001
>50	67 (40.6)	24 (14.6)	
Grade			
1	109 (66.1)	15 (9.1)	0.001
2, 3	27 (16.3)	14 (8.5)	
Myometrial invasion			
≤1/2	119 (72.1)	16 (9.7)	<0.001
>1/2	17 (10.3)	13 (7.9)	
Cervical involvement			
Absent	119 (72.1)	25 (15.2)	0.767
Present	17 (10.3)	4 (2.4)	
Peritoneal cytology			
Negative	126 (78.3)	28 (17.4)	0.591
Positive	6 (3.7)	1 (0.6)	
NA	4		
Hormone receptor status			
Negative	11 (10.5)	4 (3.8)	0.28
Positive	76 (72.4)	14 (13.3)	
NA	60		

LVSI, lymphovascular involvement; NA, not available.

Fig. 1. Survival curve by lymphovascular space involvement status.

cording to the tumor grade and depth of invasion in patients with endometrial cancer. Previous studies showed that the tumor grade and the depth of invasion [9,10], as well as LVSI [1,9], are useful predictors for the risk of lymph node metastasis. Some investigators have suggested that LVSI is associated with a risk of vaginal relapse or lymph node metastasis, but LVSI is not associated with distant metastasis in patients with endometrial cancer [2,11-13]. The presence of LVSI cannot be determined before hysterectomy. LVSI is not included among the prognostic indicators of the current Federation of Obstetrics and Gynecology (FIGO) surgical staging classification.

The incidence of LVSI in patients with endometrial cancer is reported to be about 25% when all the stages and tumor grades are included [11,14]. In previous studies, the incidence of LVSI in clinical stage I was 14%-16% [8,9,15] and it was 15.5%-32.6% in clinical stages I and II [3,16]. The incidence of LVSI was 4.3% in surgical stages I and II [17] and it was 24.6% to 34.4% when all the surgical stages were included [18,19]. In the present study, LVSI was positive in 29 patients with uterine-confined endometri-

Table 3. Factors associated with recurrence-free survival in univariate analysis (n=165)

Prognostic factors	n (%)	Recurrence-free survival	
		5-year rate (%)	P-value
Age (yr)			
≤50	74 (44.8)	100	0.028
>50	91 (55.2)	91.7	
Grade			
1	124 (75.2)	97.0	0.008
2, 3	41 (24.8)	89.7	
Myometrial invasion			
≤1/2	135 (81.8)	99.2	0.076
>1/2	30 (18.2)	87.5	
Cervical involvement			
Absent	144 (87.3)	94.7	0.923
Present	21 (12.7)	100	
Peritoneal cytology			
Negative	154 (95.7)	96.2	0.787
Positive	7 (4.3)	100	
Hormone receptor status			
Negative	15 (14.3)	82.5	0.135
Positive	90 (85.7)	95.9	
Lymphovascular space invasion			
Negative	136 (82.4)	99.0	<0.001
Positive	29 (17.6)	78.8	

Table 4. Factors associated with recurrence-free survival in multivariate analysis (n=165)

Variables	Recurrence-free survival		
	OR	95% CI	P-value
Grade 2, 3	4.124	0.78 - 21.582	0.093
LVSI presence	4.715	0.771 - 28.822	0.093
Age>50 yr	4.873	0.454 - 82.260	0.191
Myometrial invasion>1/2	0.683	0.107 - 4.375	0.683

OR, odds ratios; CI, confidence intervals; LVSI, lymphovascular involvement.

Table 5. Details of patients with recurrence

Patients	Age (yr)	Myometrial invasion	Grade	LVSI	Time to recurrence (mo)	Adjuvant treatment	Recur site
1	80	>1/2	1	-	27	None	Colon, mediastinal lymph node
2	51	<1/2	1	+	60	None	Paraortic lymph node
3	39	<1/2	3	-	67	CCRT	Lung
4	56	>1/2	2	+	15	None	Paraortic lymph node
5	56	<1/2	1	-	106	CCRT	Vagina, distal rectum, bladder, mesorectal tissue
6	57	<1/2	3	+	12	None	Liver, paraortic lymph node
7	74	>1/2	3	+	113	None	Pelvis, peritoneal seeding
8	56	>1/2	2	+	27	Chemotherapy	Vagina

LVSI, lymphovascular involvement; CCRT, concurrent chemoradiation.

oid endometrial cancer, and this was similar to the results of previous studies.

The influence of LVSI on the prognosis of patients with an early stage of endometrial cancer is not clear. LVSI was an independent factor for predicting vaginal relapse in patients with low-risk stage I disease in one study [15]. Mariani et al. [20] suggested that LVSI is strong indicator to predict extra-abdominal failure and survival in patients with positive peritoneal cytologic findings. In another study that included only patients with stage I disease of the endometrioid type, LVSI was not useful to predict vaginal relapse [21]. Another study that included stage I endometrial cancer patients reported that only deep myometrial invasion was a predictor of distant metastasis [2]. In the present study, a higher tumor grade, age > 50 years, and the presence of LVSI was associated with recurrence on univariate analysis ($P < 0.05$). However, the interaction between each histopathologic parameter also was strong and the relative importance of each histopathologic parameter as independent prognostic factors should be evaluated in a future study. Moreover, there was no significant histopathologic parameter on multivariate analysis. Higher grade and deeper myometrial invasion was not associated with prognosis in multivariate analysis in the present study. And myometrial invasion more than 1/2 can be change stages, however, deeper myometrial invasion had no significance multivariate analysis in this study. Therefore, it is uncertain that LVSI has independent prognostic significance or LVSI has an interaction with other prognostic factors.

LVSI is a certain step for tumor progression to metastasis, and it may be an indicator of the possibility of metastasis. Vascular invasion by tumor cells was an important prognostic factor in other studies for several other cancers [1,2,8] and the importance of LVSI as a predictor for lymph node metastasis was proven [1,9]. The recurrence rate in our present study was 4.8% (8 patients). The median time to recurrence was 27 months (range, 12 to 106 months). Five patients who were positive for LVSI developed recurrence at the para-aortic lymph nodes, the liver, and the vagina, and peritoneal seeding also occurred. Three patients who were negative for LVSI showed metastases to various pattern including both locoregional and distant metastases such as colon, mediastinal lymph node, lung metastasis, vagina, distal rectum, bladder, and mesorectal tissue. Three of five patients who were positive for LVSI showed paraaortic lymph node metastasis. However, the sites of recurrence showed more cases of distant metastasis rather than locoregional relapse in both groups. Therefore, each risk factor would interact rather than LVSI being a single prognostic factor. Given the association of LVSI with recurrence, postoperative adju-

vant radiotherapy for patients who are positive for LVSI with early stage endometrial cancer is questionable. There is no consensus about adjuvant therapy for treating early stage endometrial cancers with or without LVSI. Some investigators have suggested that treatment should be decided after considering other prognostic factors, because external beam pelvic radiotherapy did not have an impact on vaginal control or survival [22]. A recent meta-analysis shows that external beam pelvic radiotherapy after hysterectomy for low-risk disease increased the odds of death [23]. Therefore, the patients in this study were treated according to each clinician's decision with consideration of other prognostic pathologic variables than just LVSI.

We believe that the present study is valuable because of the relatively uniform data set, because the cases were limited to uterine-confined disease and endometrioid cytology. The limitations of this study are the small number of patients and the inconsistent surgical staging, and the fact that lymph node dissection was not done in some patients. Many patients did not undergo para-aortic lymph node dissection. Because the number of dissected lymph nodes was variable, differences of surgical skill should also be considered. Further, the modality of postoperative adjuvant treatment was not consistent.

In conclusion, LVSI was associated with other prognostic factors such as myometrial invasion, a higher tumor grade, and old age in the patients with uterine-confined endometrioid endometrial cancer. Univariate analysis showed that LVSI was associated with recurrence, but there was no statistical significance found with multivariate analysis. The precise relationship between LVSI and the outcome could have been determined if we had a larger patient population. The treatment modality for patients with uterine-confined endometrioid endometrial cancer should be determined after considering other prognostic factors along with LVSI, because LVSI influences survival by its interaction with other prognostic factors.

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자궁에 국한된 자궁내막암에서 림프혈관 침윤의 예후인자로서의 중요성

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목적

자궁에 국한된 자궁내막모양형의 자궁내막암 환자에서 림프혈관 침윤이 재발의 위험인자인지를 조사하였다.

연구방법

1998년부터 2010년까지 전자궁절제술, 양측 난소난관절제술, 복강세척 세포검사 및 림프절절제술 또는 자궁절제술, 양측 난소난관절제술, 복강세척 세포검사를 시행받은 자궁에 국한된 자궁내막모양형의 자궁내막암 환자 165명의 의무기록을 후향적으로 조사하였다. 복강세척 세포검사가 양성으로 나온 환자를 제외하지는 않았다.

결과

나이의 중간값은 52세였다(범위, 26-81세). 평균 추적기간은 46개월이었다(범위, 1-144개월). 124명(75.2%)은 보조적 치료를 받지 않았고, 41명(24.8%)은 항암화학요법, 방사선 치료, 동시 항암방사선요법의 치료를 받았다. 림프혈관 침윤은 29명(17.6%)의 환자에서 있었다. 8명(4.8%)에서 재발이 발생하였다. 단인자 분석상 50세 이상의 연령, 종양의 분화도, 림프혈관 침윤이 재발없는 생존과 연관이 있었다($P < 0.05$). 림프혈관 침윤은 종양의 분화도, 고령, 자궁근층 침윤과 같은 다른 예후 인자들과도 상호연관이 있었다. 그러나 다인자 분석에서는 통계적 의미를 보이지 않았다. 림프혈관 침윤은 재발을 예측하는 독립적 인자가 아니었다($P=0.093$).

결론

림프혈관 침윤은 자궁에 국한된 자궁내막모양형의 자궁내막암 환자에서 단인자 분석상 재발과 연관이 있는것으로 나타났으나 다인자 분석에서는 통계적 의미가 없었다. 림프혈관 침윤 그 자체로는 예후에 영향이 없는 것으로 보이며, 단독으로 치료계획을 정하거나 예후를 예측하지는 못할 것으로 생각된다.

중심단어: 자궁내막암, 림프혈관 침윤, 재발