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Lymphovascular space invasion, a prognostic marker for disease recurrence in patients with early endometrioid endometrial cancer

Inwazja przestrzeni limfatycznej jako wskaźnik prognostyczny wznowy u chorych na endometrioidalnego raka trzonu macicy we wczesnym stopniu zaawansowania

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Abstract

Aim of the study: To evaluate the clinicopathologic factors of early International Federation of Gynecology and Obstetrics (FIGO) stage I–II endometrioid endometrial cancer in a single institution and to emphasize factors contributing to recurrence. **Material and methods:** We selected several clinicopathologic factors including age, height, body weight, body mass index, cancer antigen-125, FIGO tumor grade, myometrial invasion, lymphovascular space invasion, estrogen receptor/progesterone receptor status, and adjuvant radiation therapy or systemic chemotherapy. Univariate and multivariate Cox proportional hazard model and Kaplan–Meier estimates were used for analyzing all clinicopathologic factors related to the risk of disease recurrence. **Results:** The median age was 55.05 years, and the median follow-up time was 35 months. Eleven patients (11%) showed disease recurrence, 3 patients – distant, and 8 patients – local metastasis. In univariate analysis, tumor grade ($P = 0.0045$) and lymphovascular space invasion ($P = 0.0374$) were associated with disease recurrence. Multivariate analysis demonstrated an association between any type of recurrence and lymphovascular space invasion (hazard ratio, HR, 6.308; 95% confidence interval, CI 1.851–11.484). **Conclusions:** Our study showed that the presence of lymphovascular space invasion is an important factor for disease recurrence in early endometrial cancer. Therefore, adjuvant systemic chemotherapy may be considered in patients with early endometrial cancer with lymphovascular space invasion.

Keywords: endometrial cancer, recurrence, lymphovascular space invasion

Streszczenie

Celem pracy była ocena kliniczno-patologicznych cech endometrioidalnego raka błony śluzowej trzonu macicy w stadium I–II według klasyfikacji Międzynarodowej Federacji Ginekologii i Położnictwa (International Federation of Gynecology and Obstetrics, FIGO) w jednym ośrodku oraz podkreślenie czynników wpływających na wznowę choroby. **Materiał i metody:** W pracy wybrano kilka kliniczno-patologicznych czynników, takich jak wiek, wzrost, masa ciała, wskaźnik masy ciała, wartość antygenu nowotworowego CA-125, stopień w klasyfikacji FIGO, inwazja myometrium, inwazja przestrzeni limfatycznej, status receptorów estrogenowych/progesteronowych, a także radioterapia lub chemioterapia adiuwantowa. W celu oceny wszystkich cech kliniczno-patologicznych związanych z ryzykiem nawrotu choroby zastosowano jedno- i wieloczynnikowy model proporcjonalnego ryzyka Coxa oraz analizę metodą Kaplana–Meiera. **Wyniki:** Mediana wieku wynosiła 55,05 roku, a mediana czasu obserwacji – 35 miesięcy. Nawrót choroby odnotowano u 11 chorych (11%): przerzuty odległe w 3, a wznowę miejscową w 8 przypadkach. W analizie jednoczynnikowej z nawrotem choroby powiązane były stopień złośliwości guza ($P = 0,0045$) oraz inwazja przestrzeni limfatycznej ($P = 0,0374$). Analiza wieloczynnikowa wykazała związek między każdym rodzajem nawrotu a inwazją przestrzeni limfatycznej (współczynnik ryzyka – *hazard ratio*, HR, 6,308; 95% przedział ufności CI 1,851–11,484). **Wnioski:** Wyniki niniejszego badania wskazują, że obecność inwazji przestrzeni limfatycznej jest ważnym czynnikiem nawrotu wczesnego raka endometrium. Można zatem rozważyć zastosowanie adiuwantowej chemioterapii u chorych na raka endometrium we wczesnym stopniu zaawansowania z inwazją przestrzeni limfatycznej.

Słowa kluczowe: rak błony śluzowej trzonu macicy, nawrót, inwazja przestrzeni limfatycznej

INTRODUCTION

Endometrial cancer (EM CA) is the most common gynecologic malignancy in developed countries, especially the United States, with 60,050 new diagnosed cases, 10,470 deaths and a lifetime probability of developing this cancer estimated at 1 in 36 women as of 2016 alone[1]. EM CA can be divided into two categories (type I and type II), which differ in incidence, responsiveness to estrogen, clinical characteristics, prognosis, and risk factors. Type I tumors account for about 80% of EM CA; these are grade 1–3 tumors of endometrioid histology. The most important risk factor for type I tumors is unopposed and excessive endo-/exogenous estrogen. Type II tumors include tumors of non-endometrioid type, which accounts for 10 to 20% of EM CA. Such tumors are related to endometrial atrophy; primarily surgical treatment is commonly followed by adjuvant therapy. Patients with type II tumors are at higher risk of recurrence and metastatic cancer than those with type I tumors. Typically, because patients with type I tumors experience vaginal bleeding at an early stage and are diagnosed earlier, their prognosis is better than those with type II tumors[2].

For the aforementioned reasons, the overall prognosis of EM CA is favorable; the 5-year survival rate is 84%. In addition, a lower stage of the disease according to the International Federation of Gynecology and Obstetrics (FIGO) (stages I–II) is associated with a better prognosis, with an overall 5-year survival rate of 94%[3]. Previously, many studies have shown that overall prognosis depends on many factors, including pathologic factors, such as the stage of the disease, FIGO grade, histologic type, depth of myometrial invasion (DMI), and lymphovascular space invasion (LVSI) as well as patient age at diagnosis and comorbidities[4]. These prognostic factors are criteria for assessing the risk of recurrence or persistent disease, and based on these factors, physicians decide whether adjuvant treatment should be performed following primary surgical treatment. Currently, the criteria for the administration of adjuvant therapy in early cancer are under debate. Adjuvant radiation therapy also has an effect on local recurrence of the disease but does not improve overall survival[5]. Despite having a better prognosis than other gynecologic cancers, 15–20% of patients with stage I EM CA experience a recurrence of the disease[5]. Consequently the demand for a more independent prognostic factor has been increasing, and studies are being conducted[6–9].

This study is aimed to investigate the clinicopathologic factors that affect recurrence in early type I EM CA in a single institution and to emphasize factors contributing to recurrence.

MATERIAL AND METHODS

After an Institutional Review Board approval was obtained, a single-institutional study was conducted at the Dong-A University Hospital. Our institution maintained an EM CA database of retrospectively gathered clinicopathologic data that was utilized to identify all patients with stages I–II EM CA treated at our institution from June 1995 until August 2016. All the medical records were reviewed and summarized, including operation records, pathology records, and laboratory findings. Demographics of patients, pathologic characteristics, adjuvant therapy data, and outcome (recurrence) were collected. Women of any age with a histologically proven endometrioid endometrial adenocarcinoma, postoperative FIGO stages I and II, and all grades with any myometrial invasion were eligible for this study. In the World Health Organization performance status, all patients obtained a score of 0–2. A total of 143 patients received primary surgical treatment including hysterectomy, with or without salpingo-oophorectomy/lymph node dissection (LND). Surgical staging was performed if the patient had any of the following: grade 3 lesions, grade 2 lesions >2 cm in diameter, clear cell or serous type, deep myometrial invasion (greater than 50% of the myometrium), and cervical extension[10]. Follow-up data and patient information were searched from the electronic medical records. Patients were excluded if they had histological cell types other than endometrioid carcinoma, or had a history of advanced cancer or synchronous malignancies and if they had previously received chemotherapy, radiation therapy, or hormonal therapy. Eighteen of 143 patients had non-endometrioid type tumors, 24 patients had advanced stages (stage III–IV), and one patient was diagnosed with a synchronous malignancy in the form of simultaneous ovarian cancer. As a result, 43 patients were excluded, and a total of 100 patients were enrolled.

A specialized pathologist at our institution reviewed all pathologies. Pathologic data collected included histologic type, FIGO stage, grade, presence of LVSI, DMI, and cancer antigen (CA)-125, and estrogen receptor/progesterone receptor (ER/PR) status. Assessment of risk based on age, stage, histologic grade, DMI, and LVSI was performed. Adjuvant therapy with radiation therapy and/or systemic chemotherapy was prescribed at the physician's discretion, taking into account the risk factors including FIGO grade, deep myometrial invasion, cervical or adnexal spread, and positive peritoneal cytology results[11]. For the first 2 years, the patients were assessed every three months, for the next 3 to 5 years, every six months, and then annually. At each visit, history concerning treatment morbidity was taken, and physical/pelvic examination was done. A chest radiograph and blood count as well as chemistry tests were performed at each visit. After treatment for recurrence, patients were reevaluated every 3 months for the first 2 years. Local recurrence and distant metastasis were evaluated as recurrence without distinction.

The time of recurrence is expressed in months. The primary endpoint of the study is progression-free survival. Kaplan–Meier estimates with log-rank significance tests ($P < 0.05$) were determined for time-dependent endpoints.

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Factors contributing to tumor recurrence (age, height, body weight, body mass index, CA-125, FIGO tumor grade, DMI, LVSI, ER/PR status, radiation therapy/chemotherapy) were included in Cox univariate and multivariate proportional hazard analysis. If these factors were found to have independent prognostic value ($P < 0.05$) by univariate/multivariate analysis, a hazard ratio (HR) with a 95% confidence interval (CI) was calculated. Analyses were performed using SPSS Version 22 [Copyright IBM Corporation, Data Solution Inc. and other(s), 1989, 2014].

Characteristics	Total number ($n = 100$)	Percentage (%)
Age [year, mean ± *SD*]	55 ± 9.34	-
Height [cm, mean ± *SD*]	154.0 ± 15.71	-
Weight [kg, mean ± *SD*]	61.19 ± 13.67	-
BMI [m²/kg, mean ± *SD*]	24.88 ± 4.24	-
CA-125 [U/mL, mean ± *SD*]	44.94 ± 101.60	-
FIGO stage:		
• IA	50	50
• IB	41	41
• II	9	9
FIGO grade:		
• 1	65	65
• 2	26	26
• 3	9	9
Depth of myometrial invasion:		
• confined to the endometrium	20	20
• inner half	58	58
• outer half	22	22
LVSI:		
• (+)	10	10
• (–)	90	90
ER/PR:		
• (+)	54	54
• (–)	15	15
• NC	31	31
Adjuvant treatment:		
• radiation therapy	17	17
• chemotherapy	6	6
• NAT	77	77

BMI – body mass index; **LVSI** – lymphovascular space invasion; **ER/PR** – estrogen receptor/progesterone receptor; **NC** – not checked; **NAT** – no adjuvant therapy.

Tab. 1. Demographics of patients, patterns of treatment, and clinicopathologic outcomes

RESULTS

Detailed demographics of the patients, patterns of treatment, and clinicopathologic outcomes are listed in Tab. 1. The median age at first diagnosis was 55 years (range, 25–78 years), and the median follow-up was 35 months (range, 2–155 months). The majority of the patients had grade 1 or 2 differentiated EM CA (91%). In 20 cases (20%), the tumor was confined to the endometrium, in 58 cases (58%), it invaded the inner half or less of the myometrium, and in 22 cases (22%), it involved the outer half of the myometrium. In our study, 45.5% of the cases in the recurrence group had deep myometrial invasion, compared to 36.4% in the group with myometrial invasion in the inner half. Of the 69 patients who underwent the ER/PR test, 54 patients had positive receptor results. After the primary surgery, 76 patients did not receive any adjuvant therapy, 17 patients received radiation therapy, and 7 patients received chemotherapy.

The types of primary surgery are listed in Tab. 2. Three patients underwent only hysterectomy, and 3 patients were treated with hysterectomy and bilateral pelvic lymph node dissection (BPLND) and/or para-aortic lymph node dissection (PALND). Four patients received hysterectomy and unilateral salpingo-oophorectomy (USO) and 3 patients underwent hysterectomy and USO and BPLND and/or PALND. Of the remaining 87 patients, 57 patients had staging operation including hysterectomy, bilateral salpingo-oophorectomy, and BPLND and/or PALND. Thirty patients received the same type of surgery except for LND. The disease recurred in 11 patients (11%); 8 patients had local recurrence, and 3 patients developed distant metastasis. All the cases of distant failure occurred in the lungs ($n = 3$). The median time to recurrence was 27 months (range, 6–76 months). LVSI was confirmed in 10 patients (10%). As for the recurrence rate, recurrence was more common in patients with LVSI (3/10; 30%) than in patients without LVSI (8/90; 9.4%).

Characteristics	Total number ($n = 100$)	Percentage (%)
Hysterectomy, BSO, and BPLND/PALND	57	57
Hysterectomy and BSO	30	30
Hysterectomy, USO, and BPLND/PALND	3	3
Hysterectomy and USO	4	4
Hysterectomy and BPLND/PALND	3	3
Hysterectomy only	3	3

BSO – bilateral salpingo-oophorectomy; **BPLND/PALND** – including BPLND only, PALND only, and both lymph node dissections; **USO** – unilateral salpingo-oophorectomy.

Tab. 2. Type of primary surgical treatment

Characteristics	Hazard ratio	95% CI		*P*-value
		Low	High	
Age [year]	1.049	0.920	1.197	0.4747
Height [cm]	0.869	0.743	1.016	0.0786
Weight [kg]	0.972	0.894	1.057	0.5040
BMI [m²/kg]	1.039	0.977	1.104	0.2203
CA-125 [U/mL]	0.993	0.977	1.010	0.4239
FIGO grade	2.947	1.024	8.478	0.0045
Depth of myometrial invasion	0.834	0.217	3.209	0.7913
LVSI	0.142	0.023	0.892	0.0374
ER/PR	0.000	0.000	0.000	0.9289
Adjuvant treatment:				
• radiation therapy	1.602	0.448	5.735	0.4688
• chemotherapy	2.445	0.580	10.301	0.2232

BMI – body mass index; **LVSI** – lymphovascular space invasion; **ER/PR** – estrogen receptor/progesterone receptor.

Tab. 3. Results of univariate risk analysis

Characteristics	Hazard ratio	95% CI		*P*-value
		Low	High	
Age [year]	0.745	0.500	1.110	0.1475
Height [cm]	1.688	0.913	3.121	0.0948
Weight [kg]	0.779	0.560	1.082	0.1358
BMI [m²/kg]	0.141	0.013	1.579	0.1120
CA-125 [U/mL]	0.920	0.852	0.994	0.0347
FIGO grade	0.864	0.289	1.560	0.1210
Depth of myometrial invasion	2.754	0.109	69.291	0.5382
LVSI	6.308	1.852	11.484	0.0307
ER/PR	-	-	-	-
Adjuvant treatment:				
• radiation therapy	2.974	1.642	8.103	0.0357
• chemotherapy	0.002	0.000	12.381	0.1637

BMI – body mass index; **LVSI** – lymphovascular space invasion; **ER/PR** – estrogen receptor/progesterone receptor.

Tab. 4. Results of multivariate risk analysis

Univariate analysis

FIGO grade and LVSI were associated with recurrence in a statistically significant way: FIGO grade (hazard ratio, HR, 2.947; 95% confidence interval, CI 1.024–8.478, $P = 0.0045$), LVSI (HR, 0.142; 95% CI 0.023–0.892, $P = 0.0374$) (Tab. 3). DMI, patients' age, and adjuvant chemo/radiation therapy did not reach significance as prognostic markers for recurrence ($P > 0.05$).

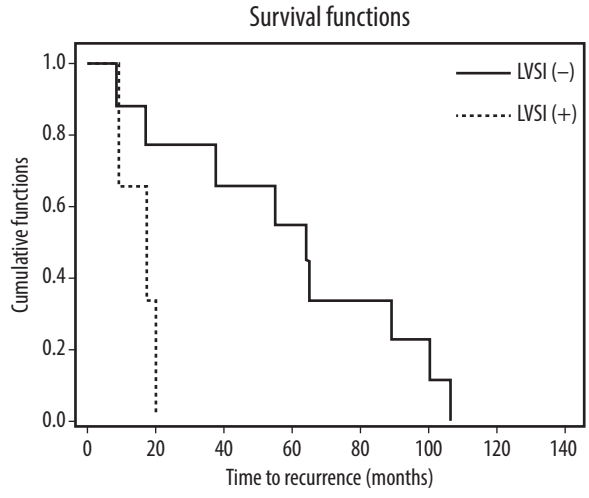
Multivariate analysis

Presence of LVSI (HR, 6.308; 95% CI 1.852–11.484, $P = 0.0307$) could be an independent strong predictor of disease recurrence (Tab. 4). Kaplan–Meier survival plot for progression-free survival was extrapolated for LVSI (Fig. 1). In LVSI-positive patients, progression-free survival was significantly reduced ($P < 0.05$). In the adjuvant radiation therapy group, the recurrence rate was statistically significantly different from that in the non-radiation therapy group ($P = 0.0357$). FIGO grade, DMI, and patients' age did not reach significance as prognostic markers for recurrence ($P > 0.05$).

DISCUSSION

In type I EM CA, prognostic factors are indispensable for determining the need for adjuvant therapy after surgery. The prognostic factors recognized to date are surgical FIGO stage, histologic type of cancer, grade of differentiation, and DMI[12]. In the present study, LVSI was a factor for predicting recurrence with statistical significance based on the multivariate analysis.

Although numerous studies have been published to support the claim that LVSI is an important prognostic factor[7–9,13–15], the significance of LVSI has been emphasized since the Gynecologic Oncology Group (GOG) 99 study was reported[16]. Based on the GOG-33, GOG-99 reanalyzed the study and observed that LVSI was a factor associated with an increase in the recurrence rate. Keys et al. first noted that LVSI became one of the crucial factors in defining risk groups, thereby changing the importance of LVSI in clinical decision-making[16,17]. Guntupalli et al. applied the "high-intermediate-risk (HIR) subgroup" of the GOG-99 study to their study and validated that the nodal disease and poor outcome were



LVSI – lymphovascular space invasion

Fig. 1. Progression-free survival of patients with and without LVSI (P < 0.05)

increased in the HIR group (95% CI 2.72–7.32, $P < 0.0001$) and the LVSI-positive group (95% CI 6.39–19.07, $P < 0.0001$), thereby emphasizing the importance of these as biomarkers of poor prognosis[14]. Similarly, of 207 cases of EM CA studied, Gilani et al. observed that LVSI was an independent factor predictive of lymph node metastasis (95% CI 1.8–22.9, $P = 0.004$)[18]. Kondalsamy-Chennakesavan et al., who studied 338 cases of EM CA, arrived at the same conclusion (95% CI 1.8–22.9, $P = 0.017$)[19].

The cure rate is high especially in early EM CA; however, it still recurs, thus eventually leading to death. Gemer et al. quantified the relative risk associated with LVSI on outcome measures in patients with stage I EM CA. In 699 stage 1 EM CA patients, 5.7% were positive for LSVI and were associated with a twofold increase in the risk of recurrence (95% CI 0.9–4.5, $P = 0.0003$), disease-specific death (95% CI 1.1–7.4, $P = 0.0007$), and overall death (95% CI 1.1–3.8, $P < 0.0001$)[20]. Even in non-surgically staged early EM CA, Nofech-Mozes et al. showed that the only prognostic factor for distant recurrence is LVSI and also suggested that this could be a significant predictor of survival rate reduction (95% CI 1.28–6.30, $P = 0.0004$)[6]. Taken together, these data show that LVSI is one of the histopathologic markers for recurrence and poor outcomes and is becoming increasingly important in treatment planning. Keys et al. demonstrated that postoperative adjuvant radiation therapy in early EM CA decreases the risk of recurrence but should be limited to patients in the HIR group[16]. Controversially, LVSI has been shown not to be a prognostic factor in other studies[21,22]. Alektiar et al. demonstrated that LVSI was associated with DMI directly and found a significant increase in the LVSI-positive frequency between EM CA that invades to one- or two-thirds[22].

The main site of local recurrence is the vagina, especially the vaginal vault. Because this site is favorable for salvage external or intracavitary radiation therapy, 75% of patients with local recurrence underwent radiation therapy for curative intent, of which 85% were cured[2]. In addition to therapeutic efficacy of radiation therapy, studies on the effect of this therapy for the prevention of recurrence have been conducted. Theoretically, assuming 100% effectiveness of brachytherapy, this might have spared three-quarters of local recurrences. However, the rate of local recurrence shows a smaller reduction than that of the control group, and a survival benefit was not expected. Therefore, in conclusion, prophylactic adjuvant radiation therapy should be applied selectively to high-risk subgroups in which uncontrolled pelvic disease is expected[5]. Similarly, ASTEC/EN.5 study suggested that external beam radiation therapy could be an effective strategy for local control, although it is difficult to expect a survival benefit in intermediate- to high-risk groups[23]. Our study showed that there was a statistically significant difference in the recurrence rate between the radiation group and non-radiation group ($P = 0.0357$). In addition, several studies have reported that adjuvant radiation therapy is effective for local control, but in the present study, the recurrence rate in the observation group was lower than that in the radiation group: 2 (13.5%) local recurrences of 15 cases in the radiation group and 6 (7.3%) local recurrences per 82 cases in the observation group. By analogy, this discrepancy could be attributed to the small sample size and to the tendency to apply radiation therapy more in patients with FIGO stage IB and above.

The strength of our study is that the research was conducted at a single institution and a pathologic review was performed by a single team, which is highly reproducible. However, this study has several limitations, for instance: the sample size was small because the study was performed at a single institution; inherent biases are common in retrospective studies; because different clinicians were involved in the study, patient heterogeneity in terms of surgical staging/adjuvant therapy may have yielded inconsistent results; there may have been differences in the timing of recurrence and the accuracy of diagnosis of recurrence because different clinicians have different follow-up appointments and varying intervals.

CONCLUSIONS

This study showed that the presence of LVSI is an important predictor for disease recurrence in early EM CA. Therefore, adjuvant systemic chemotherapy may be considered in patients with early EM CA with LVSI. Future prospective multicenter studies considering systemic chemotherapy in LVSI-positive early endometrial cancer are required to investigate improvements in recurrence and survival rates.

Conflict of interest

There are no conflicts of interest to declare.

Acknowledgments

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