A Model for Predicting Extrauterine Tumor Spread in Patients with Endometrial Cancer

Endometrium Kanserinde Ekstrauterin Tümör Yayılımını Tahmin Etmek İçin Kullanılan Bir Model

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Abstract

Objective: It was aimed to create a model using demographic, surgical and pathological factors to predict extrauterine spread in patients who underwent staging surgery with the diagnosis of endometrial cancer.

Material and Method: Included in the study were 355 patients with a final diagnosis of endometrial cancer who underwent surgery for staging purposes. The effect of surgical-prognostic factors on extrauterine spread was analyzed using univariate analysis and multivariate logistic regression analysis.

Results: Extrauterine spread was detected in 97 patients. A multivariate logistic regression model that was created to determine the factors affecting extrauterine spread identified the presence of lymphovascular invasion, cervical invasion, peritoneal cytology positivity and tumor type as independent factors. A model was created using these four independent risk factors. According to this model, the rate of extrauterine spread was 6.4% in patients who did not have the risk factors and 100% in patients who had all the risk factors ($p < 0.05$).

Conclusion: The detection of extrauterine spread is essential in planning a patient's treatment. The definition of this spread by using clinical and pathological factors would contribute to determining the appropriate therapy in a group of patients who underwent insufficient surgery or in whom surgery would otherwise cause significant morbidity.

Keywords: Endometrial cancer; Extrauterine spread; Lymphatic/nonlymphatic metastasis; Model

Özet

Amaç: Endometrium kanseri tanısı ile evreleme cerrahisi uygulanan hastalarda ekstrauterin yayılımı tahmin etmek için demografik, cerrahi ve patolojik faktörler kullanılarak bir model oluşturmak amaçlandı.

Gereç ve Yöntem: Çalışmaya endometrium kanseri tanısı alan ve evreleme cerrahisi uygulanan 355 hasta dahil edildi. Cerrahi prognostik faktörlerin ekstrauterin yayılım üzerindeki etkisi, tek değişkenli analiz ve çok değişkenli lojistik regresyon analizi kullanılarak analiz edildi.

Bulgular: 97 hastada ekstrauterin yayılım tespit edildi. Ekstrauterin yayılımı etkileyen faktörleri belirlemek için oluşturulan çok değişkenli bir lojistik regresyon modeli, lenfovasküler invazyon varlığını, servikal invazyonu, peritoneal sitoloji pozitifliğini ve tümör tipini bağımsız faktörler olarak belirledi. Bu dört bağımsız risk faktörü kullanılarak bir model oluşturulmuştur. Bu modele göre, risk faktörlerine sahip olmayan hastalarda ekstrauterin yayılım oranı %6,4, tüm risk faktörlerine sahip hastalarda %100 idi ($p<0,05$).

Sonuç: Endometrium kanseri tedavisinin planlanmasında ekstrauterin yayılımın tespiti esastır. Bu yayılımın klinik ve patolojik faktörler kullanılarak tanımlanması, yetersiz cerrahi uygulanan veya cerrahinin ciddi morbiditeye neden olacağı bir grup hastada uygun tedavinin belirlenmesine katkı sağlayacaktır.

Anahtar Sözcükler: Endometrium kanseri; Ekstrauterin yayılım; Lenfatik/Lenfatik olmayan metastaz; Model

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Introduction

Endometrial carcinoma is the invasion of endometrial tissue into the stroma, myometrium, and vascular spaces, and it is characterized by marked hyperplasia and anaplasia of the glandular elements (1). It is the most common gynecologic cancer in developed countries. Despite the lack of an effective screening test, the disease becomes symptomatic, and 70-75% of the cases are diagnosed in the early stage (2). Surgery in an early stage disease confers a high chance of survival. The five-year survival rate is 96% in patients with early-stage disease, 68% in patients with local spread, and 17% in patients with distant metastasis (3).

Endometrial cancer has been staged surgically according to the FIGO staging system since 1988. The traditional approach involves a cytological examination of the peritoneal lavage fluid, total abdominal hysterectomy, and bilateral salpingo-oophorectomy. In addition to these procedures, omentectomy and pelvic and paraaortic lymphadenectomy are performed in selected high-risk patients (3).

The limits of surgery to be performed on these patients are controversial. The controversy is mainly concerned with the inclusion of lymphadenectomy in routine surgical procedures in all patients with early-stage cancer. Pelvic and paraaortic lymphadenectomy was reported to increase morbidity despite not significantly improving the survival rates in early-stage cancer (4). There is a nonnodal extrauterine spread in approximately 10% of patients with endometrial cancer. These patients account for more than 50% of endometrial cancer-related deaths (5). The meta-analyzes found that extensive surgery involving resection of all visible tumor foci in this patient group provides survival benefit (6). In the light of these data, endometrial cancer surgery aims at offering the most probable curative therapy for the patient. If a surgical therapy is not curative, treatment aims to eliminate residual disease and guide adjuvant therapies. The presence of extrauterine spread determines the extent of surgery and the type of surgery in endometrial cancer surgery. The treatment of patients must be customized using the risk factors in predicting the presence of extrauterine spread.

The present study initially investigated the factors determining extrauterine spread using clinical and pathological data in patients with endometrial cancer undergoing surgery for staging purposes. Subsequently, a model was created to predict extrauterine spread, using demographic, surgical, and pathological factors.

Material and Method

The study included 355 patients who underwent staging surgery in a Gynecologic Oncology Clinic and who were diagnosed with stage IA-IVB endometrial cancer. The staging was performed according to the 2009 FIGO staging system. The patients diagnosed with uterine sarcoma on the examination of the paraffin-embedded tissue blocks, the patients with a sarcoma component in the tumor, the patients who received therapy before surgery, and those with a synchronous malignancy were excluded from the study. The study data were retrospectively retrieved from the hospital's database, patient files, and pathology reports. An approval was granted by the ethics committee of the hospital before the study (Number: 170 -27/12/2013).

In our clinic, the patients with a nonendometrioid adenocarcinoma, grade 2 and 3 tumor, myometrial invasion depth of ≥1/2, cervical invasion, and tumor size of greater than 2 cm on the examination of the frozen section undergo staging surgery. The staging surgery typically involves total abdominal hysterectomy + bilateral salpingo-oophorectomy + systematic pelvic and paraaortic lymphadenectomy + omentectomy (biopsy or infracolic omentectomy or total omentectomy). During intraoperative exploration, cytoreductive surgical techniques are employed in addition to staging surgery in the presence of extrauterine macroscopic pathological findings. All surgical procedures are performed by a gynecologic oncologist.

The presence of tumor in pelvic and paraaortic lymph nodes was defined as lymphatic metastasis, and the presence of tumor in extrauterine localizations (adnexa, omentum and other intra/extraabdominal metastasis) other than positive cytological findings and lymphatic metastasis was defined as non-lymphatic spread. The extrauterine spread was defined as lymphatic or non-lymphatic spread beyond the uterine corpus and cervix. Lymphovascular invasion (LVI) was defined as the presence of tumor cells attached to the vessel walls in hematoxylin-eosin-stained sections of the tumor with surrounding healthy tissues. Hysterectomy material was examined at least in four sections in the pathological examination. In the pathological examination of omentum, 2-3 sections obtained from the tumor tissue and suspicious locations and 3-5 sections randomly obtained from seemingly healthy omentum tissue were examined.

Statistical Analysis

The effect of surgical-prognostic factors on extrauterine spread was evaluated using univariate analysis and multivariate logistic regression analysis. The study data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows version 22.0 (SPSS Inc. Chicago, USA) software package. The difference between nominal values and ratios was analyzed using a non-parametric $\chi 2$ test, and parametric data were analyzed using a one-way analysis of variance (ANOVA). The univariate analysis was performed using the "log-rank" test. The "Omnibus test" and "Hosmer and Lemeshow test" were used in multivariate logistic regression analysis. The level of statistical significance was set at an alpha of 0.05.

Results

The mean age of 355 patients was 59±8.8 years (range, 32-83 years). According to the FIGO staging system, 62.5% of the patients had stage 1 disease. The mean tumor size was 43.4±26.8 mm (range, 6-330 mm). Of the patients, 283 (79.7%) had an endometrioid tumor, and 120 patients (33.8%) had grade 3 disease. Twenty patients (5.6%) did not have a myometrial invasion, 11 (3.1%) had tumor extension to the serosa. Seventy-eight patients (22%) had cervical involvement, and 68 of these patients had stromal invasion. LVI was detected in 147 patients (41.4%). Peritoneal cytology was positive in 30 (8.5%) patients.

The extrauterine spread was detected in 97 patients (27.3%). The tumor spread was non-lymphatic in 45 patients (12.7%) and lymphatic in 77 patients (21.7%). Except for

omentum and adnexa, ten patients (2.8%) had intraabdominal tumor spread, 37 patients (10.4%) had adnexal involvement, and 22 patients (6.2%) had omental metastasis. The lymphatic spread was to the paraaortic region in 49 patients (13.8%) and pelvic region in 64 patients (18%). The mean number of removed lymph nodes was 57.6±20.5 (range, 4-122). This number was 17.8 ±10 (range, 1-55) for the paraaortic region and 39.8±13.9 (range, 4-92) for the pelvic region. The mean number of metastatic lymph nodes removed was 5.7 (range, 1-32) in the paraaortic region and 4.9 (range, 1-30) in the pelvic region. The details on surgical-pathological factors are presented in Table 1.

According to the results of the univariate analysis that was made to determine the factors affecting extrauterine spread; tumor type (endometrioid vs. non-endometrioid), tumor grade (grade 1 vs. grade 2 vs. grade 3), myometrial invasion depth (no invasion vs. less than 50% invasion vs. invasion 50% or higher), uterine serosal involvement, the presence of LVI, cervical invasion, peritoneal cytology positivity and tumor size (<40 mm vs. ≥40 mm) were identified as the factors affecting extrauterine spread (Table 2).

In multivariate logistic regression analysis, the presence of LVI, cervical invasion, peritoneal cytology positivity, and tumor type were identified as independent factors affecting extrauterine spread (HR:3.486, 95%CI:1.949-6.233, p=0.009; HR:2.383, 95%CI:1.242-4.570, p<0.001; HR:17.41, 95%CI:4.780-63.43, *p<0.001*; HR:3.594, 95%CI:1.885-6.855, *p<0.001*, respectively). The results of logistic regression analysis for extrauterine spread are presented in Table 3.

A model was created using the independent risk factors for extrauterine spread in the logistic regression analysis for endometrial cancer. The rate of extrauterine spread was 6.4% in patients who did not have any of the risk factors and 100% in patients who had all the risk factors (*p<0.05*). The model created for extrauterine spread is presented in detail in Table 4.

Discussion

Although endometrial cancer is the most common gynecological malignancy, there is still a controversy over its surgical management. The most important reason for this condition is that preoperative imaging studies and endometrial biopsy fail to predict extrauterine spread. Twenty percent of patients supposed to have early-stage disease in the preoperative period are classified as having advanced-stage disease after surgery (7). A management strategy involving staging surgery in all patients results in unjustifiable morbidity and treatment costs while a strategy based on imaging studies results in an inaccurate prediction of the disease extensiveness (4, 8, 9). It is vital to detect extrauterine spread in the management of endometrial cancer in terms of determining the type of surgical procedure and adjuvant therapy.

Lymphatic spread is an important prognostic factor representing the most common extrauterine area of disease spread in endometrial cancer. Nodal metastasis is detected in 5% of women who are supposed to have low-risk endometrial cancer and 22% of women who are supposed to have moderate-risk endometrial cancer (10). It was demonstrated

Table I. Surgical and pathologic characteristics of patients.

Parameter		Mean ±SD / n	Median (Range) / %
Age		59±8.8	59 (32-83)
Tumor size (mm)		43.4±26.8	40 (6-330)
2009 FIGO stage	IA	126	35.5
	IB	96	27
	II	32	9
	IIIA	18	5.1
	IIIB	-	-
	IIIC1	24	6.8
	IIIC2	36	10.1
	IVA	1	0.3
	IVB	22	6.2
Tumor type	Endometrioid	283	79.7
	Clear cell	18	5.1
	Serous	25	7
	Mucinous	1	0.3
	Mixed	19	5.4
	Undifferentiated	9	2.5
FIGO grade	Grade 1	105	29.6
	Grade 2	130	36.6
	Grade 3	120	33.8
Myometrial invasion	No invasion	20	5.6
	<½	150	42.3
	≥½ [a]	185	52.1
Uterine serosal invasion	Negative	344	96.6
	Positive	11	3.1
Cervical invasion	Negative	277	78
	Glandular invasion	10	2.8
	Stromal invasion	68	19.2
Lympho-vascular invasion	Negative	208	58.6
	Positive	147	41.4
Peritoneal cytology	Negative	325	91.5
	Positive	30	8.5
Adnexal metastasis	Negative	318	89.6
	Positive	37	10.4
Omental metastasis	Negative	333	93.8
	Positive	22	6.2
Intra-abdominal spread b	Negative	345	97.2
	Positive	10	2.8
Extrauterine non-lymphatic spread	Negative	310	87.3
	Positive	45	12.7
Number of removed lymph node	Paraaortic	17.8±10	17 (1-55)
	Pelvic	39.8±13.9	38 (4-92)
Lymphatic metastasis	Negative	278	78.3
	Positive	77	21.7
Site of lymph node metastasis	Only paraaortic	13	3.7
	Only pelvic	28	7.9
Number of metastatic lymph nodes	Pelvic + Paraaortic	36	10.1
	Number of metastatic lymph nodes	5.7	2 (1-32)
	Pelvic	4.9	3 (1-30)
Extrauterine spread	Negative	258	72.7
	Positive	97	27.3

a: Patient with uterine serosal invasion included
b: Intraabdominal spread: Intraabdominal metastasis except omental, adnexal and lymph node metastasis

Table II. Factors determining lymphatic/non-lymphatic extrauterine metastasis.

Parameter		Lymphatic/non-lymphatic metastasis		*p*
		Negative	Positive	
		n (%)	n (%)	
Age[a]	≤59	138 (73.4)	50 (26.6)	*0.744*
	≥60	120 (71.9)	47 (28.1)	
Tumor type	Endometrioid	222 (79.6)	57 (20.4)	*<0.0001*
	Non-endometrioid	36 (47.4)	40 (52.6)	
FIGO grade	Grade 1	84 (80)	21 (20)	*<0.0001*
	Grade 2	107 (82.3)	23 (17.7)	
	Grade 3	67 (55.8)	53 (44.2)	
Myometrial invasion	No invasion	17 (85)	3 (15)	*<0.0001*
	<½	125 (83.3)	25 (16.7)	
	≥½	116 (62.7)	69 (27.3)	
Uterine serosal invasion	Negative	225 (74.1)	89 (25.9)	*0.001*
	Positive	3 (27.3)	8 (72.7)	
Lympho-vascular invasion	Negative	178 (85.6)	30 (14.4)	*<0.0001*
	Positive	80 (54.4)	67 (45.6)	
Cervical invasion	Negative	219 (79.1)	58 (20.9)	*<0.0001*
	Positive	39 (50)	39 (50)	
Peritoneal cytology	Negative	255 (78.5)	70 (21.5)	*<0.0001*
	Positive	3 (10)	27 (90)	
Tumor size (mm)[a]	≤40	156 (78.4)	43 (21.6)	*0.006*
	≥41	102 (65.4)	54 (34.6)	

[a]: Median value

Table III. Factors determining lymphatic/non-lymphatic metastasis (Logistic regression).

	B	Wald	*p*	Exp (B)	95% C.I.
Constant	-2.411	90.474	*<0.001*	0.090	
LVI	1.249	17.731	*0.009*	3.486	1.949-6.233
Cervical Invasion	0.868	6.826	*<0.001*	2.383	1.242-4.570
Peritoneal Cytology	2.857	18.765	*<0.001*	17.414	4.780-63.435
Tumor type	1.279	15.086	*<0.001*	3.594	1.885-6.855

Omnibus Test χ2:103.133, *p<0.001*; Hosmer and Lemeshow Test χ2: 1.397, *p=0.845;* LVI; lympho-vascular invasion

that lymphadenectomy does not provide a survival benefit and increases morbidity in early-stage endometrial cancer (11). Lymphadenectomy eases the selection of adjuvant therapy while causing lymphedema in 10-20% of the patients and the development of lymphocele in 10-25% of the patients (12). However, lymphadenectomy was reported to have a favorable effect on survival in a group of patients who are at high risk for extrauterine spread and in those with nodal spread (13, 14). Various factors have been described in studies to determine these high-risk groups.

Euscher et al. showed that myometrial invasion, cervical involvement, and presence of LVI are essential factors predicting extrauterine spread in patients with early-stage endometrial cancer (15). Different studies have reported

Table IV. Established model for lymphatic/non-lymphatic metastasis

LVI	Cervical Invasion	Peritoneal Cytology	Tumor Type	Lymphatic/non-lymphatic metastasis		
					n	%
Negative	Negative	Negative	Endometrioid	Negative	131	93.6
				Positive	9	6.4
			Non-endometrioid	Negative	21	72.4
				Positive	8	27.6
		Positive	Endometrioid	Negative	1	50.0
				Positive	1	50.0
			Non-endometrioid	Positive	5	100.0
	Positive	Negative	Endometrioid	Negative	22	81.5
				Positive	5	18.5
			Non-endometrioid	Negative	3	60.0
				Positive	2	40.0
Positive	Negative	Negative	Endometrioid	Negative	57	72.2
				Positive	22	27.8
			Non-endometrioid	Negative	8	61.5
				Positive	5	38.5
		Positive	Endometrioid	Negative	1	20.0
				Positive	4	80.0
			Non-endometrioid	Negative	-	-
				Positive	4	100.0
	Positive	Negative	Endometrioid	Negative	9	47.4
				Positive	10	52.6
			Non-endometrioid	Negative	4	30.8
				Positive	9	69.2
		Positive	Endometrioid	Negative	1	14.3
				Positive	6	85.7
			Non-endometrioid	Negative	-	-
				Positive	7	100.0

LVI; lympho-vascular invasion

LVI (16), tumor size (17), and tumor type (18) as important factors in determining extrauterine spread. The present study identified the presence of LVI, cervical invasion, peritoneal cytology positivity and tumor type as independent prognostic factors for predicting extrauterine spread. Our study also found that myometrial invasion and serosal involvement might be important in terms of prognosis.

There is also a controversy over the treatment of patients with endometrial cancer who were insufficiently staged (e.g., comorbidity, discordance between frozen section and final pathological diagnosis) or those who underwent hysterectomy procedure due to benign causes but incidentally detected as having a cancer. According to the American National Cancer Database, approximately 32% of patients with endometrial cancer have undergone insufficient surgery (19). The guidelines classify all patients with endometrioid type, stage 1 disease, grade1-2, myometrial invasion <1/2, and absence of LVI as having low-risk endometrial cancer, and advise follow-up without administering additional therapy (3). However, there is still an uncertainty surrounding the management of intermediate- and high-risk patients. It is stated that imaging studies or repeat staging surgery can be performed in this group of patients (3, 20).

It is not certain which surgery, chemotherapy, and radiotherapy options are the most beneficial in the

intermediate- or high-risk patients who have undergone insufficient surgery. The parameter that could clarify this uncertainty is the identification of risk factors based on the pathological findings of hysterectomy specimens and the prediction of extrauterine spread. As suggested in the PORTEC-2 study, the brachytherapy option would be preferable due to its lower side effects in patients carrying risk factors if the disease is confined to the uterus (21). In the presence of high-risk factors in patients with a condition confined to the uterus, EBRT is the standard of care, as suggested in the GOG-249 study (22). In the patients with extrauterine disease spread, a sequential combination of chemotherapy and radiotherapy modalities would be beneficial, as suggested in the PORTEC-3 study (23). All these studies have emphasized the importance of extrauterine spread in endometrial cancer. Based on the model created in the present study, the rate of extrauterine spread was found to be 6.4% in the absence of all of the risk factors (presence of LVI, non-endometrioid tumor type, peritoneal cytology positivity and cervical invasion) and 100% in the presence of all of the risk factors. The rate of extrauterine spread was 50%, particularly in the presence of peritoneal cytology positivity, despite the lack of other risk factors. The model in the present study also showed that extrauterine spread could be observed even in the absence of all risk factors. It would be reasonable to determine the treatment approach based on the reported findings of the present study without performing repeat surgery in patients who underwent insufficient surgery, particularly if there are comorbidities but no gross tumor on imaging studies. The authors recommend that the multimodal treatment approach must be adopted, particularly in high-risk patients for extrauterine spread.

Retrospective study design is the most critical limitation of the present study. Having defined extrauterine spread, a large study group, the assessment of pathology reports by experienced gynecopathologists, and the applicability of the findings to clinical practice are the strengths of the study. Also, the conduction of the study in a single-center provides the homogenization of the study population and increases the reliability of the findings.

In conclusion, the management of patients, particularly those who have undergone insufficient surgery, can be determined based on the models involving clinical and pathological data that predict extrauterine spread in endometrial cancer. The patients that are at high risk for extrauterine spread can be directed to adjuvant therapy if there is no gross tumor on the imaging studies and/or there are no comorbidities.

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