Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2024.92597

Turk J Obstet Gynecol 2024;21:37-42

A novel predictive model of lymphovascular space invasion in early-stage endometrial cancer

Erken evre endometrium kanserinde lenfovasküler alan invazyonunu tahmin edebilmek için oluşturulan yeni bir model

İbrahim Taşkum[1], Muhammed Hanifi Bademkıran[2], Furkan Çetin[3], Seyhun Sucu[2], Erkan Yergin[1], Özcan Balat[2], Halil Özkaya[3], Evren Uzun[4]

[1]*Gaziantep City Hospital, Clinic of Obstetrics and Gynecology, Gaziantep, Turkey*

[2]*Gaziantep University Faculty of Medicine, Department of Obstetrics and Gynecology, Gaziantep, Turkey*

[3]*Abdulkadir Yüksel State Hospital, Clinic of Obstetrics and Gynecology, Gaziantep, Turkey*

[4]*Gaziantep University Faculty of Medicine, Department of Medical Pathology, Gaziantep, Turkey*

Abstract

Objective: To predict lymphovascular space invasion (LVSI) positivity in early-stage (stage 1-2) endometrial cancer (EC) using a predictive model with prognostic factors of EC.

Materials and Methods: We included 461 patients who underwent total hysterectomy and bilateral salpingo-oophorectomy with pelvic-paraaortic lymphadenectomy as the primary treatment for presumed early-stage EC at our clinic between 2010 and 2020. Moreover, all surgical specimens were examined histopathologically for the positivity or negativity of LVSI, and the patients were divided into two groups based on these pathologic outcomes. Age, menopausal status, histological type (type 1-2), histological grade (grades 1-2-3), depth of myometrial invasion, and peritoneal cytology results were recorded and analyzed as clinicopathological and demographic characteristics of the patients. The Loess algorithm determined the relationship between the observed and predicted outcomes. The distinction between the algorithms was evaluated by calculating the C-index.

Results: LVSI positivity was significantly associated with advanced age, menopause, type 2 EC, advanced histological grade, malignant peritoneal cytology, cervical involvement, and a tumor exceeding 50% of the myometrial depth ($p<0.001$, respectively). Remarkably, LVSI was most strongly associated with three explanatory variables: 1- More than 50% myometrial invasion [odds ratio (OR): 3.78; 95% confidence interval (CI): 1.80-7.60], 2- Advanced histological grade [OR=1.98 (1.20-3.20) 95% CI], 3- Malignant peritoneal cytology [OR= 3.06 (1.40-6.30) 95% CI]. The penalized maximum likelihood estimation model correctly classified 87% of the included patients (C-index: 0.876).

Conclusion: Our predictive model may help predict LVSI based on different prognostic factors. The prognostic factors included in the nomogram were significantly associated with LVSI, particularly myometrial invasion depth of more than 50%, advanced histological grade, and malignant peritoneal cytology.

Keywords: Endometrial cancer, lymph node metastasis, lymphovascular space invasion, predictive model

Öz

Amaç: Bu çalışmanın amacı erken evre (evre 1-2) endometriyal kanserde (EK) lenfovasküler alan invazyonu (LVAI) pozitifliğini, EK'nin prognostik faktörlerini içeren bir prediktif model kullanarak tahmin etmektir.

Gereç ve Yöntemler: Bu çalışmaya 2010-2020 yılları arasında kliniğimizde erken evre EK tanısıyla primer tedavi olarak pelvik-paraaortik lenfadenektomi ile birlikte total histerektomi ve iki taraflı salpingo-ooferektomi uygulanan veya pelvik-paraaortik lenfadenektomi yapılan 461 hasta dahil edildi. Ayrıca tüm cerrahi örnekler LVAI pozitifliği veya negatifliği açısından histopatolojik olarak incelendi ve hastalar bu patolojik sonuçlara göre iki gruba ayrıldı. Hastaların klinikopatolojik ve demografik özellikleri olarak yaş, menopozal durum, histolojik tip (tip 1-2), histolojik derece (grade 1-2-3), miyometrial invazyon derinliği ve peritoneal sitoloji sonuçları kaydedilerek analiz edildi. Gözlemlenen ve tahmin edilen sonuçlar arasındaki ilişkiyi belirlemek için Loess algoritması kullanıldı. Algoritmalar arasındaki ayrım C-endeksi hesaplanarak değerlendirildi.

PRECIS: Predicting lymphovascular space invasion in early-stage endometrial cancer.

Address for Correspondence/Yazışma Adresi: Seyhun Sucu, MD,
Gaziantep University Faculty of Medicine, Department of Obstetrics and Gynecology, Gaziantep, Turkey
Phone: +90 532 624 00 72 **E-mail:** seyhunsucu80@gmail.com **ORCID ID:** orcid.org/0000-0001-6821-4070

Received/Geliş Tarihi: 13.01.2024 **Accepted/Kabul Tarihi:** 29.01.2024

Copyright© 2024 The Author. Published by Galenos Publishing House on behalf of Turkish Society of Obstetrics and Gynecology.
This is an open access article under the Creative Commons AttributionNonCommercial 4.0 International (CC BY-NC 4.0) License.

Bulgular: LVAI pozitifliği ileri yaş, menopoz, tip 2 EK, ileri histolojik derece, malign peritoneal sitoloji, servikal tutulum ve miyometrial derinliğin %50'sini aşan tümör ile anlamlı düzeyde ilişkiliydi. Dikkat çekici bir şekilde LVAI, üç açıklayıcı değişkenle en güçlü şekilde ilişkiliydi: 1- %50'den fazla miyometrial invazyon [odds ratio (OR): 3,78; %95 confidence interval (CI): 1,80-7,60], 2- İleri histolojik derece [OR=1,98 (1,20-3,20) %95 Cl], 3- Malign peritoneal sitoloji [OR=3,06 (1,40-6,30) %95 Cl]. Cezalandırılmış maksimum olasılık tahmini modeli, dahil edilen hastaların %87'sini doğru şekilde sınıflandırmıştır (C-endeksi: 0,876).

Sonuç: Tahmin modelimiz, farklı prognostik faktörlere dayanarak LVAI'nın tahmin edilmesine yardımcı olabilir. Nomogramda yer alan prognostik faktörler, özellikle %50'den fazla miyometrial invazyon derinliği, ileri histolojik derece ve malign peritoneal sitoloji olmak üzere LVAI ile anlamlı düzeyde ilişkiliydi.

Anahtar Kelimeler: Endometrial kanser, lenf nodu metastazı, lenfovasküler alan invazyonu, tahmin modeli

Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract in developed countries, and it is the second most common malignancy after cervical cancer in developing countries[1]. In some patients with EC, advanced age is mainly associated with higher treatment failure rates and poor survival rates[2]. Patients with EC are classically present with postmenopausal bleeding, defined as bleeding that occurs at least a year after the natural cessation of menstrual cycles[3]. The current literature offers strong evidence regarding endometrial sampling performed using Pipelle biopsy or conventional dilation and curettage as the most accurate method for EC diagnosis[4]. Staging and treatment planning for EC are generally based on the International Federation of Gynecology and Obstetrics (FIGO) guidelines. Treatment is primarily surgical, and total hysterectomy and bilateral salpingo-oophorectomy are the standard surgical approach[5]; nevertheless, the decision to perform pelvic or additional paraaortic lymphadenectomy for all patients remains questionable. Factors such as advanced age, advanced surgical stage, high-grade tumor, myometrial invasion, lymphovascular space invasion (LVSI), large tumor size, and malignant peritoneal cytology have been reported as poor prognostic factors for EC[6]. EC classification follows the FIGO guidelines, which use a three-step process to categorize the mucinous and endometrioid types according to their histological grade. However, clear, serous, squamous, undifferentiated, and small-cell ECs are not graded or considered high grade (grade 3)[7]. As the depth of invasion into the myometrium increases, so does the risk of lymphatic system invasion, extrauterine involvement, and recurrence, all of which can negatively impact prognosis[8]. LVSI is an independent risk factor for lymph node metastasis and disease recurrence[9]. EC staging now includes LVSI as an essential factor[10]. Adjuvant therapy should be considered for stage I EC patients with lymph node evaluation because of the significant prediction of LVSI for nodal recurrence and poorer overall survival[11].

In cases of EC, it has been reported that approximately 4.4% of individuals who undergo surgical staging characterize malignant peritoneal cytology[12]. However, peritoneal cytology is excluded from the current FIGO guidelines[10].

This study aimed to develop a new predictive model incorporating various prognostic factors to determine the likelihood of LVSI positivity in patients with early-stage EC. Moreover, the aim of this study is to provide clinical risk assessment counseling by using a nomogram with parameters that predict LVSI.

Materials and Methods

The Gaziantep University Faculty of Medicine Clinical Research and Ethics Committee approved this study (ethical approval no: 2022/258, date: 31.08.2022). In addition, this retrospective study was designed to follow the current guidelines of the World Medical Association's Declaration of Helsinki.

Patient Selection and Data Collection

The High-Security Hospital Data System identified 601 patients who underwent surgery for EC between 2010 and 2020 in the Department of Gynecology and Obstetrics of Gaziantep University Faculty of Medicine. Age, premenopausal or postmenopausal status, histopathological EC type (type 1 or 2), histological grade of EC (grade 1, 2, and 3), and myometrial invasion positivity (whether the tumor exceeded ½ of the myometrium) of the included patients were recorded. Further, pathology results regarding cervical involvement of EC, malignant peritoneal cytology positivity, and pelvic-paraaortic lymph node positivity were documented, and these outcomes were recorded. Patients with missing recorded data for inclusion criteria and whose final pathology result was reported as advanced-stage EC were excluded from the study. According to the final pathology results that specified early-stage (stage 1-2) EC diagnosis[10], 461 patients were included in the study.

Biostatistics

In this study, numerical variables were presented using the median (interquartile range), while categorical variables were presented as "n, (%)". Continuous variables were compared using Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical variables were analyzed using the chi-square test (χ^2). The data were summarized with descriptive statistics, including frequency, percentage (%), and mean ± standard deviation. A significance level of p-value 0.05 was considered in this study.

Candidate Predictors and Statistical Modeling

This study examined several factors as potential predictors of LVSI positivity in early-stage EC. This predictive model was designed with candidate predictors that met the necessary conditions and were selected based on previous research[13]. The seven candidate predictors for the final predictive model

included age, menopause status, histological type of EC, degree of myometrial invasion, malignant peritoneal cytology positivity, cervical involvement of EC, and histological grade of EC. No variables with very low or very high frequencies were included in the model.

This model's predicted outcome was prescribed as LVSI positivity in early-stage EC. The Loess algorithm examined the correlation between observed and predicted values. Model discrimination was estimated by calculating the C-index. A 40-bootstrap replication was used for internal validation of the expected model. Predictive model validation consisted of discrimination (Harrell's C-index) and calibration (calibration plots) using the validation set. In line with previous research[14], this study assumed that a >0.75 C-index value represented relatively good discrimination. On the basis of this predictive model, a nomogram was created. All statistical analyses were performed using R version 3.5.1 (R Statistical Software, Institute for Statistics and Mathematics, Vienna, Austria).

Results

The baseline clinical characteristics of the study groups and the comparison of all prognostic factors in patients with and without LVSI are detailed in "Table 1". LVSI positivity was not detected in 396 of 461 patients in the study. However, LVSI was positive in the pathology results of 65 patients. LVSI positivity was strongly associated with a myometrium exceeding 1/2, advanced histological grade, and malignant peritoneal cytology. Of the 65 patients with LVSI positivity, 18 (27.7%) had tumor invasion not exceeding ½ myometrium. Similarly, in 47 (72.3%) of LVSI positivity patients, the tumor did not invade beyond ½ myometrial depth. Tumor invasion did not exceed ½ myometrium in 323 (81.6%) of 396 patients without LVSI positivity. In the remaining 73 (18.4%) of patients without LVSI, the tumor extended beyond ½ myometrial depth. The results showed a significant association between patients with myometrial depth exceeding ½ and patients with LVSI positivity [odds ratio (OR): 3.78 (1.80-7.60) 95% confidence interval (CI)]. Of the 65 patients with LVSI, 7 (10.8%) had grade 1, 18 (27.7%) had grade 2, and 40 (61.5%) had grade 3. In comparison, the findings for the 396 patients without LVSI were as follows: 156 (39.4%) had grade 1, 188 (47.5%) had grade 2, and 52 (13.1%) had grade 3. These results suggest that histological grading is an important prognostic indicator for patients with LVSI positivity [1.98 (1.20-3.20) 95% CI].

Table 1. Demographic, histopathological, and prognostic factors

	LVSI positive n=65	LVSI negative n=396	p
Age [years, (mean ± SD)]	61.89±8.5	58.23±10.24	**0.006**
Menopause status, n (%)			
No	6 (9.2)	80 (20.2)	**0.03**
Yes	59 (90.8)	316 (79.8)	
Histological type of EC, n (%)			
Type 1	46 (70.8)	360 (90.9)	**<0.0001**
Type 2	19 (29.2)	36 (9.1)	
Grade, n (%)			
1	7 (10.8)	156 (39.4)	**<0.0001**
2	18 (27.7)	188 (47.5)	
3	40 (61.5)	52 (13.1)	
Degree of MI, n (%)			
<1/2	18 (27.7)	323 (81.6)	**<0.0001**
≥1/2	47 (72.3)	73 (18.4)	
MPC, n (%)			
Negative	27 (41.5)	351 (88.6)	**<0.0001**
Positive	38 (58.5)	45 (11.4)	
Cervical involvement of EC, n (%)			
Negative	42 (64.6)	357 (90.2)	**<0.0001**
Positive	23 (35.4)	39 (9.8)	

LVSI: Lymphovascular space invasion, EC: Endometrial cancer, MI: Myometrial invasion, MPC: Malign peritoneal cytology, SD: Standard deviation. Values are presented as n(%). Bold values represent p<0.05.

Upon analyzing the peritoneal cytology results of 65 patients with LVSI positivity, it was found that 27 (41.5%) had benign results and 38 (58.5%) had malignant results. In contrast, when the peritoneal cytology results of 396 patients without LVSI were examined, 351 (88.6%) had benign results and 45 (11.4%) had malignant results. Furthermore, a significant correlation was found between patients with malignant peritoneal cytology results and LVSI positivity (OR: 3.06 [1.40-6.30] 95% CI). "Table 2" presents and summarizes predictive model's ORs and CIs. A predictive model based on these candidate variables was created, with a penalized maximum likelihood estimation model correctly classifying 87% of participants. The calibration between the predicted and observed results was acceptable. A plot of the observed and expected results for LVSI positivity in early-stage EC is illustrated in "Figure 1", and a nomogram based on the final refined predictive with the candidate variables is shown in "Figure 2".

Discussion

In this study, a predictive model was created to predict the presence of LVSI in early-stage EC. Accordingly, LVSI positivity was strongly associated with myometrial invasion of more than ½, advanced histological grade, and malignant peritoneal cytology. In addition, LVSI positivity was related to the non-endometrioid type of EC, cervical stromal involvement, and post-menopausal period, according to the predictive model.

There is a discussion regarding the validity of advanced age as an independent prognostic factor; however, it is common for patients over 65 years of age to experience deep myometrial invasion, higher tumor grade, and advanced stage[15]. In the meta-analysis research by Clarke et al.[16], it was reported that early diagnosis strategies focusing on women with postmenopausal bleeding can detect 90% of EC; however, it was concluded that several women with postmenopausal bleeding may not be diagnosed with EC, remarkably. The results of the

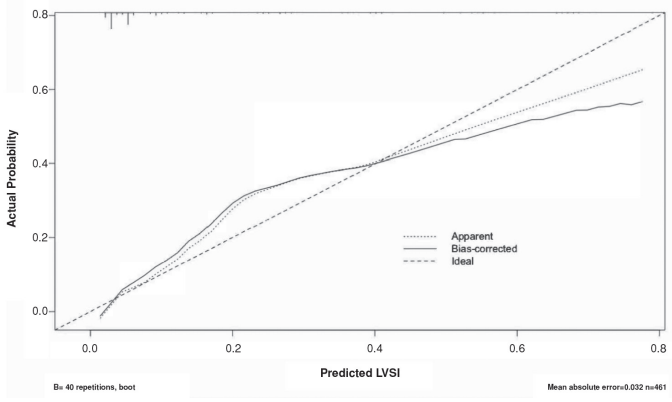

Figure 1. Calibration plot of observed results and predicted outcome to predict LVSI with prognostic factors

LVSI: Lymphovascular space invasion

Table 2. Predicting LVSI risk with prognostic factors

Variables	β-value	OR (95% CI)	p_{adj}
Age [years, (mean ± SD)]	0.009	1 (0.97-1.05)	0.63
Menopause status			
No	0.394	Reference=1	0.53
Yes		1.40 (0.43-5.1)	
Histological type of EC			
Type1	0.542	Reference=1	0.17
Type2		1.72 (0.78-3.78)	
High grade of EC	0.686	1.98 (1.20-3.20)	**0.006**
Degree of MI			
<1/2	1.33	Reference=1	**0.0002**
≥1/2		3.78 (1.80-7.60)	
MPC			
Negative	1.121	Reference=1	**0.0025**
Positive		3.06 (1.40-6.30)	
Cervical involvement of EC			
Negative	0.579	Reference=1	0.12
Positive		1.78 (0.85-3.71)	

LVSI: Lymphovascular space invasion, EC: Endometrial cancer, MI: Myometrial invasion, MPC: Malign peritoneal cytology, SD: Standard deviation, OR: Odds ratio, CI: Confidence interval, $_{Padj}$: Penalized and adjusted p value. Bold values represent p<0.05.

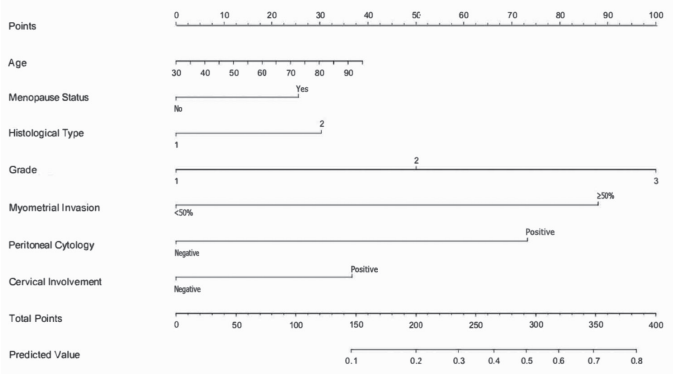

Figure 2. A nomogram based on the final refined estimates with candidate variables of early-stage EC to predict LVSI positivity

LVSI: Lymphovascular space invasion, EC: Endometrial cancer, Peritoneal Cytology Positive: Malign Peritoneal Cytology

present study indicate that LVSI positivity is more prevalent in menopausal patients who have early-stage EC, signifying a robust correlation with advanced age (p=0.006); nevertheless, there was a low level of association between age and LVSI positivity [OR: 1 (0.97-1.05) 95% CI].

Ayhan et al.[17] analyzed 912 low-risk EC patients, and LVSI positivity was detected in 53 (5.8%) patients. Their study reported that LVSI positivity was significantly associated with grade 2 EC (p<0.001), the presence of deep myometrial invasion (p=0.003), and large tumor size (p=0.005), according to the postoperative pathology results. Therefore, the grade of the tumor as a prediction factor was included in our predictive model. In a study by Doghri et al.[18], 62 patients with EC were analyzed to determine the significance of depth myometrial invasion as a prognostic factor. Consequently, their study showed that advanced invasion of the myometrium was associated with a risk of pelvic and para-aortic lymph node metastasis, which is indicated by high-grade EC. In parallel with the previous studies, the present study found a strong and significant correlation between LVSI positivity and exceeding 1-2 myometrium [OR: 3.78 (1.80-7.60) 95% CI].

In the study by Malik et al.[19], the researchers reported that approximately 75-80% of 180 patients had type 1 EC and highlighted that many patients in the early stages showed a favorable prognosis; moreover, they noted that the 5-year survival rate in patients without lymph node involvement was 96%, compared with 67% for those with involvement. In the present study, in which we compared the prognostic factors determined in early-stage EC cases, the histological type of EC showed a significant difference in LVSI positivity [OR: 1.72 (0.78-3.78) 95% CI].

Histological grade has been identified as an independent predictor of recurrence in EC[20]. Additionally, in the PORTEC 1 trial, the results of multivariate analysis confirmed the significance of grade 3 disease for locoregional recurrence[21]. The histological high grade (grade 3) and LVSI positivity were associated with a high statistical significance in the present study [OR: 1.98 (1.20-3.20) 95% CI].

In the staging system for EC, malignant peritoneal cytology is no longer sufficient to upstage the T stage, according to FIGO[10]. In a study by Scott et al.[22], malignant peritoneal cytology was not significantly associated with cure and overall survival in low- and intermediate-risk EC patients. In EC, malignant peritoneal cytology refers to tumor cells in a peritoneal fluid sample taken during surgery. This was once a component of the EC staging criteria but is no longer included in the current revision. However, many associations and organizations still recommend cytological sampling in EC surgery[23]. This study found a significant correlation between malignant peritoneal cytology and LVSI positivity [OR: 3.06 (1.40-6.30) 95% CI].

In stage 2 early-stage EC, the tumor involves the cervix but not beyond the serosa, and there is no endocervical gland involvement[10]. In a study by Toprak et al.[24], a primary tumor diameter of at least 3 cm and an LVSI of at least 50% were determined to be independent markers of cervical involvement in women with EC. Therefore, tumor diameter was not included in our predictive model; additionally, there was no endocervical gland involvement in the patients included, and the tumor did not exceed the serosa. In the present study concerning patients with early-stage EC, a noteworthy association was determined between cervical stromal involvement of EC and LVSI positivity [OR: 1.78 (0.85-3.71) 95% CI].

Study Limitations

It is essential to acknowledge that the predictive model we developed has some limitations that need to be considered. Specifically, the study was conducted retrospectively, and multiple pathologists were involved in evaluating the pathology results. Additionally, the research was conducted in a single-center setting, limiting the generalizability of our findings.

Conclusion

Age, menopausal status, histological type, tumor grade, degree of myometrial invasion, peritoneal cytology, and cervical involvement may predict LVSI positivity in early-stage EC. Clinical consultancy services can be provided by evaluating risk factors using nomograms based on predictions.

Ethics

Ethics Committee Approval: The Gaziantep University Faculty of Medicine Clinical Research and Ethics Committee approved this study (ethical approval no: 2022/258, date: 31.08.2022).

Informed Consent: All patients who participated in the study signed a consent form.

Authorship Contributions

Surgical and Medical Practices: İ.T., M.H.B., F.Ç., S.S., E.Y., Ö.B., Concept: İ.T., M.H.B., E.Y., Ö.B., Design: İ.T., M.H.B.,

H.Ö., Data Collection or Processing: İ.T., S.S., H.Ö., E.U., Analysis or Interpretation: İ.T., E.Y., Ö.B., H.Ö., E.U., Literature Search: İ.T., H.Ö., E.U., Writing: İ.T., M.H.B., F.Ç., E.U.

Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer 2016;26:2-30.
3. Sung S, Abramovitz A. Postmenopausal Bleeding. In: StatPearls. Treasure Island (FL): StatPearls Publishing.https://www.ncbi.nlm.nih.gov/books/NBK562188/ accessed September 18, 2022.
4. Sakna NA, Elgendi M, Salama MH, Zeinhom A, Labib S, Nabhan AF. Diagnostic accuracy of endometrial sampling tests for detecting endometrial cancer: a systematic review and meta-analysis. BMJ Open 2023;13:e072124.
5. Lau HY, Chen MY, Ke YM, Chen JR, Chen IH, Liou WS, et al. Outcome of ovarian preservation during surgical treatment for endometrial cancer: A Taiwanese Gynecologic Oncology Group study. Taiwan J Obstet Gynecol 2015;54:532-6.
6. Oliver-Perez MR, Padilla-Iserte P, Arencibia-Sanchez O, Martin-Arriscado C, Muruzabal JC, Diaz-Feijóo B, et al. Lymphovascular Space Invasion in Early-Stage Endometrial Cancer (LySEC): Patterns of Recurrence and Predictors. A Multicentre Retrospective Cohort Study of the Spain Gynecologic Oncology Group. Cancers (Basel) 2023;15:2612.
7. Amkreutz LCM, Pijnenborg JMA, Joosten DWL, Mertens HJMM, Van Kuijk SMJ, Engelen MJA, et al. Contribution of cervical cytology in the diagnostic work-up of patients with endometrial cancer. Cytopathol Off J Br Soc Clin Cytol 2018;29:63-70.
8. Phelippeau J, Canlorbe G, Bendifallah S, Naoura I, Lefevre M, Ballester M, et al. Preoperative diagnosis of tumor grade and type in endometrial cancer by pipelle sampling and hysteroscopy: Results of a French study. Surg Oncol 2016;25:370-7.
9. Restaino S, Tortorella L, Dinoi G, Zannoni GF, Baroni A, Capasso I, et al. Semiquantitative evaluation of lymph-vascular space invasion in patients affected by endometrial cancer: Prognostic and clinical implications. Eur J Cancer 2021;142:29-37.
10. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. Endometrial Cancer Staging Subcommittee, FIGO Women's Cancer Committee. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet 2023;162:383-94.
11. Veade AE, Foote J, Ehrisman J, Broadwater G, Davidson BA, Lee PS, et al. Associations between lymphovascular space invasion, nodal recurrence, and survival in patients with surgical stage I endometrioid endometrial adenocarcinoma. World J Surg Oncol 2019;17:80.
12. Matsuo K, Matsuzaki S, Nusbaum DJ, Machida H, Nagase Y, Grubbs BH, et al. Malignant peritoneal cytology and decreased survival of women with stage I endometrioid endometrial cancer. Eur J Cancer 2020;133:33-46.
13. Wang J, Li X, Yang X, Wang J. Development and Validation of a Nomogram Based on Metabolic Risk Score for Assessing Lymphovascular Space Invasion in Patients with Endometrial Cancer. Int J Environ Res Public Health 2022;19:15654.
14. Hu Y, You S, Yang Z, Cheng S. Nomogram predicting survival of hepatocellular carcinoma with portal vein tumour thrombus after curative resection. ANZ J Surg 2019;89:E20-5.
15. Jolly S, Vargas CE, Kumar T, Weiner SA, Brabbins DS, Chen PY, et al. The impact of age on long-term outcome in patients with endometrial cancer treated with postoperative radiation. Gynecol Oncol 2006;103:87-93.
16. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med 2018;178:1210-22.
17. Ayhan A, Şahin H, Sari ME, Yalçin I, Haberal A, Meydanli MM. Prognostic significance of lymphovascular space invasion in low-risk endometrial cancer. Int J Gynecol Cancer 2019;29:505-12.
18. Doghri R, Chaabouni S, Houcine Y, Charfi L, Boujelbene N, Driss M, et al. Evaluation of tumor-free distance and depth of myometrial invasion as prognostic factors in endometrial cancer. Mol Clin Oncol 2018;9:87-91.
19. Malik TY, Chishti U, Aziz AB, Sheikh I. Comparison of Risk Factors and Survival of Type 1 and Type II Endometrial Cancers. Pak J Med Sci 2016;32:886-90.
20. Bak SE, Yoo JG, Lee SJ, Yoon JH, Park DC, Kim SI. Prognostic significance of histological grade in low-risk endometrial cancer. Int J Med Sci 2022;19:1875-8.
21. Creutzberg CL, Nout RA, Lybeert ML, Wárlám-Rodenhuis CC, Jobsen JJ, Mens JW, et al; PORTEC Study Group. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys 2011;81:e631-8.
22. Scott SA, van der Zanden C, Cai E, McGahan CE, Kwon JS. Prognostic significance of peritoneal cytology in low-intermediate risk endometrial cancer. Gynecol Oncol 2017;145:262-8.
23. Abu-Rustum N, Yashar C, Arend R, Barber E, Bradley K, Brooks R, et al. Uterine Neoplasms, Version 1.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2023;21:181-209.
24. Toprak S, Sahin EA, Sahin H, Tohma YA, Yilmaz E, Meydanli MM. Risk factors for cervical stromal involvement in endometrioid-type endometrial cancer. Int J Gynaecol Obstet 2021;153:51-5.