

The Role of Lymphovascular Space Invasion and Cytology in the Prognosis of Endometrial Cancer

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Background: Lymphovascular space invasion (LVSI) and cytology are both independent and strong prognostic factors in endometrial cancer. This study aims to highlight the impact of LVSI and cytology positivity on prognosis, in addition to molecular classification.

Methods: A retrospective review was conducted on the records of 223 patients with endometrial cancer diagnosed between January 2011 and January 2021. The inclusion criteria stipulated that the patients were diagnosed with endometrial cancer by endometrial biopsy and were operated in the clinic. The exclusion criteria included sarcoma in the postoperative pathology report results or synchronous tumor. Staging was performed according to the Fédération internationale de gynécologie et d'obstétrique (FIGO) 2009 criteria. Cytology (using 50 cc saline) was obtained upon entry into the peritoneal cavity. In 20 patients, saline was not used due to the presence of ascites in the abdomen. The Kaplan-Meier method was employed to evaluate overall survival and progression-free survival. Survival rates were compared in terms of cytology and LVSI.

Results: After analyzing the postoperative pathology results, it was found that the mean tumor size was 4.03 ± 2.3 cm. The most common histological type was endometrioid carcinoma, with stage IA being the most common stage. Out of 223 patients with endometrial cancer, the overall survival rate was 82.4%, and the progression-free survival rate was 88.3%. For patients negative for LVSI, the progression-free survival rate was 93%, while for LVSI-positive patients, it was 77.3% ($p < 0.001$). Additionally, the progression-free survival rate for patients negative for cytology was 90.4%, whereas for cytology-positive patients, it was 77.1% ($p < 0.05$).

Conclusions: In our study, we observed that LVSI positivity and cytology positivity also reduced the overall survival rate. We aimed to highlight that, in addition to molecular classification, cytology positivity and LVSI positivity are still highly significant and independent factors in prognosis.

Keywords: endometrial carcinoma; lymphovascular space invasion; cytology; survival

Introduction

Endometrial carcinoma is the sixth most commonly diagnosed cancer in women worldwide and the 14th cause of cancer death in women [1]. The American Cancer Society reported that an estimated 61,880 new cases will be diagnosed in the United States in 2022, and 12,550 women will die from endometrial cancer [2]. The incidence of endometrial cancer is increasing due to the rise in life expectancy and obesity worldwide [3]. Lymphovascular space invasion (LVSI) is independently associated with nodal metastases, recurrence, and poor survival [4]. LVSI is defined as the presence of tumor cells in the channels surrounded by endothelium outside the main tumor in the

uterus [5]. LVSI is associated with an increased risk of disseminated disease and reduced overall survival [6]. One such prognostic factor may be malignant peritoneal cytology, which was an element of the Fédération internationale de gynécologie et d'obstétrique (FIGO) cancer staging system before the 2009 revision [7]. Peritoneal wash cytology is a diagnostic technique based on the detection of cancer cells that are shed from the primary focus and spread into the abdomen [8]. Although peritoneal cytology has been removed from the endometrial cancer staging system, National Comprehensive Cancer Network (NCCN) guidelines continue to recommend the evaluation of peritoneal cytology [9]. In this study, we aimed to emphasize the importance of LVSI and cytology in endometrial cancer.

Materials and Methods

Patients

The study was approved by Afyonkarahisar Health Sciences University Ethics Committee's decision numbered 2011-KAEK-2 and dated 03/09/2021. The study was conducted in accordance with the Declaration of Helsinki. Patients who were operated with the diagnosis of endometrial cancer between January 2011 and January 2021 were included in our study, which was designed retrospectively. The inclusion criteria for the study were that the patient was diagnosed with endometrial cancer as a result of an endometrial biopsy pathological examination and was operated on in the clinic. Exclusion criteria were sarcoma or synchronous tumor in the postoperative pathology report results and no preoperative endometrial sampling. As a result, 223 patients were included in the study. Consent was obtained from all patients during their hospitalization. The patient's age, height, and weight were recorded. The surgical procedure included a total extra fascial hysterectomy, bilateral salpingo-oophorectomy, and omental biopsy with lymph node sampling.

Cytology

Cytology was performed using 50 cc saline upon entry into the peritoneal cavity. Cases in which malignant cells were detected in the peritoneal wash cytology were considered positive. In 20 patients, saline was not used due to the presence of ascites in the abdomen. Pelvic lymph nodes were removed from the distal one-half of the common iliac artery down to the circumflex iliac vein, and nodal tissue was removed anterior to the obturator nerve and surrounding the iliac arteries and vein.

Sample Evaluation

Para-aortic lymph node sampling was performed based on the preoperative pathology results, preoperative imaging methods, and intraoperative exploration. The staging was conducted according to the FIGO 2009 criteria. Serous and clear cell cancer types were classified as Grade 3. Survival rates were compared in terms of cytology and LVSI.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics (Version 26.0. Armonk, NY, USA) for Windows. Time-to-event analyses were conducted using the Kaplan-Meier method and log-rank test. Statistical significance was defined when $p < 0.05$.

Results

The mean age of the patients was 59.7 ± 9.6 (range: 39–83 years). Out of the 223 patients with endometrial carcinoma, 126 patients (56.5%) were surgically staged

Table 1. Pathology findings.

	No. of patients	%
Surgical stage		
IA	92	41.3
IB	66	29.6
II	14	6.3
IIIA	14	6.3
IIIB	0	0
IIIC1	16	7.2
IIIC2	2	0.9
IVA	5	2.1
IVB	14	6.3
Histology		
Endometrioid adenocarcinoma	188	84.4
Clear cell carcinoma	3	1.3
Serous carcinoma	20	9
Malignant Mix Mullerian Tumor	11	4.9
Mucinous carcinoma	1	0.4
Grade		
1	85	38.1
2	79	35.4
3	59	26.5
Lymphovascular space invasion		
Negative	157	70.4
Positive	66	29.6
Myometrial invasion		
No invasion	22	9.9
<1/2	88	39.5
≥1/2	113	50.6
Cytology		
Positive	35	15.7
Negative	188	84.3
Cervical involvement		
Positive	39	17.5
Negative	184	82.5

through laparoscopy and 97 (43.5%) through laparotomy. Pelvic lymph node sampling was performed in 190 patients (85.2%), and pelvic and para-aortic lymph node sampling was performed in 33 patients (14.8%). The mean number of lymph nodes obtained was 14.11 ± 8.9 .

According to the postoperative pathology results, the mean tumor size was 4.03 ± 2.3 cm. The most common histological type was endometrioid carcinoma and stage IA was the most common stage. Lymphovascular space invasion was detected in 66 (29.6%) of the 223 cases evaluated for analysis, with 157 (70.4%) patients testing negative. Additionally, 35 (15.7%) patients had positive cytology results. The grades and staging of the postoperative pathology results of the patients are summarized in Table 1. The overall survival of endometrial cancers was 82.4%, and the recurrence-free survival was 88.3%. During the follow-up period, recurrence was found in 26 patients (Table 2). Vaginal examination and imaging methods (MRI, CT, PET-CT) were used to detect recurrence.

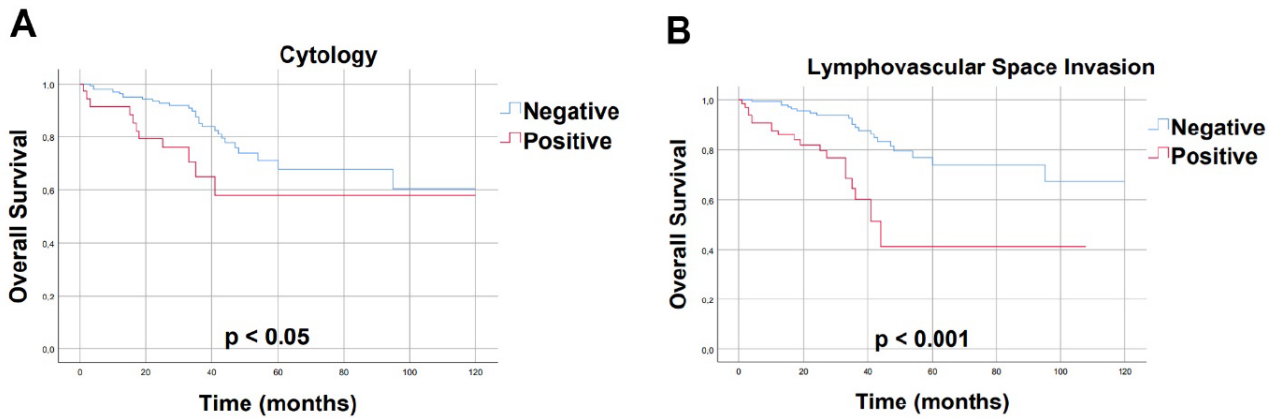


Fig. 1. Overall survival rates. (A) Overall survival rates with respect to cytology. (B) Overall survival rates with respect to lymphovascular space invasion.

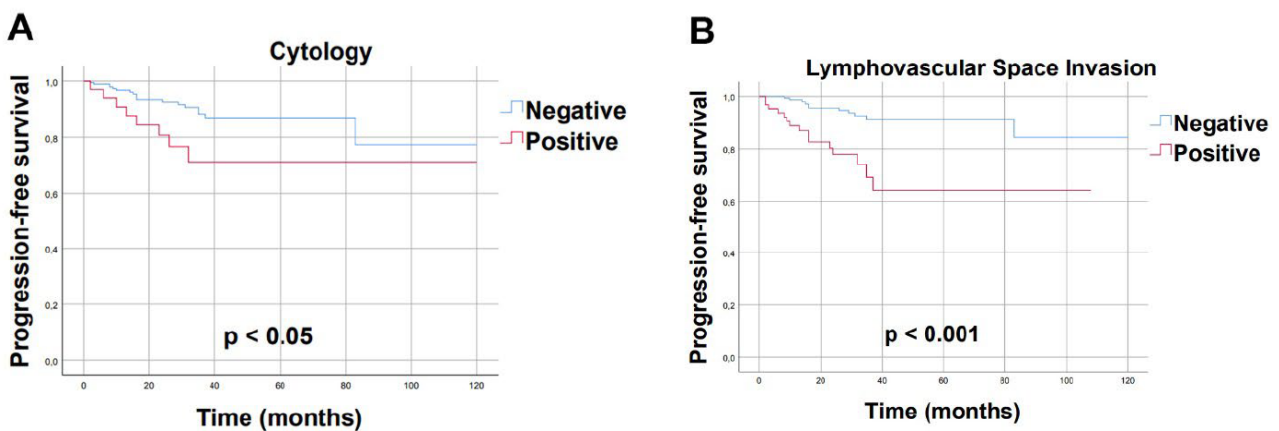


Fig. 2. Progression-free survival rates. (A) Progression-free survival rates with respect to cytology. (B) Progression-free survival rates with respect to lymphovascular space invasion.

Table 2. Cases with recurrence.

Recurrence site	No. of patients
Pelvic lymph node	4
Vaginal cuff	6
Parietal peritoneum	3
Pulmonary	8
Para-aortic lymph nodes	3
Hepatic	1
Port-site metastasis	1
Total	26

Survival rates were compared in terms of cytology and LVSI (Fig. 1). Additionally, progression-free survival rates were compared in terms of cytology and LVSI (Fig. 2). The overall 5-year survival of cytology-negative patients was 84.6%, and for cytology-positive patients, it was 68.6% ($p < 0.05$). The overall survival (OS) of LVSI-negative patients was 86.6%, while it was 71.2% in LVSI-positive patients ($p < 0.001$).

The 5-year progression-free survival (PFS) rate was 88.3%. The 5-year PFS rate was 93% for LVSI-negative

patients and 77.3% for LVSI-positive patients ($p < 0.001$). Additionally, the 5-year PFS rate was 90.4% for cytology-negative patients and 77.1% for cytology-positive patients ($p < 0.05$).

Discussion

In our study, the average age of onset of endometrial cancer was 59.7 ± 9.6 years. Endometrial cancer is typically observed in the postmenopausal period, with an average onset age of 63 years [10]. It is uncommon in women under 45 years old. We also found that survival rates were higher in patients aged 40 years and younger compared to those over 40 years old [11].

The 5-year survival rates for endometrial cancer are as follows: 74–91% for stages 1–2, 57–66% for stage 3, and 20–26% for stage 4 [9]. A recent study in Turkey reported an overall survival rate of 85% [12]. Hamilton *et al.* [13] found that the 5-year PFS was 80% for stage I/II, 29% for stage III, and 10% for stage IV. Eltabbakh *et al.* [14] reported a 5-year disease-free survival of 95.2% and an overall survival of 96.4%. In our clinic, the overall survival was 82.4%, and the progression-free survival was 88.3%.

Laparoscopy is a viable alternative to conventional laparotomy and does not worsen the prognosis of patients with early endometrial carcinoma. The 5-year PFS rates in the laparoscopy and laparotomy groups were 95.5% and 96.5%, respectively [15]. Minimally invasive techniques have recently been proven as safe alternatives for surgical staging, with less morbidity and quick recovery. A shorter hospital stay and a lack of significant difference in intra-operative complication rates have led to increased use of laparoscopy in the current approach.

It has been found that the integration of molecular classification into pathological diagnosis may be crucial for improving the prognosis assessment and clinical management of patients with endometrial cancer (EC). Piulats *et al.* [16] suggested that combining pathologic classification and the surrogate The Cancer Genome Atlas (TCGA) molecular classification for high-grade EC could be an option to improve the assessment of prognosis in EC patients. Leon-Castillo *et al.* [17] found that the molecular endometrial cancer classification has independent prognostic value among women with high-grade EC. Although molecular markers have gained prominence in recent years, classical poor prognostic factors should not be ignored and should be specifically mentioned in the pathological evaluation of each case. Raffone *et al.* [18] reported that LVSI has a prognostic value independent of TCGA signature, as well as age and adjuvant treatment, increasing the risk of death of any cause, death due to EC, and recurrent or progressive disease by 1.5–2 times. Jamieson *et al.* [19] found that molecular classification in EC was significantly associated with lymph node metastases, and molecular classification can be obtained from preoperative biopsies and used to guide surgical decision-making.

Lymphovascular space invasion is a marker of nodal disease in endometrial cancers and is considered an independent risk factor for recurrence and death in all stages of the disease [20]. In stage 1 endometrial cancer cases, lymphovascular invasion has been correlated with high mortality rates [21]. Briët *et al.* [22] reported that patients with LVSI are more likely to have pelvic lymph node metastases (PLNM) compared to those without LVSI, and relapses occur more frequently in patients with LVSI. Additionally, Hui *et al.* [23] found that abnormal p53 correlated with increased rates of local failure, and patients who had both abnormal p53 and any LVSI had worse overall survival and increased local and regional failure compared to patients without these risk factors. Similar to the literature, we found that LVSI positivity is a poor prognostic factor.

Peritoneal cytology was excluded in the FIGO 2009 staging system. However, several studies have indicated that patients with positive cytology have lower survival rates [24–26]. The National Comprehensive Cancer Network (NCCN) guidelines maintain that it should be performed in women with endometrial cancer and that the diagnostic information should be recorded, as positive cytology

is considered an adverse risk factor [27]. Although cytology does not directly affect FIGO staging, its results should still be obtained due to the adverse risk associated with positive cytology [9]. In our study, the 5-year OS of cytology-negative patients was 84.6%, while the OS of cytology-positive patients was 68.6% ($p < 0.05$). A study by Siesto *et al.* [28] showed that cytology-negative patients have higher progression-free and overall survival rates ($p < 0.001$). Matsuo *et al.* [29] reported that malignant peritoneal cytology was associated with increased all-cause mortality compared with negative peritoneal cytology. Our study, in line with the existing literature, found that cytology positivity was associated with a poor prognosis.

In 2023, FIGO published a new staging system for endometrial cancer, which now includes LVSI as part of the new staging system. However, cytology is still not included in the new staging system [30].

Our study has some limitations. The majority of our patient group has early-stage endometrial cancer, and our study is retrospective. The exclusion criteria of sarcoma or synchronous tumor in the postoperative pathology report results may have caused a higher surveillance of uterine cancers in our study, and molecular classification was not evaluated.

Conclusions

In conclusion, LVSI positivity and cytology positivity are independent and strong prognostic factors. Our study found that LVSI positivity and cytology positivity are associated with a reduction in the overall survival rate. This study emphasizes that, in addition to molecular classification, cytology positivity and LVSI positivity remain crucial in prognosis.

Availability of Data and Materials

All data are available from the corresponding author upon reasonable request.

Author Contributions

CYO: Conception and design, analysis of data, drafting of the manuscript, writing the article; DTA: Critical revision of the manuscript, control/Supervision, conception and design; NC: Acquisition of data, participated in drafting; MC: Technical and material support, analysis and interpretation of data, critical revision; FB: Statistical analysis, critical revision; SY: Control/Supervision, conception and design, critical revision; NV: Technical and material support, acquisition of data, participated in drafting; FC: Writing the article, acquisition of data. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by Afyonkarahisar Health Sciences University Ethics Committee's decision numbered 2011-KAEK-2 and dated 03/09/2021. The study was conducted in accordance with the Declaration of Helsinki. Consent was obtained from all patients during their hospitalization.

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Conflict of Interest

The authors declare no conflict of interest.

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