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The Prognostic Significance of LVSI in Early-Stage Endometrioid Endometrial Cancer: Insights into Recurrence Patterns and Survival Outcomes

Fatemeh Sadat Najib[*, **], MD, Parisa Yazdanshenas[*], MD, Mojgan Akbarzadeh Jahromi[*, ***], MD, Zahra Shiravani[***, ****♦], MD

[*]*Department of Obstetrics and Gynecology, Shiraz University of Medical Sciences, Shiraz, Iran*
[**]*Infertility Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[***] *Department of Obstetrics and Gynecology, Division of Oncology Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[****]*Maternal-Fetal Medicine Research Center, Department of Obstetrics and Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*

♦Corresponding Author
Zahra Shiravani, MD
1-Department of Obstetrics and Gynecology, Division of Oncology Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
2-Maternal-fetal medicine Research Center, Department of Obstetrics and Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz
Email: zahrashiravani@yahoo.com
shirvanizahra63@gmail.com

Abstract

Background: Endometrioid endometrial cancer (EEC) is a significant disease among women worldwide. The present study aimed to investigate the role of lymphovascular space invasion (LVSI) detection in recurrence and survival rates in patients with early-stage (stage I) EEC.

Method: This retrospective study included 234 patients diagnosed with stage I EEC. Considering the demographic information and EEC history, we evaluated the presence of LVSI and its association with recurrence rate, overall survival, and recurrence-free survival. Kaplan-Meier analysis was used to compare survival outcomes between patients with and without LVSI. Statistical analyses were conducted using SPSS software (version 22.0; IBM Corporation, USA). Kaplan-Meier analysis and log-rank tests were used for survival analysis, and $P < 0.05$ was considered to be significant.

Results: Of 234 patients, 17 relapsed and 8 died. The average time to recurrence was approximately 2.5 years, with vaginal recurrence being the most common. LVSI was identified in 7 patients and was associated with poorer overall survival, but did not predict recurrence-free survival. Patients with LVSI showed a higher risk of recurrence and shorter survival intervals. Stage IA patients with LVSI had relatively high survival probability, while stage IB (myometrial invasion ≥ 50%) patients with LVSI had much poorer outcomes.

Conclusion: LVSI is a critical prognostic factor in early-stage EEC, significantly affecting overall survival. Our study highlights the importance of advanced surveillance and more aggressive treatment for LVSI-positive patients, especially in stage IB. Standardized LVSI assessment and further research are essential to optimize patient management.

Keywords: Endometrial neoplasms, Neoplasm recurrence, Survival rate, Prognosis, LVSI

Introduction

Endometrioid Endometrial Cancer (EEC) is the sixth most common cancer among women worldwide.[1] Metastasis in EEC is the most important problem in treatment failure and patient survival. Previous studies have shown that metastasis depends on factors that fall into three categories: molecular characteristics of the cancer, hormones such as estrogen, and pro-inflammatory adipocytokines.[2, 3] Altered expression of microRNAs, which affects genes regulation, is another important factor.[4]

EEC originates from the inner lining of the uterus, the endometrium, and is often detected early due to symptoms such as irregular vaginal bleeding.[5, 6] In its early stages, cancer can be cured by surgically removing the uterus.[7] There is no standard screening test to identify EEC; However, tests such as a Pap test, transvaginal ultrasound, and endometrial biopsy may detect EEC.[6, 8] Histopathological parameters can assess risk and assess adjuvant therapy for patients with early-stage (stages I/II) EEC, including histological type, tumor grade, depth of myometrial invasion, and lymphovascular space invasion (LVSI).[9-11] LVSI is defined as the presence of tumor cells within an endothelial-lined vascular space.[12, 13]

LVSI as a prognostic factor predicts higher rates of pelvic and distant recurrence in EEC.[13] The presence of LVSI in hysterectomy specimens is graded with a two-tier scoring system, but based on studies a three-tier system (absent vs. focal vs. significant) may provide a better prognosis and more tailored approaches to adjuvant therapy.[14] LVSI has been found in 3.2%-35% of in stage I EEC, and several studies have confirmed the role of LVSI as an independent predictor of poor prognosis in patients with FIGO stage I–III EEC.[15] These studies established that LVSI was associated with a detrimental effect on disease-free survival and overall survival and a higher rate of distant recurrence and lymph node metastasis.[16, 17] In 2016, the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy and Oncology (ESTRO) and European Society of Gynecological Oncology (ESGO) consensus classified patients with low-risk features, positive LVSI, and incomplete surgical staging into an intermediate-risk class.[9]

Despite the established importance of LVSI in prognosis and treatment planning, the discrepancy in its assessment and reporting is a challenge.[12, 18, 19] Given the variability in the prevalence of LVSI and the lack of discovery of the need for adjuvant treatment or further work in patient follow-up, the present study aimed to investigate the role of LVSI diagnosis in recurrence and survival in patients with early-stage disease to address these gaps.

Method

Study design

We designed this retrospective study to investigate the incidence of LVSI histology in patients with EEC. After obtaining permission from the Medical Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1403.435), the electronic database and files of patients who underwent surgery at medical centers of

Shiraz University of Medical Sciences and were being followed up at Motahari Tumor Clinic were evaluated. We evaluated LVSI among patients with early-stage EEC, regardless of recurrence. All patient data were anonymized and de-identified prior to analysis to protect patient confidentiality. Total Abdominal Hysterectomy + Bilateral Salpingo-Oophorectomy (TAH+BSO+) Staging was done by gynecologic oncologist. Follow-up records were evaluated, and patients who failed subsequent follow-up were contacted and asked about their status and any signs or symptoms of recurrence. If it was not possible to contact the patient, the patient was excluded from the study. Pathology slides were reviewed by an expert pathologist after examining LVSI.

Patients in this study were diagnosed with EEC, stages IA, IB, and G1-3, and those underwent surgery between 2014-2020. The exclusion criteria were: 1) patients without follow-up whose contact numbers was also unavailable, 2) missing pathology report, 3) advanced stage EEC, 4) any other pathologies of EEC, 5) TAH + BSO + staging is performed by general gynecologists.

Data collection

Our data included demographic, clinical, and surgical variables, as well as patient's age at first diagnosis, year of operation, recurrence, time and location of recurrence, last follow-up, and survival. Cases were staged according to the 2018 FIGO staging system,[20] and histology and tumor grade were assessed according to the World Health Organization (WHO) classification system, 2020 edition, and FIGO criteria. According to the 2018 FIGO staging system, stage IA was defined as tumor invasion limited to less than half (< 50%) of the myometrium, and stage IB was defined as tumor invasion of half (≥ 50%) or more of the myometrium. Survival is defined as the time from surgery to the patient's death from any cause, including the tumor. In survival analysis, patients without contact at their last follow-up were censored.

LVSI assessment

LVSI was classified as present or absent, and clinicopathological factors were compared between LVSI-negative and LVSI-positive patients. Kaplan-Meier survival analyses (log-rank tests) was used to identify recurrence and survival by LVSI. Statistical analyses were conducted using SPSS software (version 22.0; IBM Corporation, USA). Kaplan-Meier analysis and log-rank tests were used for survival analysis, and $P < 0.05$ was considered to be significant.

Results

Based on the inclusion and exclusion criteria, 234 patients were evaluated in this study. The mean age of the patients was 55 years. A review of surgical history in patients with EEC showed that, on average, about six years had passed since their diagnosis. The disease stage of the patients was approximately 82% in IA and 18% in IB. The distribution of disease grade was 1, 2, and 3 in 71, 24, and 5 percent of patients, respectively (Table 1). Table 1 represents data from 234 patients diagnosed with early-stage (stage I) EEC. Two groups were defined based on the disease stage: stage IA and stage IB (FIGO stage I with myometrial invasion ≥ 50%). Within these stages, patients were further categorized by disease grade (1, 2, or 3).

Reviewing disease recurrence showed that 7.29% of patients reported positive recurrence and eight patients had died. The most common site of recurrence was the vagina, followed by the bladder and gastrointestinal tract and recurrence was recorded in patients approximately 2.5 years after surgery (Table 2).

LVSI was identified in 7 patients (3% of the study population), with focal LVSI observed in 4 cases and recurrent LVSI in 3 cases. Patients with recurrent LVSI showed significantly poorer survival outcomes

compared with patients with focal LVSI. To ensure accuracy, the differential diagnosis of LVSI was carefully performed by an expert pathologist, and LVSI was distinguished from mimics such as contractile artifact, thrombosis, and inflammation. Kaplan-Meier analysis comparing recurrence-free survival between patients with and without LVSI in early-stage EEC (Figure 1) showed no significant difference between the groups. The log-rank test for recurrence-free survival distributions confirmed that there was no significant difference ($P = 0.958$) between these groups. However, survival analysis showed that patients with recurrent LVSI had shorter time intervals to recurrence and higher recurrence rates compared with patients with focal LVSI.

Our findings highlight the importance of accurate identification and reporting of LVSI, as it plays a crucial role in the prediction and treatment planning for EEC in the early stages. The differential diagnosis of LVSI is particularly challenging and requires differentiation from artifacts such as tissue compaction, thrombosis, or inflammatory changes. This study emphasizes the need for a standardized approach to LVSI assessment to minimize interobserver variability. Furthermore, the distinction between focal and recurrent LVSI appears clinically significant, as recurrent LVSI is associated with significantly worse outcomes, including higher recurrence rates and shorter survival intervals. These findings reinforce previous research suggesting that a three-level LVSI classification system—absent, focal, and significant—may have greater prognostic value compared with a binary system.

Kaplan-Meier analysis was performed to compare survival of patients with and without LVSI in early-stage EEC (Figure 2). Patients without LVSI had a higher probability of survival over time compared with LVSI patients. The result of the log-rank test was statistically significant ($P < 0.001$), indicating a significant difference in survival between patients with and without LVSI. Specifically, patients with LVSI had higher survival rates and shorter recurrence-free intervals than patients without LVSI.

Kaplan-Meier analysis was performed to evaluate recurrence-free survival in stage 1A EEC patients, stratified by the presence of LVSI (Figure 3A). Due to the presence of multiple censored data points and the absence of duplicate events, no statistical comparisons were performed. The blue line representing patients without LVSI remained relatively high throughout the follow-up period with several censored data. The green line, which represents patients for whom LVSI data are missing, follows a similar pattern to the blue line, with a gradual decrease over time.

Kaplan-Meier analysis was performed to assess recurrence-free survival in stage IB EEC patients stratified by the presence of LVSI (Figure 3B). The blue line represents patients without LVSI and the cumulative recurrence-free survival probability shows a gradual decline over time in such a way that the censored data points (marked with a cross) represent patients who were recurrence-free at their last follow-up. The cumulative recurrence-free survival probability in the green line representing patients with LVSI is lower compared with the group without LVSI, with censored data points representing patients who were the same at their last follow-up. The log-rank test indicated a statistically significant difference between the two groups ($P < 0.001$). This result suggests that patients with LVSI have a significantly higher recurrence rate and shorter recurrence-free intervals compared with those without LVSI.

Kaplan-Meier curves were generated for survival in patients with stage 1A EEC stratified by the presence of LVSI (Figure 4 A). This design includes two groups: patients with LVSI and patients without LVSI. Both

groups had a high probability of survival during the follow-up period. The survival probability was relatively high, with no clear difference between the LVSI and non-LVSI groups over time. The presence of numerous censored data points indicates that many patients did not experience recurrence during the study period or were lost to follow-up.

The Kaplan-Meier analysis was performed to compare survival between patients with and without LVSI in stage IB EEC (Figure 4B). The survival probability for patients without LVSI remained higher over time compared with LVSI patients. Patients without LVSI (blue line) had a higher cumulative survival probability during the follow-up period, with many censored data points indicated by blue crosses. Patients with LVSI (green line) showed a lower cumulative survival probability with censored data points indicated by a green cross. The log-rank test showed a statistically significant difference in survival between the two groups ($P < 0.0001$). This result suggests that stage IB patients with LVSI have significantly higher recurrence rates and shorter recurrence-free intervals than patients without LVSI.

Discussion

This study provides valuable insights into the prognostic significance of LVSI in early-stage EEC. Among 234 patients included in the analysis, LVSI was identified in 7 cases and associated with poorer overall survival, particularly in stage IB (myometrial invasion ≥ 50%) patients, while no significant difference in recurrence-free survival was observed. The average time to recurrence was approximately 2.5 years, with vaginal recurrence being the most common. These findings emphasize the critical role of LVSI as a prognostic factor, particularly in stage IB EEC, highlighting the need for targeted surveillance and treatment protocols.

Assessing age showed the mean age of 55 years for patients. It is widely known that EEC is usually diagnosed in postmenopausal women, with less than 4 percent of patients are younger than 40 years.[21] Type I EEC, as a mainly estrogen-dependent with endometrioid morphology, account for approximately 80% of EEC usually diagnosed at an early stage and characterized by a good prognostic.[22]

EEC are usually diagnosed at an early stage with the 5-year event-free of 80 and survival rates over 95%.[9,22,23] Since all the patients we studied were in the early stages (Stage I), the results of our study were similar to other studies and had high recurrence and survival rates.

The present study showed that the mean recurrence year was approximately 2.5 years and the vagina was the most common site of recurrence. Previous research also indicated that relapse is most likely to occur within the first three years after initial treatment.[24, 25] For example, in study of the 18 recurrent cases, of the 311 women with stage I, 15 had other tumor samples were available, and the median time to recurrence among these cases was 48 months, with the longest recurrence time being 80 months.[26] The study also showed that the site of recurrence was in the vaginal cuff (53%), pelvic lymph nodes (20%), and para-aortic lymph nodes or elsewhere in the abdomen (27%). In our study, vaginal recurrence had the highest recurrence rate. Of course, other studies also showed the same result, and the interesting thing was that the probability of recovery and survival rate were higher in patients with vaginal recurrence.[24, 25] Our findings highlight the need for enhanced surveillance and potential changes to current protocols for stage I EEC patients.

Our study showed that the presence of LVSI was associated with a higher risk of recurrence and poorer survival outcomes in EEC patients. Although we did not find a significant difference in recurrence-free survival between patients with and without

LVSI, overall survival was significantly shorter in patients with LVSI. Various studies have underscored the importance of LVSI detection in patients' recurrence and survival. For example, in one study, LVSI was identified in 129 of 928 patients with EEC. This study demonstrated that significant LVSI is a strong independent prognostic factor for recurrence, metastasis, and survival.[12] Or even the number of positive LVSI vessels and the risk of pelvic lymph node recurrence were calculated in a more detailed study. This study on Danish gynecological cancer data showed that a numerical threshold (≥4 vessels with LVSI on at least one Hematoxylin and Eosin (H&E) slide) could be proposed to define clinically relevant LVSI in EEC patients.[27]

Despite the results showing that patients with LVSI had a higher risk of recurrence and shorter intervals to recurrence compared with patients without LVSI, another important aspect of our analysis was the presence of censored data points. Censored data represent patients who were lost to follow-up. Kaplan-Meier curves for stage IA highlight the favorable prognosis for patients without LVSI. The presence of several censored data points suggests that most patients should not experience a relapse by the end of the study period.

Comparing stage IA with stage IB showed that LVSI appeared to be a more important prognostic factor in stage IB compared with stage IA. In stage IA, the high recurrence-free survival rate and lack of recurrence events (censored data) suggest that LVSI does not have a significant impact on outcomes at this stage. Conversely, in stage IB, LVSI significantly affects recurrence-free survival, indicating poorer outcomes for patients with LVSI.

Although no statistical comparisons were performed in survival assessment due to the censored nature of the data, the high survival probability observed in both groups (with and without LVSI) suggests that stage IA patients generally have favorable outcomes with maximal survival during the study period. As discussed, in stage IA, high censored data points indicate that these patients are likely to be relapse-free and even alive at last follow-up.

Our results emphasize the critical role of LVSI in influencing survival rates in stage IB EEC. The significant difference in survival rates between patients with and without LVSI suggests the need for more aggressive surveillance and potential adjuvant therapy for patients with LVSI. The presence of censored data points emphasizes the importance of complete follow-up to accurately record recurrence events and survival outcomes.

The difference in the impact of LVSI on recurrence-free survival between stages IA and IB emphasizes the importance of stratifying patients by disease stage when evaluating prognostic factors. For stage IA patients, the focus should remain on maintaining a favorable prognosis, whereas for stage IB patients, identification and management of LVSI is crucial to improve outcomes.

This study has several limitations, including a relatively small sample size that may affect the generalizability of the findings, and variability in LVSI assessment methods among different pathologists, which could have influenced the results. Despite these limitations, our study demonstrates the importance of improving our understanding of the prognostic significance of LVSI and enhancing clinical management for patients with early-stage EEC. To build on these findings, future research should prioritize standardized LVSI assessment methods and larger sample sizes to provide stronger insights, while also investigating the molecular mechanisms underlying vaginal

recurrence in stage I EEC patients as a promising direction for further study.

Conclusion

The present study indicate that although LVSI does not predict recurrence-free survival, it is significantly associated with poorer overall survival in early-stage EEC. This association is particularly pronounced in stage IB patients (myometrial invasion ≥ 50%), highlighting the need for increased surveillance and more aggressive treatment protocols for LVSI-positive patients. Standardized LVSI assessment and further research are essential to optimize patient management strategies.

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Authors' Contributions

Z.Sh: Study design, experimental setup, data analysis, supervision, writing-review and editing

F.N: Study design, experimental setup, writing-review and editing, final approval

P.Y: Data collection, data analysis, writing-original draft preparation

M.A.J: Statistical analysis, data interpretation, supervision, writing-review and editing

All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Table 1. Demographic and disease characteristics of patients with early-stage (stage I) EEC

Age	Years have passed since the surgery	Disease stage		Grade of disease		
		IA	IB	1	2	3
55.12 ± 9.67	6.30 ± 6.73	82.40%	18.02%	70.81%	24.46%	4.72%

EEC: Endometrioid endometrial cancer

Table 2. Recurrence sites and time to recurrence in patients with early-stage (stage I) EEC

Site of recurrence				Year of recurrence after surgery
Vagina	Bladder, Liver, and Gastrointestinal	Pelvic and Bone	Abdomen	2.45 ± 1.84
4.29	2.14	0.85	1.28	

EEC: Endometrioid endometrial cancer

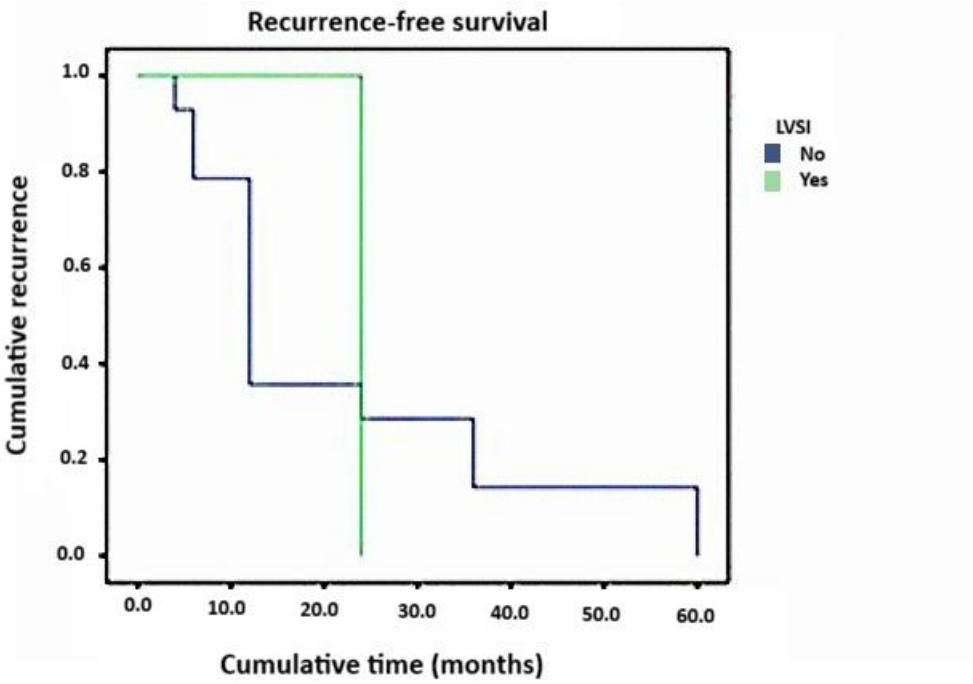

Figure 1. This figure shows the comparison of recurrence-free survival probabilities over time between patients with and without LVSI, analyzed using Kaplan-Meier methodology.
LVSI: Lymphovascular space invasion

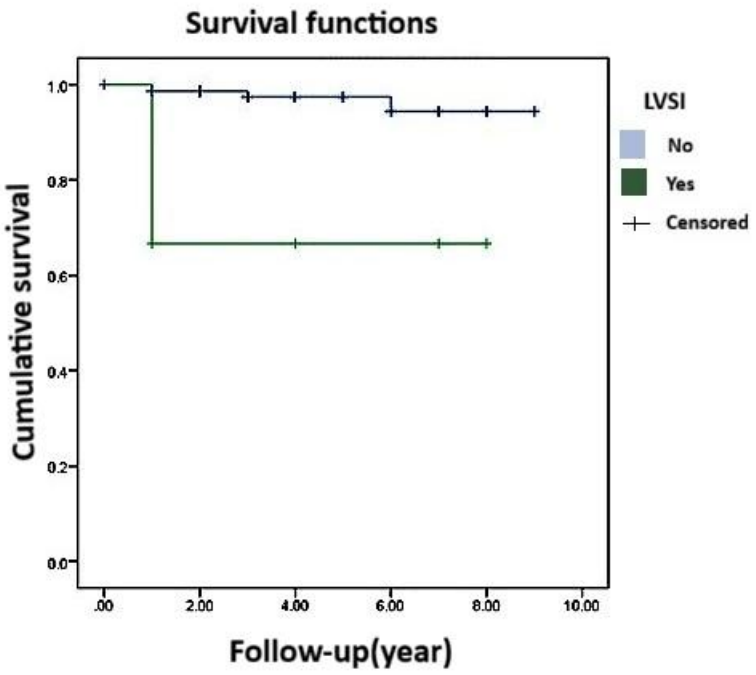

Figure 2. This figure shows Kaplan-Meier analysis of survival functions, comparing cumulative survival probabilities over time between patients with and without LVSI.
LVSI: Lymphovascular space invasion

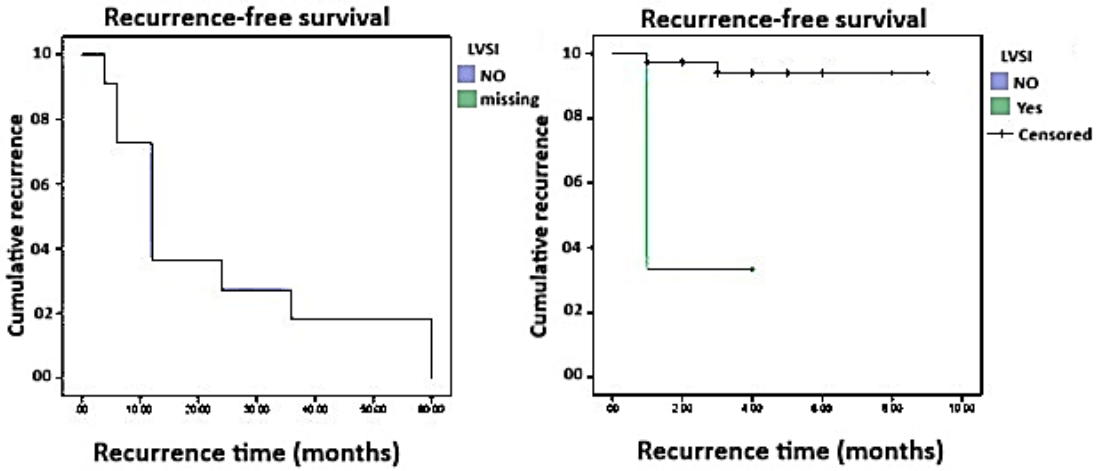

Figure 3. This figure shows Kaplan-Meier analysis of recurrence-free survival in patients with stage IA (A) and stage IB (B). The graphs compare recurrence-free survival probabilities over time between patients with and without LVSI.
LVSI: Lymphovascular space invasion

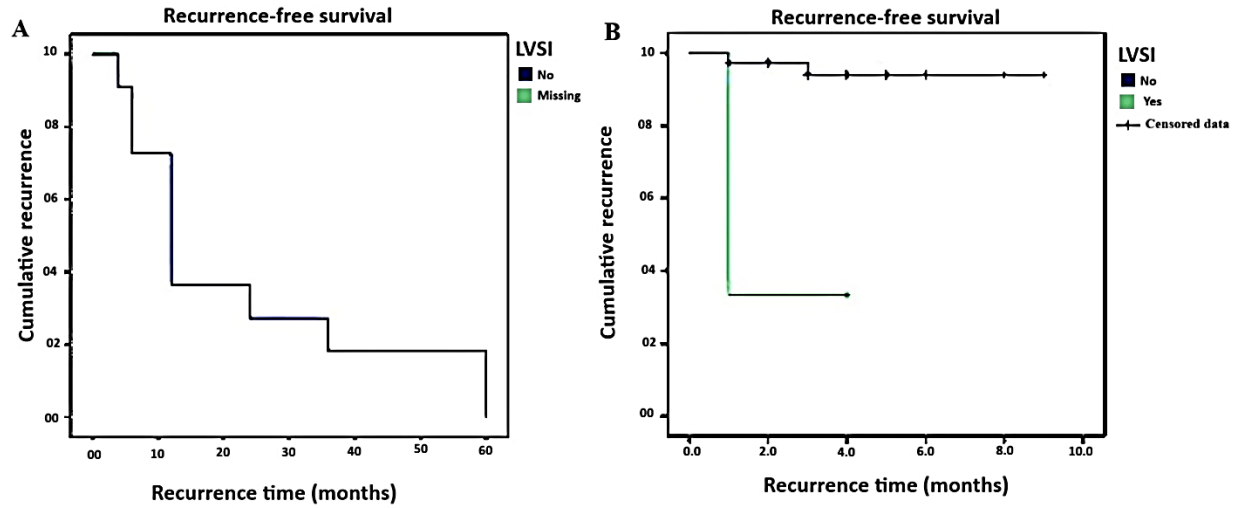

Figure 4. This figure shows Kaplan-Meier analysis of survival in patients with stage IA (A) and stage IB (B). The graphs compare overall survival probabilities over time between patients with and without LVSI.
LVSI: Lymphovascular space invasion