

The Impact of Lymphovascular Space Invasion on Recurrence and Survival in Iranian Patients With Early Stage Endometrial Cancer

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Abstract

Background: The aim of this study was to assess the impact of lymphovascular space involvement (LVSI) on recurrence and survival in early stage of endometrial cancer (EC).

Methods: Patients with EC referred to Imam Khomeini Hospital in Tehran were examined and enrolled over a 10-year period (2004 - 2015). The effect of LVSI on recurrence and overall survival was analyzed using the Kaplan-Meier and log-rank test methods.

Results: A total of 160 patients with early stage EC were identified. Out of 160 women with EC, 135 (84.4%) underwent primary surgery. One hundred and twenty-one (76.2%) patients were not found to have LVSI, whereas 38 (23.8%) were found to have LVSI. Of the 38 patients with LVSI, 21 (55.3%) had endometrioid cell type tumor, 10 (26.3%) had serous, one (2.6%) had clear cell and six (15.8%) had adeno-squamous cell type tumor.

Conclusion: The presence of LVSI represents a factor strongly associated with high risk of recurrence and poor survival in early stage EC. Patients with lower International Federation of Obstetrics and Gynecology (FIGO) stages may be at increased risk of recurrence and a poor overall survival if the pathological findings confirm the presence of LVSI. Thus, LVSI should be added to the traditional factors used to decide whether patients with early stage EC are at high risk of recurrence and adjuvant therapy planning.

Keywords: Lymphovascular space invasion; Prognostic factors; Endometrial cancer; Early stage endometrial cancer

Introduction

Endometrial cancer (EC) is the most common malignancy of women's genital system which mostly occurs in the post-menopausal era and its pathogenicity is increased with increasing age [1, 2]. Different treatment modalities for patient with EC have been introduced that consist of surgery as the standard treatment, and radiation and hormone therapy as adjuvant therapy [3]. In the past, several studies have tried to assess factors that would impact on the recurrence and survival of EC [4-7]. The most important predictive and prognostic factors in patients with EC include tumor stage, histological grade, stage of disease, depth of myometrial invasion, lymphovascular space involvement (LVSI), and cervical involvement [8-10].

LVSI, a process in which cancer cells invade vascular or lymphatic systems, represents an important prognostic factor in patients with a high incidence of relapses and poor survival [11, 12]. In spite of many evidences, LVSI was not included in the staging classification for EC reported by the International Federation of Obstetrics and Gynecology (FIGO) till 2009 [13], but it was included in the new and latest one [14, 15].

The aim of this study was to assess the impact of LVSI on recurrence and survival in the early stage of EC.

Patients and Methods

Study design and population

Patients with EC referred to Imam Khomeini Hospital in Tehran from 2004 to 2015 were examined and enrolled. The study was approved by Tehran University of Medical Sciences (TUMS) ethical committee and all patients signed informed consent before enrollment.

Inclusion criteria

Women with a histological diagnosis of the early stage of EC

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with age greater than 18 years were included.

Exclusion criteria

Women with a history of other cancers or synchronous cancer, as well as patients who did not return for follow-up were excluded.

Methods

Women with a diagnosis of EC after either endometrial biopsy or uterine curettage were subjected to surgical staging. Surgical staging included total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), and omental biopsy. Various stages were assigned using the revised FIGO staging system for EC [16]. Pelvic and para-aortic lymph node dissection was performed in the majority of patients. Prognostic factors consisted of patients' age, menopause state and pathological findings that were obtained from tumor grade, histology type, depth of myometrial invasion, LVSI, and cervical involvement. In a few patients, hormone receptor status was assessed. Non-endometrioid types such as papillary serous, clear cell, and adeno-squamous carcinoma, were also enrolled. LVSI was defined as the presence of viable tumor cells in the endothelial-lined channels, either lymphatic or capillaries, outside the tumor mass on H&E-stained sections of uterine specimens. When tumor emboli were found within a space clearly lined by endothelial cells, the tumor was considered as LVSI positive. The migration of malignant cells within the endothelium into the vascular channel was a necessary step in progression of metastatic disease.

Statistical analysis

The effect of LVSI on recurrence and overall survival was analyzed using the Kaplan-Meier and log-rank test methods. A P value < 0.05 was used to assess statistical significance. Overall survival was explained as the time from the date of surgery till the date of death. Progression-free survival was defined as the date of surgery until the date of recurrence or progression.

Results

A total of 160 patients with early stage EC were identified. Out of 160 women with EC, 135 (84.4%) underwent primary surgery. Endometrioid cell type histology was the most common cell type comprising 75.5% (120 patients), followed by serous, clear cell carcinoma and adeno-squamous cell type, respectively (Table 1). Figure 1 illustrates a case of LVSI compared to the normal subject. One hundred and twenty-one (76.2%) patients were not found to have LVSI, where 38 (23.8%) were found to have LVSI. Of the 38 patients with LVSI, 21 (55.3%) had endometrioid cell type tumor, 10 (26.3%) had serous, one (2.6%) had clear cell and six (15.8%) had adeno-squamous cell type tumor. Eighty-seven patients received adjuvant radiation

Table 1. Patients Characteristics

Variables	Number or percent
Age (median)	55.5 (range 32 - 78)
Stage of disease	
I	28 (17.5%)
IA	71 (44.4%)
IB	33 (20.6%)
III	28 (17.5%)
Total	160 (100%)
Histology	
Endometrioid	120 (75%)
Serous	17 (10.6%)
Clear cell carcinoma	10 (6.2%)
Adeno-squamous carcinoma	13 (8.1%)
Total	160 (100%)
Grading	
G1	72 (45%)
G2	43 (26.8%)
G3	24 (15%)
Other	21 (13.2%)
Total	160 (100%)
Lymph vascular space invasion	
Yes	39 (24.4%)
No	121 (75.6%)
Total	160 (100%)
Adjuvant radiation therapy	
Yes	104 (65%)
No	56 (35%)
Total	160 (100%)
Recurrence	
Yes	18 (11.3%)
No	142 (88.7%)
Total	160 (100%)

Eighty (11.3%) patients developed recurrence of disease and only two were found to have LVSI.

therapy, of whom 24 (27.6%) presented LVSI, and 63 (72.4%) were not found to have LVSI.

The median overall disease-specific survival in patients with EC and LVSI was 24 months compared with 37 months in those without LVSI (P < 0.001, Fig. 2). Therefore, LVSI in our analysis has shown to be a strong predictor of survival.

Discussion

This study that was aimed to assess the impact of LVSI on recurrence and survival in the early stage of EC, showed LVSI

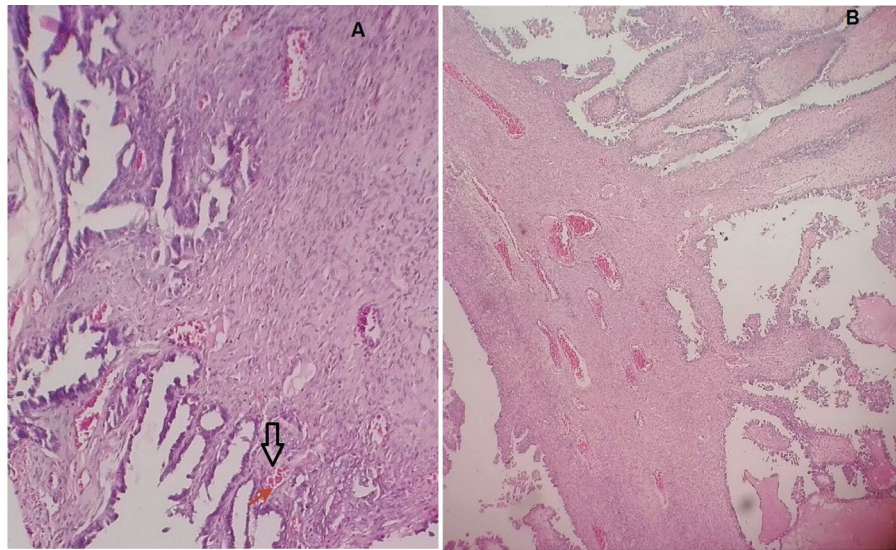


Figure 1. A case of LVSI compared to the normal subject.

to be a strong predictor of survival. EC is considered the most frequent tumor of the gynecologic tract because its incidence is gradually rising [17-19]. Several studies have investigated the role of vascular invasion as a prognostic factor for various cancers, including colorectal [20, 21], cervical [22], and breast [23] neoplasms. Moreover, in these malignancies, LVSI is considered as an important adverse and negative prognostic factor taken into consideration in clinical decision-making [24-28]. However, LVSI in EC was still not considered as a negative prognostic factor [29, 30], and was not included in the new FIGO staging classification for EC [31-33].

The incidence of LVSI was quite high in our study (23.8%) compared to previously reported studies (from 2% to 18%) [34-36]. Our finding that was collected from a single institution showed that LVSI is a predictor of a very poor survival and high risk of recurrence in EC. This finding is in agreement

with Loizzi et al on a series of 560 women with EC that also reported similar recurrence rate and poor survival [36]. Two other recent reports confirmed our findings [37, 38].

Other reports have shown neglecting results. Gadducci et al retrospectively assessed the predictive value of LVSI for the risk recurrences in patients with EC and showed that it is associated with a higher risk of distant hematogenous failure [39]. Besides, Rasool et al claimed LVSI not to be predictive of recurrence or poor outcomes [40].

Conclusion

The presence of LVSI represents a factor strongly associated with high risk of recurrence and poor survival in early stage EC. Patients with lower FIGO stages may be at increased risk of recurrence and a poor overall survival if the pathological findings confirm the presence of LVSI. Thus, LVSI should be added to the traditional factors used to decide whether patients with early stage EC are at high risk of recurrence and adjuvant therapy planning.

Conflicts of Interest

None.

Source of Funding

Tehran University of Medical Sciences (TUMS).

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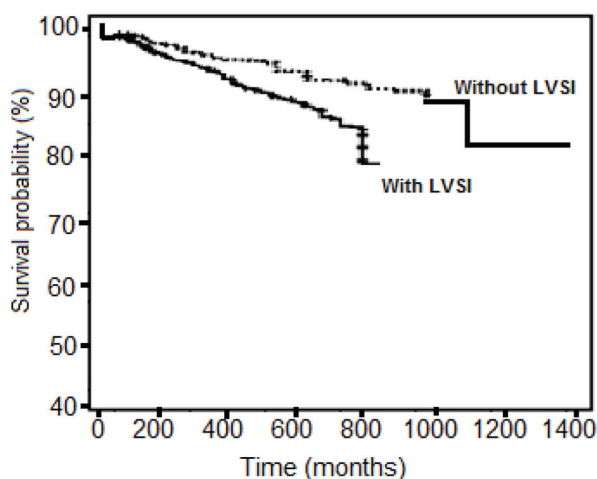


Figure 2. Kaplan-Meier analysis comparing the survival in patients with lymphovascular space involvement (LVSI) with the survival of patients without LVSI.

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