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Substantial lymph-vascular space invasion (LVSI) as predictor of distant relapse and poor prognosis in low-risk early-stage endometrial cancer

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ABSTRACT

Objective: The aim of this study is to analyze the prognostic role of lymph-vascular space invasion (LVSI), evaluated in a semi-quantitative fashion on prognosis of early stage, low risk endometrial cancer (EC).

Methods: We enrolled patients who underwent surgery for endometrial cancer between 2003 and 2018 in two referral cancer center. All patients had endometrioid EC, G1–G2, with myometrial invasion <50%, and no lymph-node involvement. LVSI was analyzed in a semi-quantitative way, according to a 3-tiered scoring system in absent, focal and substantial.

Results: Among 524 patients, any positive LVSI was found in 57 patients (10.9%) with focal LVSI (n=35, 6.7%) and substantial LVSI (n=22, 4.2%). Substantial LVSI was associated to higher rate of G2 (p<0.001), myometrial infiltration (p=0.002) and greater tumor dimensions (p=0.014). Patients with substantial LVSI were more likely to receive adjuvant treatment (6.6% vs. 52.6%, p<0.001). The 5-year OS was 99.5% in patients with absent LVSI and 70.6% in those with substantial LVSI (p<0.001). The 5-year disease free survival (DFS) was 93.6% in patients with absent LVSI and 56.5% in those with substantial LVSI (p<0.001). The rate of distant failures increased from 1.8% for absent LVSI to 22.7% for substantial LVSI (p=0.002). In univariate analysis substantial LVSI was the strongest predictor of poor overall survival (hazard ratio [HR]=11.9, p=0.001). Multivariate analysis showed that substantial LVSI was an independent predictive factor of both recurrence (HR=5.88, p=0.001) and distant failure (HR=10.6, p=0.006).

Conclusions: Substantial LVSI represents the strongest independent risk factor for decreased survival and distant relapse, indicating a role for potential hematogenous dissemination.

Keywords: Endometrial Cancer; Prognostic Factors; Neoplasm Metastasis

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INTRODUCTION

Lymph-vascular space invasion (LVSI) is a pathologic finding defined by the presence of tumor cells within lymphatic vessels and/or small capillaries, outside the main tumor. It has been found in up to 35% of endometrial cancer (EC) and in about 10%–15% of International Federation of Gynaecology and Obstetrics (FIGO) stage I EC, and its presence is frequently associated to other uterine risk factors such as high grade and deep myometrial infiltration (MI). Several studies confirmed the role of LVSI as independent predictor of poor prognosis in patients with FIGO stage I–III EC [1]. In particular, the presence of LVSI has been associated with a detrimental effect on both disease free survival (DFS) and overall survival (OS), and a higher rate of distant recurrences and lymph node (LN) metastasis. However, even in patients with negative LNs the presence of LVSI was associated to decreased survival, suggesting a role for the hematogenous dissemination. In the 2016, European Society for Medical Oncology-European Society of Gynaecological Oncology-European Society for Radiotherapy and Oncology Consensus guidelines introduced patients with low-risk features, positive LVSI and incomplete surgical staging in the high-intermediate risk class, suggesting the consideration of adjuvant treatment in those patients [2].

At this point there are 2 rising issues to be addressed: 1) it is well known that LVSI is associated to poor prognosis and higher risk of nodal metastasis. However, there are few studies in literature analyzing if the same effect of LVSI on survival is present even in lymph-node negative patients and more specifically in patients with low-risk pathologic features (i.e., superficial myometrial invasion and well-moderately differentiated grading). The clinical relevance of this issue become even more important because we are focusing on a subgroup of patients that less frequently undergo adjuvant treatment. 2) LVSI is often described in a qualitative dichotomized manner as present or absent. Due to the absence of well-defined pathologic criteria to classify LVSI in a quantitative way, there is not a consensus on this definition. However, some studies in literature tried to build a scoring system based on a quantitative analysis of the number of vessels involved [3]. Hachisuga et al. [3] classified LVSI in 3 degrees differentiating the absence, the presence of a focus around the tumor, or the presence of diffuse and multifocal LVSI around the tumor or in the myometrium. A sub-analysis of PORTEC1 and 2 study underlined the relevance of this semi-quantitative scoring system demonstrating the role of substantial LVSI in contrast to focal or absent LVSI on survival and distant metastasis [4].

The aim of this study was to evaluate the prognostic impact of a three-tiered scoring system of LVSI in patients with EC and low risk pathologic features. The originality of our study relies in the analysis of a very selected population, in order to catch purely the effect of LVSI on prognosis in patients with no other risk factors and leaving a qualitative classification in favor of a quantitative evaluation of LVSI.

MATERIALS AND METHODS

We retrospectively analyzed patients undergoing surgery for early-stage endometrial cancer at Fondazione Policlinico Universitario A. Gemelli, IRCCS in Roma between 2003 and 2018, and at A.R.N.A.S. Ospedale civico di Cristina Benfratelli in Palermo between 2016 and 2018. All patients gave their written consent to the use of clinical data for research purposes and the study was approved by the Institutional Review Board. We included in the analysis patients with endometrioid histology, well-moderately differentiated (G1–G2), superficially

infiltrating (<50% myometrial invasion) endometrial cancer. We excluded patients with type II, poorly differentiated, MI >50% or FIGO stage higher than IA EC.

1. Surgical approach

In both institutions patients underwent surgical staging including total hysterectomy with bilateral salpingo-oophorectomy. The lymph nodal status assessment changed over time. Given the low-risk features of these patients, up to 2015 the rate of systematic lymph node dissection (LND) varied according to the institutional protocols. After 2015 the development of sentinel lymph-node mapping (SLN) increased the rate of lymph nodal assessment even in low-risk patients. Surgical approach (open abdominal, laparoscopic or robotic-assisted) was individualized on the basis of surgeon preference and patient characteristics. We also collected data about adjuvant treatment, including patients who underwent external beam radiation therapy (EBRT) ± vaginal brachytherapy (VBRT), VBRT only or observation.

2. LVSI definition

In order to determine the LVSI status, pathology reports as well as hematoxylin-and-eosin (H&E) stained slides were reviewed by 2 expert pathologists (Z.G.F., A.G.), who were blind to clinical data and each other results. LVSI was recorded only if the nests of tumor cells were unequivocally lined by endothelial cells.

A 3-tiered system, based on the recommendations by Bosse et al. [4], was used for grading LVSI:
1) Absent: no LVSI
2) Focal: a single focus, consisting of 1–2 vessels involved by neoplasm was recognized around the tumor
3) Substantial: diffuse or multifocal LVSI (3 or more involved vessels) was recognized around the tumor or massive LVSI was recognized in the myometrium with a spray-like growth, regardless of the degree of myometrial invasion

These criteria for interpreting the histological findings were preventively arranged. Consensus was reached if both observers agreed. Only few cases with no consensus were discussed jointly in a multiheaded microscope until both observers reached an agreement.

3. Data collection

Demographic, surgical, and pathologic data were extracted from the medical reports. Demographic data included age and body mass index (BMI). Pathologic data included tumor dimensions (greater tumor diameter described at the pathology report), grading, and myometrial invasion (MI). Progression free survival (PFS) and overall survival (OS) were defined as the time, in months, from the date of diagnosis to the date of recurrence and death due to disease or last follow-up, respectively. Recurrences were classified as loco-regional, including vaginal and pelvic (pelvic LNs, rectum, bladder) and distant, including abdominal, para-aortic LNs and extra-abdominal recurrences (peritoneal carcinomatosis, lung, liver, bone). If both pelvic and distant recurrence happened simultaneously, the recurrence was categorized as distant.

4. Statistical analysis

Continuous variables were described as mean and standard deviation for normally distributed data, or median and interquartile range (IQR). Categorical variables were reported as frequencies and percentages. Variables were evaluated for their association with distant recurrence based on univariate logistic regression models. Associations were

summarized using the odds ratios (ORs), and corresponding 95% confidence intervals (CIs) were estimated from the final multivariable logistic regression models. Estimates of survival were calculated with the Kaplan-Meier method. Univariable and multivariable Cox regression analysis was used to calculate hazard ratio (HR) and 95% CI for factors affecting survival. Multivariable analysis included factors who reached a p-value <0.05 in the univariable analysis. All p-values were 2-sided and a value of <0.05 was considered statistically significant.

RESULTS

We enrolled 524 patients who met the inclusion criteria and underwent surgery for endometrial cancer in the 2 institutions, Fondazione Policlinco Univesitario A. Gemelli, IRCCS (n=503, 96.0%) and A.R.N.A.S. Ospedale Civico di Cristina Benfratelli (n=21, 4.0%), between 2003 and 2018. Overall, any degree of LVSI has been found in 10.9% of cases (n=57); among these 35 (6.7%) were focal and 22 (4.2%) substantial.

Mean age was 60±10.8 years, mean BMI was 28.7±7.64 kg/m². The 89.8% of patients (n=468) underwent minimally invasive surgery (laparoscopy or robotics). According to the final pathology report, the 83.8% of patients (n=439) had MI <50%, and the remaining 16.2% (n=85) did not infiltrate the myometrium. Surgical staging included LN evaluation (through systematic pelvic and/or aortic LND and or sentinel LN biopsy) in 296 patients (56.5%), while 228 patients (43.5%) underwent only hysterectomy and bilateral salpingo-oophorectomy. In the group of nodal staging, 104 patients (19.8%) underwent sentinel LN only, 58 (11.1%) had both SLN and LND and 134 (25.6%) underwent pelvic ± aortic LND.

Table 1 shows clinico-pathological characteristics according to LVSI status in the three tired scoring system. We found that patients with substantial LVSI were more likely to have also higher frequencies of MI, moderate grade (G2), greater tumor dimensions compared to patients with absent and focal LVSI. Moreover, patients with substantial LVSI were more likely to undergo adjuvant treatment (1.9% in no LVSI vs. 52.6% in substantial LVSI, p<0.001) and to experience distant recurrences (1.8% in no LVSI vs. 22.7% in substantial LVSI, p=0.002). The rate of local recurrence was not affected by the presence of LVSI instead.

Substantial LVSI was found to be a negative prognostic factor for both OS and risk of recurrence (**Fig. 1**). With a mean follow up time of 38±32.9 months, we observed a 5-years OS of 99.5%, 100%, and 70.6% (p<0.001), and a 5-years DFS of 93.6%, 92.9%, and 56.5% (p<0.001) respectively for absent, focal and substantial LVSI.

Adjuvant radiation treatment was not found to be a prognostic factor for both DFS and overall survival (OS). In the univariable Cox regression analysis, only substantial LVSI was associated to reduced OS (HR=11.7; 95% CI=2.7–50.6; p=0.001) (**Table 2**).

On multivariable analysis, only substantial LVSI, compared with focal or absent, was independently associated with reduced DFS (HR=5.95; 95% CI=2.05–17.65; p=0.001) (**Table 3**).

Table 4 shows OR for the risk of distant recurrence, unadjusted and adjusted for LVSI score and adjuvant treatment. We found that the only independent prognostic factor for distant recurrence was the presence of substantial LVSI (adjusted OR=10.65; 95% CI=2–56.7; p=0.006).

Table 1. Patient characteristics according to LVSI status

Patient characteristic	Total	Absent LVSI	Focal LVSI	Substantial LVSI	p
No. of patients	524 (100.0)	467 (89.1)	35 (6.7)	22 (4.2)	
Mean age (yr)		59.8±11	61.9±9.58	61.1±8.1	0.479
Age (yr)					0.918
<60	257 (49.0)	230 (49.3)	16 (45.7)	11 (50.0)	
≥60	267 (51.0)	237 (50.7)	19 (54.3)	11 (50.0)	
BMI					0.395
<25	129 (26.2)	116 (26.4)	8 (25.0)	5 (25.0)	
≥25 and <35	259 (52.6)	236 (53.6)	13 (40.6)	10 (50.0)	
≥35	104 (21.1)	88 (20)	11 (34.4)	5 (25.0)	
Surgical approach					0.269
Laparotomy	53 (10.2)	49 (10.6)	4 (11.4)	0	
Laparoscopy/robotic	468 (89.8)	415 (89.4)	31 (88.6)	22 (100.0)	
LN assessment					0.287
No	228 (43.5)	206 (44.1)	16 (45.7)	6 (27.3)	
Yes	296 (56.5)	261 (55.9)	19 (54.3)	16 (72.7)	
Tumor dimension (mm)					0.014
≤20	216 (43.2)	202 (45.5)	8 (23.5)	6 (27.3)	
>20	284 (56.8)	242 (54.5)	26 (76.5)	16 (72.7)	
Grading					<0.001
G1	192 (36.6)	191 (40.9)	1 (2.9)	0	
G2	332 (63.4)	276 (59.1)	34 (97.1)	22 (100.0)	
MI					0.002
No infiltration	85 (16.2)	85 (18.2)	0	0	
<50%	439 (83.8)	382 (81.8)	35 (100.0)	22 (100.0)	
Adjuvant treatment					<0.001
None	482 (93.4)	455 (98.1)	18 (54.5)	9 (47.4)	
VBRT only	25 (4.8)	7 (1.5)	13 (39.4)	5 (26.3)	
EBRT±VBRT	9 (1.8)	2 (0.4)	2 (6.1)	5 (26.3)	
Relapse					0.002
No	482 (94.7)	433 (95.6)	33 (97.1)	16 (72.7)	
Local	14 (2.8)	12 (2.6)	1 (2.9)	1 (4.5)	
Distant	13 (2.6)	8 (1.8)	0	5 (22.7)	

Values are presented as mean±standard deviation or number (%). Missing values are excluded in the analysis.
BMI, body mass index; EBRT, external beam radiation therapy; LN, lymph node; LVSI, lymph-vascular space invasion; MI, myometrial infiltration; VBRT, vaginal brachytherapy.
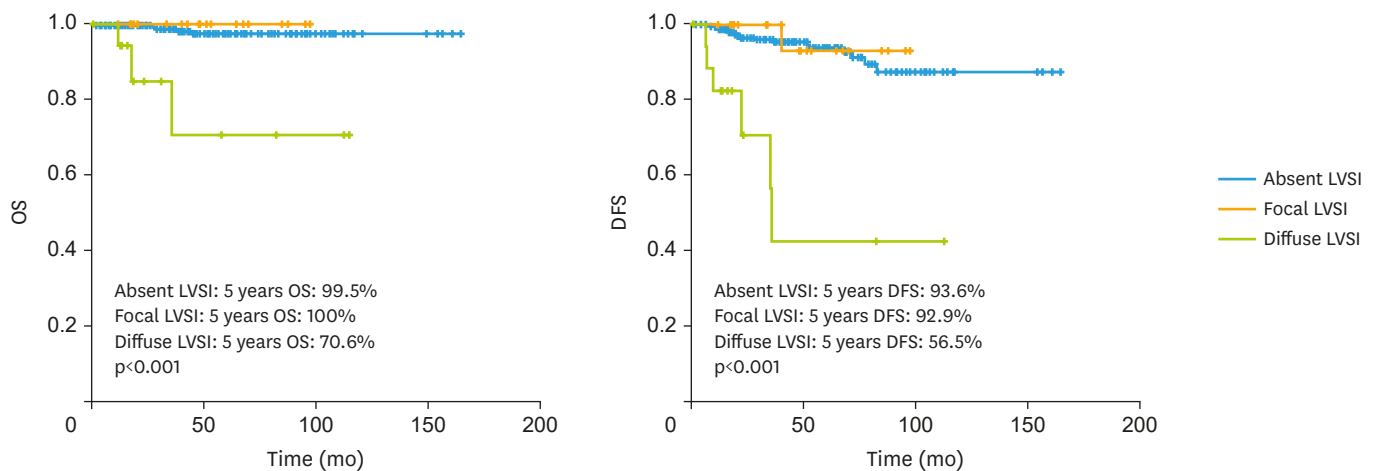

Fig. 1. Kaplan-Meier estimate of OS and DFS of the 524 patients with low-risk endometrial cancer in relation to the LVSI status. Log rank test was used to test the significance and censored patients were indicated by crosses.
DFS, disease-free survival; LVSI, lymph-vascular space invasion; OS, overall survival.

Table 2. Univariate Cox regression analysis of select covariates for DFS and OS

Characteristics	DFS		OS	
	HR (95%CI)	p	HR (95%CI)	p
Age (yr)				
<60	1		1	
>60	1.12 (0.52–2.39)	0.771	0.5 (0.12–2.01)	0.329
LVSI				
LVSI absent	1		1	
LVSI focal	0.58 (0.08–4.31)	0.592	-	
LVSI substantial	7.95 (3.18–19.86)	<0.001	11.9 (2.9–47.6)	0.001
Tumor dimensions (mm)				
<20	1		1	
>20	0.85 (0.38–1.91)	0.701	0.44 (0.1–1.85)	0.265
LND				
No	1		1	
Yes	2.62 (1.14–6.03)	0.024	2.1 (0.54–8.8)	0.274
Grading				
G1	1		1	
G2	3.28 (1.13–9.48)	0.028	1.18 (0.29–4.71)	0.818
Adjuvant treatment				
No	1		1	
Yes	2.17 (0.75–6.31)	0.153	1.4 (0.18–11.6)	0.724

Missing values are excluded in the analysis.
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LND, lymph node dissection; LVSI, lymph-vascular space invasion; OS, overall survival.

Table 3. Multivariate Cox regression analysis of predictors of recurrence

Variables	DFS		
	HR	95% CI	p
LVSI substantial	5.88	2.29–15.11	0.001
G2	2.32	0.76–7.04	0.138
LND	2.16	0.92–5.07	0.075

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LND, lymph node dissection; LVSI, lymph-vascular space invasion.

Table 4. Univariable and multivariable logistic regression analysis of risk factors for distant metastasis among patients at low risk

Characteristics	Distant recurrence (n=13)	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Age (yr)					
<60	8 (3.3)	1			
>60	5 (1.9)	0.58 (0.19–1.79)	0.340		
LVSI					
LVSI absent	8 (1.8)	1		1	
LVSI focal	0	-		-	
LVSI Substantial	5 (22.7)	16.3 (4.84–55.29)	<0.001	10.65 (2–56.69)	0.006
Tumor dimensions (mm)					
<20	4 (1.9)	1			
>20	9 (3.3)	1.73 (0.52–5.69)	0.369		
LND					
No	3 (1.4)	1			
Yes	10 (3.4)	2.5 (0.69–9.3)	0.163		
Grading					
G1	1 (0.5)	1			
G2	12 (3.7)	7.01 (0.9–54.4)	0.062		
MI					
No infiltration	0	1			
<50%	13 (3.1)	5.45 (0.32–92.6)	0.141		
Adjuvant treatment					
No	9 (1.9)	1		1	
Yes	4 (9.5)	5.35 (1.57–18.2)	0.007	2.04 (0.34–12.2)	0.435

CI, confidence interval; LND, lymph node dissection; LVSI, lymph-vascular space invasion; MI, myometrial infiltration; OR, odds ratio.

DISCUSSION

Endometrial cancer is the most frequent disease of the genital female tract carrying a relatively good prognosis, especially in early-stage of disease. However, the identification of risk factors for decreased survival is crucial specifically in those patients in which adjuvant treatment is not always recommended.

In this study we focused on the impact of a three-tiered scoring system of LVSI on prognosis in patients with low-risk endometrial cancer. We selected patients with well-moderately differentiated (G1–G2) endometrial endometrioid cancer, infiltrating less than 50% of the myometrium. Consistently with data reported in literature we found that: i) the overall rate of LVSI was 10.9% in patients with low-risk EC, among whom 6.7% were focal and 4.2% were substantial, ii) substantial LVSI is an independent risk factor for distant recurrences iii) substantial LVSI is the strongest predictor of poor prognosis in terms of OS and DFS.

LVSI has been frequently associated to lymph nodal metastasis and several high-risk pathologic features resulting consequently in poor prognosis. We specifically analyzed a very selected population, with negative LN and no other high-risk pathologic characteristics in order to catch as much as possible pure impact of LVSI on prognosis.

The presence of LVSI has been described in literature to be around the 8.9% and 13.5% [5,6] in FIGO stage I EC. However, few studies focused specifically its prevalence and prognostic impact in low-risk patients. In our study we found that 6.7% of patients had focal LVSI and 4.2% had substantial LVSI. Accordingly with our findings, these authors described increased frequencies of MI, grade 2 and recurrence rate among patients with LVSI positive. There is a significant accordance in literature on the detrimental role of LVSI on prognosis and survival, even in early-stage node negative patients [1,5-11]. However, the role of a quantitative scoring system, as independent prognostic factors for distant metastasis and OS was not extensively evaluated.

In this study, we found a significantly higher risk of recurrence and death due to disease in patients with substantial LVSI. In the multivariate analysis, substantial LVSI was the strongest independent factor for recurrence. In the univariate analysis we found a detrimental role of LN dissection on prognosis. Since nodal assessment has not been performed in a systematic way in all patients, we interpreted this data as due to a higher frequency of MI, greater tumor diameter and grade 2 among patients who underwent nodal dissection, justifying in this way the poorer prognosis of those patients.

Substantial LVSI was also the strongest independent factor for distant metastasis, despite those patients were more likely to receive adjuvant treatment.

In our study, adjuvant treatment was administered to 6.5% of the entire cohort (n=34), with an increasing rate in patients with positive LVSI compared to those with no LVSI (1.9% vs. 45.5% vs. 52.6% respectively for absent, focal or substantial LVSI, p<0.001). Accordingly with other authors we did not observe a role of adjuvant radiation on the risk of recurrence or deaths [12]. However, confirming the debated role of adjuvant radiotherapy, other authors reported the role of adjuvant radiation in the improvement of pelvic recurrence control [4,13].

The distant recurrence strongly suggests the role of hematogenous dissemination of the tumor. In a large retrospective analysis of 478 patients with early stage LVSI positive

endometrial cancer, authors did not find a prognostic role of adjuvant chemotherapy in low grade endometrial cancer with positive LVSI [14]. However, the role of adjuvant treatment in this subset of patients is still elusive.

The main limitation of this study is the retrospective nature that could have led to miss some confounding factors due to the non-homogeneity of the population (nodal staging and adjuvant treatment not standardized). However, this is the study with the largest sample size of early-stage low-risk patients, and the only study in the literature aiming to correlate a quantitative classification of LVSI to prognosis in this selected subset of patients.

The clinical and therapeutic implications of the extent of LVSI in low-risk EC needs to be further investigated, maybe our data suggest a crucial prognostic role of substantial LVSI even in patients with low-risk features. Distant metastasis advises a future focus both on molecular characterization and optimization of postoperative treatment in these patients. Waiting other definitive data on tumor profiling and risk stratification, LVSI and its pathological definition should still be considered in tailoring of adjuvant strategies.

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