Review Article

Association of Lymphovascular Space Invasion (LVSI) with Histological Tumor Grade and Myometrial Invasion in Endometrial Carcinoma: A Review Study

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Abstract

Endometrial carcinoma is one of the most frequent gynecological cancers in developed countries. Lymphovascular space invasion (LVSI), histological grade, and myometrial invasion (MMI) are important prognostic factors of endometrial carcinoma. LVSI is considered an independent poor prognostic factor in endometrial carcinoma. Based on the importance of LVSI, this study aimed to discuss the association of LVSI with tumor grade and MMI. A search of PubMed, EMBASE, Web of Science, Scopus, Google Scholar, and Cochrane Library was carried out to collect related studies. Consequently, most studies showed that LVSI is significantly associated with higher histologic grade and deep MMI.

Keywords: Endometrial neoplasms, lymphatic metastasis, myometrium, neoplasm grading, neoplasm invasiveness

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Introduction

Endometrial carcinoma is the most common cancer of the female genital tract in developed countries[1-4] with a generally good prognosis[1-3] and the sixth most frequent cancer in females with an increasing prevalence and mortality rate.[3] The American Cancer Society has assumed 66570 new cases and 12940 deaths in the United States in 2021.[5]

Principally, endometrial carcinoma involves postmenopausal females.[6] Early occurrence of symptoms and signs including spotting and postmenopausal hemorrhage results in early diagnosis, good prognosis, and up to 85% five-year survival rate.[7]

The most significant prognostic factors of endometrial carcinoma are tumor grade, International Federation of Gynecology and Obstetrics (FIGO) stage, histological subtype, depth of myometrial invasion (MMI), lymphovascular space invasion (LVSI), and age.[8]

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LVSI is characterized by the tumor cells within endothelium-lined spaces around the main tumor[9-11] that are seen typically as "free-floating" cell clusters, which frequently fit the space shape.[9,11]

The incidence of LVSI in the early stage of endometrial carcinoma is about 34%.[11] LVSI has been supposed as one of the initial events in the metastasis of endometrial carcinoma and a necessary step before lymphatic dissemination. LVSI has been meaningfully correlated with lymph node metastasis and a lower survival rate.[12-19] LVSI usually is considered an independent unfavorable factor of recurrence and survival; even in some investigations, LVSI in patients without lymph node involvement has been shown as an independent prognostic factor of survival and recurrence.[20]

MMI is identified by the endometrial cancer cell invasion into the myometrial layer.[5]

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Endometrial carcinoma is classified into two histopathological groups: low grade and high grade.[21]

Considering the significance of LVSI, depth of MMI, and grade in prognosis and survival of endometrial carcinoma, we conducted a study to evaluate the relationship between LVSI and two other important prognostic factors, including depth of MMI and grade of endometrial carcinoma.

Materials and Methods

The literature was investigated from Web of Science, PubMed, EMBASE, Scopus, Google Scholar, and Cochrane Library from April 1985 to November 2022. Only the studies published in English were included. The search terminologies consisted of "endometrial carcinoma," "endometrial tumor," "endometrial cancer," "endometrial neoplasm," "Lymphovascular Space Invasion," "LVSI," "myometrial invasion," "grading," and "classification." One author independently reviewed the literature, and another author was consulted in disagreement.

Inclusion and exclusion criteria

In this study, the following inclusion criteria were considered.

1) The studies in which the patients were only involved by endometrial carcinoma, 2) studies with adequate information on clinicopathological factors (LVSI, MMI, and tumor grading), 3) studies published exclusively in English, and 4) the types of studies consisted of cross-sectional, case–control, cohort, clinical trial, and review articles.

The following were the exclusion criteria:

1) Animal experiments, 2) unpublished studies, 3) incomplete studies, 4) case reports, and 5) studies that did not meet the expected design.

Definition, diagnosis, and grading of LVSI in endometrial carcinoma

LVSI is characterized by the collection of tumor cells in lymphatic and/or blood vessels, preferably adjacent to the vessel wall, around the main tumor.[22]

The existence of a proteinaceous substance helps in the diagnosis of a lymphatic vessel.[9,10]

Furthermore, some histological findings, for example, vicinity to an arterial or venous blood vessel or perivascular lymphocytic infiltration, have been suggested to favor LVSI.[23] Some studies have reported that perivascular lymphocytic infiltration is associated with lymphovascular space invasion, but this histologic criterion, by itself, is not diagnostic for LVSI and true tumor emboli in vessels are necessary to confirm LVSI diagnosis,[9,10] as Bosse *et al*.[24] reported perivascular lymphocytic infiltration in 32.7% of endometrial carcinomas, but only 26.4% of their cases with perivascular lymphocytic infiltration showed LVSI.

Before diagnosing LVSI, its mimickers must be excluded. The most common mimickers of LVSI include tumor cell displacement in myometrial clefts due to manipulation in surgery[25] or improper grossing[26] of a fragile, poorly fixed, or necrotic tumor. Other LVSI mimickers are stromal retraction surrounding the tumor and microcystic elongated and fragmented (MELF) pattern of invasion.[27]

In questionable cases, the immunohistochemistry (IHC) of CD31 can be used[11]; however, IHC has limited use in the diagnosis of LVSI.[28]

Because of some restrictions of the intraoperative frozen section, it is generally difficult to identify LVSI before the final pathology report.[5]

The presence or absence of LVSI must be reported in the pathology report. Moreover, it is suggested to report the location of LVSI (deep areas of myometrium, adnexa, cervix, parametrium, etc.).[28]

For scoring of LVSI in endometrial cancer, we searched the literature and found five scoring methods:

1) Qualitative two-tiered system: Most publications identified LVSI as present or absent without any more details.[24]
2) Semiquantitative three-tiered system: In 1999, Hachisuga *et al*.[22] graded LVSI as follows:
   - None: no LVSI
   - Mild: a single focus of LVSI surrounding the tumor
   - Severe (diffuse or multifocal): >1 focus of LVSI surrounding the tumor.[22]
3) Another semiquantitative three-tiered system was characterized by Bosse *et al*. in 2015[24] and the College of American Pathologists (CAP) in 2021[29]:
   - Absent: no LVSI
   - Focal or low: <3 involved vessels around the tumor
   - Substantial or extensive (diffuse or multifocal): ≥ 3 involved vessels around the tumor
4) Semiquantitative four-tiered system, classified by Fujimoto *et al*. in 2009[30]:
   - No LVSI
   - Minimal: a few vessels involved around the tumor
   - Moderate: more vessels involved around the tumor
   - Prominent: many vessels involved diffusely in the deeper areas of the myometrium

   The four-tiered system for scoring LVSI did not show stronger prognostic significance compared with the three-tiered system designed by Hachisuga *et al*.[22] due to the absence of distinction between minimal and moderate LVSI. The three-tiered system designed by Hachisuga *et al*.[22] had a significantly increased hazard ratio (HR) compared with the two-tiered system, and its prognostic importance was strongest and most relevant to the clinical aspect. In this three-tiered system, mild LVSI is defined as a single focus of LVSI, but a survey of the number of involved vessels showed an average of two involved vessels and resulted in the creation of another three-tiered system classification by Bosse *et al*.[24] Substantial LVSI using the Bosse *et al*.'s[24] three-tiered

system is defined as the strongest independent factor of prognosis for distant metastasis, pelvic recurrence, and overall survival.

5) Recently, a cutoff criterion of ≥ 4 involved vessels in at least one hematoxylin- and eosin-stained section has been suggested to identify substantial or extensive LVSI.[31] An easy prediction model for LVSI is defined as the LVSI risk index characterized by "TD×%MMI×tumor grade×cervical stromal involvement." In this index, tumor diameter (TD) and percentage of myometrial invasion (% MMI) are computed as absolute numbers.[5]

Evaluation of the depth of MMI in endometrial carcinoma

For measurement of MMI, three parameters are used: %MMI, depth of MMI in millimeters, and tumor free diameter (TFD).[32,33] Before improving a model for anticipating LVSI, it must be evaluated which of these three parameters best predicts LVSI. Kim *et al*.'s[5] study revealed %MMI as the most practical parameter among them.[5]

Ordinarily, %MMI is identified in hysterectomy specimens as less than or greater than 50% of myometrial thickness.[34]

FIGO grading system for endometrial carcinoma

Endometrial carcinoma is graded histopathologically into two main groups: low grade (FIGO G1–G2) and high grade (FIGO G3). These two grades have various biological behaviors.[2] The most common histological subtype of endometrial carcinoma is endometrioid adenocarcinoma.[35] FIGO grading system of endometrioid endometrial carcinoma is identified by the amount of solid, nonsquamous components. Grades 1, 2, and 3 are characterized by ≤5%, 6–50%, and >50% solid nonsquamous components, respectively.[35,36]

Some subtypes of endometrial carcinoma are considered as high grade. These include serous carcinoma, clear cell carcinoma, dedifferentiated carcinoma, undifferentiated carcinoma, and carcinosarcoma.[8,35]

Is there any relationship between LVSI with tumor grade and MMI?

Multiple studies have shown a positive relationship between the existence of LVSI with tumor grade and depth of MMI,[15,37,38] but the results of Motasim *et al*.[11] study are partly different. They studied LVSI in 32 patients with early-stage (stage 1), low-grade endometrioid endometrial carcinoma and observed that there is no association between LVSI and depth of MMI. This result is contrary to Tortorella *et al*.'s[39] study on 524 patients with early-stage, low-grade endometrial carcinoma that revealed a higher frequency of MMI among patients with LVSI. They reported that all patients with focal and substantial LVSI had MMI [Table 1].[39] However, regarding the association between LVSI and tumor grade, the results of the two studies by Motasim *et al*.[11] and Tortorella *et al*.[39] were in agreement with other studies. They showed a significant association between LVSI and tumor grade, as 82% of cases with LVSI were grade G2 in Motasim *et al*.'s study.[11] This proportion was higher in Tortorella *et al*.'s[39] study, which mentioned that 97.1% and 100% of patients with focal and substantial LVSI, respectively, had G2 grade carcinoma.

Table 1: Patients' characteristics according to lymphovascular space invasion

References	Characteristics	LVSI-negative	LVSI-positive
1. Tortorella *et al*.[39]	Grading		
	G1	40.9	1.75
	G2	59.5	98.2
	MMI		
	No MMI	18.2	0
	MMI <50%	81.8	100
2. Kim *et al*.[5]	Grading		
	G1	61.4	27.9
	G2	32	42.3
	G3	6.6	29.9
	MMI >50%	17	64.2
3. Watanabe *et al*.[40]	Grading		
	G1	77.4	23
	G2–G3	22.5	76.9
4. Dai *et al*.[41]	Grading		
	G1	40.55	15.49
	G2	48.73	53.52
	G3	10.72	30.99
	MMI		
	MMI <50%	81.29	52.11
	MMI ≥50%	18.71	47.87
5. Hachisuga *et al*.[22]	Grading		
	G1	53.4	13.3
	G2	33.5	44.0
	G3	13.0	42.5
	MMI		
	No MMI	49.4	1.5
	MMI ≤50%	37.5	42.5
	MMI >50%	13.0	55.9
6. Veade *et al*.[43]	Grading		
	G1	52.9	16.7
	G2	33.9	45.8
	G3	13.2	37.5
	MMI depth		
	Inner 1/3	64.3	33.3
	Middle 1/3	26.0	35.4
	Outer 1/3	9.7	31.3

Values are presented as numbers (%). LVSI: lymphovascular space invasion, MMI: myometrial invasion, G: grade

The results of Kim *et al*.'s,[5] Watanabe *et al*.'s[40] and Dai *et al*.'s[41] studies demonstrated that LVSI-positive tumors were significantly associated with higher tumor grade (*P*-value <0.001) and deep MMI (MMI >50%) (*P*-value <0.001).

Hachisuga *et al*.[22] [Table 1], Bosse *et al*.,[24] Oliver-Perez *et al*.,[42] Veade *et al*.[43] [Table 1], and Cappozi *et al*.[44] analyzed endometrial carcinoma and identified that LVSI is more

common in, or is more likely to be associated with, a higher grade and deep MMI.

More frequency of LVSI in tumors with deep MMI is quoted in other studies conducted by Wang *et al*.[45] and Dane and Bakir[46]

Important evidence of a higher rate of LVSI in higher-grade carcinomas of the endometrium is gained from the World Health Organization (WHO) classification that characterized serous carcinoma as a high-grade endometrial cancer that is associated with extensive LVSI.[35]

Also, Singh *et al*.[28] said that LVSI is an infrequent histologic finding in low-grade endometrial carcinoma.

Based on a significant and strong association between LVSI with higher tumor grade and deep MMI, these uterine factors (grade and depth of MMI) are used as indirect methods for anticipating the existence of LVSI.[5]

In summary, despite the significant association between LVSI with MMI and grade that is mentioned in many studies, it should be considered that the presence and absence of LVSI can be seen in G1 and G3 carcinomas, respectively. Also, LVSI can be present in patients with no MMI. In addition, in LVSI-negative cases, deep MMI can be present.

Conclusion

Our study showed that although scant LVSI-positive endometrial carcinomas may be associated with low-grade (G1) and superficial MMI, and also, few LVSI-negative cases may be accompanied by high tumor grade (G3) and deep MMI, in most patients with LVSI, there is a significant association between LVSI with higher histologic tumor grade and deep MMI. More evaluation is necessary regarding exceptions and different results. Moreover, considering the importance of LVSI as a prognostic factor in endometrial carcinoma, further investigations are needed to determine the role of various grades of LVSI in the selection of the type of treatment, requirement for adjuvant therapy, and the response to various treatment modalities of endometrial carcinoma.

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Conflicts of interest

There are no conflicts of interest.

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