TÜRKİYE VE DÜNYADA TIBBİ PATOLOJİ

Editör: Doç.Dr. Gülay TURAN

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İÇİNDEKİLER

CUTANEOUS LEIOMYOMA

Zeliha Çelik

1. INTRADUCTION

Leiomyomas of skin seperated three types: angioleiomyoma (AL) (vascular leiomyoma), which the superficial nodules of nevoid is usually subcutaneous, hamartomatous type derived from arrectores pilorum muscle (Pilar Leiomyoma (PL)) and Genital Leiomyoma (GL) located in the vulva, scrotum or nipple (Rosai and Ackerman's Surgical Pathology, 2011)

2. LOCALIZATION

They are most commonly found on the extensor surfaces of the extremities, followed by the trunk, head, and neck region, followed by the trunk, head and neck region. GLs can presented in the scrotum, nipple, vulva or areola (WHO, Skin tumours, 2018).

3. CLINICAL FEATURES

Cutaneous leiomyomas (CL) are flesh-coloured to brown, firm, dome-shaped papules or nodules. Multiple leiomyomas are more often painful and may be distributed in linear, segmental, or zosteriform patterns. Solitary leiomyomas are usually no larger than 20 mm. GLs are usually solitary raised to pedunculated papules or nodules, usually <20 mm but occasionally larger, and asymptomatic. Vulvar tumours may enlarge during pregnancy (WHO, Skin Tumours, 2018).

4. ETIOLOGY

Single tumours are sporadic. Multiple PLs are inherited in an autosomal dominant pattern, Heterozygous germline loss-of-function mutations in *FH*, predisposes to renal cell carcinoma and hereditary leiomyomatosis , this syndrome is rare (WHO, Skin tumours, 2018).

Increased conscious of the connection between cutaneous lesions and renal malignancy can cause to early detection. If there is more than one CL, a family history should be researched and further investigation (imaging) should be performed (Deveci et al., 2013)

Hereditary leiomyomatous renal cell carcinoma (HLRCC) is a syndrome. In this syndrome, there is a predisposition associated with CLs. Close monitoring is recommended for patients with neoplasms associated with HLRCC. (Malik et al. 2025)

5. DIAGNOSTIC MOLECULAR PATHOLOGY

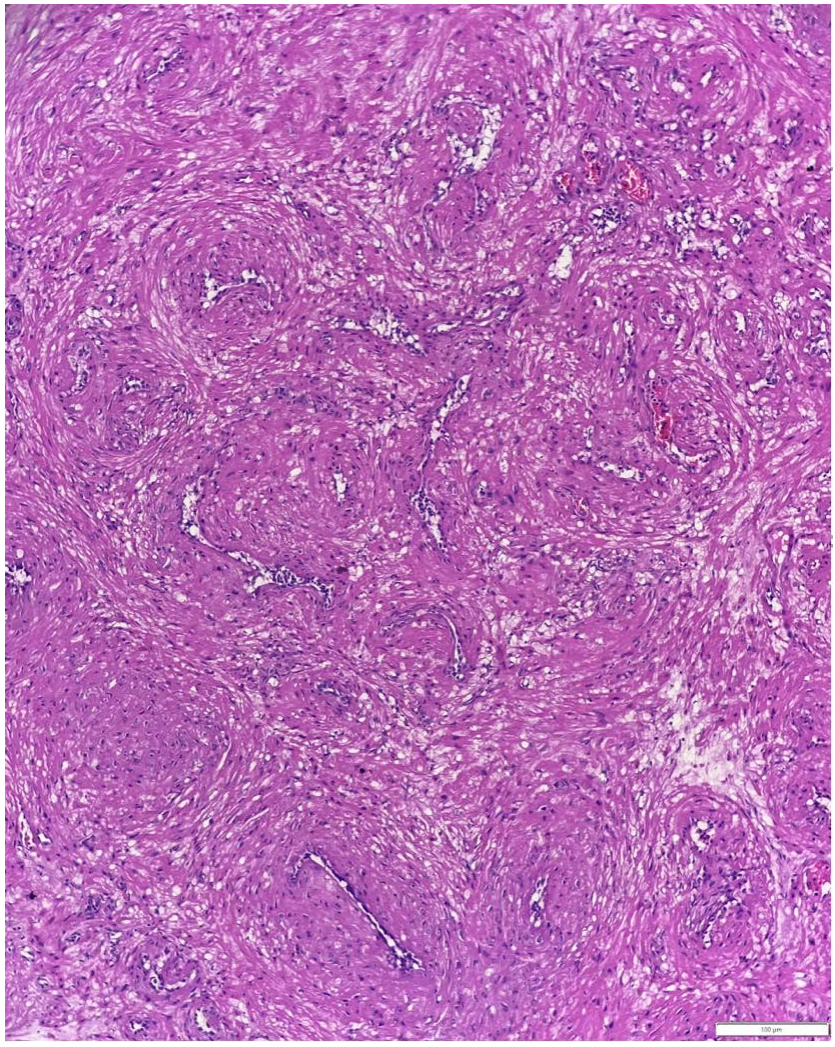
Molecular testing is not required in sporadic cases. In the familial setting, although FH and 2SC immunohistochemistry identify FH-deficient neoplasms, they do not replace genetic testing, because biallelic *FH* mutation/ inactivation can arise as a fully somatic phenomenon (WHO, Skin tumours, 2018).

6. HISTOPATHOLOGY

Piloleiomyomas, whether multiple or single, are similar in their histological appearance with GLs. They are poorly

demarcated and are composed of interlacing bundles of smooth muscle fibers. The muscle fibers composing the smooth muscle bundles are straight, they contain centrally located, blunt-edged, long, “eel-like” nuclei. Leimyomas of arrector pili origin may demonstrate a low mitotic activity of <1 per 10 high-power field, and this does not negative affect the prognosis for the patients. Pleomorphic multinucleated tumor giant cells can occur in cutaneous ‘synplastic‘ leiomyomas and pleomorphic angioleiomyoma, but more commenly in the uterus (Lever’s Histopathology of the Skin, 2009).

ALs differ from the other types of leiomyomas. They are encapsulated and contain multiple vessels, with small amounts of collagen as a rule. Veins that are present differ in size and have muscular walls of varying thickness **(Figüre-1).** There are 3 subtypes of ALs. These are cavernous type, kapillary or solid type, and venous type. In the capillary type, the vascular channels are multiple but small (Lever’s Histopathology of the Skin, 2009).



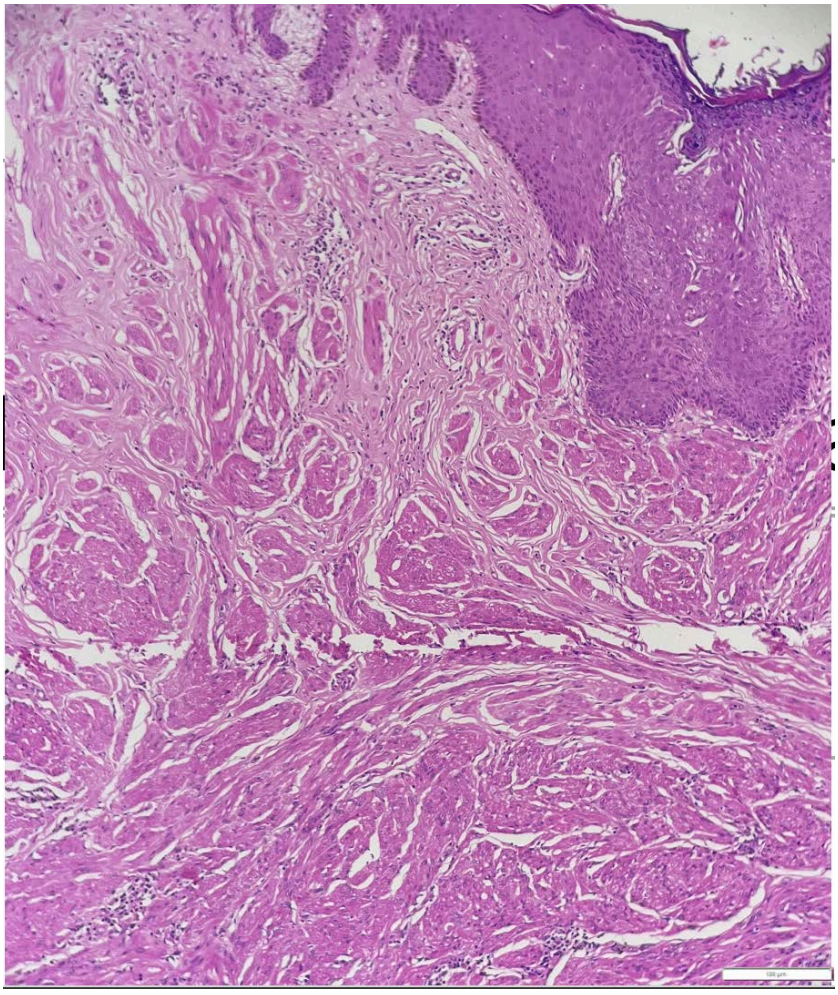
Figüre-1: Angioleiomyoma. Vascular channels of various calibers are surrounded by a proliferation of radially arranged smooth muscle cells (HEx100, Photographed from the archives of Konya Numune Hospital, Pathology Laboratory).

A study has found that of 122 cases, 37 venous in type, 11 were cavernous, and 74 were of solid type. In the study, comments were made on the histological similarity between cases with myopericytoma and concentric perivascular arrangement. In the series of 122 cases all cases were positive for calponin and actins and focally positive for h-caldesmon. The myopericytomas stained fort he actins and calponin, But they were negative for desmin (Weedon's Skin Pathology, 2016).

Dermoscopy of PL shows changes similar to those of dermatofibroma, including a hypopigmented area and a peripheral pigmented network. Some lesions also show a circular or elongated hyperpigmented structure within the central hypopigmented area; the latter could be due to focally compact hyperkeratosis or related to scratching (Weedon's Skin Pathology, 2016).

Scrotal leiomyomas have illdefined or infiltrative margins. They are more cellular with rarely mitoses. Dartoic muscle is seen beside to the tumor. Male genital leiomyomas may be androgen receptor positive. Cases may express estrogen and progesterone receptors, but this expression is not expected in PLs. A small number of mitoses may be present (Weedon's Skin Pathology, 2016).

The GLs includes masses arising from the dartos muscle of the scrotum or from the labia majora, beside those derived from the mammilary muscle of the nipple in male anf female. GL is the least occurring type of CL and epidemiological tendencies are inadequate. The nipple and groin lesions are generally solitary asymptomatic masses. They are sometimes painful, either spontaneously or in response to cold. Nipple leiomyomas are generally smaller than 2 cm in diameter **(Figüre-2)** (Khachemoune et al. 2005).



Figüre-2: Genital Leiomyoma**.** Interlacing bundles of smooth muscle fibers with in which varying amounts of collagen bundles (HEx100, Photographed from the archives of Konya Numune Hospital Pathology Laboratory).

In females, it has been claimed to be related to estrogen and progesterone. Other causes are trauma and certain drugs like

oral contraceptives. Nipple leiomyomas are also seen in males, associated with gynecomastia, or idiopathic (Cho et al. 2012).

7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of leiomyoma is not difficult. Other differential diagnosis are smooth muscle hamartoma and dermatomyofibroma. Dermatomyofibroma showing a myofibroblastic proliferation with bundles of spindle cells in a parallel arrangement to the epidermis. There is no strong or messy coloring for Desmin. Leiomyomas may demonstration nuclear palisading. Schwannomas are encapsulated and diffusely immunoreactive for S100 protein, and also myoid markers are negative. Finally, cytological atypia, mitotic activity, or necrosis should suggest an atypical intradermal smooth muscle neoplasm or a well-differentiated leiomyosarcoma (Dermatopathology, Foundations in Dignostic Pathology, 2016).

Leiomyosarcomas are cellular, larger, mitotically active and may contain areas of necrosis. Cutaneous leiomyosarcomas often recur. Some of the recently reported cases have occurred as multiple nodules in HIV-infected patients and have been associated with EBV (Rosai and Ackerman's Surgical Pathology, 2011).

In a study conducted by Yokohama et al. 34 cases of subcutaneous and cutaneus leiomyomas were described. These were consist of 12 cases of PL and 22 of GL (vulva, areola, nipple, perianal region, scrotum). 13 cases of 22 GLs occurred in the vulva. 4 cases of pilar arrector origin had multiple lesions. The tumor occurred in adult females with an approximate sex ratio of 3:1 (26 females and 8 males). The average age of patients of leiomyoma is 46.8 years (ranged in age from 26 to 77). According

to Yokoyama et al. Cutaneous leiomyomas are surely rare in occurrence, excluding ALs (Yokoyama et al., 1987).

ALs were found primarily in the inferior extremities and feet, without gender differences. The average size was 1 cm. The most common clinical symptom was localized pain, present in 78% of cases (n = 65); with a mean follow-up of six years, no recurrence or malignant transformation was observed in any of the patients. ALs were found entirely in subcutaneous tissue in 80.2% of cases. The most common form of LA was solid (67.6%), followed by venous (28.3%) and cavernous (4.1%). 14.5% of cases exhibited features of two or three of the described patterns simultaneously. There was no internal neoplasia associated with LG. Scrotal lesions were the most frequent (n = 10), followed by areolas (n = 4) and vulvar lesions (n = 1). The mean size of scrotal lesions was 2.1 cm, areolas 0.67 cm, and vulvar lesions 1 cm. There was no clinical recurrence after two years of follow-up (Yokoyama et al., 1987).

In a study conducted by Aqullo et al. a total of 255 cases were included in the study that could be evaluated for review: 75 patients with 88 (34.5%) PL, 152 (59.6%) AL, and 15 (5.9%) LG (ten scrotal, four areolar, and one vulvar). The most frequent location of PL was the superior extremities and trunk. The mean clinical size was 0.73 cm, similar in multiple and solitary forms, median 0.6 cm). Most PLs were located in the reticular and superficial papillary dermis (39.2%), in the full dermis (24.1%), and in the reticular dermis (13.9%). 45.2% were painful upon friction or pressure (Agullo Perez et al, 2021)

If there is pain associated with the lesions, in the differential diagnosis include: endometrioma, blue rubber bleb nevus, glomus tumors, neurilemmoma, neuromas, granular cell tumor, angiolipomas, and eccrine spiradenomas (Bernett et al. 2025).

In general, uterine leiomyomas associated with the FH mutation are more numerous, larger (up to 10 cm), require hysterectomy and develop at a younger age. However, concerning feature of an FH mutation is its association with a renal cell carcinoma (papillary renal cell carcinoma, type 2) that develops in nearly 15% of patients. Unfortunately, in these patients who develop renal cell carcinoma, approximately 50% have metastases at the time of diagnosis (Bernett et al. 2025).

If PLs result from a genetic syndrome, they usually appear early in life, with an average age of onset of lesions of 25 years, ranges from 10 to 50 years old (Bernett et al. 2025).

8. TREATMENT

Leiomyomas are a benign tumor. Excision is performed for a definitive diagnosis or for other cosmetic reasons (Dermatopathology, Foundations in Dignostic Pathology, 2016).

Pharmacological therapy may be mentioned for patients who are not accepted to be surgical candidates (i.e possibility of recurrence, widespread PLs or extensive). Most therapies, such as nitroglycerin, doxazosin, and nifedipine reducing contraction of the smooth muscle of the pilosebaceous unit. Pregabalin, Duloxetine, and Gabapentin can be used for pain treatment. The results of botulinum toxin injection treatment for lesions are not clear (Bernett et al. 2025).

9.CONLUSION

Cutaneous leiomyomas are rare conditions. Their recognition is important because they can be associated with syndromes and because of the malignancies included in their differential diagnosis.

References:

- Agulló Pérez AD, Resano Abárzuza MA, Córdoba Iturriagagoitia A, Aisa Rivera G, Patiño García A, Yanguas Bayona JI. [Cutaneous leiomyomas: a clinicpathological and epidemiological review]. An Sist Sanit Navar. 2021 Aug 19;44(2):163-176. Spanish. doi: 10.23938/ASSN.0914.

- Bernett CN, Mammino JJ. Cutaneous Leiomyomas. 2023 Aug 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.

-Cho HJ, Kim SH, Kang BJ, Kim H, Song BJ, Lee AW. Leiomyoma of the nipple diagnosed by MRI. Acta Radiol Short Rep. 2012 Oct 1;1(9):arsr.2012.120025. doi: 10.1258/arsr.2012.120025.

-Dermatopathology, a volume in the series, Foundations in Dignostic Pathology (2016), Second Edition, p: 556-558)

-Deveci U, Kapakli MS, Altintoprak F, Cayırcı M, Manukyan MN, Kebudi A. Bilateral nipple leiomyoma. Case Rep Surg. 2013; 2013:475215. doi: 10.1155/2013/475215.

- Khachemoune A, Rodriguez C, Lyle S, Jiang SB. Genital leiomyoma: surgical excision for both diagnosis and treatment of a unilateral leiomyoma of the male nipple. Dermatol Online J. 2005 Mar 1;11(1):20. doi.org/10.5070/D33c544905.

-Lever's Histopathology of the Skin (2009), Tenth Ed., David E. Elder, USA, p:1076-1080

- Malik K, Patel P, Chen J, Khachemoune A. Leiomyoma cutis: a focused review on presentation, management, and association with malignancy. Am J Clin Dermatol. 2015 Feb;16(1):35-46. doi: 10.1007/s40257-015-0112-1.

-Rosai and Ackerman's Surgical Pathology, (2011), Tenth Edition, Juan Rosai, USA, MOSBY Elsevier, p:181-182)

-Weedon's Skin Pathology. 4th ed. James W. Patterson, 2016. p: 1030-1033.

- World Healht Organization (WHO) (2018). 4th ed. Skin Tumours. (Section Editor: Folpe A. Fullen D.R.), IARC Press (p:328-329).

- Yokoyama R, Hashimoto H, Daimaru Y, Enjoji M. Superficial leiomyomas. A clinicopathologic study of 34 cases. Acta Pathol Jpn. 1987 Sep;37(9):1415-22.

LYMPHOVASCULAR INVASION IN ENDOMETRIAL CANCER: A COMPREHENSIVE ANALYSIS FROM PATHOLOGICAL FOUNDATIONS TO CURRENT STAGING AND CLINICAL MANAGEMENT

Naile KÖKBUDAK

1. Introduction

Endometrial cancer remains the most common malignancy of the female genital system in developed countries, and its incidence is increasing at an alarming rate globally. When examining the underlying dynamics of this increase, factors such as the obesity pandemic brought about by modern lifestyles, the rise in the prevalence of metabolic syndrome, and increased life expectancy stand out as playing a critical role in the pathogenesis of estrogen-dependent neoplasms (1). Although endometrial cancer is often detected at an early stage confined to the uterus due to its early symptom of postmenopausal bleeding and has excellent survival rates with curative surgery, epidemiological data show that a significant proportion of patients (15-20%) face the risk of recurrence, distant metastasis, and disease-related mortality. This clinical dilemma-the unexpected aggressive course observed in a cancer type considered to have a good prognosis-has prompted pathologists and oncologists to search for biomarkers that can more accurately predict the tumor's biological behavior.

1.1. Epidemiology and Prognostic Factors in Endometrial Cancer

One of the most critical parameters whose importance has been increasingly recognized in recent studies is “Lymphovascular Space Invasion (LVSI).” LVSI is the first and most decisive step in the passage of tumor cells from their primary foci into the systemic circulation and lymphatic network. Accepted as a trigger for the metastatic process in tumor biology, this parameter is more than just a histopathological finding; it is concrete evidence of the tumor's invasive capacity and interaction with the microenvironment.

In the past, LVSI was considered a secondary risk factor that was excluded from staging systems and only mentioned as present or absent in pathology reports; today, in light of molecular pathology and large-scale randomized controlled trials, it has become a prognostic factor that directly alters staging (FIGO 2023) and can independently guide adjuvant treatment decisions (ESGO-ESTRO-ESP guidelines) (2,3). Particularly in today's practice, where sentinel lymph node (SLN) procedures or surveillance without lymphadenectomy are increasingly used to avoid the morbidity of lymph node dissection, the presence of LVSI in the uterine specimen has become the strongest indicator of occult metastasis risk (4).

2. The Biological Basis of Lymphovascular Invasion and the Metastatic Process

2.1. Tumor Microenvironment and the Mechanism of Vascular Invasion

LVSI is not a passive event, but rather the result of a dynamic interaction between tumor cells and host tissue. Endometrial cancer cells activate a program called Epithelial-Mesenchymal Transition (EMT) to gain invasive capacity. During this process, the expression of E-cadherin, which provides intercellular connections, decreases, while mesenchymal markers such as vimentin and N-cadherin increase. These cells, which gain the ability to move, progress into the stroma by breaking down the basement membrane and extracellular matrix through the proteolytic enzymes (matrix metalloproteinases - MMPs) they secrete.

However, stromal invasion alone is insufficient for metastasis. Tumor cells must enter the lumen of lymphatic or blood vessels (intravasation). The endometrium and myometrium possess a rich lymphatic and vascular network. Lymphangiogenesis developing particularly in the peritumoral area provides transport pathways for tumor cells. The secretion of growth factors such as VEGF-C and VEGF-D by tumor cells triggers lymphatic vessel proliferation and dilation by stimulating the VEGFR-3 receptor on the lymphatic endothelium. Dilated and increased permeability of peritumoral lymphatics facilitates the entry of tumor cells (5).

2.2. Formation of Tumor Emboli

Tumor cells entering the vascular lumen encounter mechanical stress in circulation and immune system attacks by NK cells. The tumor emboli we see under the microscope in LVSI diagnosis are actually a defense mechanism developed by tumor cells against these threats. Instead of circulating individually, the cells form clusters and camouflage themselves by covering themselves with platelets and fibrin. These emboli are not merely passively drifting structures, but biologically active units that play a role in preparing the metastatic process.

The presence of LVSI indicates not only that the tumor has spread anatomically, but also that it exhibits a biologically aggressive behavior pattern (such as p53 mutation or high proliferation index). Indeed, studies have demonstrated that LVSI positivity correlates strongly with other poor prognostic factors such as histological grade, deep myometrial invasion, and lymph node metastasis. More importantly, however, multivariate analyses show that LVSI has a negative impact on disease-free survival (DFS) and overall survival (OS), independent of all other factors. This confirms that LVSI is an independent marker reflecting the tumor's capacity for systemic spread (6).

3. Histopathological Diagnosis

In pathology practice, LVSI diagnosis is one of the areas with the lowest interobserver agreement and the most frequent source of debate. Studies showing kappa values ranging from 0.4 to 0.6 demonstrate that pathologists can reach different conclusions when examining the same section (7). The main reason for this lack of agreement is the presence of numerous histological artifacts that mimic LVSI.

3.1. Standard Diagnostic Criteria

To establish a definitive LVSI diagnosis in hematoxylin-eosin (H&E) stained sections, the following criteria must be meticulously evaluated (8):

1. Endothelial Lining: The space occupied by the tumor cell cluster must be lined by flat endothelial cells. A slight protrusion of the endothelial nuclei toward the lumen is a diagnostic clue.

2. Intraluminal Location: The tumor group must be located within the vessel lumen. This group may float freely or be attached to the vessel wall at one point.

3. Peripheral Response: Lymphocytes, erythrocytes, or eosinophilic proteinaceous material representing lymphatic fluid may be present accompanying tumor cells within the vessel lumen.

4. Mismatched Shape: The shape of the tumor embolism should differ from the shape of the vascular space it occupies. If the tumor group completely fills the space like a puzzle piece or precisely follows its contours, this indicates an artifact rather than invasion.

3.2. Differential Diagnosis

A false-positive LVSI diagnosis may lead to the patient being unnecessarily classified as stage II or III and exposed to toxic treatments (radiotherapy/chemotherapy). A false-negative diagnosis, on the other hand, may result in a high-risk patient being left untreated. Therefore, awareness of mimics is of vital importance (9).

3.2.1. Retraction Artifact

During tissue tracking, formalin fixation and alcohol dehydration cause the tumor tissue to shrink and separate from the surrounding stroma. This separation results in clear spaces around the tumor islands. These spaces may resemble lymphatic channels under the microscope. In retraction artifact, the resulting void is not lined with endothelium. The most important clue is the mirror image; that is, the shape of the void exactly follows the shape of the tumor island. Furthermore, retraction is typically observed in the center of the tumor and over large areas, whereas true LVSI is more commonly seen at the peripheral invasive margins of the tumor (10).

3.2.2. MELF Pattern (Microcystic, Elongated, Fragmented)

MELF, a specific invasion pattern seen in endometrioid carcinomas, is characterized by glands acquiring a microcystic, elongated, and fragmented structure and spreading into the stroma. This pattern is usually surrounded by a fibromyxoid stroma and an inflammatory response. Tumor cells exhibiting the MELF pattern are cytokeratin 7 (CK7) positive but may take on a histiocyte-like morphology. Glands exhibiting the MELF pattern may mimic lymphatic vessel endothelium with their thinned epithelia and flattened cells. Furthermore, the actual incidence of LVSI in MELF areas is quite high. The MELF gland itself should not be interpreted as vascular invasion, but the presence of the MELF pattern should be considered a warning sign, prompting a more careful search for actual vascular invasion in that area (11). Studies suggest that the presence of the MELF pattern is associated with lymph node metastasis, but this is likely due to the accompanying intense LVSI rather than the MELF structures

themselves (12).

3.2.3. Iatrogenic Displacement

Uterine manipulators used particularly in laparoscopic and robotic surgery, the application of pressurized gas, or the fragmentation of the tumor during surgery can mechanically push tumor fragments into vascular lumens. Such artificial emboli are generally not adherent to the vessel wall and lack surrounding fibrin or tissue reaction. Furthermore, their appearance as isolated foci in deep myometrial vessels or large vessels near the serosa, where the tumor would not normally reach, should raise suspicion. Mechanical displacement does not affect prognosis and should not be reported as LVSI (13).

3.3. The Role of Immunohistochemistry: D2-40, CD31, CD34

In cases where standard H&E staining is insufficient, immunohistochemistry (IHC) becomes a critical problem solver.

D2-40 (Podoplanin): An IHC marker with high specificity for lymphatic endothelial cells. It is considered the gold standard for distinguishing retraction artifacts from true lymphatic invasion. Retraction spaces are not stained with D2-40, whereas the walls of true lymphatic channels are stained (14).

These are pan-endothelial IHC markers. They stain blood vessels strongly but may stain lymphatics weakly or cross-react with fibroblasts in the stroma. Therefore, these two markers are not as reliable as D2-40 in lymphatic invasion studies (15).

In routine practice, applying IHC to every case is not sustainable in terms of cost and workload. However, studies have shown that the use of D2-40 increases the detection rate of LVSI and that a significant proportion of cases reported as suspicious with H&E are actually artifacts (16). Therefore, FIGO and CAP guidelines recommend IHC confirmation only when a “substantial” LVSI diagnosis is to be made and this diagnosis will fundamentally change the patient's treatment (e.g., radiotherapy decision), not to prevent false positives, but to avoid mandatory routine use (17,18).

4. Quantitative Assessment

One of the most significant changes in pathology literature over the past decade has been the recognition that LVSI should be assessed quantitatively rather than simply as a presence or absence parameter. This change is based on retrospective analyses of PORTEC studies (4).

4.1. The Concept of “Substantial” LVSI

In the PORTEC-1 and PORTEC-2 studies, when patients with LVSI were examined, it was noted that the risk of recurrence in patients with invasion in only 1-2 vessels was similar to that in patients with no invasion. In contrast, the risk increased dramatically in patients with widespread vascular involvement. This observation led to the distinction between “Focal” and “Substantial” (extensive/significant) (16).

4.2. Threshold Value

The threshold value to be used for Substantial LVSI has been debated for a long time. Some pathology communities and older studies have suggested a ≥3 vessel threshold. However, the most recent and comprehensive data indicate that the ≥5 vessel threshold has the highest prognostic discriminatory power. The FIGO 2023 Staging System and the World Health Organization (WHO) 2020 classification have adopted the criterion of 5 or more vessels as the official threshold value based on this evidence (1,2) (Table 1).

Table 1: LVSI Classification According to Current Guidelines

Category	**Definition (WHO / FIGO 2023)**	**Microscopic Characteristics**	**Clinical Risk Level**
Negative	No invasion	-	Low Risk
Focal	**< 5 vessel involvement**	Usually in a single focus, 1-4 vessels at the invasive border.	Low / Neutral Risk (Similar to Negative)
Substantial	**≥ 5 vessel involvement**	It is usually multifocal, widespread, and may also occur in deep myometrial areas.	High Risk (Independent prognostic factor)

4.3. Clinical Implications of PORTEC Data

In PORTEC analyses, the presence of substantial LVSI increases the risk of pelvic recurrence from 5% to the 25-30% range. In patients with focal LVSI, this rate is around 5-6%. These data demonstrate that focal LVSI can be managed as if it were clinically absent, but substantial LVSI requires aggressive treatment. This distinction aims to protect thousands of patients from the side effects of unnecessary radiotherapy while ensuring that patients who are truly at risk receive the appropriate treatment (4,16).

5. FIGO 2023 Staging System

The International Federation of Gynecology and Obstetrics (FIGO) has revolutionized the management of endometrial cancer with its new staging system published in 2023. The most striking aspect of this update is that pathological and molecular characteristics now directly determine the stage, taking precedence over anatomical spread (1,2).

5.1. Transition from Anatomical Staging to Histological Staging

In the old system (FIGO 2009), staging was based entirely on where the tumor had spread anatomically (half of the myometrium, cervix, serosa, etc.). Although LVSI was known to be a factor affecting prognosis, it did not change the stage. FIGO 2023, however, also classifies the tumor based on its biological behavior. Histological types are divided into two categories: “Aggressive” (Serous, Clear Cell, Grade 3 Endometrioid, Carcinosarcoma) and “Non-aggressive” (Grade 1-2 Endometrioid).

5.2. Stage Upgrading Mechanism: From Stage I to IIB

The integration of LVSI into staging has produced dramatic results, particularly in early-stage “non-aggressive” tumors. According to FIGO 2023 rules:

-**Stage IA and IB:** Only Grade 1-2 endometrioid carcinomas that are LVSI Negative or Focal may remain in this stage.

-**Stage IIB:** If Substantial LVSI is present, the patient is directly classified as Stage IIB, regardless of myometrial invasion depth (even if it is only in the polyp), provided the histological type is non-aggressive (Grade 1-2).

This rule is the clearest evidence of how the pathology report changes the clinical outcome. For example, a patient without myometrial invasion (formerly Stage IA) who is reported to have tumor emboli in ≥5 vessels is now Stage IIB. This change results in the patient receiving pelvic radiotherapy and potentially chemotherapy instead of being followed with surgery alone. This approach aims to neutralize the high risk of pelvic recurrence and distant metastasis created by substantial LVSI with aggressive treatment (19).

6. LVSI in the Era of Molecular Classification

The Cancer Genome Atlas (TCGA) project has established a genetic basis for prognosis prediction by dividing endometrial cancer into four molecular subtypes (POLE, MMRd, NSMP, p53 abnormal) (8).

6.1. TCGA Groups and the Relationship with LVSI

In this molecular era, LVSI, a microscopic finding, remains important, but its impact varies depending on the molecular group.

-**POLE Mutated (Ultramutated) Group:** Has an excellent prognosis. LVSI may be present in this group, but studies show that the presence of LVSI in POLE mutant patients does not worsen the prognosis. The strong anti-tumor immune response resulting from the tumor's high mutation burden may prevent systemic spread even in the presence of vascular invasion. Therefore, treatment de-escalation can be safely considered in POLE mutant patients even in the presence of LVSI (20).

-**MMR Deficiency (dMMR / MSI-H) Group:** In this group, LVSI is associated with poor prognosis. Substantial LVSI, in particular, increases the risk of lymph node metastasis. However, the sensitivity of dMMR tumors to immunotherapy (checkpoint inhibitors)

offers new treatment options in LVSI-positive recurrence cases (21).

-**p53 Abnormal (Serous-like) Group:** This is the group with the worst prognosis. The frequency of LVSI is very high. However, the main factor determining prognosis in this group is usually the genomic instability caused by p53 mutation. Nevertheless, LVSI is an indicator of disease spread (22).

-**NSMP (No Specific Molecular Profile / p53 wild-type) Group:** LVSI is the most critical marker in this group, which constitutes the largest portion (50%) of endometrial cancers. Since molecular features are neutral, the main factors determining prognosis are grade and LVSI. Studies have shown that the presence of substantial LVSI in the NSMP group increases the risk of recurrence by 7.5 times. In this group, the treatment decision is almost entirely dependent on the pathologist's LVSI report (8,23).

7. Clinical Management and Adjuvant Treatment Algorithms

The inclusion of LVSI in staging and the increased importance of its quantity have reshaped clinical guidelines (ESGO-ESTRO-ESP) (3).

7.1. ESGO-ESTRO-ESP Guidelines

European guidelines classify patients into risk groups when deciding on adjuvant therapy (3):

-**Low Risk**: Stage I, Grade 1-2, LVSI Negative. (Treatment: Follow-up only)

-**Intermediate Risk:** Stage IB, Grade 1-2, LVSI Negative. (Treatment: Vaginal Brachytherapy (VBT) is recommended. Focal LVSI is generally managed in this category or in the low-risk category).

-**High-Intermediate Risk:** This group is defined by substantial LVSI. The presence of substantial LVSI in stage I endometrioid cancer places the patient directly into this risk group. (Treatment: VBT alone is insufficient for these patients because substantial LVSI increases the risk of pelvic recurrence. Therefore, External Pelvic Radiotherapy (EBRT) is the standard recommendation. When combined with certain high-risk features (e.g., Grade 3 + Substantial LVSI), adjuvant chemotherapy may also be added to the treatment.)

-**High Risk:** Advanced stages or aggressive histologies (Serous, p53 abn).

7.2. Management of Patients with Negative Lymph Nodes

Even in patients who have undergone lymphadenectomy and whose lymph nodes are pathologically negative (pN0), the presence of substantial LVSI in the uterus is a sign of poor prognosis. This may indicate the presence of micrometastases in the lymphatic system that cannot be removed surgically or hematogenous spread. Studies in “node-negative” cases emphasize that the presence of substantial LVSI increases the risk of distant metastasis and mortality; therefore, these patients are candidates for adjuvant systemic therapy or radiotherapy even if they are pN0 (6,10,19,24).

7.3. Fertility-Preserving Approaches

In young patients and women who wish to preserve their fertility, uterine preservation with progestin therapy may be considered. However, patient selection is critical for this approach. Guidelines indicate that ideal candidates for fertility-preserving therapy are those with tumors that are limited to the endometrium (Stage IA1), Grade 1, and LVSI Negative. The presence of LVSI constitutes a strong contraindication for fertility-sparing treatment, as it indicates a high risk of myometrial invasion and extrauterine spread.

8. Conclusion

LVSI is one of the most strategic parameters in modern gynecological pathology for endometrial cancer. As discussed in this book chapter, LVSI is no longer just a microscopic detail but a prognostic factor that directly determines the stage (FIGO 2023), risk group (ESGO-ESTRO-ESP), and treatment selection (Observation vs. Radiotherapy/Chemotherapy).

Quantity should be specified in pathology reports. LVSI should no longer be reported as “Present/Absent,” but rather as “Absent / Focal (<5) / Substantial (≥5).”

Be cautious of mimics, be alert for MELF patterns and retraction artifacts, and consider immunohistochemical confirmation (D2-40) if a substantial diagnosis is to be made and this will change the patient's treatment.

When reporting substantial LVSI, the pathologist should be aware that this will be interpreted by the clinician as an upgrade in stage (IIB) and will change the treatment regimen.

In conclusion, the accurate diagnosis and reporting of LVSI plays a vital role in improving the survival of patients with endometrial cancer and avoiding the toxicity of unnecessary treatments. In the future, the integration of artificial intelligence-supported digital pathology tools into this field is expected to make LVSI assessment more standardized and objective.

REFERENCES

1. Berek, J. S., Matias-Guiu, X., Creutzberg, C., Fotopoulou, C., Gaffney, D., Kehoe, S., Lindemann, K., Mutch, D., Concin, N., & Endometrial Cancer Staging Subcommittee, FIGO Women's Cancer Committee (2023). FIGO staging of endometrial cancer: 2023. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 162(2), 383–394. https://doi.org/10.1002/ijgo.14923
2. Menendez-Santos, M., Gonzalez-Baerga, C., Taher, D., Waters, R., Virarkar, M., & Bhosale, P. (2024). Endometrial Cancer: 2023 Revised FIGO Staging System and the Role of Imaging. Cancers, 16(10), 1869. https://doi.org/10.3390/cancers16101869
3. Concin, N., Matias-Guiu, X., Vergote, I., Cibula, D., Mirza, M. R., Marnitz, S., Ledermann, J., Bosse, T., Chargari, C., Fagotti, A., Fotopoulou, C., Gonzalez Martin, A., Lax, S., Lorusso, D., Marth, C., Morice, P., Nout, R. A., O'Donnell, D., Querleu, D., Raspollini, M. R., Creutzberg, C. L. (2021). ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. International journal of

gynecological cancer : official journal of the International Gynecological Cancer Society, 31(1), 12–39. https://doi.org/10.1136/ijgc-2020-002230.
4. Bosse, T., Peters, E. E., Creutzberg, C. L., Jürgenliemk-Schulz, I. M., Jobsen, J. J., Mens, J. W., Lutgens, L. C., van der Steen-Banasik, E. M., Smit, V. T., & Nout, R. A. (2015). Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer-A pooled analysis of PORTEC 1 and 2 trials. European journal of cancer (Oxford, England : 1990), 51(13), 1742–1750. https://doi.org/10.1016/j.ejca.2015.05.015
5. Ogunmuyiwa, J., & Williams, V. (2024). Emerging Advances in Endometrial Cancer: Integration of Molecular Classification into Staging for Enhanced Prognostic Accuracy and Implications for Racial Disparities. Cancers, 16(6), 1172. https://doi.org/10.3390/cancers16061172
6. Yalcin, Y., Kosan, B., Yalcin, S., Abay, M., & Ozerkan, K. (2025). The Impact of Lymphovascular Space Invasion on Recurrence and Survival in FIGO Stage I Node-Negative Endometrioid Endometrial Cancer. Journal of clinical medicine, 14(18), 6535. https://doi.org/10.3390/jcm14186535
7. Zheng, Q., Shao, D., Shu, J., Zhang, Q., Huang, M., Wang, D., & Zou, D. (2025). The impact of integrated genomic analysis on molecular classifications and prognostic risk stratification in endometrial cancer: a Chinese experience. Frontiers in oncology, 15, 1541562. https://doi.org/10.3389/fonc.2025.1541562
8. Alexa, M., Hasenburg, A., & Battista, M. J. (2021). The TCGA Molecular Classification of Endometrial Cancer and Its Possible Impact on Adjuvant Treatment Decisions. Cancers, 13(6), 1478. https://doi.org/10.3390/cancers13061478
9. Üyük, C., Kantarcıoğlu, S. C., & Yavuzcan, A. (2023). Endometrium kanserinde lenfovasküler saha invazyonu ile kötü prognostik faktörlerinin ilişkisinin incelenmesi. Türk Jinekolojik Onkoloji Dergisi, 23(3), 58-65. https://doi.org/10.59215/trsgo.1312688
10. Cusano, E., Myers, V., Samant, R., Sudai, T., Keller, A., Le, T., E, C., Grimes, S., & Xu, Y. (2018). Prognostic Significance of Lymphovascular Space Invasion in the Absence of Lymph Node Metastases in Early-Stage Endometrial Cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society, 28(5), 890–894. https://doi.org/10.1097/IGC.0000000000001229
11. Sun, B., Zhang, X., Dong, Y., Li, X., Yang, X., Zhao, L., Wang, J., & Cheng, Y. (2024). Prognostic significance of lymphovascular space invasion in early-stage low-grade endometrioid endometrial cancer: a fifteen-year retrospective Chinese cohort study. World journal of surgical oncology, 22(1), 203. https://doi.org/10.1186/s12957-024-03483-6
12. Sun, B., Zhang, X., Dong, Y., Li, X., Yang, X., Zhao, L., Wang, J., & Cheng, Y. (2024). Prognostic significance of lymphovascular space invasion in early-stage low-grade endometrioid endometrial cancer: a fifteen-year retrospective Chinese cohort study. World journal of surgical oncology, 22(1), 203. https://doi.org/10.1186/s12957-024-03483-6
13. Kim, S., Park, H. K., Jung, H. Y., Lee, S. Y., Min, K. W., Kim, W. Y., Han, H. S., Kim, W. S., Hwang, T. S., & Lim, S. D. (2013). ERG Immunohistochemistry as an Endothelial Marker for Assessing Lymphovascular Invasion. Korean journal of pathology, 47(4), 355–364. https://doi.org/10.4132/KoreanJPathol.2013.47.4.355
14. Peters, E. E. M., Bartosch, C., McCluggage, W. G., Genestie, C., Lax, S. F., Nout, R., Oosting, J., Singh, N., Smit, H. C. S. H., Smit, V. T. H. B. M., Van de Vijver, K. K., & Bosse, T. (2019). Reproducibility of lymphovascular space invasion (LVSI) assessment

in endometrial cancer. Histopathology, 75(1), 128–136. https://doi.org/10.1111/his.13871
15. Eminović, S., Babarović, E., Klarić, M., & Fučkar Čupić, D. (2024). Blood Vessel Invasion Is an Independent Prognostic Factor in Endometrial Endometrioid Carcinoma Compared to Lymph Vessel Invasion and Myometrial Invasion Pattern. Cancers, 16(13), 2385. https://doi.org/10.3390/cancers16132385
16. Van den Heerik, A. S. V. M., Aiyer, K. T. S., Stelloo, E., Jürgenliemk-Schulz, I. M., Lutgens, L. C. H. W., Jobsen, J. J., Mens, J. W. M., van der Steen-Banasik, E. M., Creutzberg, C. L., Smit, V. T. H. B. M., Horeweg, N., & Bosse, T. (2022). Microcystic elongated and fragmented (MELF) pattern of invasion: Molecular features and prognostic significance in the PORTEC-1 and -2 trials. Gynecologic oncology, 166(3), 530–537. https://doi.org/10.1016/j.ygyno.2022.06.027
17. Momeni M, Chary M, Tran A, et al. (2025) Immunohistochemistry Does Not Improve Reliability of Diagnosis of Lymphovascular Space Invasion in Endometrial Cancer. Int J Pathol Clin Res11:163. doi.org/10.23937/2469-5807/1510163
18. Peters, E. E. M., Nucci, M. R., Gilks, C. B., McCluggage, W. G., & Bosse, T. (2025). Practical guidance for assessing and reporting lymphovascular space invasion (LVSI) in endometrial carcinoma. Histopathology, 86(2), 173–182. https://doi.org/10.1111/his.15272
19. Avcı F. (2025). Correspondence on "Oncologic outcomes based on lymphovascular space invasion in node- negative FIGO 2009 stage I endometrioid endometrial adenocarcinoma: a multicenter retrospective cohort study" by Dagher et al. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society, 35(1), 100045. https://doi.org/10.1016/j.ijgc.2024.100045
20. Jumaah, A. S., Al-Haddad, H. S., McAllister, K. A., & Yasseen, A. A. (2022). The clinicopathology and survival characteristics of patients with POLE proofreading mutations in endometrial carcinoma: A systematic review and meta-analysis. PloS one, 17(2), e0263585. https://doi.org/10.1371/journal.pone.0263585
21. Yin, X., Luo, B., & Li, Y. (2025). Meta-analysis of the clinicopathologic features of endometrial cancer molecular staging. Frontiers in oncology, 14, 1510102. https://doi.org/10.3389/fonc.2024.1510102
22. Siegenthaler, F., Epstein, E., Büchi, C. A., Gmür, A., Saner, F. A. C. M., Rau, T. T., Carlson, J. W., Mueller, M. D., & Imboden, S. (2023). Prognostic value of lymphovascular space invasion according to the molecular subgroups in endometrial cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society, 33(11), 1702–1707. https://doi.org/10.1136/ijgc-2023-004606
23. Cancer Genome Atlas Research Network, Kandoth, C., Schultz, N., Cherniack, A. D., Akbani, R., Liu, Y., Shen, H., Robertson, A. G., Pashtan, I., Shen, R., Benz, C. C., Yau, C., Laird, P. W., Ding, L., Zhang, W., Mills, G. B., Kucherlapati, R., Mardis, E. R., & Levine, D. A. (2013). Integrated genomic characterization of endometrial carcinoma. Nature, 497(7447), 67–73. https://doi.org/10.1038/nature12113
24. Pifer, P. M., Jaishankar, S., Bhargava, R., Schad, M. D., Keller, A., Musunuru, H. B., Cohen, M., Sukumvanich, P., Courtney-Brooks, M., Boisen, M., Berger, J. L., Olawaiye, A., Lesnock, J., Edwards, R., Taylor, S., Vargo, J. A., & Beriwal, S. (2023). Is Substantial Lymphovascular Space Invasion Prognostic in Patients With Pathologically Lymph Node-Negative Endometrial Cancer?. International journal of radiation oncology, biology, physics, 117(1), 148–153. https://doi.org/10.1016/j.ijrobp.2023.02.053

TÜRKİYE VE DÜNYADA

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