Lymphovascular space invasion in node-negative endometrial cancer: what was old is new again

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Received 28 August 2024
Accepted 29 August 2024

The presence of lymphovascular space invasion (LVSI) impacts outcomes in early endometrial cancer, yet defining and identifying LVSI remains challenging. Numerous studies demonstrate the association between LVSI and lymph node metastasis, distant disease, and recurrence. Consequently, LVSI has been integrated into the European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology (ESGO/ESTRO/ESP) treatment guidelines and the International Federation of Gynecology and Obstetrics (FIGO) 2023 staging for endometrial cancer.[1 2] Traditionally assessed as present/absent, then subjectively as no, focal, or substantial, LVSI has evolved into a semi-quantified measure to better distinguish between borderline cases and inform adjuvant treatment decisions.[3] As Dagher et al elegantly outline, the quantification reproducibility remains modest, with obstacles in diagnosis arising from fixation artifacts, LVSI definition nuances, and the small number of cases near the cut-off point. There is also ongoing debate over the appropriate cut-off for defining substantial LVSI, with different studies ranging from two to five vessel involvement.[1]

This month's lead article examines whether the current World Health Organization (WHO) classification of LVSI into no/focal (<5 vessels) and substantial/extensive (≥5 vessels) provides meaningful prognostic separation and should be included in endometrial cancer staging.[4] They performed an international multi-institutional retrospective cohort study of 1555 patients with FIGO 2009 stage I endometrioid endometrial cancer who had undergone hysterectomy and lymph node analysis. Patients were categorized into three groups: no LVSI, focal LVSI (1–4 vessels), and substantial LVSI (≥5 vessels). Five-year progression-free survival was significantly higher in patients with no LVSI (90.7%) than in those with focal (70.5%) or substantial LVSI (68.7%) (p<0.001), and any presence of LVSI was associated with a higher risk of progression or death. Importantly, the difference in the adjusted hazard risk between focal and substantial LVSI was minimal (1.18, p=0.049). Approximately 20% of patients received adjuvant therapy, with the modality decided on an individual basis and following local center guidelines.

We congratulate the authors for addressing the critical piece missing from the PORTEC analyses informing the quantified approach to LVSI—namely, lymph node assessment.[3] Previously, Jorge et al found a 3–16-fold increased risk of lymph node positivity in patients with any LVSI, underscoring the incomplete story told by our current data.[5] Dagher et al address this problem by including only patients who successfully underwent sentinel lymph node biopsy and/or lymphadenectomy and are truly node-negative.[4] Before we can confidently use substantial LVSI alone to increase a patient's stage as in the FIGO 2023 staging, it is essential that we pursue more robust data on LVSI quantification in well-staged populations. These data have crucial implications for prognostication, staging, and the individualization of post-surgical therapy in endometrial cancer.

The increasing use of molecular analysis to guide treatment as in the RAINBO trial will provide further clarification of the true role of quantified LVSI.[6] At the same time, our understanding of the interplay between isolated tumor cells and LVSI will improve with ongoing prospective analysis and will be able to be incorporated into future staging guidelines.[7] Given the current challenges, advances, and compelling evidence presented in this month's lead article, perhaps the traditional two-tiered LVSI measurement system (present vs absent) currently serves patients best.

Contributors Both authors contributed to the writing of this manuscript. GG is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

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► http://dx.doi.org/10.1136/ijgc-2024-005746

To cite: Glaser G, Shahi M. *Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2024-006067

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