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Assessment of lymphovascular invasion in early stage endometrial carcinoma -a retrospective study

Ambreen Moatasim*, Zujajah Hameed and Imran Ahmad

Abstract

Introduction: Endometrial carcinoma is associated with several known prognostic factors. Recently, lymphovascular invasion (LVI) has gained a prominent position in the risk assessment of early endometrioid endometrial carcinoma, in identifying patients who can benefit from adjuvant radiation therapy. This study aims to assess LVI in early-stage endometrioid endometrial carcinoma accurately with emphasis on its extent /grading. We also propose a few local recommendations for improving LVI reproducibility in endometrial carcinoma to guide future studies.

Methods: The duration of this retrospective study was 2 years. Early-stage I (Ia and Ib), and grade 1 and 2 endometrioid endometrial carcinomas were included. 03 reviewers independently recorded their findings on H&E stained slides. LVI was graded as none, focal and substantial. In discordant cases, immunohistochemical stain CD 31 was used.
All the data was entered in the statistical software SPSS version 26 and analyzed for frequencies. The relationships between various histological parameters assessed and the degree of reproducibility for LVI amongst various observers were also determined.

Results: Out of a total of 70 cases of endometrioid carcinoma diagnosed on hysterectomy specimen, only 32 met our inclusion criteria. The rate of LVI positivity was 6.3 %, 34.4 %, and 37.5 % respectively for reviewers 1, 2, and 3. The degree of reproducibility in LVI assessment and LVI grading was significant amongst reviewers 2 and 3. Also, a significant association was drawn between tumor grade and LVI.

Conclusion: Despite limitations in our study we recommend including both LVI assessment and grading in routine reporting formats locally. By adding a second reviewer in LVI assessment and using CD31 in discrepant cases LVI positivity can be significantly increased.

Keywords: Endometrioid carcinoma, LVI, Reproducibility, Grading

Introduction

Endometrial cancer is the most common gynecological malignancy in developed countries. The majority of the women are diagnosed at an early stage with an overall good prognosis. In Pakistani women, endometrial cancer is the third most common gynecologic malignancy after cervix and ovary (Ferlay et al. 2015).

The International Federation of Obstetrics and Gynecology (FIGO) Cancer Report published in 2018 on Cancer of the Corpus Uteri, identified four histological parameters including tumor grade 3 (poorly differentiated), lymphovascular space invasion, non-endometrioid histology, and cervical stromal involvement as predictors of poor prognosis (Amant 2018).

Lymphovascular invasion (LVI), defined as the presence of tumor cells within endothelial-lined spaces within the uterine wall outside the main tumor, is an independent poor prognostic factor in early-stage

* Correspondence: ambreen.moatasim@gmail.com
Shifa International Hospital Ltd, Pitras Bukhari Road, Sector H-8/4, Islamabad, Pakistan

endometrial cancer due to its association with nodal metastasis and disease recurrence in some studies (Guntupalli et al. 2012).

The ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer in 2016 recommended adjuvant radiation treatment for patients with grade 1 or 2, stage I Endometrioid endometrial cancer (EEC) in the presence of unequivocal LVI, independent of the depth of myometrial invasion (Colombo et al. 2016).

The objective of this retrospective study was to assess LVI in early-stage (Stage 1), grade 1 and 2 endometrioid endometrial cancer, diagnosed over a period of 2 years. The frequency, extent, and reproducibility of LVI were determined.

Materials and Methods

This retrospective study was carried out at Shifa International Hospital, Islamabad. The duration of the study was two years. During this period all the cases of endometrioid carcinoma diagnosed on hysterectomy specimens were retrieved from the archives along with their original reports. Only stage I (Ia and Ib), and grade 1 and 2 endometrioid carcinomas were included. All cases with a higher stage and grade and carcinomas diagnosed on endometrial biopsies were excluded from the study. Histologic variants like serous and clear cell carcinoma were also excluded from the study. Patient age, number of sections examined, histologic grade, and depth of myometrial invasion was recorded from previous biopsy reports.

03 reviewers, all general Histopathologists, independently examined Hematoxylin and eosin (H&E) stained slides and recorded their findings. To ensure patient confidentiality and to reduce bias, H & E slides with accompanying study proforma were circulated amongst reviewers, without original reports. Since it was a retrospective study, the first reviewer was taken as the original reporting pathologist and the information recorded by reviewer number one was obtained from the previous reports. The other two reviewers, although non-specialists but having an interest in gynecological pathology were kept unaware of the original findings, independently recorded and graded LVI.

LVI was recorded in the myometrial wall outside the main tumor and was defined as cohesive aggregates of tumor cells located inside a vascular space lined by endothelial cells and preferentially juxtaposed to the vessel wall, outside the main tumor. LVI was graded as None, Focal (defined as 'the presence of a single focus of LVI around the tumor'), Fig. 1, and Substantial (defined as 'diffuse or multifocal, ≥ 2 foci of LVI around the tumor) (Hachisuga et al. 1999), Fig.2. Caution was exercised to differentiate true LVI from its potential mimics like retraction artifacts (no endothelial lining), artefactual tumor displacement, and MELF pattern.

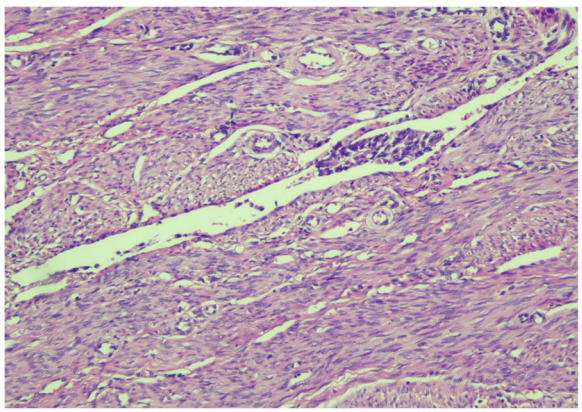

Fig. 1 Focal lymphovascular invasion is defined as 'the presence of a single focus of LVI around the tumor' (H & E X 10 M)

In doubtful cases, immunohistochemical stain CD 31 (JC70) mouse monoclonal antibody by ventana was used (Fig. 3).

All the data was entered into the statistical software SPSS version 26 and analyzed. Frequencies relating to patient age, tumor grade, depth of myometrial invasion, and LVI were calculated. Fisher exact and Chi-square tests were applied to determine the statistical relationship between the number of sections examined, myometrial depth, and tumor grade with lymphovascular invasion. Statistical significance was considered at $P< 0.05$. Kappa values were calculated to determine the reproducibility of LVI amongst various observers. A kappa value of 0.60 to 0.80 was considered a good interobserver agreement while 0.80 to 1.00 was considered as a very good/excellent agreement (Cicchetti 1994).

Results

From April 2018 to April 2020 a total of 70 cases of endometrioid carcinoma were diagnosed on

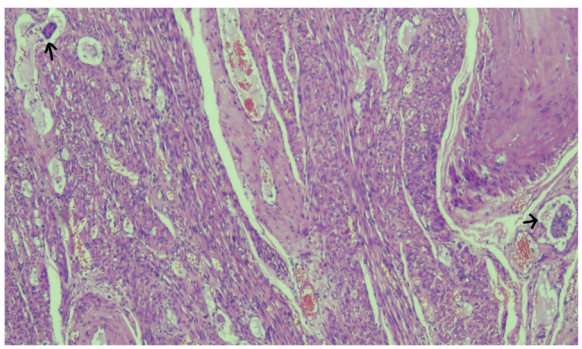

Fig. 2 Substantial lymphovascular invasion defined as 'diffuse or multifocal, ≥ 2 foci of LVI around the tumor, arrows (H & E X 10 M)

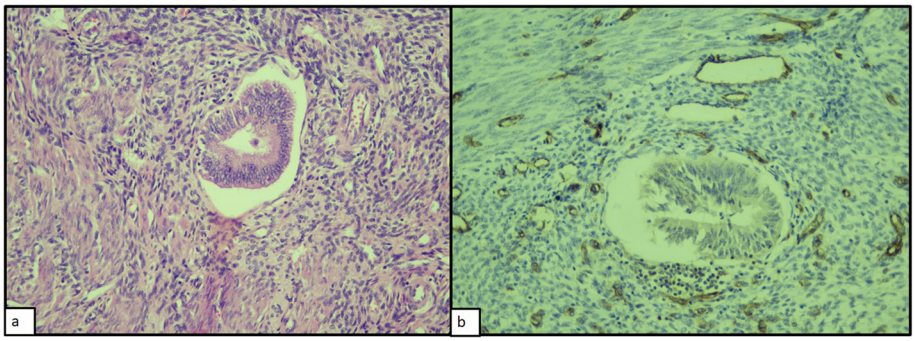

Fig. 3 Potential mimic of LVI: **a** retraction cleft with no endothelial lining (H & E X 20 M). **b** Confirmed by immunohistochemical stain CD31

hysterectomy specimens. Out of these only 32 met the inclusion criteria. The age range was from 43 to 89 with a mean age of 60.53 years. Grade 1 and 2 endometrioid carcinomas comprised of an equal number of cases that is 16 each. As far as the depth of myometrial invasion was considered, 25 cases (78.1 %) displayed less than 50 % myometrial invasion (stage Ia) and 7 (21.9 %) showed more than 50 % myometrial invasion (stage Ib).

The number of sections examined ranged from 2 to 19 with a mean of 8.94. The number of sections examined per cm of the tumor ranged from 1 to 14/cm with a median of 2.5 sections/cm of tumor. Table 1 illustrates the clinicopathologic characteristics of the cases included in our study.

The rate of LVI positivity was 6.3 %, 34.4 %, and 37.5 % respectively for reviewers 1, 2, and 3. As far as the grading of LVI was concerned, reviewer 1 noted no LVI in 30(93.8 %) and substantial in 2 cases (6.3 %). Reviewer 2 detected no LVI in 21(65.6 %), focal in 5 (15.6 %) and substantial in 6 (18.8 %); whereas reviewer 3 found no LVI in 20(62.5 %), focal in 4 (12.5 %) and substantial in 8 (25.0 %) cases.

There were four (12 %) discordant cases amongst reviewers 2 and 3. In one out of four cases (3 %), there was disagreement in focal vs. substantial while in the rest of the three (9 %) the disagreement was related to absence vs. focal/substantial invasion. In all these cases Immunohistochemical marker CD31 was used to differentiate true LVI from its potential mimics. The final results after Immunohistochemistry are displayed in Table 2. After rectification, the total number of cases with lymphovascular invasion was 11 (34.4 %) with 3 cases (27 %) showing focal and 8 (73 %) showing substantial LVI.

An association between the number of sections examined and consensual rectified lymphovascular invasion was determined by applying Fisher exact and Chi-square tests. The p-value was 0.114 which was statistically insignificant and hence no association can be drawn between LVI and the number of sections examined. Similarly no association could be drawn between patient age and LVI ($p = 0.307$) or depth of myometrial invasion and LVI ($p = 0.544$). However, an association was seen between tumor grade and LVI ($p = 0.012$). 9/11 (82 %) cases displaying lymphovascular invasion were histologically grade 2 tumors.

The reviewers 1 and 2 (κ= 0.246), and reviewers 1 and 3 (κ = 0.216) showed poor interobserver agreement for LVI assessment whereas reviewers 2 and 3 showed excellent agreement (κ = 0.761).

Discussion

Endometrial carcinoma is the most common malignancy of the female genital tract in the developed countries.

Table 1 Clinicopathologic characteristics of 32 cases included in the study

Age	Minimum (years)	Maximum (years)	Mean (years)
	43	89	60.53
Tumor size	**Minimum (cm)**	**Maximum (cm)**	**Median (cm)**
	1.0	5.0	3.2
Section/ cm of tumor	**Minimum/cm**	**Maximum/ cm**	**Median/cm**
	1.1	14	2.5
Myometrial depth of invasion	**Less than 50 % (Stage Ia)**		**More than 50 % (Stage Ib)**
	25 (78.1 %)		7 (21.9 %)
Tumor grade	**Grade 1**		**Grade 2**
	16 (50 %)		16 (50 %)

Table 2 LVI Positivity amongst reviewers before and after Immunohistochemistry

LVI	Reviewer 1 [*n* = 32(%)]	Reviewer 2 [*n* = 32(%)]		Reviewer 3 [*n* = 32(%)]	
		Without IHC	With IHC	Without IHC	With IHC
None	30 (93.8 %)	21 (65.6 %)	21 (65.6 %)	20(62.5 %)	21 (65.6 %)
Present	2 (6.3 %)	11 (34.4 %)	11 (34.4 %)	12 (37.5 %)	11 (34.4 %)
LVI Grade		**Without IHC**	**With IHC**	**Without IHC**	**With IHC**
None	30 (93.8 %)	21 (65.6 %)	21 (65.6 %)	20 (62.5 %)	21 (65.6 %)
Focal	0	5 (15.6 %)	3 (9.4 %)	4 (12.5 %)	3 (9.4 %)
Substantial	2 (6.3 %)	6 (18.8 %)	8 (25.0 %)	8 (25.0)	8 (25.0 %)

The majority of patients with early-stage endometrial cancer have an excellent prognosis with a low risk of recurrence and are managed by surgery alone (Amant et al. 2005).

No internationally accepted guidelines are available regarding grossing of the specimen with endometrial cancer, nevertheless it is generally accepted that a thorough gross examination can help to optimize diagnosis, staging and prognosis. In a recently published article by international society of gynecologic pathologists, recommendations regarding grossing and processing of endometrial cancer specimen have been published in order to facilitate cancer reporting (Malpica 2019).

For endometrial cancer, amongst the known prognostic factors are included histological type, tumor stage, size, grade, cervical involvement, depth of myometrial invasion and lymphovascular invasion. (Amant 2018; Euscher et al. 2013)The significance of LVI is related to its association with nodal metastasis and disease recurrence in some studies (Guntupalli et al. 2012) and has gained a prominent position in risk assessment for endometrial cancer.

The combination of above mentioned histologic prognostic factors have been used to stratify early-stage endometrial cancer into low-risk (LR), intermediate risk, high–intermediate risk (HIR), and high-risk (HR), to identify patients at risk of recurrence and who can benefit from adjuvant therapy (Colombo et al. 2016). Compared with the ESMO risk group classification (Colombo et al. 2013), the adverse prognostic role of LVI has been recognized by the ESMO-ESGO-ESTRO Consensus Conference (Colombo et al. 2016). Adjuvant radiation treatment is now recommended for high-intermediate risk group: patients with stage I endometrioid carcinoma, grade 1–2, with LVI unequivocally positive, regardless of the depth of invasion.

From the above statement, it is apparent that LVI should be unequivocally present that is, beyond any ambiguity. The ambiguity can result from potential mimics of LVI. The most frequently encountered LVI mimic is artefactual tumor displacement within myometrial clefts or large endothelial-lined vessels. This may result from surgical manipulation (Logani et al. 2008)or inappropriate grossing (Kitahara et al. 2009) of a friable tumor and usually occurs in poorly fixed or necrotic tumors. Another common artifact is stromal retraction around the tumor mimicking LVI (Fig.3). 'Microcystic elongated and fragmented (MELF)-type invasion (Murray et al. 2003), may also be another potential LVI mimicker. The true from pseudoinvasion can be differentiated by adhering strictly to the histologic criteria defined as cohesive aggregates of tumor cells located inside a vascular space lined by endothelial cells and preferentially juxtaposed to the vessel wall, outside the main tumor.

Apart from a few large institutes in Pakistan, the lymphovascular invasion is not routinely reported in cases of endometrial carcinoma. Our article emphasizes the importance of routine reporting of LVI not only due to prognostic reasons but also due to the impact on management.

The usual treatment offered to patients of endometrial carcinoma is total abdominal hysterectomy with bilateral salpingo-oophorectomy. Patients with lymphovascular invasion can benefit from adjuvant radiotherapy. Recently, sentinel lymph node dissection is recognized as a treatment modality in such patients. In case of failure of mapping a systematic lymphadenectomy is recommended even though the chances of lymph node involvement are low. In a study by Capozzi et al. (Capozzi et al. 2020), a preoperative lymphovascular invasion score is devised to determine the true probability of LVI and hence the likelihood of lymph node involvement that can guide the surgeon in planning the correct management, avoiding unnecessary overtreatment in case of low scores (Capozzi et al. 2020).

The prevalence of LVI in stage I endometrial cancer varies from 3.2 to 35 % (O'Brien et al. 2009; Rasool et al. 2010). In our study the LVI positivity for the three reviewers was 6.3 %, 34.4 %, and 37.5 % respectively. The detection rate of LVI can be improved by adding a reviewer apart from the reporting pathologist. The low LVI positivity for the first reviewer, in this study, is related to multiple factors including the fact that it is a retrospective study and the first reviewer being the

primary reporting pathologist might have overlooked LVI while reporting other histologic parameters, since general pathologists at times do not specifically look for LVI; whereas the other two reviewers in our study were specifically concentrating on the lymphovascular invasion. Also, LVI mimickers including retraction clefts and artefactual tumor displacement within vessels may have resulted in confusion. Thirdly, immunohistochemistry CD31 was not routinely performed in challenging cases at the time of initial reporting. After the introduction of additional reviewers, though not trained gynecological pathologists but with a special interest in gynecological pathology, overall positivity of LVI increased from 6.3 to 37.5 %. The reproducibility of LVI assessment has been studied in other tumors like colorectal carcinoma (Harris et al. 2008), hepatocellular carcinoma(Fan et al. 2010), and squamous cell carcinoma (Beggan et al. 2016). To our knowledge, only a few studies are available that have studied the reproducibility of LVI assessment in endometrial cancer (Peters et al. 2019; Guan et al. 2011; de Boer et al. 2018). The interobserver reproducibility of LVI assessment and LVI grading in endometrial cancer was substantial (ICC = 0.64,$P < 0.001$) and (ICC = 0.62, $P< 0.001$) respectively in a study by Peters E E M et al. (Peters et al. 2019). de Boer SM et al. (de Boer et al. 2018)reviewed tumor characteristics including LVI as part of an upfront pathology review before randomization in the PORTEC-3 trial. A high rate of interobserver agreement was found between the original pathology report and central review for lymphovascular space invasion ($\kappa = 0.72$). In the study by Guan H et al. (Guan et al. 2011) LVI was assessed in 254 cases of endometrial carcinoma by four pathologists resulting in a disappointing k-value of 0.23 for LVI. In our study reproducibility of LVI assessment was excellent amongst reviewers 2 and 3.

The purpose of retaining the first reviewer in our study is to create a comparison and to bring home the message that by giving only little extra attention to LVI, while routine reporting; one can positively contribute towards patient management.

A three-tiered LVI grading system (none, focal and substantial) has been proposed in a recent study (Bosse et al. 2015). Focal LVI was defined as 'single focus of LVI around a tumor' and substantial LVI as 'diffuse or multifocal LVI around a tumor'. The study used a pooled PORTEC biobank and showed that substantial LVI is a highly significant risk factor for pelvic and distant recurrence. In our study, a significant agreement was seen between reviewers 2 and 3 for LVI grading. Since substantial LVI has a prognostic significance and is considerably reproducible, the LVI grading can easily be incorporated in the pathology report to guide further management. In our study, there were 3 cases (27 %) of focal and 8 (73 %) of substantial LVI.

In this study no association could be drawn between LVI with patient age, the number of sections examined, and depth of myometrial invasion. However, there was a significant association between tumor grade and LVI. Out of 11 cases showing LVI, 9 (82 %) were grade 2 tumors.

The major weaknesses of our study are its retrospective nature and the small number of cases. This is related to the low reported frequency of endometrial carcinoma in Pakistan and more than half of these patients presenting with a high grade and stage, the reason being reluctance to seek specialized help due to ignorance and limited financial resources. Another shortcoming of this study was that there was no gold standard for LVI assessment.

An additional ongoing prospective study is recommended to verify our results. Another limitation of the study is that the first reviewer was the original reporting pathologist while the other two retrospectively reviewed the cases. They were specifically asked to comment on certain parameters including the presence of LVI and its grading, which introduced some bias in our study.

Conclusions

Despite the limitations of our study, we were able to make some recommendations to guide future studies. Since substantial, unequivocal LVI has a prognostic significance in risk stratification of early-stage endometrial carcinoma, for adjuvant radiation therapy, we recommend including both LVI assessment and grading in routine reporting formats.

In most cases, LVI can be easily detected on H&E stained slides. By adding a second reviewer for LVI assessment, the rate of positivity can be significantly enhanced as the chance of missing an LVI by a single reviewer, not trained in gynecological pathology, is higher. In discrepant cases and cases with significant artifacts, CD31 immunostaining can resolve the problem.

Abbreviations

LVI: Lymphovascular invasion; EEC: Endometrioid endometrial carcinoma; H&E: Hematoxylin and eosin; MELF: Microcystic, elongated, and fragmented pattern; ICC: Intra-Class Correlation

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Author contributions

AM: conception, acquisition, analysis, interpretation of data; has drafted the work and has approved the submitted version. ZH: analysis, interpretation of data; has drafted the work and has approved the submitted version. IA: analysis, interpretation of data; and has approved the submitted version.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to hospital privacy policy but can be made available from the corresponding author on reasonable request and after approval from IRB & EC.

Declarations

Ethics approval and consent to participate
The research has been approved by the Institutional Review Board and Ethics Committee (IRB &EC), Shifa International Hospitals Limited.

Consent for publication
The manuscript does not contain data from any person, and hence the above statement is "Not applicable".

Competing interests
The authors declare that they have no competing interests.

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