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DEMYSTIFYING THE ENIGMA OF MELF AND LYMPHOVASCULAR INVASION IN ENDOMETRIAL CARCINOMA – AN IN DEPTH ANALYSIS

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ABSTRACT :
INTRODUCTION :
Endometrial carcinoma is impacted by various prognostic factors, among which lymphovascular invasion (LVI) has recently added prominence in evaluating the hazard associated with early endometrioid endometrial carcinoma and in determining the potential benefits of adjuvant radiation therapy for patients.In order to accurately evaluate LVI in early-stage endometrioid endometrial cancer, this study focuses on grading and determining its extent.. Additionally, the study proposes local recommendations aimed at enhancing the repeatablity of LVI evaluation in endometrial carcinoma, offering insights to plan further investigation activities.
MATERIALS AND METHODS :
In this retrospective study spanning two years, cases included early-stage Ia and Ib endometrioid endometrial carcinomas of grade 1 and 2. Three independent reviewers meticulously documented their observations based on H&E stained slides, categorizing LVI as absent, focal, or significant. In samples where discrepancies arose, the immunohistochemical stain CD 31 was utilized for further clarification. All data were meticulously entered into SPSS version 26 for comprehensive statistical analysis, including frequency distributions and evaluations of the associations with different histological factors and the consistency of LVI assessments among different researchers.
RESULTS :
Among the initial 70 samples of endometrioid carcinoma identified in hysterectomy specimens, only 32 cases satisfied the stringent inclusion criteria for this study. The rates of LVI positivity varied among reviewers, with percentages of 6.3%, 34.4%, and 37.5% respectively for reviewers 1, 2, and 3. Notably, significant consistency was observed in LVI evaluation and categorizing specifically between assessors 2 and 3. Furthermore, a statistically noteworthy correlation was established amongst tumor grade and the presence of LVI.
CONCLUSION :
In spite of inherent restrictions in our study, we advocate for the routine inclusion of both LVI evaluation and its grading in local result protocols. We suggest implementing a dual-reviewer system for LVI assessment and employing CD 31 staining in cases where discrepancies in LVI status occur, as these measures have the potential to substantially enhance the detection of LVI(1). These recommendations aim to standardize and improve the accuracy of LVI evaluation in clinical practice, potentially influencing treatment decisions in early-stage endometrial carcinoma.
KEYWORDS : Lymphovasular invasion , Well being , Microcystic Pattern .

INTRODUCTION :

Cancer endometrium is the leading malignant cancer in developed countries, usually diagnosed at early stage and frequently linked to a positive prognosis (1,2). Among women from Pakistan cancer endometrum is 3rd commonest cancer among women behind cervical & ovarian cancers. The 2018 FIGO Cancer Report regarding Corpus Uteri Cancer recognized 4 histological elements—poorly differentiated stage, non-endometrioid histology, lymphovascular invasion and cervical stroma association—as factors linked to a worse prognosis. Lymphovascular invasion (LVI) in initial stages of cancer endometrium is defined by the existence of malignant cells located inside endothelial-lined areas in the wall of uterus, extending beyond the primary malignancy. It is regarded as a separate negative prognostic

factor because of its link to nodal metastasis and the likelihood of disease recurrence, as shown by several studies on patient outcomes (3).

The 2016 ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer advised that people affected with initial stages of cancer endometrium should undergo adjuvant radiation therapy if clear lymphovascular invasion (LVI) is detected, irrespective of the extent of myometrial invasion(4). Our research work was done retrospectively to evaluate lymphovascular invasion (LVI) in initial stage (grade one and two) endometrial cancer cases identified over a two-year timeframe(5). The research aimed to evaluate the prevalence, scope, and uniformity of LVI evaluations(6).

MATERIALS AND METHODS :

This retrospective research was done at Saveetha Medical College and Research Institute in Thandalam over a duration of two years. All instances of endometrioid cancer found in hysterectomy specimens during this time was recovered from the records and actual reports. The research solely encompassed instances of stage I (Ia and Ib) and grade 1 and 2 endometrioid carcinomas. The study excluded patients diagnosed with advanced stages or grades and carcinomas identified through endometrial biopsies.

Histological types like serous and clear cell carcinoma were omitted from the research work. Age, number of sections analysed, grade of histology and extent of myometrial incursion were documented according to earlier biopsy results. Each histopathologist reviewed hematoxylin and eosin (H&E) stained slides independently & documented the observations. To preserve patient privacy and decrease bias, H&E slides was distributed to assessors, excluding the actual results. In this retrospective analysis, the 1st assessor was deemed the main evalauting pathologist, and the data documented by 1st assessor was recovered from the stored or saved documents. Lymphovascular invasion (LVI) was documented in the myometrium beyond the primary malignancy. It is marked by unified groups of malignant cells situated inside vascular spaces bordered by endothelial cells, usually located next to the vessel wall exterior to primary malignancy. LVI was categorized into two groups: None and Focal, where Focal is defined as having one area of LVI around the tumor.

The results collected was analysed using SPSS version 26. The patient's age, grade of maligancy, distance of myometrial incursion, and frequencies of lymphovascular invasion (LVI) were assessed. Chi-square tests was employed to evaluate the correlation among the various factors taken for analysis. $P < 0.05$ was considered significant. Kappa values were computed to assess the consistency of LVI evaluations among various observers. A kappa score ranging from 0.60 to 0.80 suggested decent interobserver consistency, whereas a score from 0.80 to 1.00 showed very good or excellent consistency.

RESULTS :

Between April 2018 and April 2020, 70 cases of endometrioid carcinoma were identified from specimens obtained during hysterectomies. Nonetheless, just 32 cases satisfied the inclusion criteria for our research. The patients' ages varied between 43 and 89 years, averaging at 60.53 yrs. Grade 1 and Grade 2 endometrioid carcinomas both included 16 cases, indicating an even distribution.

TABLE 1

MELF and LVI Invasion

	Count of MELF	Count of LVI	P-Value
YES	39.135	45.93	<0.001
NO	4.57	2.353	0.406

In terms length of invasion into myometrium , twenty five samples (78.1%) demonstrated fewer than 50% incursion (stage Ia), whereas seven cases (21.9%) indicated greater than 50% incursion (stage Ib). The quantity of fragments analyzed varied between 2 and 19, averaging 8.94 sections. The examination rate was noted to vary between 1 and 14 sections for each centimeter of tumor, with a middle value of 2.5 sections per centimeter.

TABLE 2 –AGE AND SIZE OF TUMOUR

AGE	MINIMUM(YEARS)	MAXIMUM(YEARS)	MEAN (YEARS)
	40	75	57.5 Years
Tumor Size	MINIMUM(CM)	MAXIMUM(CM)	
	1.5	4.5	3.0
Section/cm of tumors	MINIMUM(CM)	MAXIMUM(CM)	
	1.3	15	

TABLE 3: DEPTH OF INVASION & GRADING

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%)

DISCUSSION :

Carcinoma endometrium is the maximum prevalent tumor of reproductive tract in women in urbanized nations, primarily managed by surgery due to its generally favorable prognosis in early stages(1).Despite lacking universally accepted guidelines for specimen handling, thorough gross examination is widely acknowledged to enhance diagnostic accuracy, staging, and prognostication. In view of Global health, the International Society of

Gynecologic Pathologists published references to standardize the making and handling of endometrial cancer specimens (2)

Prognostic indicators in endometrial cancer encompass histopathological type, stage of malignancy, dimension, status, association of cervix, distance of invasion of myometrium and lymphovascular invasion (LVI) (7). The importance of LVI stems from its connection to nodal metastasis and disease relapse, which affects risk stratification and informs decisions regarding adjuvant therapy(8).

LVI can be challenging to identify due to potential mimics such as tumor displacement artifacts or stromal retraction, impacting accurate diagnosis and subsequent management decisions(9). Methods like immunohistochemistry with CD31 may aid in distinguishing true LVI from mimickers like microcystic elongated and fragmented (MELF)-type invasion .

Regular recording of LVI is crucial not only for predictive details but also for guiding treatment strategies, including adjuvant radiotherapy. Recent advances, such as preoperative LVI scoring systems, aim to refine risk stratification and treatment planning, avoiding unnecessary interventions(10).

Despite varying reported prevalences of LVI in stage I endometrial cancer, its accurate assessment remains pivotal. In our study, involving retrospective evaluation by multiple reviewers, we observed an increase in LVI detection rates from 6.3% to 37.5%, highlighting the benefit of additional reviewer perspectives(8) . Interobserver reproducibility in LVI assessment was found to be substantial, underscoring its reliability in clinical decision-making

Our study's retrospective design and limited case numbers are acknowledged limitations, it underscores the importance of diligent LVI assessment in endometrial carcinoma. Future prospective reseearch is required to confirm above conclusions and further refine management protocols(2).

CONCLUSION :

Although our study had some limitations, we could formulate numerous suggestions for forthcoming research and clinical application. Considering the prognostic importance of marked and clear lymphovascular invasion (LVI) in the hazard evaluation of primary stage of endometrial cancer, we suggest that standard pathology reporting formats should incorporate both LVI evaluation and grading when relevant.

In many instances, LVI can be readily identified on hematoxylin and eosin (H&E) stained slides. Enhancing LVI detection rates can be achieved by incorporating a second reviewer specifically focused on LVI assessment, particularly since non-specialized pathologists may overlook LVI. In cases where discrepancies arise or significant artifacts are present, CD31 immunostaining can be employed to clarify the presence of true LVI versus mimics.

Our study underscores the importance of meticulous LVI assessment in endometrial cancer pathology reports to ensure accurate risk stratification and guide appropriate adjuvant therapy decisions. Future studies should further explore these recommendations to validate their impact on clinical outcomes and refine management protocols.

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