Original Article

A Study on Efficacy of Verhoeff Van Gieson Elastic Stain and CD34 Immunohistochemistry in Identification of Extramural Vascular Invasion in Colorectal Cancers

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Abstract

Background: Colorectal cancer (CRC) is the third most common malignancy worldwide and the second leading cause of cancer-related deaths, mainly due to late-stage diagnosis and recurrence. Lymphovascular invasion (LVI), particularly extramural vascular invasion (EMVI), is a strong prognostic marker linked to metastasis and poorer survival outcomes. However, EMVI detection is often underreported due to variability in diagnostic techniques, making accurate identification crucial for guiding adjuvant therapy decisions. This study aims to compare the efficacy of hematoxylin and eosin (H&E) staining, Verhoeff Van Gieson (VVG) elastic staining, and CD34 immunohistochemistry (IHC) in detecting EMVI in colorectal cancer specimens.

Methods: This is a cross-sectional study of 72 colorectal cancer patients conducted at a tertiary referral center in Kerala, South India, over a period of 18 months. EMVI was assessed using H&E, VVG, and CD34 stains, and detection rates were compared using SPSS 23.0 version.

Result: H&E staining identified EMVI in 10 cases (14%), VVG in 15 cases (21%), and CD34 IHC in 7 cases (9.7%), with significant differences between methods. VVG staining had the highest detection rate and was significantly associated with lymph node metastasis (p=0.024) and advanced AJCC stages (p=0.017).

Conclusion: VVG elastic staining enhances EMVI detection in colorectal cancer compared to H&E. The use of CD34 IHC, while less effective and more resource-intensive, is not recommended for routine EMVI detection due to its lower sensitivity and technical complexity.

Keywords: colorectal carcinoma; immunohistochemistry; elastic fibres; hematoxylin

Introduction

Colorectal cancer (CRC) is the third most prevalent cancer worldwide, responsible for 9.6% of all cases and the second leading cause of cancer-related deaths. In 2022, it accounted for 9.3% of cancer fatalities.[1] Projections suggest that incidence could more than double by 2035, particularly in less developed regions.[2]

CRC arises from genetic or epigenetic changes in the glandular epithelium of the large intestine, leading to adenoma formation and eventually carcinoma.[2, 3] A key aspect of CRC's metastatic potential is its ability to invade blood and lymphatic vessels. The local extent and vascular invasion (VI) significantly influences staging and prognosis.[3, 4] The venous invasion can be classified as either extramural, occurring beyond the muscularis propria, or intramural, involving the submucosa or muscularis propria.[5]

The Royal College of Pathologists (RCPath) defines venous or large vessel invasion in CRC as tumors involving endothelium-lined spaces, with an identifiable smooth muscle layer or elastic lamina. Circumscribed tumor nodules surrounded by elastic lamina on H&E or elastic stain are also considered venous invasion. Venous invasion is suspected when two key signs are observed: the "orphan artery sign," where a tumor deposit is adjacent to an artery without a corresponding vein, and the "protruding tongue sign," where smooth tumor tongues extend into pericolic or perirectal fat.[5, 9]

While the clinical significance of intramural vascular invasion (IMVI) is debated, extramural vascular invasion (EMVI) is more clearly associated with adverse outcomes and is recommended for routine reporting in CRC. EMVI serves as a strong predictor of poor prognosis, linked to advanced tumor stage, lymph node metastasis, and aggressive disease features.[10, 11] However, variability in detection methods and lack of standardization complicate the accurate assessment of vascular invasion.

Traditional detection methods, such as hematoxylin and eosin (H&E) staining, often struggle to differentiate between lymphatic and blood vessels, leading to misidentification of vascular invasion. Recent advancements, including elastic staining techniques like Verhoeff Van Gieson (VVG), significantly enhance detection by highlighting elastic fibers in venous walls, achieving a 2-3 fold increase in detection rates compared to H&E.[12, 13, 14] Additionally, immunohistochemistry (IHC) with endothelial markers like CD34 and CD31 improves differentiation between blood and lymphatic vessels.[15] This study aims to compare the effectiveness of H&E, VVG, and CD34 IHC in detecting extramural vascular invasion (EMVI) in colorectal carcinoma, addressing the critical need for improved standardization in vascular invasion assessment.

Materials and Methods

This study was a hospital-based descriptive cross-sectional analysis conducted over 18 months from November 2022–May 2024. Seventy-two colorectal carcinoma resection specimens received at the Department of Pathology of our institution were included in the study using consecutive sampling. The sample size was calculated at a 5% significance level based on Duduyemi et al.[15], using the formula with , , and , yielding a required sample size of 72 cases. Only resection specimens from patients with a confirmed diagnosis of colorectal carcinoma were selected. Specimens from patients who had undergone prior surgeries or received neoadjuvant chemotherapy or radiotherapy were excluded to eliminate potential biases related to treatment effects.

Histological diagnosis of colorectal carcinoma was made on well-oriented, formalin-fixed, paraffin-embedded sections stained with hematoxylin and eosin (H&E). Each case was thoroughly reviewed for the presence of extramural vascular invasion (EMVI). In instances where EMVI was not detected on H&E, sections containing suspicious areas in the peritumoral tissue or the section with the deepest invasive tumor front were selected for further evaluation. The corresponding paraffin blocks were retrieved, sectioned, and stained with Verhoeff Van Gieson elastic stain and CD34 immunohistochemistry (IHC) using a mouse monoclonal anti-CD34 antibody (clone QBEnd/10). These newly stained slides were carefully evaluated for EMVI, and the findings were verified by an expert pathologist. All data were systematically recorded using a proforma. Statistical analysis was performed using SPSS 23.0 version, with continuous variables expressed as means and categorical variables as percentages. The Fischer exact test was used to compare the efficacy of H&E, VVG, and CD34 IHC in detecting vascular invasion, with significance set at $p < 0.05$. The association between EMVI and various prognostic clinicopathological parameters were also studied.

Results

The mean age of the study population was 63 years, ranging from 21 to 84 years, with the highest number of cases in the 61-70 age group (31 cases, 43%). The male-to-female ratio was 1:1.48. Most cases were in the left colon (38 cases, 52.8%), followed by the right colon (25 cases, 34.7%), and the rectum (9 cases, 12.5%). The sigmoid colon had the highest number of cases (16 cases), followed by the ascending colon (13 cases). The rectum and rectosigmoid each accounted for 9 cases, while the caecum had the fewest, with 5 cases. The distribution of cases based on histologic types is given in Table 1.

Table 1: Distribution of cases

Histologic type	Frequency	Percentage (%)
Adenocarcinoma- NOS	59	81.9
Adenocarcinoma with mucinous component	8	11.1
MiNEN	1	1.4
Mucinous adenocarcinoma	3	4.2
Signet ring cell carcinoma	1	1.4
Total	72	100.0

Using the AJCC 8th edition TNM staging system, most tumors in the cohort were classified as T3 (55 cases, 76.4%),

indicating invasion beyond the muscularis propria, while T2 tumors comprised 9 cases (12.5%), and T4a and T4b stages accounted for 6 (8.3%) and 2 (2.8%) cases, respectively. Regional lymph node metastasis was observed in 34 cases (47.2%), primarily within the N1 category (22 cases, 30.6%), with fewer cases in N2 (10 cases, 13.9%), and 38 cases (52.8%) were node-negative (N0). Distant metastasis was rare, present in only one patient (1.4%) with liver involvement (M1). Histologically, the majority of tumors were moderately differentiated (Grade 2; 60 cases, 83.3%). Regarding overall stage grouping, Stage IIA was most frequent (30 cases, 41.7%), followed by Stage IIIB (26 cases, 36.1%), with no cases identified in Stage IVB or IVC.

Among the 72 cases, EMVI was identified in 10 cases using H&E, 15 cases using VVG, and 7 cases using CD34 IHC (Table 2). A comparison between H&E and VVG (Table 3), revealed that VVG detected EMVI in a significantly higher number of cases (p = 0.0001). Similarly, while comparing VVG to CD34 IHC (Table 4), VVG demonstrated superior sensitivity in detecting EMVI, with the difference again being statistically significant (p = 0.0001). These findings highlight the greater efficacy of VVG in detecting EMVI compared to both H&E and CD34 IHC.

Table 2: Frequency of EMVI detection by H&E, VVG and CD34.

EMVI	H&E	VVG	CD34
Positive	10 (14%)	15 (21%)	7 (9.7%)
Negative	62 (86%)	57 (79%)	65 (90.3%)
Total	72	72	72

Table 3: Comparison of EMVI detection by H&E with VVG and CD34 (P = 0.0001).

	EMVI with VVG		EMVI with CD34	
EMVI with H&E	Positive	Negative	Positive	Negative
Positive	7	3	6	4
Negative	8	54	1	61
Total	15	57	7	65

Table 4: Comparison of EMVI detection by VVG with CD34 (P = 0.0001).

EMVI with VVG	EMVI with CD34 Positive	EMVI with CD34 Negative	Total
Positive	7	8	15
Negative	0	57	57
Total	7	65	72

Assessing the association between EMVI detected by VVG stain and clinicopathological variables revealed that the highest number of EMVI-positive cases occurred in the 61-70 age group. This finding reflects the overall age distribution of the study population. However, no significant associations were found between EMVI and age (p = 0.759), gender (p = 0.218), or tumor location (p = 0.660).

In this cohort, 59 of the 72 cases were classified as adenocarcinoma NOS, with 12 cases EMVI-positive and 47 cases EMVI-negative. Notably, all cases of signet ring cell carcinoma and mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) were EMVI-positive, suggesting a potential link between these histologic types and EMVI (p = 0.036). However, these findings should be interpreted with caution due to the limited representation of these histologic types in the study.

No significant associations were found between EMVI and tumor stage (p = 0.299) or histologic grade (p = 0.170). In contrast, a significant association was identified between EMVI and lymph node metastasis (p = 0.024), with 12 of the 15 EMVI-positive cases showing nodal involvement. Furthermore, EMVI-positive cases were more frequently observed in advanced AJCC stages (IIIB and IIIC), with no EMVI-positive cases detected in Stage I, IIB, IIC, or IVA. Overall, a statistically significant association was noted between EMVI and advanced tumor stage (p = 0.017).

Discussion

Vascular invasion, particularly extramural vascular invasion (EMVI), is a well-established predictor of poor prognosis and aggressive behavior in CRC, regardless of tumor stage.[15, 16, 17, 18] However, detection rates of vascular invasion (VI) vary significantly across studies. In this cohort, VVG staining detected EMVI in 21% of cases, compared to 14% with H&E and 9.7% with CD34 IHC. VVG demonstrated a 1.5-fold increase in EMVI detection over H&E, and a 1.4-fold decrease was noted with CD34 compared to H&E. This indicates higher sensitivity of VVG in identifying EMVI and thus may be more effective for routine use than H&E or CD34 IHC.

These findings are consistent with the literature, where studies like those by Liu and Polydorides have shown that using elastic stains significantly increase EMVI detection. Liu and Polydorides found a 1.3-fold increase in EMVI-positive cases with elastin stains.[19] Similarly, Bogner et al. demonstrated that elastic staining identified vascular invasion in 67.1% of cases, compared to 27.45% with H&E, effectively doubling the detection rate.[20] These studies support the idea that elastic stains can enhance the identification of vascular invasion, improving diagnostic accuracy in CRC.

However, there are differing views on the routine use of elastic stains. Talbot et al. argue that elastic stains should be used selectively, as they found no significant challenges in diagnosing vascular invasion with H&E alone. They reserved the use of elastic stains for cases where the diagnosis was equivocal.[14, 21] Similarly, Kingston et al. expressed concerns about the specificity of elastic stains as these fibres are widely distributed within the intestinal wall and can lead to false positives.[20, 22]

In contrast, CD34 IHC showed a lower detection rate of EMVI in this study. Similar findings were noted in studies by Gama et al., which found that CD34 staining did not outperform H&E in hepatocellular carcinoma cases.[23] Harris et al. also reported that IHC, including markers like D2-40 and CD31, did not improve the consistency of VI diagnosis in CRC cases when compared to H&E alone.[24] Their findings also underscore the variability in VI detection even among experienced pathologists and highlight the limitations of relying solely on IHC for vascular invasion diagnosis.

Another recent study by Leone et al. discussed endothelial-to-mesenchymal transition (EndMT), which supports our findings.[25] This process highlights how endothelial cells can respond to stress or disease by transforming into mesenchymal cells. The vascular endothelium is dynamic and can influence its environment by releasing molecules like nitric oxide and prostacyclin. During EndMT, endothelial cells lose markers such as CD31, CD34 and acquire mesenchymal markers like FSP1 (Fibroblast-Specific Protein-1), alpha-SMA (alpha Smooth Muscle Actin), vimentin and N-cadherin, primarily under the influence of TGF-β. Other modulators of EndMT are hypoxia, EC metabolic alterations such as endothelial fatty acid oxidation, and epigenetic regulators including microRNAs. This phenomenon is observed across various cancers, including colorectal cancer[26] pancreatic cancer, lung cancer, glioblastoma, esophageal cancer, oral squamous carcinoma, and breast cancer.[25]

In our study, six cases that were positive on H&E (Figure 1) were also detected by VVG staining (Figure 2, left) and CD34 immunohistochemistry (Figure 2, right), highlighting the concordance across all three staining methods in these instances. Additionally, VVG identified eight further cases missed by H&E, suggesting superior sensitivity. However, three cases that were positive on H&E were negative on both VVG and CD34, and one case was positive on H&E and VVG but negative on CD34, reflecting occasional discrepancies among the staining techniques in detecting extramural vascular invasion (EMVI).

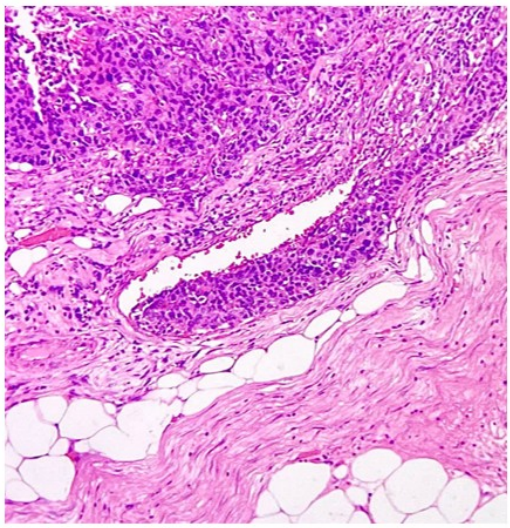

Figure 1: Case 64 – EMVI with protruding tongue morphology identified using H&E stain (100X).

The discrepant result with H&E can be attributed to retraction artifacts and its inability to reliably distinguish lymphatic from venous invasion (Figure 3). VVG, by selectively highlighting elastic fibers (Figure 4, left), predominantly identifies venous structures and excludes lymphatics, as reported by Howlette et al. and Gonzalez et al.[9, 27] However, VVG's limitation lies in detecting small veins that lack elastic fibers, potentially leading to false negatives.

CD34 staining offers an advantage in marking vascular endothelial cells (Figure 4, right), distinguishing them from lymphatics. However, its variability in detecting different vessel types in various organs, as noted by Baumhueter et al., Müller et al., and Pusztaszeri et al.[28, 29, 30], may affect its detection rate. Factors such as endothelial-mesenchymal transition and tumor microenvironment interactions can also lead to CD34 negativity, reducing sensitivity.[25] Additionally,

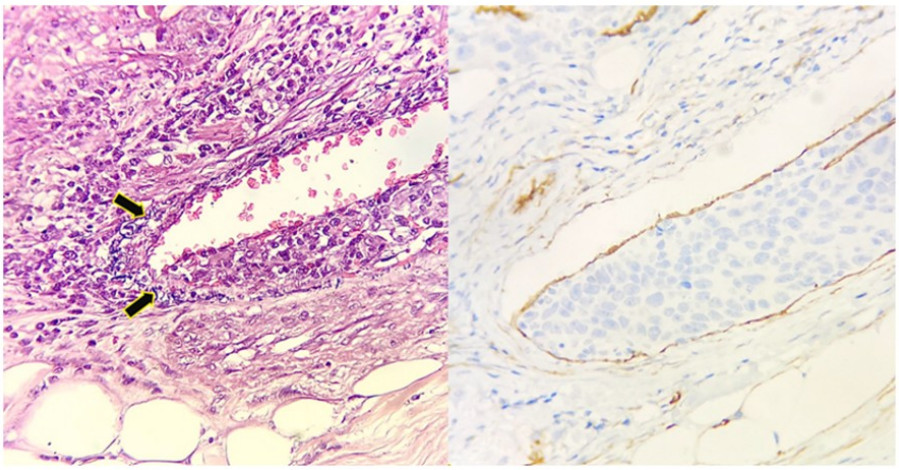

Figure 2: Case 64 – VVG stain highlighting disrupted elastic fibres in the vessel wall (400X) on left and CD34 IHC highlighting the vascular endothelial cells (400X) on right.

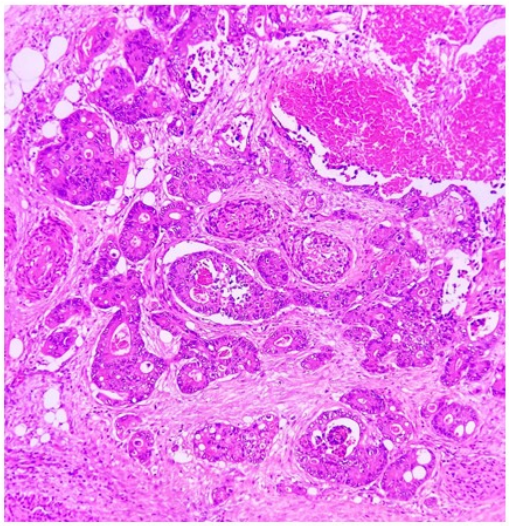

Figure 3: Case 23 – EMVI overlooked on H&E stain, misinterpreted as a retraction artifact (100X).

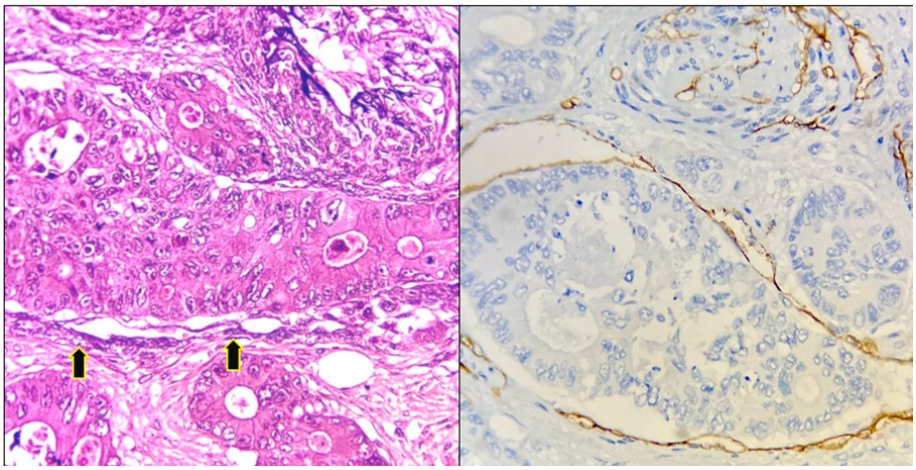

Figure 4: Case 23 – VVG stain selectively highlighting elastic fibers (left), while CD34 demonstrates vascular endothelial cells (right) (400×).

CD34 expression in stromal progenitor cells may lead to non-specific staining in certain tissue contexts, as described by previous studies.[31, 32]

Interestingly, cases that were negative on VVG were also negative on CD34, underscoring the specificity of CD34 staining. One case was CD34-positive but H&E-negative, suggesting a potential complementary role for CD34 in detecting EMVI.

However, the risk of false positives due to stromal positivity remains a concern, as noted by some authors.[31]

Limitations of the study

This is a single tertiary care center-based study, hence the findings may not be extrapolated to a broader population.

Although 3-4 H&E-stained sections were examined for EMVI in each case, VVG and CD34 staining were performed on only one slide, focusing on suspicious areas or the deepest invasive front.

Traditional perpendicular sectioning of tumors was followed, which transects fewer veins. Tangential sectioning at the outer tumor border may have increased EMVI detection as it transects more number of veins.

The strong association between EMVI and histologic types like MiNEN, signet ring cell carcinoma, and mucinous carcinoma should be interpreted with caution, as the representative cases were too few.

Challenges faced during the study

Quality of VVG stain – Interpretation of VVG stain can be extremely difficult unless good quality sections and proper staining techniques are used. Under-differentiation or thicker sections can result in overstained sections, while over-differentiation can lead to the loss of elastin staining in smaller vessels.

Interpretation of CD34 stains can present difficulties due to the variability in the staining patterns. Close review with H&E stained sections is required to avoid false-positive results.

Conclusion

The use of VVG elastic stain significantly improves the detection of extramural vascular invasion in colorectal cancers. It is cost effective, simple and reduces the diagnostic time. This method enhances diagnostic accuracy, minimizes variability, and increases efficiency, leading to better patient care. In contrast, CD34 immunohistochemistry is less reliable for detecting EMVI. Tumors often alter or destroy the endothelium and CD34 staining varies across vessel types, which further diminishes its reliability. Additionally, immunohistochemical techniques are more expensive, labour-intensive, and challenging to evaluate. Based on our findings, we do not recommend CD34 IHC for detecting EMVI.

Acknowledgements: Approval of the research protocol – Ethical approval for the study was obtained from the Institutional Research and Ethics Committee (Approval No: 17/EC/22/AIMS-69) prior to commencement of the research. Informed Consent – Written informed consent was obtained from all subjects involved in the study. Registry and the Registration No. of the study/Trial – Not Applicable. Animal Studies – Not Applicable.

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Competing Interests: None.

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