LYMPHOVASCULAR AND PERINEURAL INVASION IN VIRUS-ASSOCIATED RECTAL ADENOCARCINOMA: A PATHOMORPHOLOGICAL STUDY

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ABSTRACT

Background: Lymphovascular invasion (LVI) and perineural invasion (PNI) are important histopathological features associated with tumor progression and metastatic potential in rectal adenocarcinoma. However, their relationship with viral status remains insufficiently characterized.

Objective: To investigate the morphological characteristics of LVI and PNI in virus-positive and virus-negative rectal adenocarcinomas using an integrated histopathological, immunohistochemical, and molecular approach.

Methods: Tumor specimens will be evaluated using routine histopathology, selected immunohistochemical markers, and molecular assays for viral detection. Morphological findings will be correlated with clinicopathological parameters.

Conclusion: The study is expected to clarify the association between viral status and invasive tumor features and to support the development of a more comprehensive approach to pathological assessment and prognostic stratification in rectal adenocarcinoma.

Keywords: rectal adenocarcinoma; HPV; EBV; HCMV; virus-associated cancer; lymphovascular invasion; perineural invasion; pathomorphology; immunohistochemistry; prognosis.

INTRODUCTION

Colorectal cancer is one of the most common malignant neoplasms worldwide and remains an important cause of cancer-related mortality. According to GLOBOCAN 2024, more than 2 million colorectal cancer cases and approximately 917,895 deaths were recorded globally. Although the development of colorectal cancer is multifactorial, infectious agents have attracted increasing scientific interest.

Human papillomavirus, Epstein–Barr virus, and human cytomegalovirus have been investigated in relation to colorectal carcinogenesis. HPV, particularly high-risk genotypes, may influence cell-cycle regulation through viral oncoproteins E6 and E7, which interfere with p53 and retinoblastoma protein pathways. However, detection of viral DNA or proteins alone does not establish a causal relationship, and the biological significance of viral infection remains an active area of investigation.

A 2026 systematic review and meta-analysis reported an increased association between HPV infection and colorectal cancer, while previous meta-analyses also demonstrated substantial heterogeneity between geographic populations. EBV has likewise been detected in a proportion of colorectal cancer cases, although prevalence estimates vary considerably. HCMV has been discussed as a possible modifier of tumor-associated inflammation and immune responses.

LVI represents the presence of tumor cells within lymphatic or blood vascular spaces and is strongly associated with regional lymph-node involvement and distant metastatic spread. PNI is characterized by tumor invasion of, around, or through peripheral nerves and is considered an important adverse prognostic factor in colorectal cancer. Both findings may reflect a biologically aggressive tumor phenotype.

Despite the growing literature on viral infection and on LVI/PNI separately, relatively few studies have systematically evaluated the relationship between viral status and these invasive morphological patterns specifically in rectal adenocarcinoma. Therefore, integrated pathomorphological investigation may provide additional information for risk stratification.

AIM OF THE STUDY

To comprehensively investigate the pathomorphological features of lymphovascular and perineural invasion in virus-associated rectal cancer and determine their relationships with tumor biological characteristics, local invasion, metastatic potential, and clinical-prognostic parameters, with the subsequent development of an improved pathomorphological and prognostic algorithm.

OBJECTIVES

1. To analyze clinical and morphological characteristics according to age, sex, tumor location, histological type, differentiation, and TNM stage.
2. To detect viral infection and viral types, particularly HPV, using molecular-genetic andimmunohistochemical methods.
3. To determine the frequency and extent of LVI and distinguish lymphatic from blood-vesselinvolvement.
4. To characterize the morphology and extent of PNI.
5. To assess CD31, CD34, ERG, D2-40, S100, SOX10, and PGP9.5 expression.
6. To study epithelial–mesenchymal transition, proliferation, and invasive activity using E-cadherin,N-cadherin, vimentin, MMP-2, MMP-9, Ki-67, and p53.
7. To correlate LVI and PNI with lymph-node metastasis, local tumor spread, growth pattern, anddifferentiation.
8. To compare the prognostic significance of these parameters in virus-positive and virus-negativegroups.

9. To develop an integrated pathomorphological-prognostic algorithm.

MATERIALS AND METHODS

The study is planned on archival and current biopsy and surgical specimens obtained from patients with rectal cancer during 2016–2026 at pathology and oncology institutions. Histological sections will be stained with hematoxylin and eosin and examined according to standard pathological criteria.

Immunohistochemistry will be used to identify vascular and lymphatic structures (CD31, CD34, ERG, D2-40), neural structures (S100, SOX10, PGP9.5), epithelial–mesenchymal transition (E-cadherin, N-cadherin, vimentin), extracellular-matrix remodeling (MMP-2 and MMP-9), proliferative activity (Ki-67), and p53 expression. Molecular-genetic methods will be applied for detection of viral infection, with special attention to high-risk HPV genotypes.

Digital morphometry will be used to quantify relevant morphological and immunohistochemical parameters. Statistical analysis will include group comparisons, correlation analysis, and, where adequate follow-up is available, survival analysis and multivariable prognostic modeling.

EXPECTED RESULTS AND SCIENTIFIC NOVELTY

The study is expected to identify differences in the frequency, distribution, and morphological characteristics of LVI and PNI between virus-positive and virus-negative rectal adenocarcinomas. Immunohistochemical characterization may improve detection of subtle lymphatic, vascular, and perineural invasion that can be difficult to recognize on routine hematoxylin–eosin sections.

It is also expected that selected viral-positive tumors may demonstrate features of a more invasive phenotype, including increased proliferative activity, altered expression of adhesion molecules, extracellular-matrix remodeling, and epithelial–mesenchymal transition. Such relationships will be interpreted as associations rather than proof of direct viral causation.

The combination of viral status, LVI, PNI, molecular markers, TNM stage, and lymph-node status may allow identification of patients with a particularly high-risk pathological profile and provide a basis for an integrated prognostic algorithm.

CLINICAL AND PRACTICAL SIGNIFICANCE

The proposed approach may improve routine pathological evaluation of rectal cancer by combining conventional morphology with targeted immunohistochemistry and molecular testing. Use of CD31, CD34, ERG, and D2-40 may facilitate assessment of vascular and lymphatic invasion, while S100, SOX10, and PGP9.5 may improve recognition of perineural invasion.

The results may be useful for pathologists and oncologists in estimating metastatic risk, stratifying patients according to pathological aggressiveness, and selecting patients who may require closer clinical follow-up. Regional data from Uzbek clinical material may also contribute to the broader understanding of virus-associated colorectal cancer.

DISCUSSION

The biological interaction between viral infection and tumor invasion is complex. In HPV-associated lesions, E6/E7-mediated disruption of p53 and pRb pathways may promote cellular proliferation and resistance to apoptosis. Changes in adhesion molecules and extracellular-matrix degradation may additionally facilitate tumor-cell migration. However, viral detection should not be interpreted independently of tumor morphology and clinical context.

PNI may involve complex interactions between tumor cells and nerves, including signaling pathways involving nerve growth factor/TrkA, BDNF/TrkB, GDNF/GFRα, NCAM, and L1CAM. LVI and PNI may therefore represent different manifestations of a common aggressive tumor phenotype. Their combined assessment may provide more prognostic information than either parameter alone.

A major strength of the proposed study is the integration of viral status with detailed pathological assessment. Such an approach may help clarify whether virus-positive tumors demonstrate reproducible differences in invasive behavior and whether these differences have independent prognostic significance.

CONCLUSION

Virus-associated rectal cancer represents a clinically and biologically relevant research area. Lymphovascular and perineural invasion are important morphological indicators of tumor aggressiveness and metastatic potential. A combined assessment of viral infection, LVI, PNI, immunohistochemical markers, and conventional clinicopathological parameters may improve pathological risk stratification and contribute to development of a more informative prognostic algorithm. Further prospective and molecular studies are required to clarify the causal role of viral infection in rectal carcinogenesis.

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