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MORPHOLOGICAL, IMMUNOHISTOCHEMICAL AND MOLECULAR PROGNOSTIC MARKERS IN COLORECTAL CANCER

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Abstract
The article presents the results of an analysis of current data on the prognostic significance of morphological, immunohistochemical, and molecular markers in colorectal cancer. A narrative review of scientific publications from 2009 to 2024 was conducted, focusing on tumor morphology, CDX2 expression, immunohistochemical markers (PD-L1, HLA-G, CD3, CD8), microsatellite instability, and the molecular classification CMS. It was shown that morphological parameters (degree of differentiation, tumor budding, lymphovascular and perineural invasion) retain high prognostic value, often exceeding the isolated loss of CDX2. A comprehensive assessment of immunohistochemical and molecular indicators (MSI, KRAS, BRAF, CIMP, CMS) improves the accuracy of recurrence risk prediction. The findings indicate the promise of integrating morphological, immunohistochemical, and molecular characteristics for the personalization of colorectal cancer treatment.

Keywords: Colorectal cancer; prognostic markers; CDX2; tumor budding; immunohistochemistry; microsatellite instability; molecular classification; personalized medicine.

Introduction
Colorectal cancer (CRC) is one of the most common malignant neoplasms and represents a significant global healthcare problem. The disease is characterized by pronounced clinical, morphological, and molecular heterogeneity. Patients with similar anatomical stages of the disease may have substantially different clinical outcomes, treatment response, and recurrence risk [1].
Traditional prognostic assessment of CRC is mainly based on clinicopathological parameters, including depth of tumor invasion, regional lymph node involvement,

and the presence of distant metastases. Although the TNM staging system remains fundamental for clinical decision-making, anatomical staging alone is insufficient to fully reflect the biological behavior of colorectal tumors. The development and progression of CRC are determined by multiple factors, including histopathological characteristics, genetic and epigenetic alterations, the tumor immune response, and the composition of the tumor microenvironment. For this reason, modern oncological pathology is increasingly focused on identifying additional prognostic biomarkers capable of improving patient stratification. Morphological parameters, such as tumor differentiation grade, tumor budding, and lymphovascular and perineural invasion, remain important indicators of tumor aggressiveness [1].

At the same time, immunohistochemical markers, including CDX2, PD-L1, HLA-G, CD3 and CD8, can provide additional information about tumor differentiation and the interaction between malignant cells and the immune system [2, 4].

Molecular characteristics, including microsatellite instability (MSI), KRAS and BRAF mutations, the CpG island methylator phenotype (CIMP), and consensus molecular subtypes (CMS), further contribute to the biological characterization of CRC [3, 5].

Integration of different levels of information is particularly important in the context of personalized medicine. A comprehensive understanding of tumor morphology, its immune phenotype, and its molecular profile can improve prognosis and support the selection of individualized therapeutic strategies. The aim of this literature review was to analyze current data on the prognostic significance of morphological, immunohistochemical, and molecular markers in colorectal cancer and to assess their potential role in the personalized management of patients.

Materials and Methods

To summarize current data on prognostic markers in colorectal cancer, a narrative literature review was conducted. Scientific publications published between 2009 and 2024 were selected for analysis. The reviewed publications included original research articles and contemporary reviews devoted to the prognostic and molecular characteristics of colorectal cancer. The selected studies focused on the following areas: morphological prognostic features [1]; tumor budding [1]; lymphovascular and perineural invasion [1]; CDX2 expression and loss [2, 3]; microsatellite instability [3, 5]; PD-L1 and HLA-G [4]; the immune markers CD3 and CD8 [4]; KRAS and BRAF molecular alterations [5]; the CIMP phenotype [5]; the CMS molecular classification [5]; and approaches to personalized treatment. The selected

publications were analyzed comparatively. The data obtained were grouped into three main categories:

1. Morphological prognostic factors;
2. Immunohistochemical prognostic markers;
3. Molecular prognostic markers and classifications.

The results of the reviewed studies were compared with respect to their prognostic significance, association with clinicopathological characteristics, and potential value for personalized treatment.

Results

Analysis of the selected literature showed that traditional morphological characteristics remain important predictors of the biological behavior of colorectal cancer. The most significant morphological prognostic parameters include: tumor differentiation grade; tumor budding; lymphovascular invasion; perineural invasion; regional lymph node status; histological subtype [1].

According to Chen, K., Collins, G., Wang, H., & Toh, J. W. T. (2021), tumor budding — the presence of single tumor cells or small clusters of malignant cells at the invasive tumor front — is considered an indicator of increased invasiveness and metastatic potential [1]. Lymphovascular and perineural invasion are also associated with more aggressive tumor behavior and an increased risk of progression and recurrence. These morphological parameters retain significant prognostic value even in the era of molecular oncology, especially when combined with immunohistochemical and molecular characteristics [1, 3].

The studies by Baba, Y. et al. (2009) CDX2 — a transcription factor involved in the differentiation of intestinal epithelium and widely used as an immunohistochemical marker of gastrointestinal tumors — are of particular interest. Analysis of data from 621 patients showed that loss of expression of CDX2 was associated with a low degree of tumor differentiation, a more advanced disease stage, specific molecular alterations, and the phenotype CIMP [2].

These data suggest that loss of CDX2 may reflect unfavorable biological tumor characteristics, although its prognostic value remains complex. A study of more than 1000 CRC cases showed that loss of CDX2 was more frequently observed in MSI-H status and unfavorable histopathological features [3], but in several analyses, traditional morphological parameters (differentiation grade, tumor budding, histological subtype) demonstrated greater prognostic significance than isolated CDX2 loss [3]. This indicates that CDX2 should not be regarded as a universal independent marker — its value is greater when interpreted together with

morphological and molecular characteristics. One study examined a combination of immunohistochemical markers: PD-L1; HLA-G; CDX2; CD3; CD8 [4]. Comprehensive assessment of several markers improved recurrence prediction compared with the use of a single biomarker [4]: CD3 and CD8 reflect the T-cell immune response, while PD-L1 and HLA-G reflect mechanisms of tumor immune evasion.

Dunne, P. D., & Arends, M. J. (2024) suggest that such a multi-marker assessment can provide a more complete prognostic profile and support the development of personalized treatment strategies. The main molecular characteristics of prognostic relevance include microsatellite instability (MSI), KRAS and BRAF mutations, the CIMP phenotype, consensus molecular subtypes (CMS), and characteristics of the tumor immune microenvironment [5]. Tumors with high microsatellite instability are associated with defects in DNA mismatch repair and exhibit specific biological and immunological features; MSI status has both prognostic and therapeutic significance, influencing the potential response to immunotherapy [5].

The CMS classification divides colorectal cancer into biologically distinct subtypes that differ in mechanisms of carcinogenesis, microenvironment, prognosis, and response to therapy [5].

Summarizing the reviewed publications, an evolution in the understanding of CRC prognostic markers can be traced. The study “Pathological Features and Prognostication in Colorectal Cancer” (2021) [1] showed that a comprehensive assessment of tumor morphology together with biomarkers substantially improves prognostic accuracy compared with the isolated analysis of individual parameters. The earlier work “Relationship of CDX2 Loss with Molecular Features and Prognosis in Colorectal Cancer” (2009) [2] laid the foundation for the study of CDX2, establishing an association between its loss and low differentiation grade, more advanced stage, and the CIMP phenotype.

Building on this topic, «Loss of CDX2 in Colorectal Cancer is Associated with Histopathologic Subtypes and Microsatellite Instability but is Prognostically Inferior to Hematoxylin-Eosin-Based Morphologic Parameters from the WHO Classification» (2021) [3] showed that traditional morphological parameters have greater prognostic significance than isolated CDX2 loss, despite its association with histopathological subtypes and MSI status. A different direction is presented in «An Exploration of Immunohistochemistry-Based Prognostic Markers in Patients Undergoing Curative Resections for Colon Cancer» (2022) [4], where a comprehensive multi-marker assessment (PD-L1, HLA-G, CDX2, CD3, CD8)

improved recurrence prediction compared with the analysis of individual biomarkers.

Finally, the most recent work — «Molecular Pathological Classification of Colorectal Cancer — An Update» (2024) [5] — summarizes advances in the molecular classification of CRC, emphasizing the significance of MSI status, CMS subtypes, and tumor microenvironment characteristics for prognosis and treatment selection.

Thus, the reviewed studies (2009–2024) demonstrate an evolution in the understanding of CRC prognostic markers — from isolated morphological and immunohistochemical characteristics to comprehensive integrative models.

Discussion

The results of the reviewed studies show that the prognosis of colorectal cancer cannot be reliably determined using a single biological marker. Morphological characteristics remain the foundation of prognostic assessment. Tumor differentiation grade, tumor budding, and lymphovascular and perineural invasion provide important information about tumor aggressiveness and metastatic potential [1]. At the same time, immunohistochemical and molecular characteristics provide additional information that cannot be obtained through traditional histopathological examination alone.

The role of CDX2 illustrates the complexity of modern prognostic assessment. Loss of CDX2 expression is associated with unfavorable clinicopathological and molecular features, including low differentiation grade, advanced disease, and MSI-related characteristics [2, 3]. However, comparative data show that traditional morphological parameters may have greater prognostic significance than isolated CDX2 loss [3]. This emphasizes that individual biomarkers should not be interpreted independently.

Rather, their prognostic value should be assessed in the context of the overall morphological and molecular profile of the tumor. Assessment of several immunohistochemical markers can provide additional prognostic information. A comprehensive evaluation of PD-L1, HLA-G, CDX2, CD3, and CD8 can improve recurrence prediction [4], while simultaneously reflecting tumor differentiation, immune system activation, and mechanisms of immune evasion.

Molecular classification represents another important component of modern CRC prognostic assessment. MSI status, KRAS and BRAF mutations, the CIMP phenotype, and CMS classification provide information about the biological characteristics of the tumor and may help predict treatment response [5]. Integration of these different types of information is particularly important for personalized

medicine. A patient-oriented prognostic model may include: clinical characteristics + morphological features + immunohistochemical profile + molecular alterations.

Such an integrated approach may allow more accurate classification of patients according to the risk of recurrence and progression. However, a number of limitations remain. The studies included in this review differed in design, sample size, biomarkers studied, and evaluation methods. In addition, clinical implementation of complex biomarker panels requires standardization of laboratory methods and interpretation criteria. Further prospective studies are needed to validate integrated prognostic models and determine their practical value in everyday clinical practice.

Conclusion

Current data demonstrate that the prognosis of colorectal cancer is determined by a complex interplay of morphological, immunohistochemical, and molecular characteristics. Morphological parameters, including tumor differentiation grade, tumor budding, and lymphovascular and perineural invasion, remain fundamental prognostic factors [1].

Immunohistochemical markers, including CDX2, PD-L1, HLA-G, CD3 and CD8, provide additional information about tumor differentiation and the interaction between malignant cells and the immune microenvironment [4].

Molecular characteristics, including MSI, KRAS, BRAF, CIMP and subtypes CMS, contribute to the understanding of tumor biology and can help inform decisions on personalized treatment [5].

The most promising approach is the integration of morphological, immunohistochemical, and molecular data into a single prognostic model. Such an approach may improve risk stratification, recurrence prediction, and the selection of individualized treatment strategies for patients with colorectal cancer. Future studies should focus on the development and validation of standardized integrated prognostic algorithms that can be effectively implemented in everyday clinical practice.

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