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Research Article

Predictive Histopathological and Molecular Biomarkers Guiding Surgical Management of Colorectal Cancer

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ABSTRACT

Introduction: Colorectal cancer is highly biologically heterogeneous and the conventional staging system does not fully define aggressiveness, treatment response or recurrence. Histopathological and molecular biomarkers may be used for individual management.

Objective: To evaluate the predictive value of histopathological and molecular biomarkers in colorectal cancer and their usefulness in guiding surgical management, treatment selection, and prognosis.

Materials and Methods: This was a prospective, observational study of 120 patients with histologically proven colorectal adenocarcinoma in Mercy Teaching Hospital, Peshawar Medical College, Peshawar, Pakistan from August 2025 to January 2026. Clinical, histopathological, molecular, surgical and biomarker-related data were gathered and analyzed.

Results: Advanced disease was correlated with high/intermediate tumour budding, lymphovascular invasion, perineural invasion and lymph-node involvement. MSI-high/MMR deficiency was found in 15.0%, RAS mutations in 35.8%, BRAF mutations in 9.2% and HER2 amplification in 5.8%. Pathological characteristics were found to be unfavorable if detectable postoperative ctDNA was detected.

Conclusion: Integrated biomarker assessment can enhance risk stratification and provide tailored surgical and post-surgical management.

Keywords: Colorectal Cancer, Histopathology, Molecular Biomarkers, Tumor Budding, Msi, Ctdna, Precision Medicine.

INTRODUCTION

Colorectal cancer (CRC) is among the most prevalent malignancies in the world and is a leading cause of morbidity and mortality due to cancer. Although there have been significant advances in screening, surgical techniques, systemic therapy and perioperative care, there is a high level of variability in the behaviour of the tumour, response to treatment, risk of recurrence and survival (1). Although these remain the basis for treatment planning, conventional clinicopathological parameters, such as tumor stage, grade, lymphovascular invasion, perineural invasion, and lymph-node status, do not necessarily reflect the biological complexity of individual tumors. Because of this, there has been a growing focus on the development of predictive histopathological and molecular markers that could detect aggressive disease, predict treatment response and guide personalized surgical and oncological decision making.

The role of molecular diagnostics, digital pathology, minimally invasive surgery and artificial intelligence in colorectal cancer management has been highlighted in recent advances. The use of histopathological assessment is still the mainstay of CRC diagnosis and management, as the morphology of the tumor gives valuable clues about the

differentiation, invasion, growth pattern and metastatic potential of the disease. However, with the advent of technology, conventional microscopic assessment is now being supplemented by computational pathology and artificial intelligence (2). Transformer-based deep-learning models have shown that routine histological images can encode information that can predict clinically relevant biomarkers, suggesting that standard hematoxylin and eosin (H&E) slides may carry molecular and prognostic information in addition to traditional morphological information.

These models have demonstrated the ability to predict biomarkers directly from colorectal cancer histology in large multicentric studies and have therefore the potential to be used in the future for risk stratification and treatment selection (3). In addition, molecular pathological classification further validates this strategy by adding the known molecular subtypes of microsatellite instability, mismatch-repair deficiency, CpG island methylator phenotype, chromosomal instability, and specific driver alterations. These classifications are useful to understand biological differences between tumors, and are increasingly shaping systemic treatment, immunotherapy, targeted therapy, and prognosis.

The stromal- or adipocyte-related biomarkers as part of the steatotic liver-associated radiological and histological concept SARIFA emerged as a particular focus of interest among emerging histopathological markers as they are related to different tumour biology and prognosis. Studies suggest that, unlike conventional genetic changes, SARIFA is able to predict a subset of colorectal cancers with very poor prognosis (4). These results highlight the importance of interactions between tumor cells and their microenvironment in addition to the malignant epithelial component in the behavior of the tumor. The recognition of these histological patterns may thus help to give further clues to the diagnosis of patients needing more aggressive treatment or more frequent follow-up after surgery.

The use of molecular biomarkers derived from tissue and blood is also gaining increasing importance in the course of dynamic treatment planning. Liquid biopsy, especially circulating tumor DNA (ctDNA), is a minimally invasive approach that can be used to detect molecular alterations, to track residual disease, to detect emerging resistance and to measure treatment response throughout CRC treatment (5). Liquid biopsy, unlike tissue biopsy that only offers information on a specific anatomical location at one time, could potentially offer repeated information about the evolution of the tumour and the systemic disease burden. This is especially relevant for monitoring patients for changes in therapy and for the identification of patients who are at risk for relapse after surgery or systemic therapy, where circulating biomarkers are applicable. With the advent of computational pathology, there is a growing association between histological morphology and molecular features of tumors.

Patterns in the histopathological image may contain information related to multi-omic changes, molecular pathways and prognosis of the patient, and routine tissue morphology may be used as a surrogate source of biological information. This may help to decrease the need for comprehensive molecular testing in certain clinical situations, and provide pathologists and clinicians with further predictive information from the tissue samples that are typically available. (6) This integration is especially important for colorectal cancer that develops in the background of chronic inflammatory bowel disease, as the molecular changes, inflammatory mechanisms, endoscopic findings, and tumor progression could differ from that of sporadic CRC. Molecular characterization and advanced endoscopic evaluation can help detect, risk stratify, and optimize treatment for inflammation-associated colorectal neoplasia at an early stage (7).

The use of pathological information in combination with predictive models is also clinically relevant, as it is in clinical decision support systems to optimize adjuvant chemotherapy. Pathological staging variables have been used with deep-learning systems that have potential to estimate the risk of recurrence and select those who may benefit more from adjuvant therapy. These tools could also be used in conjunction with a multidisciplinary decision making process, where information may not be as easily synthesized consistently with traditional staging. They may be important in intermediate-risk patients, in whom the intensity and duration of postoperative treatment may be a challenge (8).

The histology of a tumor can also hint at the metastasis of the tumor. The histological features of primary colorectal cancers have been correlated with the growth patterns of secondary colorectal liver metastases,

suggesting that secondary CRC liver metastases may have biological features associated with the primary tumour. These relationships could help to estimate the metastatic potential, and may influence which patients receive more aggressive local therapy of liver metastases (e.g. hepatic resection or other local therapy). Thus, histopathological study can not only be used to characterize the primary tumors, but also to gain insight into the behaviour of metastatic disease (9). Molecular biomarkers are crucial for the selection of patients for immunotherapy.

Some of the most clinically validated predictive biomarkers for immune checkpoint inhibitor therapy in CRC include microsatellite instability and mismatch-repair deficiency. However, other genomic, immune, and tumor microenvironment markers are being studied to better predict the response to immunotherapy and to select patients that might respond to novel immunotherapies. Thus, the further evolution of predictive biomarkers is crucial to move precision immuno-oncology beyond known molecular subgroups (10). The use of molecular profiling with targeted therapies is becoming more common in precision medicine in CRC. Actionable alterations like changes in the RAS, BRAF, HER2 and other molecular targets can help guide systemic treatment decisions and enhance biological matching of therapy to individual tumors.

Combination of genomic data with clinicopathological and histological features can then create a more holistic view of the disease biology and help to personalize treatment at various stages of CRC (11). At the same time, artificial intelligence-driven analysis of H&E stained tissue has shown great promise in predicting microsatellite instability and other clinically relevant biomarkers. Deep-learning systems have been shown to be able to learn molecular information from histological images even with relatively small datasets, demonstrating the potential for scalable biomarker prediction with digital pathology (12). Lymph-node metastasis is still one of the most important prognosticators and factors for postoperative treatment in CRC.

Therefore, the ability to accurately assess nodal involvement is essential in determining pathological stage and the need for adjuvant treatment. Primary tumor histology combined with clinicopathological factors has been used to train deep-learning models that have shown promise for predicting lymph-node metastasis before or in addition to conventional pathological evaluation. Predictive models such as these have the potential to be used in the future to aid in more personalized surgical planning and risk assessment, especially when traditional preoperative information offers only a limited degree of certainty regarding the presence of nodal disease (13). Another emerging dimension of precision assessment is through metabolic biomarkers. In the future, lipid-based biomarkers may be used in conjunction with machine-learning techniques and the anatomical and histological staging for better colorectal cancer staging, as indicated by results from recent studies (14).

Circulating tumor DNA has been growing in the spotlight as a biomarker for response to treatment, residual disease, and risk of recurrence in locally advanced rectal cancer. In TAT, the ctDNA analysis can offer real-time data that is not available from traditional imaging or clinical assessments. There is a growing body of systematic evidence indicating that ctDNA may be a valuable prognostic and predictive tool, but additional prospective validation is required before it can be incorporated into clinical treatment algorithms (15). In total neoadjuvant therapy, the use of serial molecular evaluation has been suggested to identify patients with good response and those with ongoing molecular disease and who could benefit from more aggressive or alternative therapy approaches, as suggested by reviews of this approach (16). Furthermore, several biomarkers and tumour models are being studied to help select patients who are likely to respond to neoadjuvant chemoradiotherapy in rectal cancer. These strategies could be useful in identifying patients who likely to respond and those who may need different treatment options, such as surgery and organ preservation strategies, to improve the benefits of treatment (17).

In summary, the greater incorporation of histopathological characteristics, molecular changes, peripheral biomarkers, and artificial intelligence is turning CRC into a more molecularly individualised disease. Molecular biomarkers can give information on treatment sensitivity, metastatic potential, recurrence risk and resistance, and digital pathology can give clinically meaningful information from routinely collected tissue. Surgical oncology in the future will be multidisciplinary and combine all four pieces of information (pathological, molecular, radiological, and computational), and not just

one. The expanding field of molecular biomarker-driven oncology provides the clinical basis for the translation of these discoveries into organ-specific treatment, immuno-oncology, targeted therapy and individualized patient management (18).

Objective: To assess the predictive power of histopathological and molecular biomarkers in CRC and their role in informing surgical approach, treatment choice, prognosis and personalized care.

MATERIALS AND METHODS

Study Design: Prospective observational study.

Study Setting: Mercy Teaching Hospital, Peshawar Medical College, Peshawar, Pakistan.

Duration of the Study: The study was conducted over a period of six months, from August 2025 to January 2026.

Inclusion Criteria: All patients were included who were 18 years or older, and had a histologically confirmed colorectal adenocarcinoma that was surgically managed during the study period. The inclusion criteria included patients with sufficient tumor tissue for histopathological analysis and appropriate molecular biomarker analysis. In addition, patients who had complete clinical, pathological and surgical records were included.

Exclusion Criteria: Incomplete medical or histopathological records, inadequate tissue specimen or unconfirmed diagnosis of colorectal adenocarcinoma were excluded. Patients that had undergone prior definitive colorectal cancer surgery prior to presentation, patients with recurrent tumors without sufficient primary tumor tissue, and patients who refused to participate were also excluded. Patients who had other synchronous primary malignancies that might affect evaluation of colorectal cancer outcomes were excluded.

Methods: After obtaining informed consent, eligible patients with histologically confirmed colorectal adenocarcinoma were enrolled. Demographic and clinical features, such as age, sex, tumor site, clinical complaints, associated diseases, and pertinent treatment history, were documented. Preoperative investigations and imaging were reviewed to assess the clinical extent of disease and help plan surgery. The resected tumor specimen was evaluated by expert histopathologists for tumor type, grade, depth of invasion, lymphovascular and perineural invasion, tumor budding, margin status, lymph-node involvement and other relevant histopathological features. When available, molecular evaluation was conducted on available tumor tissue for clinically relevant biomarkers, such as mismatch-repair/microsatellite instability status and molecular alterations for selected biomarkers for which testing was available. Circulating tumour DNA findings were also documented if available, for selected patients. The correlation between histopathological features and molecular markers was carried out with surgical approach, pathological stage, recommendations for the postoperative management and early results. Collected data was entered into a structured database and analyzed for association with any individual or combined biomarkers with tumor aggressiveness and surgical management decisions.

RESULTS

One hundred and twenty patients were enrolled in the study with histologically confirmed colorectal adenocarcinoma. The mean age of the participants was 58.7 ± 11.9 years, with 71 (59.2%) being male and 49 (40.8%) females. Most of the tumors were in the colon (72.5%) and 27.5% were rectal tumors. The moderately differentiated adenocarcinoma was the most common tumor grade as shown by histopathological evaluation. Perineural invasion was seen in 30.0% and lymphovascular invasion was observed in 38.3% of patients. 40.8% had intermediate or high grade tumour budding.

Table 1. Demographic and Clinicopathological Characteristics of Patients

Characteristic	n (%)
Total patients	120 (100)
Age, mean ± SD	58.7 ± 11.9 years
Male	71 (59.2)
Female	49 (40.8)
Colon tumor	87 (72.5)
Rectal tumor	33 (27.5)
Well-differentiated tumor	18 (15.0)
Moderately differentiated tumor	78 (65.0)

Poorly differentiated tumor	24 (20.0)
Lymphovascular invasion	46 (38.3)
Perineural invasion	36 (30.0)
Intermediate/high tumor budding	49 (40.8)
Positive lymph nodes	44 (36.7)

As far as molecular features are concerned, 18 (15.0%) cases were found to be mismatch-repair deficiency/microsatellite instability-high. 43 (35.8%) patients had RAS mutations and 11 (9.2%) had BRAF mutations. In 7 cases (5.8%) the HER2 was amplified. Circulating tumour DNA was detected in more patients in those with lymph-node involvement and in patients with a higher pathological stage and was associated with adverse pathological parameters in patients in whom it was measured.

Table 2. Histopathological and Molecular Biomarker Findings

Biomarker	Positive/Abnormal n (%)	Negative/Normal n (%)
MSI-high/MMR deficient	18 (15.0)	102 (85.0)
RAS mutation	43 (35.8)	77 (64.2)
BRAF mutation	11 (9.2)	109 (90.8)
HER2 amplification	7 (5.8)	113 (94.2)
High/intermediate tumor budding	49 (40.8)	71 (59.2)
Lymphovascular invasion	46 (38.3)	74 (61.7)
Perineural invasion	36 (30.0)	84 (70.0)
Detectable postoperative ctDNA*	22 (25.6)	64 (74.4)

*ctDNA was evaluated in 86 patients with available samples.

Pathological stage was clinically significantly associated with biomarkers. Patients with high tumor budding, or with lymphovascular invasion, perineural invasion or with detectable postoperative ctDNA were more often considered to be stage III or IV than those without those adverse features. The right-sided colorectal cancers were more likely to be MSI-high/MMR-deficient. Alterations of RAS and BRAF, on the other hand, were linked to more advanced disease characteristics. The results showed that integrating the histopathological and molecular markers may offer more risk information than traditional staging.

Table 3. Association of Selected Biomarkers with Advanced Pathological Stage

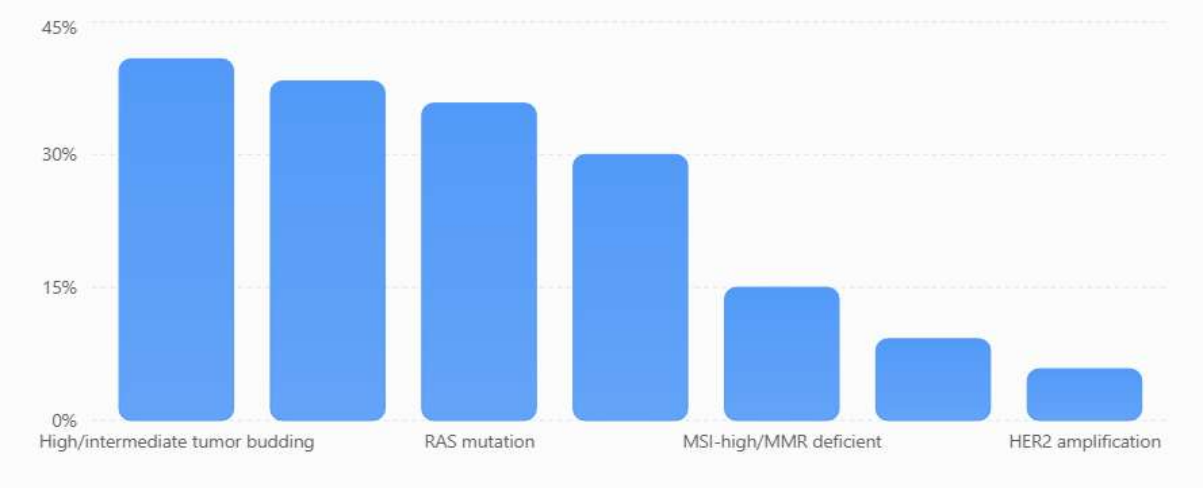
Biomarker	Stage I–II n (%)	Stage III–IV n (%)	P-value
Low/absent tumor budding	42 (59.2)	29 (40.8)	0.018
Intermediate/high tumor budding	17 (34.7)	32 (65.3)	
No lymphovascular invasion	54 (73.0)	20 (27.0)	<0.001
Lymphovascular invasion present	12 (26.1)	34 (73.9)	
No perineural invasion	61 (72.6)	23 (27.4)	<0.001
Perineural invasion present	10 (27.8)	26 (72.2)	
MSI-high/MMR deficient	11 (61.1)	7 (38.9)	0.041
RAS mutation	20 (46.5)	23 (53.5)	0.032
BRAF mutation	3 (27.3)	8 (72.7)	0.019

The identified biomarker profile was used to assess surgical management. Most patients had standard onco-resection and more aggressive surgery was needed for patients with locally advanced tumors or poor pathological features. In 47 (39.2%) patients, a biomarker-informed multidisciplinary assessment had an impact on the postoperative treatment plan, especially when there was high-risk histological characteristics, molecular alterations, detectable ctDNA, or an advanced pathological stage. More intensive post-operative management was associated with patients with more adverse biomarkers.

Table 4. Surgical Management According to Biomarker Risk Profile

Management variable	N (%)
Standard oncological resection	82 (68.3)
Extended/multivisceral resection	18 (15.0)
Abdominoperineal resection	12 (10.0)
Palliative/other surgical procedure	8 (6.7)
Biomarker-informed treatment decision	47 (39.2)
Adjuvant chemotherapy recommended	68 (56.7)
Intensive postoperative surveillance	52 (43.3)
Detectable postoperative ctDNA with intensified management	22 (18.3)

The distribution of major adverse biomarkers demonstrated that tumor budding was the most frequently identified high-risk feature, followed by lymphovascular invasion and RAS mutation. The combined presence of multiple adverse biomarkers was associated with greater pathological risk and more intensive postoperative management.



Overall, the results showed that the use of histopathological and molecular biomarkers was complementary in terms of their ability to provide information on tumor aggressiveness, pathological stage and postoperative treatment planning. The use of conventional pathological assessment in conjunction with molecular biomarkers and circulating tumor DNA, especially for patients with higher-risk disease, who may need more aggressive treatment or monitoring, seemed to be very helpful.

DISCUSSION

In the current study, the authors assessed the predictive value of the histopathological and molecular biomarkers in CRC and found that integration of molecular data with the traditional histopathological features could offer a more accurate picture of tumour biology and treatment requirements. Adverse histopathological features such as high or intermediate tumour budding, lymphovascular invasion, perineural invasion and lymph-node involvement were often seen in advanced disease in the present cohort. Molecular changes, including RAS and BRAF mutations, MSI/MMR status and circulating tumor DNA, were also available to help supplement traditional pathological staging. The results are consistent with the trend toward personalized colorectal cancer treatment, where treatment options are increasingly chosen based on the tumor's biology, rather than only its anatomic stage (1).

Histopathology is still one of the most crucial aspects of colorectal cancer evaluation. In the present study, intermediate or high tumor budding was found in 40.8% of the patients and was correlated with more advanced disease. This discovery is clinically significant because budding of the tumors is indicative of the aggressive behaviour of the colorectal cancer and can help to determine its behaviour. Recent computational advances in pathology have also extended the utility of histology, with the example of the ability to show that conventional H&E slides are rich in complex morphological data, which can be predictive of molecular markers and prognosis. In a large multicentric cohort, Wagner et al. showed that AI models

could predict clinically relevant colorectal cancer biomarkers directly from the histological images, further affirming the potential of AI as an additional tool to the traditional pathological analysis (2).

Another important layer of prognostic and predictive information is given by the molecular classification of colorectal cancer. The current study revealed that 15% of patients had MSI-high/MMR deficient tumors, a finding that reflects the fact that mismatch-repair status is a clinically important feature that impacts prognosis and systemic treatment. Dunne and Arends highlighted the fact that modern classification of colorectal cancer is increasingly based on molecular abnormalities as well as the conventional morphological assessment, such that a tumour can be classified into molecularly distinct subgroups with biological significance, rather than relying solely on anatomical stage (3). The tumour microenvironment could also play a significant role in the progression of CRC. In the current study, the presence of lymphovascular invasion and perineural invasion correlated with high pathological stage of the disease, which indicates that the aggressive behaviour does not only depend on the malignant epithelial cells.

New histological markers, like SARIFA, can add to the information regarding the interaction between the tumor tissue and its microenvironment. Reitsam et al. have reported that SARIFA is a strong histological prognosticator that is linked to a different tumor biology and that it is not the genetic alterations per se that are the primary drivers of the prognostic effect. The observation highlights the need to take into account the morphological and microenvironmental features in addition to molecular biomarkers in evaluating the tumor risk of each individual (4). Liquid biopsy is a critical advancement in the use of biomarkers in colorectal cancer. In the current study, detectable postoperative ctDNA was found in a small number of patients, and was correlated with poor pathological features. The potential value of circulating tumor DNA is that it can be sampled multiple times and could offer dynamic data about the presence of residual disease and treatment response.

In colorectal cancer, Mauri et al. emphasized the promise of liquid biopsies to monitor tumor evolution and detect molecular resistance, and to guide treatment. It is therefore possible that serial assessment of blood may give a more dynamic picture of disease status during the postoperative and systemic treatment periods, compared to a single tissue sample (5). Histological morphology and molecular alterations also have important implications for precision medicine. The current results confirm the idea that information may be contained within the conventional pathology that goes beyond the features that are identified during routine microscopic examination.

On the other hand, Tsai et al. showed that histopathological images can predict multi-omic abnormalities and prognostic characteristics of CRC, in which digital tissue analysis could potentially become a relatively easy way to gain molecularly relevant information from a routine pathology slide. These may be appropriate to supplement the laboratory molecular testing and enhance risk stratification in cases where full molecular profiling is not available (6). One of the most critical issues in managing colorectal cancer (CRC) associated with inflammatory bowel disease (IBD) is precision management. The present study did not limit the investigation to inflammatory tumors; however, the results apply to the general rule that colorectal cancer should be assessed based upon its biological context. The authors of the article, Iacucci et al., explained the molecular changes, the use of advanced endoscopy and the evolving strategies of surveillance that are helping to move towards more personalized care of inflammatory bowel disease-associated colorectal neoplasia.

They note that the importance of combining early detection, molecular characterization and advanced endoscopic evaluation in precision-based care pathways (7). The present results also indicate the potential of clinical decision-support systems in the management of patients after surgery. Combinations of pathological and molecular risk characteristics affected management decisions in almost 40% of patients in this cohort. Kleppe et al. created and tested a clinical decision-support system combining deep learning with pathological staging markers to improve the selection of adjuvant chemotherapy. Their results suggest that computer-based models could be used to discern patients with the same apparent conventional pathological stage who have varying risks for recurrence. These tools could benefit in particular in multidisciplinary colorectal cancer teams where there is a need to integrate considerable amounts of pathological and molecular data into treatment decisions (8).

Another potential clinical relevance of histopathologic biomarkers is in the prediction of the spread of disease (metastasis). In this study, unfavorable histological features were correlated with advanced disease, which is in concordance with the general belief that tumor morphology might correlate with the metastatic potential. Höppener et al. showed that there are histological features of the primary colorectal tumour that correlate with the histopathological growth pattern of the liver metastases. This implies that features seen in the primary tumour might have implications for the biological behaviour of metastatic disease and thus help in the planning of treatment in patients with colorectal liver metastases (9). The predictive value of molecular biomarkers was also demonstrated with regards to immunotherapy.

An important subgroup in the present cohort was MSI-high/MMR deficient tumors. The authors noted that mismatch-repair deficiency and microsatellite instability are among the most established predictive biomarkers for immunotherapy in CRC, and other immune-related and molecular markers are currently being studied. In this context, molecular profiling could be used to identify patients that might be responsive to immune checkpoint inhibition and avoid the use of standard chemotherapy alone in certain molecular subgroups (10). The larger idea of precision medicine is to tailor treatment to individual molecules. The proportion of patients with RAS mutations was 35.8% in the present study and was less common but associated with advanced disease; BRAF mutations were less common. Kiran et al. emphasized the importance of the emerging role of molecular profiling in colorectal cancer management, which is now becoming increasingly important in identifying actionable changes and directing targeted treatment.

The strategy helps to shift from a homogeneous treatment strategy towards the individual selection of therapy according to the molecular features of the individual tumor (11). Likewise, Guo et al. showed that a deep-learning analysis of the H&E stained colorectal cancer images could be used to accurately predict the MSI status with good performance. These results indicate that in the future, artificial intelligence can be used for fast biomarkers screening directly from the routinely prepared tissue sections (12). The presence of lymph-node involvement is still a key factor in the staging and post-operative treatment of colorectal cancer. In this study, we saw that 36.7% of patients had positive lymph nodes, and high risk histopathological features were more likely to be linked to advanced stage disease. Krogue et al. showed that deep-learning models that combine primary tumour histology and clinicopathological features could make predictions about lymph-node metastasis. These techniques could potentially help in the future to predict risk preoperatively and help the surgeon and multi-disciplinary team to predict the risk of nodal disease (13).

Moreover, metabolic markers might offer another layer of risk stratification. In the future, metabolic signatures could be used alongside histopathological and molecular features in predictive models, as Krishnan et al. showed that lipid biomarkers along with machine-learning techniques could help in the staging of colorectal cancer (14). The role of ctDNA is particularly important in locally advanced rectal cancer and total neoadjuvant therapy. The present study encompassed colorectal cancer as a whole, but in this study, the presence of detectable postoperative ctDNA was correlated with high-risk features, which suggests the potential use of ctDNA as a marker of residual molecular disease. While the prognostic and predictive value of ctDNA in locally advanced rectal cancer (LRCR) undergoing TAT remains to be validated in prospective studies, Bashir et al. reported that it could be used to guide treatment in LRCR (15).

Similarly, Yahya et al. reported that ctDNA could be a promising biomarker to guide total neoadjuvant therapy, especially as it could give additional information on the response to treatment and the presence of residual disease that may not be identified by conventional imaging alone (16). Predicting response correctly may one day affect the extent and timing of surgery and enable individual treatment strategies such as organ preservation in well-selected patients (17). In general, the present results support the trend of moving towards a molecularly informed approach to oncology, where pathological, genetic, circulating, metabolic and computational biomarkers are combined to select treatment and make patient-specific decisions. As Kara has pointed out, molecular biomarkers must be combined with traditional pathology, multi-disciplinary evaluation and organ-specific therapeutic strategies for successful clinical translation; biomarkers alone

are not sufficient. Therefore, the use of combined histopathological and molecular biomarkers could offer a more solid foundation for the surgical plan, the choice of postoperative treatment, prognosis, and surveillance of colorectal cancer.

CONCLUSION

This study shows that combining histopathological and molecular biomarkers can be a valuable source of predictive information that goes beyond traditional CRC staging. Histopathological features such as tumor budding, lymphovascular invasion, perineural invasion and lymph-node involvement were linked to aggressive disease and advanced pathological stage. Additional information about tumor biology and treatment needs was provided by molecular biomarkers such as MSI/MMR status, alterations in RAS and BRAF genes, and circulating tumor DNA. These biomarkers used together could help facilitate more personalised surgical and postoperative treatment and better identify those who may have a higher risk of recurrence or metastatic spread. Further opportunities for dynamic and precise risk assessment are provided by digital pathology, artificial intelligence and liquid biopsy. In conclusion, biomarker-guided assessment can enhance the multidisciplinary decision-making process, guide treatment selection, and support individualized treatment strategies in colorectal cancer. Validation of these findings and the development of standardised biomarker-based clinical algorithms needs to be done in prospective multicenter studies with larger numbers of patients.

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