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Perspective

The Function of Biomarkers in Colorectal Liver Metastases Management

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Abstract

Patients with Colorectal Liver Metastases (CRLM) now have a 5-year overall survival rate above 50% thanks to new systemic treatments paired with surgical therapy. For patients with unresectable CRLM, a wide range of liver-directed treatments have enhanced local disease control. Sadly, a sizeable percentage of patients who have curative-intent hepatectomy experience a disease recurrence. Traditional indicators do not properly risk-stratify and prognosticate CRLM patients. We now know much more about the pathophysiology and tumours microenvironment features of CRLM because to developments in molecular sequencing technologies over the past few decades. These investigations have uncovered biomarkers that could help guide treatment choices for CRLM patients. National and societal standards have taken actionable indicators including *RAS* and BRAF mutations, microsatellite instability/mismatch repair status, and tumours mutational burden into account. To assess their clinical value, other biomarkers, such as circulating tumours DNA and radiomic characteristics, are now being researched. Reliable biomarkers are required to help clinicians create patient-specific management strategies due to the abundance of therapeutic modalities and paucity of data on timing and sequencing.

Keywords: Colorectal cancer • Colorectal liver metastasis • Biomarker

Introduction

The main cause of cancer-related morbidity and mortality worldwide is Colorectal Cancer (CRC). Advances in CRC screening and multidisciplinary therapy have significantly improved mortality rates, particularly among patients living in highly developed countries where mortality rates have fallen in recent years, even though the global incidence is still rising, disproportionately so in low- and middle-income countries. Despite these advancements, CRC continues to rank second in the United States for cancer-related death. Roughly 50% of CRC patients develop metastatic liver disease. While 20%-34% of CRC patients have synchronous liver disease, the majority of Colorectal Liver Metastases (CRLM) develop metachronously after treatment for loco regional CRC. In cont*ras*t to patients with metachronous CRLM, those with synchronous disease are more likely to have multiple liver lesions and bilobar disease, which portends a worse prognosis. Unfortunately, at presentation, 80%-90% of CRLM patients had an incurable liver condition. Patients who do not have surgery had a much poorer 5-year survival rate. Therefore, metastatic liver disease is the main cause of death in most CRC patients.

Both curative purpose surgery and perioperative systemic therapy are currently included in the standard of care for patients with resectable CRLM. Improvements in resection rates have been achieved while perioperative morbidity and mortality following liver surgery have been significantly decreased. Long-term patient outcomes are dramatically improved following complete surgical resection with negative margins and adequate liver remnant. According to recent meta-analyses, certain individuals with solitary liver metastases who underwent resection and the proper perioperative systemic medication had a median 5-year survival rate ranging from 38%-71%.

However, within 2 years of surgery, 50% of individuals experience recurring illness. Many of these individuals have an incurable condition, even if some of them are eligible for greater resection. Liver-directed therapy offer local disease management for patients with unresectable CRLM and, in some circumstances, may help patients develop resectable disease. Hepatic Artery Infusion (HAI), radio embolization (Y-90), ablation, and external beam radiation (such as Conformal Radiation Treatment [CRT], Stereotactic Body Radiation Therapy [SBRT], and Intensity-Modulated Radiation Therapy [IMRT]) are examples of liver-directed therapies. Surgery is still the gold standard of treatment, but there are still concerns about the selection and timing of liver-directed medicines as well as the perioperative administration of systemic medications.

The ability to identify the genetic variations relevant for CRC carcinogenesis has substantially enhanced our understanding of CRC pathophysiology thanks to developments in Next-Generation Sequencing (NGS) and computational data analytics. These molecular biomarkers offer clinicians potentially useful information, together with the developing disciplines of radiomics and artificial intelligence. Certain biomarkers, such as *RAS*, BRAF, and Mismatch Repair (MMR) status, are taken into account in the current treatment algorithms for patients with CRLM. Other biomarkers are actively being researched in clinical studies but need to have their clinical value validated. Here, we describe how biomarkers are currently used to monitor patients with CRLM.

Tumour Morphology

Significant predictive information is provided by tumours morphology, which also directs clinical judgement. Resectability is determined by the size, quantity, and proximity to vascular structures, and margin-negative resection is a key component linked to long-term survival. Additionally, combined surgical/ablation techniques are informed by lesion size, depth from the periphery, and vascular proximity to give definitive care and spare liver parenchyma in the event that a future hepatectomy may be required to remove recurring disease. Second, predictive discriminatory abilities for long-term survival outcomes are shown by morphology-based grading systems. Based on previous research that included patients with hepatocellular carcinoma, Sasaki et al. recently created a Tumours Burden Score (TBS) utilizing simply the number of lesions and maximal tumours size. Higher TBS scores were associated with shorter 5-year survival among patients following hepatectomy for CRLM, according to external validation on 2 cohorts. This method of reliable 5-year survival categorization was shown to be based on the TBS.

Patients with resectable and non-resectable illnesses who had radiographic response rates of CRLM while receiving systemic or liver-directed therapy had better disease-free and overall survival. A Pathologic Complete Response (PCR), which ranges from 24%-96% (median 77.5%) in patients with a complete radiographic response (i.e., vanishing liver metastases) following therapy but is still undetected with intraoperative ultrasonography.

Additionally, patients with resectable cancer who had therapy and went from having unresectable illness to resectable disease had better survival rates than patients who did not show a radiological response and remained unresectable. Additionally, the histological growth patterns of CRLM that were examined after resection offer a predictive value for overall survival.

Researchers have looked into Artificial Intelligence (AI)-based approaches like machine learning in response to the expanding volume of clinical data produced by the digitalization of healthcare. Although it is not a biomarker in and of itself, AI maximizes the utility of the data by taking into account all relevant data in an unbiased, unsupervised manner with the capacity to constantly enhance predictions. When 1406 patients with CRLM underwent liver resection, the long-term results were predicted using a novel machine learning method. As a "biomarker," tumours morphology has numerous substantial drawbacks. The resectability of a tumours may only be inferred from its morphology. For instance, different institutions have different definitions of resectability, sometimes relying more on the skill of the surgeon than morphological traits. The 10%-15% of individuals with a resectable disease who get a resection but later experience an early recurrence and pass away from cancer provide little insight into their condition, according to tumours morphology. While changes in tumours morphology based on serial imaging offer useful information about the therapeutic response during treatment, it does a poor job of predicting the therapeutic response to systemic therapy before treatment even begins, let alone identifying which systemic therapy may offer the best results for a given patient.

Molecular Biomarkers

When describing mutations related to K*RAS*, *APC*, and TP53 at different phases of CRC carcinogenesis in 1988, invasive carcinoma arises from adenomatous polyps by the successive accumulation of somatic mutations in numerous genes was proposed. Since the creation of NGS technology, the study of oncogenesis has improved significantly thanks to methods including whole-genome, whole-exome, and targeted sequencing, which have identified a variety of genetic changes.

A fraction of CRC cells develops the ability to escape the main tumours, travel through the extracellular matrix and surrounding tissue, intravasate, survive transit through the blood, extravasate, and eventually populate the liver. This process requires molecular changes that result in a biologically aggressive and phenotypically unique disease entity.

Not all genomic modifications are associated with predictable adjustments in biological activity. The molecular processes that take place between gene expression and illness manifestation are made clearer by proteomics. Recent proteome profiling investigations, particularly in proteins linked to the extracellular matrix, energy metabolism, and immune-cell-related migration, have identified distinct protein and post-translational changes found in metastatic CRC cancers. We go over major genomic, proteomic, and post-translational alterations in CRLM formation in the section that follows.

Genomic Biomarkers

One-third of patients with CRC metastases had mutations that could be corrected, according to genome-wide sequencing studies. All patients with metastatic CRC should be tested for *RAS* (*KRAS* and *NRAS*), *BRAF* mutations, and *HER2* amplifications, either individually or as part of an *NGS* panel, according to the most recent National Comprehensive Cancer Network (NCCN) guidelines. All patients who have just been diagnosed with CRC should also be tested for MMR or Microsatellite Instability (MSI).

Gain-of-function activity in the MAPK pathway is the mechanism by which mutations in the *RAS* proto-oncogene family, most notably *KRAS, NRAS,* and *HRAS*, cause uncontrolled cell proliferation. Up to 52% of individuals with *CRLM* have *RAS* mutations, and there is a strong correlation between the underlying tumours and *CRLM*. Compared to people with wild-type *RAS*, patients with *RAS*-mutated *CRLM* have considerably lower recurrence-free and overall survival rates. Patients with *RAS* mutations soon develop resistance to Epidermal Growth Factor Receptor (EGFR) antibody treatment as a result of the activation of the MAPK pathway. Cetuximab and panitumumab, anti-EGFR antibody drugs, are therefore solely advised for the treatment of K*RAS* and N*RAS* wild-type cancers. .

Furthermore, compared to RAS-wild-type *CRLM*, *RAS*-mutated *CRL*M exhibit more migratory or invasive behavior, leading to the growth of local tumours and a higher incidence of micro metastasis. As a result, these tumours had a double the rate of positive surgical margins following hepatectomy and a shorter median negative margin. Smaller *RAS*-mutated *CRLMs* treated with ablation therapy exhibit similar outcomes. The ideal negative margin distance for patients with *CRLM* is still up for debate. Patients with RAS-mutated CRLM had equally bad outcomes between the R0 and R1 resection groups, but patients with wild-type RAS CRLM benefited from negative surgical margins. The ideal surgical margin in K*RAS*-variant CRLM was recently determined using AI-based analytics on a study of 1843 patients with CRLM who received curative-intent surgery. For K*RAS*-variant CRLM, the AI model recommended an ideal margin width of 7 mm. The extension from 1 mm to 7 mm contributed less to the improvement in survival than the 1 mm margin, which was where the majority of the associated lengthening of survival was observed. Before trying surgical resection with a curative goal, individuals with *RAS*-mutated tumours should ultimately show disease stability on systemic therapy and be free of additional poor prognostic markers.

BRAF has become known as a very bad prognostic sign in the MAPK pathway. Of patients with CRLM, 5% have BRAF mutations. Over 90% of these mutations are caused by BRAFV600E, which has valine in place of glutamic acid at codon 600. Rarely do patients with BRAF-mutated CRC have lone liver metastases. Furthermore, compared to patients with wild-type BRAF, median recurrence-free survival and overall survival after curative-intent hepatectomy are only half as high in patients who have a small percentage of patients who have resectable cancer. Patients with a BRAF mutation, like those with *RAS*-mutated CRC, do not react to anti-EGFR therapy unless it is combined with a BRAF inhibitor. Patients with non-BRAFV600E mutations may experience better results than even patients with wild-type BRAF, despite the fact that the data are confined to small trials. 2%-3% of metastatic CRCs exhibit HER2 amplification, a targetable variation in the MAPK pathway. The low prevalence of HER2 amplification in CRC cases, despite the fact that it has been extensively researched in breast cancer, prevents confidence claims about the predictive impact of HER2 amplification. In terms of targeted therapeutics, phase 2 trials suggest the use of a dual HER2 blockade in HER2-amplified metastatic CRC that has received a lot of prior treatment. But only HER2-amplified tumours that are simultaneously *RAS* and BRAF wild-type are appropriate for anti-HER2 therapy.

MSI is present in 5% of individuals with metastatic CRC who have defective DNA Mismatch Repair (dMMR). Germline mutations, such as Lynch disease, or spontaneous promoter hyper methylation and silence of the MMR gene MLH1 cause changes in the MMR system. One-third of dMMR patients have sporadic mutations, which are strongly related with BRAFV600E mutations and have a worse prognosis than those with a genetic dMMR. While dMMR status in metastatic CRC resulted in a worse prognosis compared to proficient MMR tumours, it is associated with lower metastatic potential and a positive prognosis in early-stage CRC. Additionally, regardless of the dMMR status, patients with metastatic CRC might have a significant tumours mutation burden that results in MSI. High tumours mutational load patients may also gain from ICI therapy.

Four of the top five most mutated genes, *APC*, *TP53*, *PIK3CA*, and *SMAD4*, are among the genomic alterations revealed in metastatic CRC that are sadly the majority of which lack a targeted therapy. The prognostic value of these mutations can be determined by understanding their state. *TP53* and *RAS* mutations together have poorer prognostic consequences than each mutation alone. Patients with CRLM that has both mutations specifically have significantly lower overall survival and recurrence-free survival rates. Patients with tumours carrying both an *APC* and a *PIK3CA* mutation experience a similar trend. A worse prognosis results from the combined effects of these mutations on chemoresistance. It should come as no surprise that cancers with mutations in both an oncogene (*KRAS, PIK3CA*) and a tumours suppressor gene (*TP53, APC*) are more physiologically aggressive, resulting in earlier disease recurrence and mortality.

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