

A Narrative Review on the Current Application of Biomarkers in the Management of Colorectal Cancer

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Abstract

Currently a wide range of biomarkers and potential biomarkers exist across a variety of fields for the management of colorectal cancer. These can be a specific molecule or a radiographical finding and can predict outcome or response to treatment. The field is being developed along several fronts with many new innovations happening in the last few years however few have made it into routine clinical practice with others requiring validation.

The evolving markers of significance are; MicroRNA, epithelial-to-mesenchymal-transition, imaging and metabolic with several sub-divisions depending on the pathway effected. This review will provide a narrative appraisal of our current understanding and clinical application of these biomarkers.

Keywords: Imaging biomarkers; Molecular biomarkers; Colorectal cancer diagnosis; Prognosis

Background

Colorectal cancer is one of the most common types of cancer, and leading causes of cancer-related deaths in both genders worldwide [1]. In 2017, there will be an estimated 135,430 new cases of colorectal cancer diagnosed, with 39,220 new cases of rectal cancer specifically [2]. Disease management for patients with colorectal cancer have improved significantly in the past 2 decades, and treatment plans have become more personalized to optimize care [3]. Biomarkers are a way to use more personalized information to improve patient care, help determine the patient's prognosis and guide the ideal treatment plan to improve cancer specific survival. The National Cancer Institute defines a biomarker as a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process [4]. (NCI dictionary of cancer terms. Biomarker. Available online at: <http://www.cancer.gov/dictionary?cdrid=45618>). In cancer, biomarkers can be objectively measured and evaluated as an indicator(s) of normal biological processes, or pharmacological responses to a therapeutic intervention [5,6]. The ideal biomarkers can help determine predisposition for treatment, early detection of disease, and assessment of prognosis [7]. In this submission, we review the growing evidence for using biomarkers as a tool for these processes and responses in colorectal cancer. For this summation, the biomarkers are broadly grouped into metabolic, molecular, and imaging categories.

Metabolic Biomarkers

Colorectal cancer results from complex interactions between inherited susceptibility, inflammatory conditions, and environmental/lifestyle-related risk factors, where diet and body habitus have a major impact. The hypothesis that diet and related metabolic, anthropometric and hormonal markers impacted cancer development was originally proposed in the 1940s [8]. Many studies that followed supported the association of elevated body mass index (BMI), metabolic disorders including hyperglycemia, hyperinsulinemia, dyslipidemia, type 2 diabetes, and hypertension and visceral adiposity with the risk of CRC and colon carcinogenesis [9]. Adipose tissue, which is viewed like glandular tissue, performing endocrine, paracrine and autocrine functions, has been found key in the process of neoplastic transformation, especially in inhibiting the anti-lipolytic effect of insulin [10-15]. Two specific hormonal systems, adipokines and the insulin/insulin-like

growth factor (IGF) axis, are the most studied metabolic biomarkers of CRC [16,17]. The systems regulate processes including glucose and lipid metabolism, inflammation, angiogenesis, and cell proliferation [18]. Studies have found they markers in these systems impact risk clinical behavior, and mortality. To date, serum adiponectin, leptin, resistin and visfatin levels (and its receptors) are validated metabolic biomarkers of CRC. High concentrations of serum HDL are associated with a decreased risk of CRC, while increased circulating IGF1 levels and an increased IGF1/IGFBP3 ratio are associated with a higher risk of CRC. Hyperinsulinemia and hyperglycemia are associated with higher mortality from CRC, and increased HbA1C levels are an independent predictor of aggressive clinical behavior in CRC patients. Conversely, high IGF2 levels are associated with improved overall survival in CRC patients [17]. Further studies will determine the independent role of these possible biomarkers and their impact on rectal cancer specifically.

A hybrid of the molecular and metabolic biomarker fields is metabolomics. Metabolomics provides a systematic, time-dependent measurement of metabolic shifts occurring in response to drugs, environmental stimuli or disease [19-29]. It offers a functional view of system activity by showing all micromolecular data downstream of the genome and proteome [30]. This wider view of system activity past macromolecules such as DNA and RNA could facilitate personalized approaches for colorectal cancer diagnosis, prognosis and therapeutic personalisation [22,28].

Molecular Biomarkers

Molecular biomarkers grew out of the pathways for colorectal cancer development. There are 3 distinct paths: chromosomal instability causing mutations in oncogenes, epigenetic methylation of varying genes, and

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microsatellite instability resulting from defective DNA repair. The epidermal growth factor receptor (EGFR) pathway has proved the most clinically relevant molecule involved in the chromosomal instability pathway. In fact, the development of biomarkers in colorectal cancer stemmed from the benefits demonstrated with KRAS and microsatellite instability testing [10,11,23,24]. Mutation of some of the components of KRAS on the EGFR pathway, including KRAS and NRAS codons 12 and 13 of exon 2, 59 and 61 of exon 3, and 117 and 146 of exon 4, render the malignant cells resistant to anti-EGFR therapies like Cetuximab and Panitumumab. This has a direct impact on patient care [25-27]. As a result, screening of KRAS/NRAS mutation status is mandatory prior to the start of treatment. This is also a therapeutic target, with monoclonal antibody therapies targeting the epidermal growth factor receptor (EGFR) that binds the EGFR extracellular domain, blocking EGFR signalling pathways; knowledge of the mutational status of genes in this pathway serve as predictive biomarkers of response to these therapies [25-27]. In the future, this could be an avenue for imaging biomarkers, as up regulation of EGF could potentially be measured. Other mutations in genes of the EGFR signalling pathways may affect response of CRC to anti-EGFR antibody therapies, including involving other exons of KRAS, NRAS, BRAF, PIK3CA, and PTEN. Further research will evolve on their role and guidelines addressing the molecular testing of EGFR pathway genes beyond KRAS.

Microsatellite instability (MSI) is a hypermutable phenotype caused by the loss of DNA mismatch repair activity. MSI is detected in about 15% of all colorectal cancers; 3% are of these are associated with Lynch syndrome and the other 12% are caused by sporadic, acquired hypermethylation of the promoter of the MLH1, MSH2, MSH6, or PMS2, most commonly [28]. MSI status also has a correlation with outcome, and MSI high or low is a useful molecular marker to stratify stage II colorectal cancer, as node negative colorectal cancer patients with MSI-high tumours have been shown to have a better outcome than patients with MSH-low tumours; adjuvant chemotherapy is usually not indicated in these cases [29,30]. Thus, it is recommended that clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification [31].

MicroRNAs (miRNAs) are short, noncoding RNAs that regulate gene expression through post-transcriptional interactions with mRNA [32]. They have the potential to impact a vast range of downstream effects, and may act as either oncogenes or tumour suppressors, depending on the target proteins affected. Thus, miRNAs are directly involved in multiple biological pathways that can influence carcinogenesis and progression [33-35]. Their role has been described in breast and lung cancer, and continued work has shown mutated miRNAs have been found in multiple targets linked to cancerous transformation in general, such as p53 and EGFR [36-39]. Further exploration of the role of miRNA involvement has promise with as a miRNAs as a clinically relevant biomarker to predict tumour staging and response to treatment in colorectal cancer [37,38].

Imaging Biomarkers

Imaging biomarkers provide a way to objectively measure tumour response to a therapeutic intervention and potentially detect early disease, in a non-invasive manner. The simplest imaging biomarker is tumour size, which can be reliably measured on CT or MRI [40,41]. Reduction in tumour size correlates with a positive response to neoadjuvant treatment and improved survival [42]. Using the blood flow on dynamic contrast enhanced CT or MRI scans as a surrogate for angiogenesis has been correlated with the development of

metastases and decreased survival, and may have benefit as an imaging biomarker [43-46]. Other variables seen specifically on MRI following chemoradiotherapy, such as the degree of fibrosis, correlates with the histopathological tumour regression grade, and can be applied to determine the timing or need for surgical management [47]. Another variable on MRI, extramural venous invasion (EMVI), has been shown to be an independent indicator of prognosis and may be a valuable biomarker [48].

Specific CT and MRI types may hold additional benefit as a marker for response and prognosis. While T2 weighted MRI is the standard for evaluating staging and response to therapy in rectal cancer, the diffusion weighted imaging (DWI) sequences may add additional value for evaluation after response to chemoradiotherapy [49,50]. DWI analyses water molecules during MRI acquisition and can highlight cell death and vascular alterations typically before size changes occur [51-53]. In addition, contrast enhanced CT measuring tumour heterogeneity could emerge as a biomarker for prognosis. Study has found tumours demonstrating less heterogeneity were associated with poorer survival, supporting the use texture analysis to staging contrast-enhanced CT, and possibly serve as a prognostic biomarker in colorectal cancer [54].

One method of measuring response is through metabolism, as with positron emission tomography (PET) scans. The concept of altered cancer metabolism, described as the Warburg effect, where cancer cells preferentially convert glucose into lactate even in the presence of abundant oxygen, has been validated in a variety of cancer subtypes [55-58]. This serves as the support for using [18F]-fluorodeoxyglucose (FDG) enhanced positron emission tomography (FDG-PET) imaging of solid tumours, which shows glycolytic flux [54,59]. Other modalities are harnessing this metabolic effect with other imaging tools to provide value, such as the combined PET/CT to predict early recurrence in the treatment of liver metastases, and application of PET/MR to provide information on tumour staging, response to neoadjuvant therapy, and disease recurrence [60,61]. Further studies are needed to define the true benefit of these studies in colorectal cancer care. The metabolism can be seen in a dynamic fashion, combining tissue specific spectra with chemometric data as a real-time imaging biomarker, as with high resolution nuclear magnetic resonance spectroscopy (HR-MAS NMR). To date, HR MAS NMR has shown reductions in lipids and glucose with increase of taurine, lactate and glycine in cancerous rectal mucosa [62]. This holds promise in developing targeted agents for rectal cancer [63].

Conclusion

Multiple types of biomarkers exist that have a variety of clinical applications, but few are currently used in routine practice. The ideal biomarkers for cancer have applications in determining predisposition, early detection, assessment of prognosis, and drug response [64]. However, much work is needed to fully develop these potentially useful markers. As the discovery, validation, and application of biomarkers continue to grow, future focused trials are required to determine their role in colorectal cancer management and outcomes.

Conflict of Interests

None

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None

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