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The current value of determining the mismatch repair status of colorectal cancer: A rationale for routine testing

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ABSTRACT

Colorectal Cancer (CRC) is the third most prevalent cancer in men and women. Up to 15% of CRCs display microsatellite instability (MSI). MSI is reflective of a deficient mismatch repair (MMR) system and is most commonly caused by hypermethylation of the MLH1 promoter. However, it may also be due to autosomal dominant constitutional mutations in DNA MMR, termed Lynch Syndrome. MSI may be diagnosed via polymerase chain reaction (PCR) or alternatively, immunohistochemistry (IHC) can identify MMR deficiency (dMMR). Many institutions now advocate universal tumor screening of CRC via either PCR for MSI or IHC for dMMR to guide Lynch Syndrome testing. The association of sporadic MSI with methylation of the MLH1 promoter and an activating BRAF mutation may offer further exclusion criteria for genetic testing. Aside from screening for Lynch syndrome, MMR testing is important because of its prognostic and therapeutic implications. Several studies have shown MSI CRCs exhibit different clinicopathological features and prognosis compared to microsatellite-stable (MSS) CRCs. For example, response to conventional chemotherapy has been reported to be less in MSI tumours. More recently, MSI tumours have been shown to be responsive to immune-checkpoint inhibition providing a novel therapeutic strategy. This provides a rationale for routine testing for MSI or dMMR in CRC.

1. Introduction

Colorectal Cancer (CRC) is the third most prevalent cancer in men and women (Siegel et al., 2012). It accounts for approximately 50,000 deaths each year in the United States (Siegel et al., 2012; Winawer et al., 2003). The reduction in death rates for CRC reflects improvements in earlier cancer detection and management, in combination with an increased understanding of the molecular and genetic basis of the disease (Hagan et al., 2013). It is now apparent that CRC is a heterogeneous disease characterised by a number of molecular subtypes (Guinney et al., 2015). Traditionally two major pathogenetic pathways have been implicated in the development of CRC: the chromosomal instability (CIN) and microsatellite instability (MSI) pathways (Cunningham et al., 2010; Ogino et al., 2011; Shi and Washington, 2012). CIN has recently been subdivided into three further consensus molecular subtypes (CMS), each with distinguishing features: CMS2 ("canonical"), epithelial, marked WNT and MYC signalling activation; CMS3 ("metabolic"), epithelial and evident metabolic dysregulation; and CMS4 ("mesenchymal"), prominent transforming growth factor–β activation, stromal invasion and angiogenesis (Guinney et al., 2015).

Mismatch repair deficient (dMMR) or MSI tumours, on the other hand, represented in the CMS1 ("microsatellite instability, hypermutated, immune") subtype, occur when there is deficiency in MMR proteins, generally due to sporadic epigenetic silencing (e.g. by hypermethylation) or by constitutional mutations (e.g. in Lynch syndrome). Diagnosis of MSI is via polymerase chain reaction (PCR) amplification of specific microsatellite repeats. Alternatively, immunohistochemistry (IHC) can confirm the presence or absence of MMR proteins. Sporadic MSI occurs in both CRC and extracolonic malignancies, particularly endometrial cancer (Bruegl et al., 2014; Haraldsdottir et al., 2014). Lynch syndrome (formerly hereditary non-polyposis colorectal cancer [HNPCC]) is the most common heritable cancer predisposition syndrome and is characterised by an increased predisposition to certain cancers, most notably CRC (Vasen et al., 2007). Lynch syndrome tumours are caused by autosomal dominant mutations in the DNA MMR system (Bonadona et al., 2011; Jass, 2007; Kovacs et al., 2009; Lagerstedt Robinson et al., 2007; Ligtenberg et al., 2009; Lynch et al., 2009; van der Klift et al., 2005).

A traditional third or "alternate" molecular CRC pathway, the "serrated pathway", is characterised by DNA hypermethylation at specific regulatory sites, enriched in CpG motifs (CpG islands) in the promoter regions of tumor suppressor genes (Toyota et al., 1999). There is some overlap between this CpG island methylator phenotype (CIMP) and sporadic MSI cancers due to their association with methylation of the MLH1 promoter and an activating *BRAF* mutation (Kane et al., 1997). However, *BRAF* mutation is rare in tumours due to germline deficiency (Lagerstedt Robinson et al., 2007). Thus, BRAF testing or methylation analysis of the MLH1 promoter may offer exclusion criteria for Lynch syndrome genetic testing (EGAPP, 2009).

At present there are four major reasons why clinicians may be interested in assessing MSI/MMR status in the CRC patient.

1. The detection of Lynch Syndrome – the role of MMR as a genetic marker of Lynch Syndrome is well established. Both MSI detection and IHC are highly sensitive methods for the identification of a defective MMR system and guide clinicians towards informative, cost-effective genetic testing. These patients benefit from increased surveillance (Jarvinen et al., 2000; Jarvinen et al., 1995), prophylactic aspirin (Burn et al., 2011) and more radical surgery, (Heneghan et al., 2015; Vasen et al., 2013) and may also require different approaches to adjuvant therapy (Le et al., 2015; Sinicrope and Yang, 2011).
2. Prognosis – Several studies have shown dMMR CRC has a better prognosis than MMR proficient (pMMR) CRC (Gavin et al., 2013; Guastadisegni et al., 2010; Klingbiel et al., 2015; Popat et al., 2005; Roth et al., 2010; Sinicrope et al., 2015). MSI tumours are less prone to lymph node (Mohan et al., 2016) and synchronous liver metastasis (Nordholm-Carstensen et al., 2015). However, in metastatic disease MSI seems to confer a negative prognosis. (Goldstein et al., 2014; Mohan et al., 2016; Tran et al., 2011) Grade is not associated with prognosis in dMMR (Mohan et al., 2016; Rosty et al., 2014; Ward et al., 2001).
3. Chemotherapy response – Although with conflicting results, a large amount of preclinical and clinical evidence suggests a possible reduced response to 5-FU based chemotherapy in dMMR tumours (Benatti et al., 2005; Hutchins et al., 2011; Ribic et al.,