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Title:

Deficient mismatch repair testing in colorectal cancer: more than just screening for Lynch syndrome

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None.

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Around 3% of colorectal cancer is associated with a germline mutation in the mismatch repair genes characteristic of Lynch syndrome (LS). In February 2017, the National Institute for Health and Care Excellence (NICE) in the UK issued guidance recommending that all newly diagnosed CRC should be screened for possible LS by testing the tumour tissue for either mismatch repair deficiency by immunohistochemistry or microsatellite instability. These tests should be followed by BRAF mutational testing and MLH1 promoter methylation analysis as appropriate to screen out cases of 'sporadic' deficient mismatch repair (dMMR) and identify patients who are more likely to have LS so that they can be referred to clinical genetics services for counselling and germline investigation. Histopathologists are ideally placed to lead and deliver this screening by initiating testing as soon as a positive diagnosis is made, preferably on a diagnostic biopsy specimen. In the UK immunohistochemistry is readily available in pathology laboratories and BRAF/methylation testing can be performed through the regional genomic laboratory hub.

The NICE guidance was introduced following analysis showing significant clinical and cost effectiveness to screening all colorectal cancer patients at diagnosis rather than a subset at increased risk. Whilst patients with LS often present with tumours earlier in life in the context of a positive family history, a significant number present at a later age resulting in many cases remaining undiagnosed. LS patients have an increased risk of a number of different tumours including gastrointestinal, gynaecological, skin and brain cancers. The risk of second cancers is also significant. The definitive identification of LS therefore enables individuals to undergo appropriate surveillance and also testing of wider family members.

Confirmation of LS at diagnosis also opens up the opportunity to modify the primary cancer surgery to reduce the risks of subsequent tumour development e.g. total colectomy plus or minus hysterectomy, depending on the clinical circumstances.

Of the patients screened at diagnosis, around 15% will show evidence of dMMR, although this is dependent on the site of the cancer with the majority of cases located in the right colon [1]. Only around 20% of dMMR is likely to be related to LS with the majority of cases caused by somatic events, usually hypermethylation of the MLH1 promoter region leading to loss of gene function. Whilst NICE guidance highlights the importance of screening to identify possible LS, there is also emerging clinical benefit to identifying patients with 'sporadic' dMMR. Firstly, there is good evidence that patients with dMMR have a better prognosis stage for stage. In stage II/III disease, the QUASAR trial demonstrated that dMMR tumours are associated with half the rate of recurrence when compared to patients with proficient mismatch repair (pMMR) [1]. The proportion of stage IV cancers with dMMR is significantly reduced at 5%, in keeping with a lower risk of disease progression, however once the tumour has metastasised dMMR patients have a poorer prognosis than those with pMMR [2].

The predictive effect of dMMR is still debated although most studies suggest a poorer response to adjuvant chemotherapy when compared to pMMR, at least when using single agent fluoropyrimidines [3]. Over recent months, the mismatch repair status is therefore frequently sought by the colorectal cancer multidisciplinary team when making adjuvant therapy decisions, with some withholding chemotherapy altogether in dMMR or use of a second drug e.g. oxaliplatin if high risk features are present. What is increasingly clear is that dMMR is a positive predictive marker of response to immunotherapy due to the higher tumour mutational burden and associated neoantigens making them sensitive to immune checkpoint blockade [4]. Given the current expense of immunotherapy, a reliable predictive marker is essential and prospective clinical trials are ongoing. Trials of neoadjuvant immunotherapy in dMMR cancers have also shown early evidence of benefit with a significant response in the primary tumour.

With a strong association between dMMR and prognosis, response to adjuvant chemotherapy, benefit from immunotherapy and identification of patients with LS, there is clear evidence for routine mismatch repair testing of all colorectal cancers at histopathological diagnosis. Despite the introduction of the 2017 NICE guidance, a 2018 freedom of information request sent to NHS hospitals in England by Bowel Cancer UK showed that 83% of centres are not currently performing testing. This was reported to be

primarily due to lack of identified funding and insufficient staff resources. It is therefore essential that colorectal cancer multidisciplinary teams recognise the clinical importance of dMMR testing and develop a local business case and/or work with commissioners and hospital managements to ensure that these important analyses are undertaken and reported alongside standard histopathological reporting.

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