An Audit of Mismatch Repair Protein Testing in Colorectal Carcinoma in MMUH in 2020

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Background

Mismatch repair deficiency (dMMR) leading to microsatellite instability (MSI-H) occurs in approximately 15% of all colorectal cancers and can be due to germline mutations in MMR genes (Lynch Syndrome) or epigenetic silencing of MLH1 by hypermethylation[1]. Tumours with dMMR are more likely to respond to immune checkpoint inhibitors and do not benefit from 5FU based chemotherapy [2,3]. Reflex testing for MMR protein expression by immunohistochemistry (IHC) on all colorectal cancers has now become standard in many cancer centres due to the associated increased pick up rate of Lynch syndrome and the treatment implications for patients. Reflex testing with MMR IHC on all colorectal carcinomas began in MMUH in November 2019 with follow up molecular tests ordered as per the algorithm in Figure 3.

Aims

To assess the rate of MMR testing and follow up testing, as indicated by the algorithm, in MMUH in 2020. Figures from 2019 were also collected to allow a comparison.

Standards

While no official standards exist, many national guidelines recommend performing MMR IHC on all new cases of colorectal carcinoma.

Methods

A search was performed on the laboratory information system for all colorectal adenocarcinoma cases in 2019 and 2020 using SNOMED codes. This list was evaluated and all new diagnoses were entered into a spreadsheet. Pathology reports were reviewed to determine if MMR IHC was performed. Where appropriate, reports were also reviewed to determine if other molecular tests were performed e.g. MSI PCR, BRAF, MLH1 hypermethylation.

Results

There were 106 cases of colorectal adenocarcinoma in 2020 of which 104 (98%) had MMR IHC performed. The two cases that were missed were subsequently tested and found to have a normal staining profile. For comparison, in 2019, there were 110 colorectal adenocarcinomas of which 76 (69%) had MMR testing performed.

Of the 106 cases in 2020, 15 (14.4%) were dMMR compared to 11/76 (14.5%) in 2019.

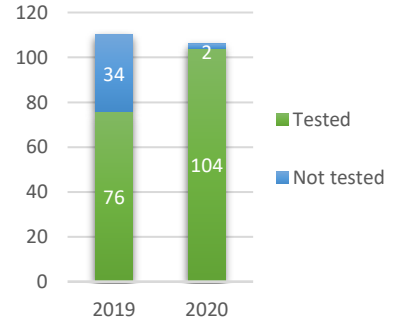
The breakdown of the 15 dMMR cases are as follows:

- 12 cases with PMS2 and MLH1 loss, all of which were due to MLH1 hypermethylation (8 with BRAF mutations and 4 BRAF wild type with MLH1 hypermethylation confirmed).
- Two cases with MSH2 and MSH6 loss (referred for germline testing)
- One case with solitary PMS2 loss (referred for germline testing)

Issues identified:

- BRAF mutation analysis had not been ordered on a case with PMS2 and MLH1 loss. This was ordered and showed a BRAF mutation favouring a sporadic tumour.
- MLH1 methylation testing had been performed on one case but the test result had not been entered onto the lab information system. This was updated during the audit.

Figure 1: Rates of MMR testing on colorectal carcinoma cases in 2019 and 2020



Results

Figure 2: Breakdown of MMR IHC results in 2020 cases

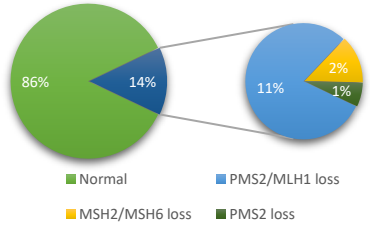
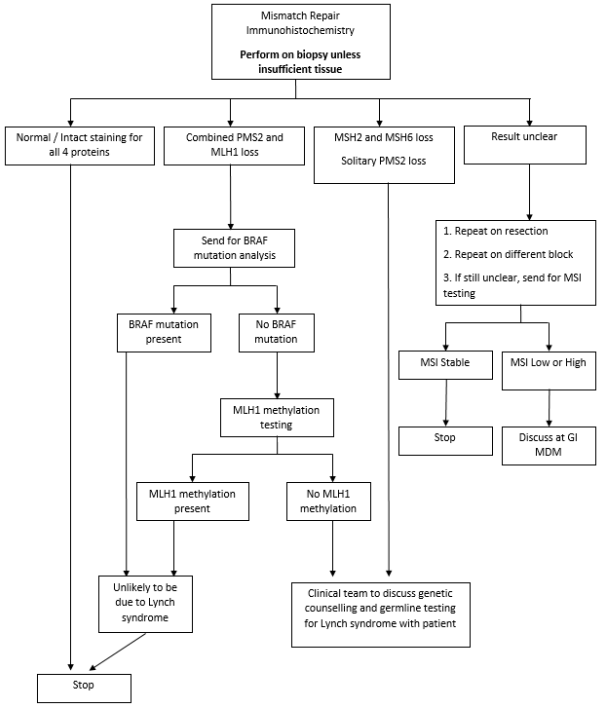


Figure 3: Algorithm for testing for dMMR and MSI-H



Conclusions

1.9% of cases of colorectal carcinoma in 2020 did not have reflex MMR testing, a marked improvement from 30.9% of cases in 2019. MMR testing was subsequently performed meaning that 100% of colorectal carcinoma specimens were tested for MMR IHC in 2020. The algorithm for molecular testing in dMMR patients was not followed in one case. This was subsequently performed and showed a BRAF mutation indicating a sporadic tumour. 3/106 (3%) patients were referred to the Family Screening Clinic for germline testing for Lynch syndrome based on their MMR IHC results.

Recommendations

1. Measures have been put in place in the laboratory to ensure that tests performed by external providers are followed up on.
2. BRAF testing will be performed in-house in 2021, reducing the potential for error.
3. Template reporting of MMR IHC will be introduced in 2021 to include the email address of the Family Screening Clinic to ensure patients are appropriately referred for assessment.

Re-audit

We will be repeating this audit on an annual basis to ensure that reflex testing is performed and algorithms are adhered to.

References

1. Ionov Y, Peinado MA, Malkhosyan S, Shibata D, Perucho M. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nature 1993; 363; 558–561.
2. Le DT, Durham JN, Smith KN et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017; 357; 409–413.
3. Sargent DJ, Marsoni S, Monges G et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J. Clin. Oncol. 2010; 28; 3219–3226.