p16 and BRAF Immunohistochemistry as a screening assay in MLH-1 deficient colorectal cancer

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Background: Hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome is the most common hereditary colorectal cancer, it is caused by germline mutation in DNA mismatch repair (MMR) genes (MLH-1, PMS-2, MSH2, and MSH6). Identification of the newly diagnosed HNPCC patients is important and cost-effective in the aspect of patient outcomes and public health. We designed this study to use p16 and BRAF immunohistochemistry (IHC) for screening sporadic MLH-1 deficient patients from the germline MLH-1 mutant patients. We also investigated the clinicopathological characteristics between deficient-MMR and proficient-MMR groups and their survival outcomes.

Method: The patient's FFPE tissue blocks with loss of MLH-1 were tested for p16 and BRAF immunohistochemistry. All patients were also tested for germline MLH-1 mutation. The correlation between IHC and mutation study was assessed later. The correlation between clinicopathological data, mismatch repair status and survival outcomes were analyzed.

Results: In 37 out of 196 colorectal cancer patients had deficient-MMR status and 22 from the 37 patients had loss of MLH-1 expression by IHC. We investigated 15 from the 22 patients whom tissue archives were available for screening by p16 and BRAF immunohistochemistry. Eight patients with positive IHC tests and 1 patient with negative IHC tests were analyzed for germline MLH-1 mutation. Only the patient with negative IHC testing consistently showed negative germline MLH-1 mutation testing. The p16 and BRAF IHC testing had sensitivity of 100%, with 50% specificity. The colorectal cancer staging is balanced between both deficient-MMR and proficient-MMR groups, but the survival is better in deficient-MMR group, consists with the previous studies.

Conclusions: In patient with MLH-1 loss, p16 and BRAF testing can correctly exclude sporadic deficient-MMR with 100% negative predictive value. This can expedite the initiation of new screening before germline MLH-1 mutation testing. Patients’ survival were longer in deficient-MMR patients compared with proficient-MMR patients. However, this is a small study and we believe that a larger trial is warranted to confirm the results.