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# Molecular profiling of colorectal cancer within South Africa

**McCabe, Michelle**

**2024**
https://hdl.handle.net/10539/37588

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Abstract:

There is a global requirement to characterize colorectal cancer (CRC) by molecular subtyping within subpopulations for the assignment of relevant therapies to improve prediction outcomes. Previous CRC studies conducted within South Africa (SA) have mainly been epidemiological, and subtyping limited to immunohistochemistry (IHC) protein expression analysis. The conclusions from these reports provided limited insight and lacked supportive molecular investigations in the development of CRC specifically within our population.

CRC develops through 3 main molecular pathways; i.e. (1) Chromosomal instability (CIN) (75-85%), (2) Microsatellite Instability (MSI) (~15%), and (3) CpG Island Methylator Phenotype (CIMP) (15-20%) pathway. This study descriptively analyses histopathological and molecular information of CRC patients in a 5-year study cohort (2011-2015), by assessing MSI status to ascertain unique features associated with different population groups, particularly within the African population. This study showed a large proportion (37%) of African CRC patients present with early disease onset (<50 years) in comparison to other ethnic group (OEG) patients (15%). Molecular characterization of CRC revealed MSI CRC within African patients occurred at an increased frequency compared to other ethnic groups (15% vs 8%), lacked a BRAFV600E mutation, and the dominant deficient (d) mismatch repair (MMR) profile was dMSH2 and dMSH6, suggesting hereditary Lynch Syndrome (LS) as the dominant pathway of disease development. These results are unique, as international findings demonstrate, 75% of MSI-CRC are sporadic, associated with dMLH1 and BRAFV00E mutations. OEG SA patients however were mostly associated with MLH1 and BRAFV600E mutations, and therefore follow the more well-established sporadic MSI pathway. Further insight gained through universal MSI screening was the ability to differentiate MSI-H versus MSS and MSI-L CRC. MSS/MSI-L CRC categorized by tumour site (left versus right) and ethnicity revealed unique histopathological features associated with left-sided CRC (LCC) in African patients compared to OEG patients. In addition,

a higher proportion of MSI-L LCC was seen in African patients associated with more advanced disease stage and unique molecular and histopathological features. These findings suggest MSI CRC found in African patients is predominantly of a hereditary form, and further variant screening analysis to determine causative germline pathogenic variants are required. MSS CRC particularly within the left colon, was associated with unique histopathological features in the African population group, suggesting an alternative carcinogenic pathway of development when compared to OEG patients. MSI-L CRC also illustrated unique features at this site in African patients, and suggest this to be a completely separate molecular subtype. Deeper molecular characterization by next generation sequencing, including somatic and germline cancer gene screening is required to provide more insight into the different molecular subtypes and pathways in the development of CRC within the SA. This research will therefore direct better clinical management strategies, improving diagnosis, genetic counselling and testing strategies, prognosis, treatment outcomes, survival, and the overall burden associated with the disease within SA.