EDITORIAL

Molecular Markers in Colorectal Carcinoma – Transforming Prognostication and Therapy in Malaysia.

Colorectal cancer (CRC) remains a formidable health challenge in Malaysia, contributing to 13.5% of all newly diagnosed cancers (2012-2026), ranking as the second most common malignancy. Alarmingly, survival outcomes remain poor, with a median survival of just 24 months and a 5-year survival rate of only 18.4% [1]. These sobering statistics underscore the urgent need for precision oncology strategies to improve patient outcomes. As a molecularly heterogeneous disease, CRC has distinct genetic and epigenetic alterations influencing tumour behaviour, treatment response, and prognosis. The advent of next-generation sequencing (NGS) and immunohistochemistry (IHC) has enabled the classification of CRC based on molecular subtypes, facilitating precision oncology. The evolution of molecular pathology classification systems from The Cancer Genome Atlas (TCGA, 2012), Consensus Molecular Subtypes (CMS, 2015), Colorectal Intrinsic Subtypes (CRIS, 2016), Single Cell Intrinsic CMS (iCMS, 2022) and to the latest Pathway Derived Subtypes (PDS, 2024) has revolutionised our understanding of CRC biology [2]. This editorial note discusses briefly a few molecular markers in CRC, their prognostic significance, and clinical implications for personalised therapy.

RAS/RAF Mutations (KRAS, NRAS, BRAF): KRAS and NRAS mutations are detected in 40-50% and 1.2-4.2% of CRC, respectively. Survival of KRAS and BRAF V600E mutation in the microsatellite stable (MSS) CRC, is better than in the microsatellite instability-high (MSI-H) CRC [3]. KRAS and NRAS mutations predict resistance to anti-epidermal growth factor receptor (anti-EGFR) therapy. Emerging data suggest that KRAS/BRAF wild-type MSS tumours may derive benefits from EGFR inhibition, reinforcing the need for routine molecular testing [4].

Microsatellite Instability-High (MSI-H)/Mismatch Repair Deficient (dMMR): MSI-H/dMMR tumours occur in ~15% of sporadic CRCs and exhibit a favourable prognosis in their early stages. MSI-H tumours display high tumour mutational burden, making them exquisitely sensitive to treatment with immune checkpoint inhibitors (pembrolizumab, nivolumab) [5]. Hence, MSI-H testing is important to identify patients for these immunotherapies, which will dramatically improve survival outcomes [4,5].

***TP 53* and Adenomatous Polyposis Coli (APC) Mutations:** *TP53* is mutated in 60% of CRC, with most being missense substitutions at position R175 or R273. *TP53* mutations correlate with aggressive tumour behaviour, metastasis, resistance to 5-fluorouracil, and dismal survival, underscoring their role as a poor prognostic marker [6]. APC mutations are seen in 70-80% of CRC, are early events in CRC, and drive the canonical (β-catenin-dependent) Wnt signaling pathway activation. Recent evidence suggests APC and *TP53* mutations help to predict cetuximab sensitivity, offering new avenues for personalized therapy and better patient outcomes [6].

Human Epidermal Growth Factor Receptor 2 (HER2) Amplification: CRC with HER2 amplification is seen in 3-5%, are associated with aggressive behaviour, brain metastasis and worse outcomes. Dual HER2 blockade (trastuzumab and pertuzumab) has

shown promise in metastatic HER2 CRC, mirroring advances in breast and gastric cancers [7].

While molecular diagnostics have transformed CRC management, several challenges persist in Malaysia, notably, limited access to NGS and biomarker testing in routine practice, and high costs of targeted therapies. To bridge these limitations, the molecular testing facilities in public hospitals should be expanded, and there should be integration of molecular biomarkers into the national CRC treatment protocols. Molecular stratification, guided by KRAS, BRAF, MSI, *TP53*, APC, and HER2 status, is essential for optimizing outcomes.

Keywords: *BRAF, Colorectal carcinoma, KRAS, MSI-H, Precision oncology.*

Editor-in-Chief:
Assoc Professor Dr Roswati Muhammad Noor
Faculty of Medicine, UniKL RCMP, Ipoh, Perak
Email: roswati@unikl.edu.my

References

[1]. Ministry of Health Malaysia. National strategic plan for colorectal cancer (NSPCRC) 2021 – 2025. (2021). pp. 1–68.

[2]. Dunne, P. D., & Arends, M. J. (2024). *Virchows Archiv*, *484*(2), 273-285. doi:https://doi.org/10.1007/s00428-024-03746-3

[3]. Taieb J, et al. Ann Oncol. 2023 Nov;34(11):1025-1034. doi: 10.1016/j.annonc.2023.08.006.

[4]. DeStefanis RA, et al Curr Colorectal Cancer Rep. 2019 Apr;15(2):61-69. doi: 10.1007/s11888-019-00430-6. Epub 2019 Mar 20.

[5]. Kang S, et al. Medicine (Baltimore). 2018 Mar;97(9):e0019. doi: 10.1097/MD.0000000000010019.

[6]. Thota R, et al. Cancers (Basel). 2021 Oct 27;13(21):5394. doi: 10.3390/cancers13215394.

[7]. artore-Bianchi A, et l. Lancet Oncol. 2016 Jun;17(6):738-746. doi: 10.1016/S1470-2045(16)00150-9. Epub 2016 Apr 20. Erratum in: Lancet Oncol. 2016 Oct;17(10):e420. doi: 10.1016/S1470-2045(16)30463-6.