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Comparative effectiveness and safety of first-line systemic anti-cancer treatments of metastatic colorectal cancer: a systematic review and meta-analysis.
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Abstract title: comparative effectiveness and safety of first-line systemic anti-cancer treatments of metastatic colorectal cancer: a systematic review and meta-analysis

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Background: metastatic colorectal cancer (mCRC) is characterised by multiple treatment strategies. Randomised clinical trials are not always aligned with the clinical practice, and greater use of real-world (RW) studies has been suggested to inform health care decisions by providing results that reflect RW practice. The purpose of this systematic review and meta-analysis was to provide a synthesis of the available RW evidence on the effectiveness and safety of first-line systemic anti-cancer therapies (SACTs) in patients with mCRC.

Methods: relevant databases were searched from inception until July 2021. Inclusion criteria were observational studies; published in English; patients ≥ 18 years; mCRC; first-line SACT for treatment of mCRC. No restrictions were placed on the country of publication. The effectiveness outcomes included overall survival (OS), the primary outcome, and progression-free survival (PFS). Safety was assessed by the occurrence of grade 3 or 4 adverse effects based on the national cancer institute common terminology criteria for adverse events (NCI CTCAE). The results were synthesised using a random-effect meta-analysis model based on Hazard ratio and 95% confidence interval (95% CI) for survival outcomes, while risk ratio and 95% CI was used for safety outcome. Subgroup analysis was performed to explore differences between different treatment strategies. Heterogeneity was assessed using I^2.

Results: The search strategy identified 5662 studies, of which 31 met the inclusion criteria and were included in the overall survival meta-analysis. The pooled hazard ratio for overall survival, including all SACTs, was 1.19 (1.1-1.29). The overall heterogeneity of included studies was 76.6%. Subgroup analysis identified a significant difference between different treatment comparisons (p =0.01). The pooled overall survival was significant for chemotherapy only versus Bevacizumab+ chemotherapy (pooled estimate: 1.15 (1.05-1.26).

For PFS, 20 studies were included in the meta-analysis. The pooled hazard ratio, including all SACTs, was 1.19 (1.08- 1.3), with an overall heterogeneity of the included studies was 64.4%. subgroup analysis showed a significant difference between different comparisons (p=0.001). the pooled PFS was significant for: (1) chemotherapy only versus bevacizumab+ chemotherapy (pooled estimate: 1.36 (1.05-1.26) and (2) bevacizumab+ irinotecan-based chemotherapy versus bevacizumab+ oxaliplatin-based chemotherapy (pooled estimate: 1.22 (1.07-1.38).

For the safety outcomes, 14 studies were included in the meta-analysis. The pooled relative risk of haematological and non-haematological toxicities was 1.25 (0.89-1.76) and 1.03 (0.73-1.46), respectively, with no statistically significant difference between different treatment strategies for the haematological toxicities (p > 0.05). However, the pooled estimate for non-haematological toxicities was significant for two subgroups (1) bevacizumab+ XELIRI versus bevacizumab+ FOLFIRI (pooled estimate 1.66 (1.03-2.7). and bevacizumab+ FOLFOXIRI versus bevacizumab+ XELOXIRI (pooled estimate: 3.5 (1.9-6.4).

Conclusion: The results indicated a survival benefit for bevacizumab with additional non-haematological toxicities for several combinations involving bevacizumab used in first-line settings of mCRC treatment. Although the survival benefit may appear clinically modest, bevacizumab offers hope for increased survival for patients with mCRC.