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GLP-1 Receptor Agonists and Colorectal Cancer Outcomes: A Multinational Cohort Study

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Abstract

Background

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with reduced cancer incidence in large observational studies, yet cancer-specific outcome data in patients with established colorectal cancer (CRC) remain sparse. Most prior analyses lack active comparator designs and conflate cancer prevention with post-diagnosis treatment effects. We compared CRC-related outcomes in patients receiving GLP-1RAs versus sodium-glucose cotransporter-2 inhibitors (SGLT2is) using a propensity score-matched, active-comparator, new-user design.

Methods

We conducted a retrospective cohort study using the TriNetX Research Network (113 US healthcare organizations). Adults aged 18 years or older with a diagnosis of colorectal malignancy (ICD-10-CM C18, C19, C20) who initiated a GLP-1RA (semaglutide, tirzepatide, liraglutide, dulaglutide, exenatide, or lixisenatide) or an SGLT2i (empagliflozin, dapagliflozin, canagliflozin, or ertugliflozin) before or within six months of first CRC diagnosis were included. Mutually exclusive medication exposure was enforced. Pre-specified 1:1 propensity score matching on demographics, comorbidity burden,

and medication class was performed. Outcomes included any metastatic progression, site-specific metastases (liver, peritoneal, pulmonary, bone, brain), cancer cachexia and weight loss, intestinal obstruction, venous thromboembolism (VTE), and all-cause mortality, evaluated over a 1,825-day follow-up window. Risk analysis, Kaplan-Meier survival analysis, and Cox proportional hazards regression were performed.

Results

After 1:1 propensity score matching, 4,503 patients per cohort were analyzed. Baseline characteristics were well-balanced across all covariates (all standardized differences <0.02). GLP-1RA users had a significantly lower risk of any metastatic progression (HR 0.867, 95% CI 0.775-0.970; $p=0.013$), liver metastasis (HR 0.784, 95% CI 0.662-0.928; $p=0.005$), peritoneal metastasis (HR 0.741, 95% CI 0.588-0.935; $p=0.011$), cancer cachexia and weight loss (HR 0.724, 95% CI 0.597-0.877; $p=0.001$), and all-cause mortality (HR 0.788, 95% CI 0.714-0.870; $p<0.001$) compared to SGLT2i users. No significant differences were observed for pulmonary, bone, or brain metastasis, intestinal obstruction, or VTE.

Conclusion

In a large, propensity score-matched, active-comparator cohort of CRC patients, GLP-1RA use was associated with lower risks of metastatic

progression, cancer-associated cachexia, and all-cause mortality compared to SGLT2i use. These findings extend the emerging biology of GLP-

1RA anticancer effects into the post-diagnosis setting and support prospective evaluation of GLP-1RAs as adjunctive therapy in CRC.

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