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Original Research

Clinicopathological differences and survival outcomes with first-line therapy in patients with left-sided colon cancer and rectal cancer: Pooled analysis of 2879 patients from AGITG (MAX), COIN, FOCUS2, OPUS, CRYSTAL and COIN-B trials in the ARCAD database☆

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Abstract ***Purpose:*** Patients with left-sided colon tumours have better survival and respond differently to biologics compared with patients with right-sided tumours. Left-sided colon tumours and rectal cancers are often grouped together. Herein, we examined the clinicopathological differences and outcomes between left-sided colon and rectal cancers.
Patients and methods: Data from 2879 metastatic colorectal cancer patients enrolled on six first-line clinical trials during 2004–2010 were pooled. Patients were included if the primary tumour origin was clearly defined. Progression-free survival (PFS) and overall survival (OS) were compared in the two groups after adjusting for patient and tumour characteristics, metastatic sites and the first-line regimen.
Results: In total, 1374 patients with metastatic left-sided colon cancer and 1505 patients with metastatic rectal cancers were evaluated. Left-sided colon cancer patients were more likely to be female (40.1% versus 32.6%; $P < 0.0001$) and older (31.0% $\geq$ 70 years versus 25.8%; $P = 0.0033$) compared with rectal cancers patients. Patients with left-sided colon cancer had higher rates of liver metastases (80.9% versus 72.3%, $P < 0.0001$) but lower rates of lung metastases (34.2% versus 53.8%, $P < 0.0001$). *KRAS* mutations were slightly less frequent among left-sided tumours (34.8% versus 40.5%; $P = 0.0103$). Patients with left-sided tumours had approximately similar PFS (median 7.4 versus 6.9 months; hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.87–1.03; $P = 0.1998$) and OS (median 17.4 versus 16.6 months; HR 0.99, 95% CI 0.91–1.07; $P = 0.7597$) compared with rectal cancer patients.
Conclusion: The site of tumour origin within the left side was not prognostic of outcomes. Moreover, neither bevacizumab nor cetuximab impacted, differently, the findings of the comparisons in outcomes between patients with left-sided colon tumours or rectal cancers.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death in the USA [1,2]. The standard first-line treatment for metastatic colorectal cancer (mCRC) is combination chemotherapy with an oxaliplatin- or irinotecan-based fluoropyrimidine-containing regimen, commonly combined with a biological agent—either the anti-vascular endothelial growth factor (VEGF) inhibitor bevacizumab, or, for patients with RAS wild-type tumours only, the anti-EGFR inhibitors cetuximab or panitumumab.

Until recently, bevacizumab and cetuximab were believed to have comparable efficacy when added to chemotherapy in the frontline treatment of RAS wild-type patients [3]. However, this belief has now changed in light of the retrospective analyses of the pivotal CALGB/SWOG 80405 and FIRE-3 studies [4,5]. The authors reported that in the first-line treatment of mCRC patients, the anatomic location of the primary tumour within the colon not only has an impact on patient survival but also on response to biological therapy: patients with right-sided primary tumours (from caecum to proximal transverse colon) have inferior overall survival (OS) and do not appear to benefit from first-line use of anti-epidermal growth factor receptor (EGFR) therapy as patients do with left-sided tumours (distal transverse to sigmoid colon and rectum) [4,5]. Similar results were seen in other studies including a meta-analysis of FIRE-3/AIO KRK0306, CALGB/SWOG 80405 and the PEAK study [5–8].

Hence, tumour location (right versus left) has emerged as an important prognostic and predictive factor in the treatment of mCRC, and shortly thereafter guidelines were updated to highlight the prognostic and predictive role of primary tumour location and to suggest that the site of tumour origin should be taken into account when selecting biological therapy in patients with RAS wild-type tumours [9,10].

In the context of the aforementioned sidedness analyses, patients with metastatic left-sided colon tumours (distal transverse to sigmoid colon) and rectal cancers have been grouped together as one entity.

However, clinical differences have been observed between patients with left-sided colon tumours and rectal