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Original Research

The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials

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Abstract ***Background:*** Retrospective subgroup analyses suggest that primary tumour location (PTL) has a prognostic importance and relates to response to targeted therapy.
Methods: We conducted a meta-analysis of first-line clinical trials available up to October 2016, which assessed the relevance of PTL in patients with metastatic colorectal cancer (mCRC). Right- and left-sided colorectal cancers were differentiated (RC and LC).
Results: In 13 first-line randomised controlled trials and one prospective pharmacogenetic study, RC was associated with a significantly worse prognosis compared with LC (hazard ratio [HR] for overall survival: 1.56; 95% confidence interval [CI]: 1.43–1.70; $P < 0.0001$). A meta-analysis of PRIME and CRYSTAL study suggests that PTL was predictive of survival benefit from addition of anti-EGFR antibody to standard chemotherapy in patients with RAS wild-type tumour (overall survival, HR for LC: 0.69; 95% CI: 0.58–0.83; $P < 0.0001$ and HR for RC: 0.96; 95% CI: 0.68–1.35; $P = 0.802$). A meta-analysis of FIRE-3/AIO KRK0306, CALGB/SWOG 80405 and PEAK study indicates that patients with RAS wild-type LC had a significantly greater survival benefit from anti-EGFR treatment compared with anti-VEGF treatment when added to standard chemotherapy (HR 0.71; 95% CI: 0.58–0.85;

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P = 0.0003). By contrast, in patients with RC, benefit from standard therapy was poor and bevacizumab-based treatment was numerically associated with longer survival (HR 1.3; 95% CI: 0.97–1.74; P = 0.081).
Conclusions: The present meta-analysis demonstrates that PTL is prognostic in mCRC. Further, it supports the conclusion that patients with left-sided RAS wild-type mCRC should be preferentially treated with an anti-EGFR antibody. In right-sided mCRC, chemotherapy plus bevacizumab is a treatment option, but optimal treatment has yet to be defined.

1. Background

Tumours arising from different regions of the colon are clinically and molecularly distinct [1–5]. Beside differences in the luminal content (e.g. bacterial flora), this might reflect also the ontogenesis with left-sided colon tumours (LC) deriving from the embryonic hindgut and right-sided colon tumours (RC) deriving from the embryonic midgut [6,7]. As the embryological demarcation line at the distal third of the colon transversum is difficult to determine in retrospective analyses, the splenic flexure was used for differentiation of LC and RC in most of the available clinical reports. Characteristics of LC and RC differ substantially in several aspects. RC is more often found in female patients, it is more frequently characterised by higher TNM stage at first diagnosis, by mucinous histology and greater immunogenicity. It more frequently shows microsatellite instability due to a genetic or epigenetic inactivation of DNA mismatch-repair enzymes. In addition, RC more often shows activating mutations of RAS, BRAF and PIK3CA genes. In contrast, LC is characterised by a more frequent occurrence of chromosomal instability and a gene expression profile corresponding to an activation of the epithelial growth factor receptor (EGFR) pathway [1,8,9].

The differing molecular characteristics translate into a differential clinical outcome with RC displaying a markedly worse prognosis [1,8,10–21]. Nevertheless, primary tumour location (PTL) has not been used as a stratification factor in clinical trials so far.

Besides its prognostic relevance, several retrospective analyses suggest that PTL may also be predictive of treatment benefit from targeted therapy with anti-EGFR and anti-VEGF directed agents [11,19,21–26]. However, differences in study results may be attributable to sample size, heterogeneity in treatment and limited information on molecular and pathological features [14–16,27]. On this basis, the present study performed a meta-analysis of prospective clinical trials. The aims were to evaluate the prognostic and predictive relevance for targeted therapy with anti-EGFR and anti-VEGF antibodies in patients with mCRC.

2. Material and methods

2.1. Search strategy and selection criteria

A PubMed-based search including the following search terms was conducted in October 2016: colon cancer, colorectal cancer, metastatic colorectal cancer, mCRC as well as primary tumour location, left-sided tumour, right-sided tumour, sidedness. Relevant MeSH terms (Medical Subject Headings) were used where possible. No restrictions were placed on the searches. The titles and abstracts of all remaining citations were reviewed and irrelevant citations were discarded. Potentially relevant studies were retrieved in full text and assessed. Hand searches of the reference lists of the relevant reports were carried out to identify any relevant studies that were missed with the search strategy. Further, major oncological conferences such as the American Society of Clinical Oncology, European Society for Medical Oncology and World Gastrointestinal Cancer Conferences were searched manually. If multiple reports referred to the same data, the report containing the most recent data was included into the analyses. From the results obtained, first-line randomised controlled trials (RCTs) and prospective clinical trials evaluating the relevance of PTL in mCRC were selected for a meta-analytic evaluation.

2.2. Objectives

The primary objective of the meta-analysis was to evaluate the impact of PTL on overall survival (OS) and progression-free survival (PFS) in relation to the applied treatment. Overall response rate (ORR) was considered where data were available.

2.3. Analyses

Time to event outcomes (OS and PFS) were reported using medians and HRs with corresponding 95% CIs and P-values where available. For ORR, medians and odds ratios (ORs) along with 95% CIs and P-values