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Review

Early tumour shrinkage as a prognostic factor and surrogate end-point in colorectal cancer: A systematic review and pooled-analysis

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Abstract ***Purpose:*** Early tumour shrinkage (ETS), defined as a reduction of at least 20% in tumour size at first reassessment, has been recently investigated retrospectively in first-line trials of metastatic colorectal cancer (CRC), and appears to be associated with better outcomes. We have performed a systematic review and meta-analysis of published trials to evaluate the prognostic value of ETS in CRC in terms of overall survival (OS) and progression-free survival (PFS).

Material and methods: An electronic search of the PubMed, SCOPUS, EMBASE, the Web of Science, and the Cochrane Central Register of Controlled Trial databases identified trials that compared outcomes of patients with or without ETS during first-line chemotherapy for metastatic CRC. The OS, reported as a hazard ratio (HR) with a 95% confidence interval (CI), was the primary outcome measure; the correlation coefficient (R) between ETS with median OS was also estimated.

Results: Twenty-one trials from 10 publications were analysed. Overall, patients with ETS were associated with a better OS (HR, 0.58; 95% CI, 0.53 to 0.64; $P < 0.00001$) and PFS (HR, 0.57; 95% CI, 0.47–0.69; $P < 0.00001$) compared with patients who were early non-responders. However, ETS was poorly correlated with OS in terms of surrogacy ($R = 0.37$; 95% CI - 0.31–0.78; $P = 0.28$).

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Conclusions: ETS is a good prognostic factor but an inappropriate surrogate for predicting outcome in CRC patients. These findings support ETS as prognostic tool in ascertaining earlier non-responders; however, its role as a surrogate end-point deserves further evaluation.

1. Introduction

The prognosis of metastatic colorectal cancer (CRC) has greatly improved by the addition of targeted agents to standard chemotherapy regimens. Currently, a median survival of over 30 months is achieved in clinical trials, especially in patients with *RAS* wild-type status, and who are potentially eligible for anti-epidermal growth factor receptor (*EGFR*) treatment [1]. Early prognostic factors and reproducible surrogate end-points are urgently needed for both clinical trial design, and eventually, selection of the treatment strategies. In fact, phase III trials rarely satisfy the primary end-point of overall survival (OS) because of the influence of post-progression survival, which may dilute the potential benefits of first-line therapy [2]. Consequently, intermediate (surrogate) end-points are necessary to verify the efficacy of experimental treatments, thus reducing costs, number of patients and time necessary for conducting trials and obtaining drug approval. In the interim, an early indicator of effectiveness (biochemical, morphological, or functional) could permit the rapid evaluation of treatment activity, driving the continuation of care, and might help to estimate prognosis based on the velocity or depth of tumour regression.

The disease control rate, represented by the sum of complete and partial response (RR) plus disease stability, or even a minimal shrinkage in tumour size represents a valid prognostic indicator in solid tumours treated with anti-angiogenic drugs. Early tumour shrinkage (ETS), defined as a 10–20% reduction in the sum of largest diameters of target lesions estimated during early radiological assessment (usually after 6–8 weeks from treatment initiation), appears to represent a strong prognostic factor in renal cell carcinoma and hepatocellular carcinoma [3–5].

In first-line trials carried out in CRC, the RR was not validated as an accurate surrogate of OS, as demonstrated by Tange et al. and Buyse et al. [6,7]. However, several retrospective analyses of randomised studies suggested that an ETS of at least 20% was associated with improved OS, independent of the treatment arm [8–10]. The present meta-analysis was aimed at evaluating the prognostic significance of ETS in metastatic CRC patients treated with first-line chemotherapy (with or without targeted agents) in clinical trials, and at determining whether ETS was a surrogate end-point for OS, towards evaluating its applicability in future trials.

2. Methods

2.1. Search strategy and selection criteria

We conducted an electronic search on studies evaluating the effect of ETS on patient survival. We searched PubMed, SCOPUS, The Cochrane Register of Controlled Trials, Web of Science, and EMBASE using the terms 'early tumour shrinkage' and 'colorectal cancer' (search details: 'Rectal Neoplasms' [Mesh] OR 'Colorectal Neoplasms' [Mesh] AND (early[All Fields] AND ('tumour' [All Fields] OR 'neoplasms' [MeSH Terms] OR 'neoplasms' [All Fields] OR 'tumour' [All Fields]) AND shrinkage[All Fields]) for articles published from inception to October 2014. We initially focused our search on the research title, followed by the abstract, and finally full texts were reviewed if they qualified as relevant reports. All the references within the review papers and original reports were checked for identifying additional relevant studies during the systematic review. Randomised or prospective studies evaluating the prognosis of CRC patients treated with first-line chemotherapy (with or without targeted agents) and obtaining an ETS after 6–8/9 weeks from treatment initiation were identified. Furthermore conference abstracts retrieved from SCOPUS, EMBASE and Web of Science were evaluated for inclusion criteria. For studies including an anti-*EGFR* therapy, only survival data of wild-type *(K)RAS* patients were considered, if available. Only articles published in the English language were retrieved. Studies were excluded if they did not contain an analysis of survival, were not first-line trials, lacked comparison between ETS, or lacked data on ETS. This study follows guidelines by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement.

2.2. Data extraction

Two independent reviewers (FP and FP) reviewed each publication for eligibility and extracted required data. For each study, data on the number of patients and study treatment in each arm, median OS, hazard ratio (HR) and median progression-free survival (PFS) for randomised controlled trials (RCTs), number of patients with and without ETS and study design were obtained, and a consensus was achieved on all items. Duplication of data was avoided by referencing the author's name and the name of the research centres.