



Review

Reporting of patient characteristics and stratification factors in phase 3 trials investigating first-line systemic treatment of metastatic colorectal cancer: A systematic review



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Abstract Background: Patient characteristics and stratification factors are important factors influencing trial outcomes. Uniform reporting on these parameters would facilitate cross-study comparisons and extrapolation of trial results to clinical practice. In 2007, standardisation on patient characteristics reporting and stratification in metastatic colorectal cancer (mCRC) trials was proposed. We investigated the reporting of prognostic factors and implementation of this proposal in mCRC trials published from 2005 to 2016.

Methods: We searched PubMed and Embase (January 2005 – June 2016) for first-line phase 3 mCRC trials. Patient characteristics reporting and use of stratification factors were extracted and analysed for adherence to the proposal from 2007.

Results: Sixty-seven trials (35,315 patients) were identified, reporting 48 different patient characteristics (median: 9 [range: 5–18] per study). Age, gender, performance status (PS), primary tumour site and adjuvant chemotherapy were frequently reported (87%–100%), in contrast to

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laboratory values, such as alkaline phosphatase, lactate dehydrogenase and white blood cell count (10%–25%). We identified 29 different stratification factors (median: 3 [range: 1–9] per study). The most common strata were PS and treatment centre (>60%). A median of 8/12 (range: 4–11) of the proposed parameters was reported. Although the percentage of studies reporting each factor slightly increased over time, there was no significant correlation between publication year and adherence to the proposal from 2007.

Conclusions: We observed persistent heterogeneity in the reporting of patient characteristics and use of stratification factors in first-line mCRC trials. The proposal from 2007 has not led to increased uniformity of patient characteristics reporting and use of stratification over time. There is an urgent need to address this issue to improve the interpretation of trial results. © 2018 Elsevier Ltd. All rights reserved.

1. Introduction

Randomised controlled trials are considered the gold standard for evaluating the efficacy of new treatment strategies. Patient characteristics are probably the most important factors determining trial outcomes, since many characteristics are of prognostic value. Randomisation of a sufficient number of patients increases the odds of balanced distribution of potential prognostic factors. In addition, stratification can be used to balance several key prognostic factors between treatment arms, which also reduces the risk of bias in pre-planned subgroup analysis. For statistical efficiency, the number of strata is usually kept to a minimum [1,2], which requires the challenging task of identifying a minimal set of clinically relevant variables to use as stratification factors. In many cases, prognostic factors have a stronger impact on survival than any available treatment regimen. Therefore, uniform trial reporting of patient characteristics and use of stratification factors is essential to enable a valid comparison of treatment arms, to facilitate cross-study comparisons and to evaluate whether study populations are representative of the general patient population.

Sørbye *et al.* [3] observed considerable heterogeneity in the reporting of patient characteristics and use of stratification factors in metastatic colorectal cancer (mCRC) trials published between 2001 and 2005, indicating a lack of consensus on the importance and use of prognostic factors. The authors found that only gender, age, performance status (PS), prior adjuvant therapy, site and location of metastases were frequently reported in the trials. Other prognostic factors were often missing, particularly laboratory values. The authors proposed a standardisation of patient characteristics reporting and stratification factors (Table 1). The adoption of these recommendations in mCRC trials published in more recent years has not been evaluated.

The aims of this systematic review are (1) to provide an overview of the reporting of patient characteristics and stratification factors in phase 3 mCRC trials of first-line systemic treatment published between 2005 and 2016; (2) to analyse whether standardisation of reporting of patient characteristics and stratification factors as

proposed by Sørbye *et al.* [3] has been used in trials published since 2009; and (3) to investigate the reporting of other prognostic factors that may have become relevant in the light of new treatment strategies.

2. Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [4].

2.1. Search strategy

We performed a systematic literature search in PubMed and Embase on June 6, 2016 to identify mCRC studies published in English between January 2005 and June 2016. The search strategy included ‘metastasis’, ‘colorectal’, ‘cancer’ and ‘phase 3 trial’ as keywords

Table 1
Suggested patient characteristics and stratification factors in studies of medical treatment of metastatic colorectal cancer [3].

Patient characteristics	
Age	Median
Gender	
Performance status (PS)	ECOG or WHO. PS 0, 1 and 2
Site of primary tumour	Colon versus rectum
Surgery of primary tumour	
Prior adjuvant chemotherapy	
Prior radiotherapy	
Metastatic sites	1 versus > 1
Location of metastases	Liver versus other
Lactate dehydrogenase (LDH)	>UNL or 1.5 UNL
Alkaline phosphatase (ALP)	>UNL
White blood cell count	>10 × 10 ⁹ /l
Stratification factors	
Centre	
PS	
Laboratory value	ALP or LDH
Number of metastatic sites	1 versus > 1
<i>For later line trials</i>	
Prior chemotherapy or targeted therapy	
Feasibility of metastasectomy after systemic treatment	If applicable

ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; UNL, upper normal limit.

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