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Does a patient's self-reported health-related quality of life predict survival beyond key biomedical data in advanced colorectal cancer?

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ABSTRACT

The purpose of this study was to determine whether baseline patients' self reported health-related quality of life (HRQOL) parameters could predict survival beyond key biomedical prognostic factors in patients with metastatic colorectal cancer. The analysis was conducted on 299 patients. HRQOL baseline scores were assessed using the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core30 (EORTC QLQ-C30). The Cox proportional hazards regression model was used for both univariate and multivariate analyses of survival. In addition, a bootstrap resampling technique was used to assess the stability of the outcomes.

The final multivariate Cox regression model retained four variables as independent prognostic factors for survival: white blood cell (WBC) count with a hazard ratio (HR) of 1.961 (95% CI, 1.439–2.672; $P < 0.001$), alkaline phosphatase with HR = 1.509 (95% CI, 1.126–2.022; $P = 0.005$), number of sites involved with HR = 1.108 (95% CI, 1.024–1.198; $P = 0.01$) and the patient's score on the social functioning scale with HR = 0.991 (95% CI, 0.987–0.996; $P < 0.001$) which translates into a 9% decrease in the patient's hazard of death for any 10 point increase. The independent prognostic importance of social functioning and the stability of the final Cox regression model were also confirmed by the additional bootstrap model averaging analysis, based on 1000 bootstrap-generated samples. The results suggest that social functioning, acts as a prognostic measure of survival beyond a number of previously known biomedical parameters.

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1. Introduction

Colorectal cancer ranks second in terms of both incidence and mortality in more developed countries. Over 940,000 new colorectal cancer cases are diagnosed worldwide each year, which accounts for some 492,000 deaths [1]. Despite some advances made in the treatment of colorectal cancer, more than half of colorectal cancer patients die from metastatic disease [2].

Several studies have identified prognostic factors for survival in colorectal cancer. Recently, a large pivotal multivariate analysis of 3825 metastatic colorectal cancer patients, identified four key biomedical parameters: performance status, white blood cell (WBC) count, alkaline phosphatase and the number of involved metastatic sites [3]. The identification of independent prognostic factors could have important implications for routine clinical practice and research for many reasons, including a helpful guide in treatment decision making. In advanced-disease settings, this information could also assist clinicians to recalibrate clinical prediction of survival and optimize the use of palliative care [4]. From a clinical research perspective, the identification of prognostic factors for survival could better help stratify patients into randomized clinical trials and aid the interpretation of results in a more transparent way.

The general literature on this topic has traditionally investigated biomedical variables. However, a growing number of studies have also focused on investigating the prognostic value of patient self reported health-related quality of life (HRQOL) parameters. Over the last few years, methodologically robust studies have shown that HRQOL parameters predict length of survival beyond important traditional clinical variables. This evidence has been reproduced in various advanced cancer populations, including breast [5], lung [6], melanoma [7], prostate [8], and gastric cancer [9].

In light of this recent literature, the objective of this research was to evaluate if baseline HRQOL parameters could predict overall survival beyond a number of previously known key biomedical prognostic variables, in metastatic colorectal cancer patients. Very few studies have been conducted to investigate the value of HRQOL as a prognostic factor in colorectal cancer; available results are limited by small sample sizes or inadequate statistical control of known biomedical prognostic factors [10,11]. Furthermore, because of possible harmful multicollinearity, which may occur when including HRQOL variables for prognostic factor analysis, it might become difficult to disentangle its influence and thus obtain a reasonably precise estimate of the separate effects of the single predictor variables [12]. This is the first large international study investigating the prognostic value of HRQOL parameters in metastatic colorectal cancer, which also takes into account such problems as possible model selection instability.

2. Patients and methods

2.1. Study design

This work is based on data from a prospective multicenter randomized controlled trial (RCT) in advanced colorectal cancer patients, conducted by the European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal Group (EORTC Study 40952). Fifty-nine institutions participated, enrolling patients from seven countries. The primary endpoint of the trial was overall survival (OS), with HRQOL included as a secondary endpoint. In total, 497 patients with previously untreated metastatic colorectal cancer were randomly allocated into three arms: those receiving bolus fluorouracil (FU) 425 mg/m^2 intravenously + leucovorin (LV) 20 mg/m^2 on days 1–5 and repeated on day 28 (FU + LV), or FU 2600 mg/m^2 as 24-h infusion alone (FU_{24h}), or in combination with 500 mg/m^2 LV (FU_{24h} + LV) – all given weekly 6× followed by a 2-week rest period. After a median follow-up of more than three years, survival did not significantly differ between treatment groups (median FU + LV, 11.1 months; FU_{24h}, 13.0 months and FU_{24h} + LV, 13.7 months; $P = 0.72$). Full details of treatment schedule and treatment-related clinical outcomes have been previously reported [13].

2.2. Patients

To be eligible for inclusion in the trial, patients had to be diagnosed with adenocarcinoma of the colon or rectum, beyond a curative option by surgery. Patients were required to have a performance status of 2 or less, no previous chemotherapy for metastatic disease (with the exception of previous adjuvant treatment if it was completed at least 6 months before inclusion). Eligible patients were randomly assigned centrally after stratification for the following factors: institution, World Health Organization (WHO) performance status (0, 1 vs. 2), tumour assessability (measurable vs. nonmeasurable) and prior adjuvant pre-treatment (yes vs. no). The study, approved by the EORTC protocol review committee and the ethics committee of each participating center, was conducted in compliance with the Helsinki declaration. All patients provided written informed consent. Plausibility of the data was checked for all centers by the study coordinators.

2.3. HRQOL baseline assessment and variables examined

Baseline HRQOL was measured using the EORTC Quality of Life Questionnaire-Core 30 (version 2.0) (EORTC QLQ-C30), an internationally validated HRQOL questionnaire suitable for use with a generic cancer population. It is available in several languages and has proven robust psychometric properties [14]. Assessments were performed at baseline considering a time window of 15 days before or after randomization, but in any case before treatment start. To maximize compliance and minimize error variance, due to uncontrolled differences in the timing or other external aspects of the assessments, HRQOL data collection was an integral part of the clinical trial [15]. Wherever possible, the questionnaires were administered at the clinic, in a room where the patient would not be disturbed. EORTC guidelines for administering questionnaires were provided, ensuring a standard approach to the collection of HRQOL data. The EORTC QLQ-C30 scores were calculated using the recommended EORTC procedures [16]. These involved transformation of raw scores into a linear scale ranging from 0 to 100. In the case of missing items within a scale, the scale score was calculated using only those for