European Journal of Cancer 101 (2018) 105–113

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Impact of primary tumour location and RAS/BRAF mutational status in metastatic colorectal cancer treated with first-line regimens containing oxaliplatin and bevacizumab: Prognostic factors from the AIO KRK0207 first-line and maintenance therapy trial

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Received 12 February 2018; received in revised form 12 June 2018; accepted 14 June 2018

KEYWORDS
Colorectal cancer;
Prognostic factors;
Primary tumour

Abstract ***Background:*** The major prognostic relevance of primary tumour location (LPT) in advanced colorectal cancer was shown in large retrospective studies, but quantitative estimates are highly heterogeneous, and there is still limited information about its impact within the framework of biomarker-guided treatment strategies. Therefore, we analysed LPT in relation

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https://doi.org/10.1016/j.ejca.2018.06.015

location;
RAS mutation;
BRAF mutation;
Bevacizumab;
Overall survival;
First-line therapy

to other clinical and molecular parameters, based on mature survival data from the recent randomised AIO KRK0207 trial.

Methods: Patients uniformly received first-line induction treatment with a combination of bevacizumab, oxaliplatin and fluoropyrimidine. LPT was retrospectively determined using surgical reports, pathology reports and endoscopy reports. The prognostic analyses were performed using Kaplan–Meier estimations and log-rank tests, while hazard ratios (HRs) and multivariable results were derived from Cox models.

Results: Among 754 patients with unequivocal information on LPT, patients with left-sided tumours showed a median overall survival of 24.8 months compared with the right-sided cohort with 18.4 months (HR: 1.54, 95% confidence interval: 1.30–1.81, $P < 0.0001$). In a multivariable model, LPT proved to be the strongest prognosticator (HR 1.60), with performance status, number of metastatic sites, baseline carcinoembryonic antigen (CEA) and platelets independently retaining prognostic significance. In the subgroup of patients with known RAS/BRAF status (n = 567, 75%), a BRAF mutation showed the greatest unfavourable impact (HR 3.16). Although BRAF is strongly correlated to LPT, the latter remained a significant prognosticator in the BRAF wild-type subgroup. In contrast, no major impact of LPT was seen on tumours carrying RAS mutations.

Conclusions: Within the framework of a uniform treatment strategy according to the current standards, LPT proved to have an important, although not solely dominating, relevance for survival prognosis. Its impact seems to be low in tumours with a RAS mutation.

Registration: ClinicalTrials.gov NCT00973609.

1. Introduction

Colorectal cancer (CRC) ranks among the most frequent types of malignant neoplasms in both sexes and accounts for a high proportion of cancer mortality worldwide [1]. Therefore, numerous study cohorts and retrospective series have been analysed to predict the survival probability based on the characteristics of the patient and his/her cancer. In the prebiomarker era, this resulted in the development of prognostic scores for stage IV patients, such as those of Köhne [2] or GERCOR [3], established in the first decade of the 21st century. However, owing to the improvement of the diagnostic and therapeutic armamentarium in the recent decades, the overall survival (OS) times after the detection of distant metastases showed a distinct increase, from a median of about 1 year in the 5-fluorouracil (5-FU) era to about 30 months nowadays [4].

As a consequence, the relative prognostic impact of various patient and tumour characteristics may also have changed over time. The era of exploding development of knowledge and procedures on the molecular and cellular level resulted in a waterfall of biomarker information of potential prognostic and predictive relevance. Nevertheless, up to now, few molecular biomarkers could be shown to have major prognostic impact [5]. On the other hand, surprisingly, the importance of a relatively 'trivial', easy-to-collect dichotomous information, readily available in all patients after initial staging, had been missed in the established prognostic profiling systems mentioned previously. Only since the beginning of this decade, the location of the primary tumour (LPT) on the right or left side of the colorectal anatomy was recognised as of utmost importance.

A recently published large meta-analysis on tumour sidedness and prognosis, based predominantly on retrospective series [6], showed a statistically convincing result on the bottom line, but an extreme level of effect heterogeneity between the individual studies. This remained largely unexplained by the authors despite subgrouping and meta-regression procedures, focussing on race, stage, pretreatment, study design and sample size or decade of diagnosis. Further meta-analyses have focussed on RAS wild-type patients [7,8] and on the efficacy of adding bevacizumab to first-line chemotherapy in relation to tumour sidedness [5]. Data on patients treated with first-line oxaliplatin plus fluoropyrimidine (FP), with RAS and BRAF status available but including also patients carrying the respective mutations, are rare. Although sidedness data are available from the NO16966 trial, one has to keep in mind that this trial was recruiting more than a decade ago when RAS mutational analysis was not yet available. Therefore, further prognostic profile analyses of data from large controlled trials including well-characterised patients treated according to the current standards are warranted.

As previously published [9], the main objective of AIO KRK0207 was the randomised comparison of three different maintenance strategies in patients having achieved at least a stabilisation of metastatic disease after induction chemotherapy: either no continuation of