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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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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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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

therapy or bevacizumab alone or any FP plus bevacizumab. With respect to OS, the results were comparable in the three arms. However, all patients were enrolled and adequately documented after the initial diagnosis of dissemination and uniformly received 24 weeks of a combination therapy including FP, oxaliplatin and bevacizumab. Thus, our data allowed for the prognostic analysis of OS in a representative population of patients with metastatic CRC without any biomarker-based selection, receiving a three-drug combination corresponding to the present guidelines, including a vascular endothelial growth factor (VEGF)–targeted component. Because this is a major difference to the majority of recently published analyses of randomised trials on the impact of LPT, focussing on the RAS wild-type subpopulation only [8,10,11], detailed prognostic factor analyses of our study population should give rise to further important insights.

2. Material and methods

2.1. Study design and participants

AIO KRK0207 was an open-label, randomised multicentred phase 3 trial. Study design, eligibility criteria, ethical approvals, informed consent, treatment regimens and additional information on diagnostic, therapeutic and follow-up procedures as well as the primary outcome of the trial, comparing the different maintenance strategies, were reported elsewhere [9].

Eligible patients were registered for the trial before starting an induction regimen consisting of any FP (infusional or capecitabine), oxaliplatin and bevacizumab, eventually followed by randomised maintenance and reinduction strategies of differing intensity. OS data were updated by December 2016, extending the data lock of the initial publication (December 2014). Except for LPT, all data were retrieved from the main trial database of KRK0207 [9].

2.2. Categorisation of the primary tumour localisation/ biomarker data

LPT was retrospectively determined using reports on surgery, pathology and endoscopy. Right-sided primary tumours were defined as located in the caecum, ascending colon and transverse colon up to the splenic flexure. Left colon was defined as splenic flexure, descending and sigmoid colon and rectum, in accordance with recent publications [10,11]. Patients with synchronous tumours located in the left and right colon or patients in whom primary tumour location could not be determined were scored as undetermined or missing. Although not required by the initial protocol, tumour samples were retrieved for central examination of the RAS and BRAF status (Institute of Pathology, Ruhr-University Bochum, Germany), whenever possible. Formalin-fixed paraffin-embedded tissue was microdissected and cut. DNA was extracted using the DNA Purification Kit (Promega; Madison). Mutational analysis was performed stepwise using the pyrosequencing technique (Q24, Qiagen, Hilden). In the first step, the mutational status of the codon 12 and 13 of the KRAS gene was determined. In the second step, the mutational status of codons 59, 61, 117 and 146 and the mutation hotspots of the NRAS gene in exons 2–4 were analysed (p.G12, p.G13, p.A59, p.Q61, p.K117 and p.A146).

2.3. Statistical aspects

All analyses, including the resulting *P*-values, are of exploratory nature and hypothesis generating. Therefore, adjustments for multiple testing were neither preplanned nor performed. Nevertheless, within the scope of this analysis, the term 'significant' is used in case of $P < 0.05$.

OS was calculated from the study recruitment (or date of randomisation in the analyses of the maintenance subpopulation) to death or censored at the time point of the last valid observation without the respective event. Survival curves and medians were estimated according to Kaplan–Meier. Univariable analyses were performed using the log-rank test. The Cox proportional hazard model [12] was applied for multivariable analysis, based on the patients with a complete set of covariates, with *P*-values derived from Wald tests and initially including all covariates with a prospectively defined univariable P level < 0.1. Subsequently, the model was reduced by stepwise exclusion of the covariate with the highest *P*-value, until only factors with $P \leq 0.1$ remained. All hazard ratios (HRs) and confidence intervals (CIs) reported are derived from Cox models. All presented *P*-values are two sided.

3. Results

3.1. Correlation of location of the primary tumour with other baseline characteristics

In 754 of 825 enrolled patients, LPT could be unequivocally allocated to the left (n = 525, 70%) or right side (n = 229, 30%). The distribution of major baseline characteristics of potential prognostic relevance in the subgroups according to anatomic side is displayed in Table 1. LPT was more often on the right in women. An impaired performance status and synchronous distant metastases, usually determining a higher risk, showed a discernable, albeit only weak to moderate, association with LPT on the right. On the other hand, high carcinoembryonic antigen (CEA) values were more often found in patients with tumours on the left. The most distinct correlation was detected in the molecular level,

Table 1
Correlation of location of the primary tumour with other baseline characteristics.

Characteristic	Left side (n = 525)	Right side (n = 229)	Side undefined, unknown (n = 71)	Total (n/%)	p[a]
Age (years)					
Mean ± SD	63.4 ± 10.1	64.2 ± 10.5	64 ± 9.9	63.7 ± 10.2	
Median	65	66	67	65	
Range	32–82	23–83	43–81	23–83	
≤70 years	364 (69%)	147 (64%)	45 (63%)	556 (67%)	
>70 years	161 (31%)	82 (36%)	26 (37%)	269 (33%)	0.18
Sex					
Male	353 (67%)	129 (56%)	47 (66%)	529 (64%)	
Female	172 (33%)	100 (44%)	24 (34%)	296 (36%)	0.0050
Performance status (n = 796)					
ECOG 0	301 (59%)	108 (49%)	39 (57%)	448 (56%)	
ECOG 1–2	207 (41%)	111 (51%)	30 (43%)	348 (44%)	0.015
Time of metastasis					
Synchronous	418 (80%)	199 (87%)	59 (83%)	676 (82%)	
Metachronous	107 (20%)	30 (13%)	12 (17%)	149 (18%)	0.018
Adjuvant chemotherapy					
No	448 (85%)	213 (93%)	65 (92%)	726 (88%)	
Yes	77 (15%)	16 (7%)	6 (8%)	99 (12%)	0.0036
No. of metastatic sites (n = 819)					
1	223 (43%)	107 (47%)	27 (39%)	357 (44%)	
>1	300 (57%)	120 (53%)	42 (61%)	462 (56%)	0.26
CEA at baseline (n = 737)					
≤20 ng/ml	156 (33%)	85 (41%)	16 (28%)	257 (35%)	
>20 ng/ml	315 (67%)	123 (59%)	42 (72%)	480 (65%)	0.056
Platelets at baseline (n = 815)					
≤ULN	376 (72%)	159 (71%)	46 (65%)	581 (71%)	
>ULN	143 (28%)	66 (29%)	25 (35%)	234 (29%)	0.66
RAS/BRAF status (n = 567)					
Wild type	175 (46%)	34 (22%)	12 (39%)	221 (39%)	
RAS mutation	191 (51%)	85 (54%)	17 (55%)	293 (52%)	0.51
BRAF mutation	12 (3%)	39 (25%)	2 (6%)	53 (9%)	<0.0001
RAS or BRAF mutation	203 (54%)	124 (78%)	19 (61%)	346 (61%)	<0.0001

ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of the site-specific normal range; CEA, carcinoembryonic antigen.
[a] Fisher's exact test for association with the left or right side; patients with undefined/unknown side were excluded.

with BRAF mutations being a rare finding in left-sided tumours. In contrast, RAS mutations of any subtype were equally common in both cohorts.

3.2. Univariable prognostic analyses on OS

With a maximum follow-up duration of more than 80 months and the death event recorded in 702/825 patients (85%), the mature data on OS from recruitment, in the total evaluable study population, showed a median of 21.5 months. As to be expected, the 472 patients qualifying for randomisation lived distinctly longer with a median of 26.8 months compared with a median of 13.2 months in the remaining 353 patients not randomised to maintenance strategy, for various reasons.

Among 754 patients with unequivocal information on LPT, patients with left-sided tumours showed a median OS of 24.8 months compared with the right-sided cohort with 18.4 months. The corresponding univariable HR was 1.54 (95% CI: 1.30–1.81, $P < 0.0001$; Fig. 1A). This and other variables with a statistically significant prognostic impact are shown in Table 2. Neither age cohorts nor previous adjuvant chemotherapy were of prognostic relevance. In the subcohort of 576 patients (70%) with information on the RAS/BRAF(V600E) mutational status available from centralised reference pathology, both mutation of RAS (any location) and, outstandingly, of BRAF proved to be associated with poor prognosis (Table 2; Fig. 1B).

3.3. Multivariable prognostic analyses on OS

In the Cox model including all univariably significant parameters (excluding molecular markers because of the relatively high proportion of missing information), female sex and synchronous metastasis did not exhibit independent prognostic relevance (Table 2). However, the other five parameters, that is, performance status, number of metastatic sites, LPT, CEA and platelets at baseline, retained their impact on mortality risk. Location of the primary tumour seems to be the factor of utmost importance; however, the resulting impact sizes, that is, HRs, all fell within a rather narrow range from 1.32 to 1.60.

This result of rather comparable, independent importance suggested to allocate risk points, one to each

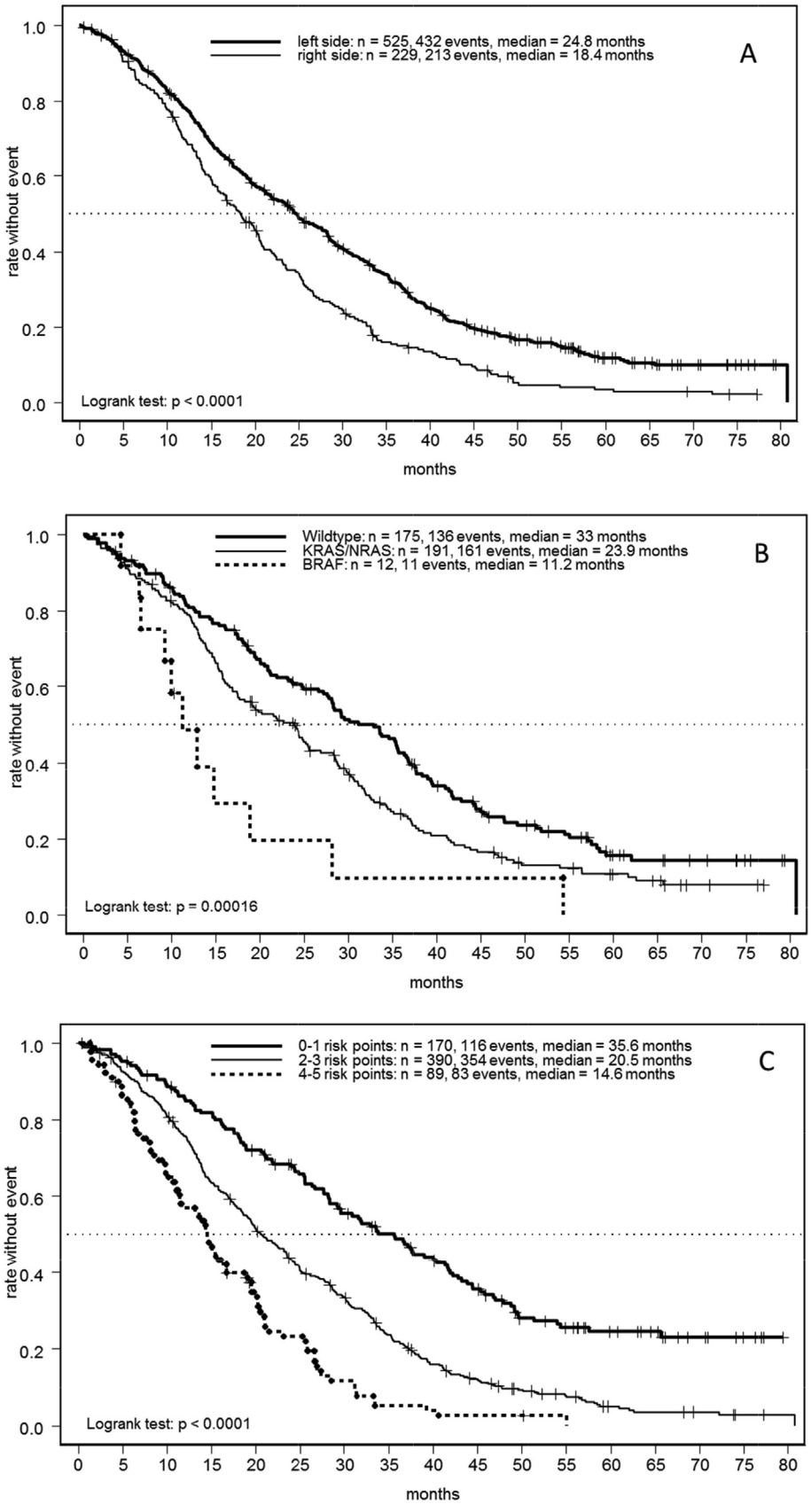

Fig. 1. Kaplan–Meier estimation of overall survival (A) by location of the primary tumour (left versus right), (B) by any RAS mutation, BRAF (V 600E) mutation and wild-type tumours and (C) by prognostic score group.

Table 2
Analysis of prognostic factors for overall survival from recruitment for first-line therapy.

Prognostic factor (first group mentioned is reference for HR)	Univariable[a] median; months (95% CI), *P*	Multivariable, full model (n = 649); HR (95% CI), *P*	Multivariable, reduced model (n = 649); HR (95% CI), *P*
Sex: male versus female	23.2 (20.7–25.1) versus 19.5 (17.4–23.2), $P = 0.030$	1.02 (0.86–1.22), $P = 0.81$	–
ECOG performance: 0–1 versus 2-4	25.6 (24.2–28.4) versus 17.0 (15.1–19.8), $P < 0.0001$	1.48 (1.25–1.76), $P < 0.0001$	1.49 (1.25–1.77) $P < 0.0001$
Time of metastasis: synchronous versus metachronous	20.5 (18.8–22.4) versus 28.5 (24.4–33.6), $P = 0.0015$	0.89 (0.71–1.12), $P = 0.33$	–
Number of metastatic sites: 1 versus > 1	24.6 (21.3–28.2) versus 19.8 (18.4–22.6), $P = 0.00014$	1.42 (1.19–1.69), $P < 0.0001$	1.42 (1.19–1.69), $P < 0.0001$
CEA at baseline: ≤ 20 ng/mL versus > 20 ng/mL	28.2 (23.9–32.8) versus 19.5 (17.2–21.0), $P < 0.0001$	1.53 (1.27–1.84), $P < 0.0001$	1.55 (1.29–1.86), $P < 0.0001$
Platelets at baseline: ≤ ULN versus > ULN	23.9 (21.8–26.4) versus 18.1 (15.7–20.0), $P < 0.0001$	1.29 (1.06–1.57), $P = 0.012$	1.32 (1.10–1.60), $P = 0.0036$
Primary tumour location: left versus right	24.8 (21.9–28.2) versus 18.4 (15.8–20.5), $P < 0.0001$	1.58 (1.32–1.90), $P < 0.0001$	1.60 (1.33 – 1.92), $P < 0.0001$
Mutational status: all wild type versus RAS versus BRAF	33.0 (27.9–36.6) versus 23.9 (17.7–28.4) versus 11.2 (9.3- undefined), $P < 0.0001$	–	–

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval; ULN, upper limit of the site-specific normal range; –, not included in model.
[a] Only variables with $P < 0.1$ were presented (see text). The number of patients varies between 825 and 576 (molecular markers) due to missing values in some parameters.

of the factors, adding up to a scale ranging from zero to five. Fig. 1C shows the clear-cut OS distinction between patients with 0–1, 2–3 or 4–5 risk points ($P < 0.0001$).

The negative impact on survival of any RAS or BRAF mutation in the overall population was highly significant (HR = 1.49, 95% CI: 1.24–1.80, $P < 0.0001$). If patients with a BRAF mutation were excluded from the analysis, any RAS mutation showed a lesser impact, albeit still significant (HR = 1.35, 95% CI: 1.11–1.64; $P = 0.0022$). This was similarly detected in the subgroup of left-sided tumours (Fig. 2A), with an HR of 1.42 for all wild-type versus any RAS mutation (95% CI: 1.13–1.79; $P = 0.0026$). Remarkably, this trend could not be shown, or is numerically even reversed, in right-sided tumours (Fig. 2B; HR = 0.89, 95% CI: 0.58–1.35; $P = 0.57$). The other way round, patients with an all–wild-type tumour exhibited a strong prognostic impact of LPT (HR = 1.83, 95% CI: 1.23–2.72), while in tumours with a RAS mutation, no impact of LPT could be confirmed (HR = 1.09, 95% CI: 0.83–1.43).

In a Cox model of 465 patients with all the respective covariates available, including the five independent parameters described in Table 2, the additionally incorporated term of any RAS/BRAF mutation showed an HR of 1.32 (95% CI: 1.06–1.63), with all of the other five covariates remaining significant (Supplementary Table S1, available at the *European Journal of Cancer* [*EJC*] online). However, if RAS and BRAF mutations were addressed as separate factors, the latter had the by far strongest unfavourable impact (HR = 3.16, 95% CI: 2.17–4.60; $P < 0.0001$), while the former did not retain statistical significance (HR = 1.22, 95% CI: 0.98–1.52; $P = 0.080$).

As tumour sidedness and BRAF mutational status are strongly correlated (Table 1), we multivariably addressed the relevance of the anatomical site in patients with BRAF wild-type tumours only: right-sided location remained an indicator of poor prognosis even in this subpopulation (HR = 1.40, 95% CI: 1.09–1.79; $P = 0.0084$), with all the other four factors identified above similarly retaining their significance (Supplementary Table S2, available at the *EJC* online).

4. Discussion

There is a growing consensus that primary tumour location is an important factor for the general prognosis of a patient and is also contributing to the guidance of targeted therapy. However, LPT only presents a surrogate marker for complex, and still heterogeneous, molecular patterns associated predominantly with the respective location, with details not yet fully understood [13,14]. The rate of 30% of right-sided tumours detected in our study corresponds well to the findings in other large studies focussing on patients selected for VEGF- or epidermal growth factor receptor (EGFR)–targeted combinations [5,7]. In an exclusively RAS wild-type population, the proportion seems to be somewhat lower, that is, about 24% [8].

The prognostic impact of LPT seems to be rather independent of, or not fully captured by, other conventional or molecular variables. Although shown qualitatively in most series, its quantitative effect size is subject to a huge amount of heterogeneity, as has become evident in recent reviews [15] and meta-analyses [6,7]. Beyond the biomarker-driven selection of data

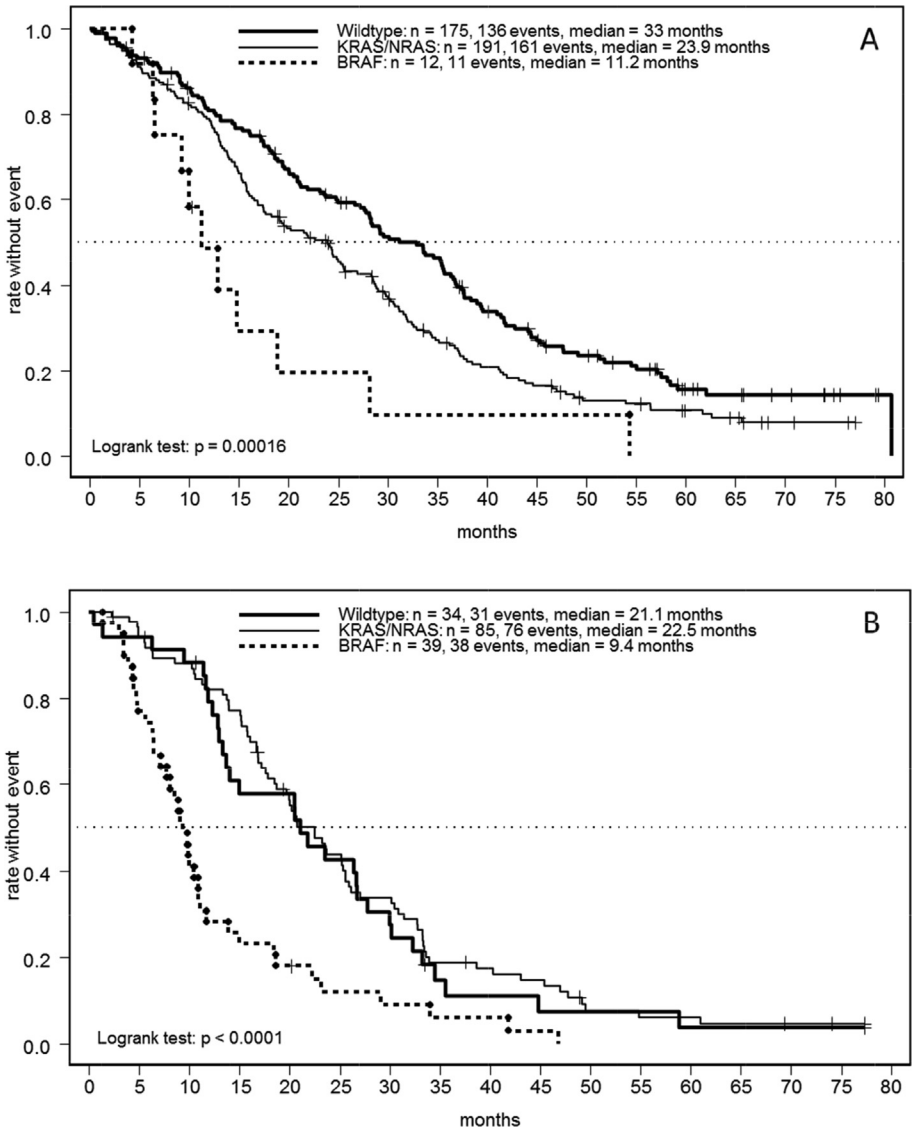

Fig. 2. Kaplan–Meier estimation of overall survival by any RAS mutation, BRAF (V 600E) mutation, (A) in the subgroup of left-sided tumours and (B) in the subgroup of right-sided tumours.

sources, this heterogeneity may also be due to the therapeutic approach in the respective studies, that is, with/without targeted agents or whether addressing the EGFR or VEGF target [7,16].

The largely unrestricted inclusion of a total of 66 studies in the large meta-analysis by Petrelli *et al.* [6] resulted in a rather small increase of mortality risk for right-sided tumours of 22%, but this estimate is hampered by an unexplained heterogeneity of $I^2 = 97\%$. The recent meta-analysis by Holch *et al.* [7], exclusively focussing on prospective first-line studies in metastatic disease, showed a much larger prognostic difference. Although the disposition of trials is somewhat disproportionally inclined to a RAS wild-type population, the finding of an HR = 1.54 (fixed-effect model), with acceptable heterogeneity ($I^2 = 16\%$), corresponds well to the findings of our analysis (1.54 univariably and 1.60 multivariably).

In studies investigating VEGF-targeted first-line treatment, the univariable impact sizes of a right location were HR = 1.41, 1.82 and 2.27 in the studies NO16966, AVF2107g and PROVETTA, respectively [5], mirroring the findings of our analysis. NO169966 had an oxaliplatin backbone, similar to this study. The similar prognostic information (HR 1.41 and 1.54, respectively) could be suggestive of a differential effect of different chemotherapy backbones. As all of our analysed patients received bevacizumab, we cannot contribute to the still somewhat contradictory evidence on a possible interaction between VEGF antibody treatment and LPT [13,16].

Furthermore, our trial is the first one to provide data on the prognostic impact of RAS/BRAF mutational status in this unselected cohort of patients. The data suggest that the strong prognostic effect of LPT is mainly located in the RAS wild-type population.

Although most tumours with BRAF mutations are located proximally, an additional unfavourable impact of LPT was retained in this biomarker subgroup.

Several prognostic scores for metastatic CRC have been developed during the last two decades, markedly differing in the individual parameters incorporated [2,3,17]. While the most established one, the Köhne Score, was based on data from the 5-FU era, it proved to be also valid in populations treated with irinotecan or oxaliplatin [18,19]. Nevertheless, even before taking LPT into account, its relevance in the era of targeted biotherapies was strongly questioned [20,21], notably due to a lack of discrimination between the low and intermediate risk group. The numerical combination of 'risk points' derived from the five independent (conventional) prognostic factors in our multivariable model yielded a distinct separation into three groups. However, this approach requires prospective confirmation in a validation sample.

A major limitation of this analysis is its retrospective nature. Some variables, notably LPT and molecular markers, were not available for all patients, due to the retroactive data collection, leading to decreased event numbers in multivariable models. As in most studies on tumour sidedness, the demarcation line between left and right may be suboptimally defined and differing from the underlying embryology.

In conclusion, our study enlarged the body of evidence on tumour sidedness in patients with metastatic CRC, who were prospectively selected, observed and uniformly treated with a triple combination, specifically including an oxaliplatin-based chemotherapy with bevacizumab. It confirmed the important, although not solely dominating, relevance of LPT for the survival prognosis, but at the same time suggests interactions with biomarkers, such as the RAS mutational status. A plethora of recent [5,14,22,23] and ongoing activities will further elucidate the molecular variability of advanced CRC originating from the different anatomic sites.

Conflict of interest statement

S.H.-B. is an advisory board member of Amgen, Chugai, BMS, Lilly and Merck. S.N.-D. received honoraria from Baxalta, BMS and Ipsen and is an advisory board member of BMS. A.H. received honoraria from Roche. U.G. received honoraria from Roche, Sanofi, Amgen, Merck and Servier. A.R.-S. received honoraria from Amgen, Roche, Pfizer, Sanofi-Aventis and Merck and is an advisory board member of Amgen, Roche, Pfizer, Sanofi-Aventis and Merck. B.K. received honoraria from BMS and Roche and travel costs from Janssen. S.-E.A.-B. received honoraria and research grants Roche . A.T. received honoraria from Amgen, Roche, Merck Serono and Sanofi-Aventis. D.A. received honoraria from Bayer, Biocompatibles, Lilly, Merck, MSD, Roche, Sanofi, Servier and Sirtex and is an advisory board member of Bayer, Lilly, Merck, Roche, Sanofi, Servier, Sirtex and Terumo. The other authors declare that they have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.06.015.

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