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REVIEW ARTICLE

Anna Janiak, Joanna Połowinczak-Przybyłek, Rafał Czyżykowski, Piotr Potemski

Chemotherapy Clinic, Oncology Department, Medical University of Lodz, Poland
Nicolaus Copernicus Multidisciplinary Centre of Oncology and Traumatology in Lodz, Poland

Clinical significance of primary tumour location in colorectal cancer — a review

Address for correspondence:
Lek. Anna Janiak
Klinika Chemioterapii Nowotworów,
Katedra Onkologii, Uniwersytet Medyczny
w Łodzi; Wojewódzkie Wielospecjalistyczne
Centrum Onkologii i Traumatologii
im. Mikołaja Kopernika w Łodzi
e-mail: a.janiak@yahoo.com

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ABSTRACT

Colorectal cancer (CRC) is one of the most common malignant neoplasms worldwide. The heterogeneous course of disease, as well as, genetic and molecular differences between tumours localized in different parts of the large intestine, resulted in an attempt to evaluate the significance of the primary tumour location and divide colorectal cancer into right- and left-sided. The results of the retrospective analyses of the phase III studies indicate that the right-sided location is a negative prognostic factor in stage IV and III of disease. The benefit of adding an anti-EGFR antibody to the first-line palliative chemotherapy was clearly demonstrated for patients with primary tumour located on the left side and the effect of treatment seems to be better than anti-VEGF therapy combined with chemotherapy. Treatement results of patients with right-sided primary tumour location are worse regardless of the type of treatment. In patients with right-sided cancer, it seems that bevacizumab treatment might be more beneficial in comparison with anti-EGFR therapy, although these suggestions are based on small groups of patients. The efficacy of bevacizumab seems to be independent of primary tumour location. It is still unclear whether the primary tumour location should be considered as an independent prognostic or predictive factor, or rather it is necessary to look for specific genetic and molecular disorders responsible for demonstrated and possible differences.

Key words: colorectal cancer, primary tumour location, chemotherapy, cetuximab, panitumumab, bevacizumab

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Introduction

Colorectal cancer (CRC) is one of the most common malignant neoplasms worldwide with 1.8 million new cases and 880 000 of cancer deaths reported yearly [1]. Two entities with different management recommendations are discerned — colon cancer and rectal cancer [2]. Heterogeneous course of the disease and differences in the response to treatment in colorectal cancers with similar clinicopathological features caused a search for a biological explanation of this phenomenon [3–10]. An international consortium, whose goal was, among others, the unification of the current state of knowledge, identification of the most homogeneous genetic tumours, and characterisation of mechanisms crucial for the functioning of cancer, distinguished — based on the analysis of the gene expression profiles — four molecular subtypes of colorectal cancer with different prognosis (CMS, consensus molecular subtype): CMS1 — immune, CMS2 — canonical, CMS3 — metabolic, CMS4 — mesenchymal [11]. Nevertheless, this classification is not used in clinical practice. Easily accessible predictive biomarkers for treatment and prognostic factors are requested and most commonly investigated are *RAS*, *BRAF* mutation and microsatellite instability (MSI) [12]. Recently, a subject of great interest is the clinical significance of the primary tumour location of colorectal cancer and division depending on the location of the primary tumour on right- and left-sided colorectal cancer.

Sidedness definition, clinicopathological and molecular profile according to the side of the tumour

The sidedness definitions differ. Referring to embryology, the right side of the large intestine origins from the midgut, is supplied with the superior mesenteric artery and consists of the caecum, ascending colon, hepatic flexure and proximal two-thirds of the transverse colon. The left side of the large intestine which derives from hindgut is vascularised by the inferior mesenteric artery and includes distal third part of transverse colon, splenic flexure, descending colon, sigmoid colon and rectum [13]. However, the lack of precise data concerning tumour location in the transverse colon generally makes the embryological division impossible to apply. This is the reason that some authors exclude transverse colon from the research [14], but the majority include it in right-sided colorectal cancer group [15–17].

Patients with right-sided colorectal cancer (RC) are more often women and elderly people. Lynch syndrome is more frequent and the mutations of *BRAF, KRAS, PIK3CA, PTEN, CTNNB1, ATM* and *BRCA1* genes are more common. A greater number of somatic mutations (TML, tumour mutational load) may indicate that this cancer is more immunogenic. In contrast, left-sided colorectal cancer (LC) more often affects men and younger people. There is a greater incidence of familial adenomatous polyposis (FAP), genetic mutations in *APC, TP53, NRAS* and amplification of *EGFR* and *HER2.* Common features for right-sided tumours are MSI, CMS1 subtype, CMS3, CpG island methylator phenotype (CIMP-H), mucinous histology, and for left-sided: CMS2 subtype and chromosomal instability (CIN) [18–20].

In the study evaluating the immunological tumour microenvironment (TME) (n = 638) in RC, a larger infiltration of immune cells most frequently by T lymphocytes and a higher level of immune system activation were observed. In contrast, in LC, more CD56 + NK lymphocytes were detected. The elevated level of vascular endothelial growth factor type A (VEGF-A) on the right side was associated with decreased activity of CD8 + T lymphocytes [21].

Patients with primary RC have shorter survival. It is uncertain, whether the worse prognosis is the result of known, unfavorable prognostic factors which appear more frequently on the right side, or the right-sided location itself. Some data indicate that after exclusion from the analysis patients with V600 *BRAF* mutation [22] or patients with *BRAF* mutation and mucinous subtype [17], people with RC still have a worse prognosis. However, in some studies in which RC was associated with a worse prognosis in the entire studied group, after adjustment for clinicopathological factors [23] or the presence of *BRAF* and *RAS* mutations [24], location of the primary tumour did not affect survival.

Analysis of the first-line treatment of metastatic colorectal cancer

According to the obvious differences between RC and LC, the scientists performed some retrospective analyses of the previously carried out prospective clinical trials in the first-line setting. The most frequent analyzed studies, considering the impact of the primary tumour location on the survival of patients without *RAS* mutation, were: four phase III trials (CRYSTAL, PRIME, FIRE-3 and CALGB/SWOG 80405), and one phase II trial (PEAK). CRYSTAL and PRIME trials compared a combination of chemotherapy and anti-epidermal growth factor receptor (EGFR) antibody to chemotherapy alone; the others i.e. FIRE-3, CALGB/SWOG 80405 and PEAK compared two different strategies — anti-EGFR to anti-VEGF treatment, both combined with chemotherapy. These retrospective studies proved a negative prognostic value of RC. Differences in impact caused by adding a molecular-targeted drug on progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) depending on the tumour side were also observed.

In a group of 364 *RAS* wild-type patients in CRYSTAL study, the addition of cetuximab to chemotherapy prolonged survival in LC (n = 280). The median PFS reached 12.0 months for FOLFIRI with cetuximab (n = 142) comparing to 8.9 months for chemotherapy alone (n = 138) (HR = 0.50; 95% CI: 0.34–0.72; $p < 0.01$), and the median OS was 28.7 and 21.7 months, respectively (HR = 0.65; 95% CI: 0.50–0.86; $p < 0.02$). In RC (n = 84) no clear benefit from anti-EGFR therapy was observed; the median PFS of patients treated with chemotherapy and antibody (n = 33) reached 8.1 months in comparison to 7.1 months for patients treated with chemotherapy alone (n = 51) (HR = 0.87; 95% CI: 0.47–1.62; p = 0.66), and the median OS was 18.5 and 15.0 months, respectively (HR = 1.08; 95% Cl: 0.65–1.81; p = 0.76). The addition of cetuximab in LC had a positive impact on ORR (73% *vs.* 41%; OR = 3.99; 95% CI: 2.40–6.62; $p < 0.001$), while in RC this effect was not obvious (ORR 42% *vs.* 33%; OR = 1.45; 95% CI: 0.58–3.64; p = 0.43) [15].

For 328 patients with LC participating in the PRIME trial, the median PFS reached 12.9 months for FOLFOX regimen with panitumumab (n = 169) compared to 9.2 months in chemotherapy alone group (n = 159) (HR = 0.72; 95% CI: 0.57–0.90; $p < 0.005$), the median OS was 30.3 and 23.6 months, respectively (HR = 0.73; 95% CI: 0.57–0.93; $p < 0.011$). For 88 patients with RC the median PFS was 7.5 months in panitumumab-chemotherapy group (n = 39) and 7.0 months in

chemotherapy alone arm (n = 49) (HR = 0.80; 95% CI: 0.51–1.26), the median OS was 15.4 and 11.1 months, respectively (HR = 0.87; 95% Cl: 0.55–1.37). In LC, ORR was significantly higher for chemotherapy with panitumumab than for chemotherapy (68% *vs.* 53%; OR = 1.91; 95% CI: 1.18–3.07), but in RC the difference was not significant (42% *vs.* 35%; OR = 1.36; 95% CI: 0.51–3.62) [16].

In both above-mentioned studies, the beneficial effect of the addition of an anti-EGFR drug on PFS, OS, and ORR was obvious in patients with LC. In patients with RC, no clear benefit was observed. However, it should be emphasized that the number of patients was low, and randomisation was not stratified for a primary tumour location. Thus, some significant differences between compared groups regarding other predictive and prognostic factors can not excluded.

In the retrospective analysis in *RAS* wild-type population (n = 400) of the FIRE-3 trial, cetuximab and bevacizumab combined with FOLFIRI regimen were compared. Patients with LC cancer (n = 306) treated with cetuximab (n = 157) lived significantly longer than those treated with bevacizumab (n = 149) (median OS 38.3 *vs.* 28.0 months; HR = 0.63, 95% CI: 0.48–0.85, p = 0.002). There were no significant differences in PFS and ORR. In patients with RC (n = 88) there were no significant differences; the median OS was 23.0 months for bevacizumab (n = 50) and 18.3 months for cetuximab (n = 38) (HR = 1.31, 95% CI: 0.81–2.11, p = 0.28) [15].

In a retrospective analysis of the phase II PEAK study, 143 patients without *RAS* mutation were treated using FOLFOX with panitumumab (n = 75) or with bevacizumab (n = 68). There were no significant differences between the treatment arms in terms of PFS and OS, irrespectively of the primary location, although the difference in PFS in favour of the anti-EGFR treatment in patients with LC almost reached a level of statistical significance [16].

In the US CALGB/SWOG 80405 trial, which included 1137 *KRAS* wild-type patients, the cetuximab + FOLFIRI/FOLFOX was compared to bevacizumab + FOLFIRI/FOLFOX [25]. The authors of the study presented the result of an interaction test suggesting that tumour location may affect the effectiveness of a biological agent in relation to OS and PFS. Treatment with cetuximab seemed to be more beneficial for LC, whereas bevacizumab treatment for RC [26]. For LC patients, the median OS with cetuximab treatment reached 39.3 months, and with bevacizumab 32.6 months (HR = 0.77; 95% CI: 0.59–0.99, p = 0.04). For RC patients, the median OS was 13.7 and 29.2 months, respectively (HR = 1.36, 95% CI: 0.93–1.99, p = 0.10). These results could be inter preted as a possibility of greater benefit form cetuximab treatment in the LC and from bevacizumab in the RC [27]. Furthermore, it is noteworthy that a majority of patients in CALGB/SWOG 80405 trial received FOLFOX regimen — in the NO16966 phase III clinical trial the addition of bevacizumab to 1. line oxaliplatin-based chemotherapy did not prolong OS [28].

Considering presented data, some aspects need to be strongly emphasised; a retrospective character of the analysis, the loss of a randomisation effect and a disproportion in numbers of patients between compared groups (sample size over four times smaller for a right-side location). Moreover, these data usually did not take into account *BRAF* mutation status. It is noteworthy, that V600 *BRAF* mutation is usually considered as a negative predictor for anti-EGFR therapy, and it is more common in cancers located on the right side of the colon.

A few reliable data referring to the efficacy of an antibody against vascular endothelial growth factor (VEGF) added to chemotherapy regarding primary tumour location in colorectal cancer is available. From the analysis of three trials: PROVETTA cohort pharmacogenetic trial without a control arm (n = 200; FOLFIRI + bevacizumab) and two phase III randomised trials: AVF2017g (n = 599) and NO16966 (n = 1269), where bevacizumab with chemotherapy was compared to chemotherapy — IFL and FOLFOX/XELOX, respectively, a consistent conclusion about RC as a negative prognostic factor was drowned [17]. OS hazard ratios for left vs right side were: in the AVF2107g trial — 0.55 (95% CI: 0.43–0.70, p < 0.001), in the NO16966 trial — 0.71 (95% CI: 0.62–0.82; p < 0.001), and in the PROVETTA trial — 0.44 (95% CI: 0.28–0.70; p < 0.001). PFS hazard ratios for left vs right side were: in the AVF2107g trial — 0.68 (95% CI: 0.55–0.83, p < 0.001), in the NO16966 trial — 0.90 (95% CI: 0.79–1.03; p = 0.12), and in the PROVETTA trial — 0.52 (95% CI: 0.36–0.75; p < 0.001). Due to the availability of both clinical and molecular data in the PROVETTA trial, the poor prognostic value of RC was proven not only for the entire population but also was confirmed after excluding patients with already known other negative prognostic factors, such as *BRAF* mutation and mucinous histology. The authors of the AVF2017g and NO16966 trials have not posed the question of whether the addition of bevacizumab is more beneficial in cancers with a primary tumour located on the right or the left side. The only reliable information is coming from a negative test for interaction showing that the efficacy of bevacizumab added to chemotherapy does not depend on primary tumour location [17].

There is one prospective Chinese trial involving patients treated only with bevacizumab with chemotherapy, where in the subgroup analysis bevacizumab combined with FOLFIRI regimen, produced better PFS in LC than in RC patients. However, there were only 28 patients in this subgroup, and the population

was imbalanced according to age and sites of metastases. The authors followed their trial by a meta-analysis of 21 studies with 4416 patients treated with anti-VEGF agent and chemotherapy in first or second-line. The outcomes suggested that primary tumour location may have the impact on bevacizumab treatment favouring the left side over the right side according to ORR, PFS and OS result in the overall population, as well as, in *RAS*/*BRAF* wide type population [29].

Meta-analysis — stage IV colorectal cancer

Several meta-analyses focusing on the impact of primary tumour location were conducted. One of them included thirteen phase III trials and one prospective pharmacogenetic trial, all were published until October 2016 and concerned the first-line palliative systemic treatment of colorectal cancer. It confirmed that patients with RC, which represented 27% cases (18–41%) have worse prognosis than patients with LC irrespectively to the applied treatment (OS HR = 1.56, 95% CI: 1.43–1.70, p < 0.0001; PFS HR = 1.33, 95% CI: 1.20–1.48, p < 0.0001).

The predictive value of primary tumour location for anti-EGFR therapy was based on a meta-analysis of CRYSTAL and PRIME trials. Significant clinical benefit from adding the antibody to chemotherapy in OS, PFS and ORR was demonstrated only for patients with LC (OS HR = 0.69; 95% CI = 0.58–0.83 p < 0.0001, PFS HR = 0.62; 95% CI = 0.44–0.88, p < 0.008; ORR odds ratio 2.69; 95% CI = 1.3–5.57; p < 0.007).

A direct comparison of anti-EGFR with anti-VEGF treatment, both in combination with chemotherapy, was based on a meta-analysis of three trials: FIRE-3, PEAK, CALGB/SWOG80405. For LC patients anti-EGFR therapy was more effective than anti-VEGF therapy. Significant differences were observed in OS and ORR (OS HR = 0.71; 95% CI: 0.58–0.85, p < 0.0003; ORR = 1.49; 95% CI: 1.16–1.09, p < 0.002). Patients with RC seemed to benefit less from molecular targeted therapies. When anti-EGFR and anti-VEGF strategies were compared in patients with RC, better results were obtained for bevacizumab in combination with chemotherapy for PFS only (HR = 1.53; 95% CI: 1.16–2.01, p < 0.003) [30].

In 2018, another meta-analysis consisted of seven trials (COIN, CRYSTAL, OPUS, PRIME, PEAK, FIRE-3, and CALGB/SWOG 80405) including 3805 patients was published. An obvious limitation was a low percentage of patients crossed-over to molecular therapies in the subsequent lines (36.6% received bevacizumab, and 33.2% — anti-EGFR). Conclusions referring to primary tumour location indicate that LC patients treated with anti-EGFR antibody combined with chemotherapy have significantly better OS in comparison to chemotherapy alone (CRYSTAL, PRIME) (HR = 0.69; CI: 0.54–0.83), or to chemotherapy with bevacizumab (HR = 0.70; CI: 0.54–0.85), while the opposite but non-significant trend was observed in RC (HR = 1.29; CI: 0.81–1.77) (PEAK, FIRE-3, CALGB/SWOG 80405) [27].

A recent meta-analysis of fifteen trials of the first-line treatment was published in 2020. The subgroup analysis of LC *RAS* wide type patients showed that every agent (bevacizumab, panitumumab, cetuximab) added to chemotherapy produced a significant benefit over chemotherapy alone in ORR (odds ratio = 1.92; 95% CI: 1.26–2.91, OR = 2.04; 95% CI: 1.37–3.06, OR = 3.0; 95% CI: 2.17–4.13, respectively). Compared to chemotherapy alone, both panitumumab and cetuximab produced better PFS (HR = 0.52; 95% CI: 0.34–0.79; HR = 0.48; 95% CI: 0.34–067, respectively), and OS (HR = 0.59, 95% CI: 0.39–0.91; HR = 0.48, 95% CI: 0.34–0.66, respectively). Cetuximab showed significant benefits on all efficacy outcomes, compared to bevacizumab (ORR odd ratio = 1.56; 95 % CI: 1.15–2.13; PFS HR = 0.71; 95% CI: 0.52–0.96; OS HR = 0.55; 95% CI: 0.40–0.75). In RC *RAS* wide type patients, no significant differences between these therapies on ORR and OS were found. However, PFS was significantly better for bevacizumab than for cetuximab or chemotherapy alone (HR = 2.24, 95% CI: 1.35–3.73; HR = 0.31, 95% CI: 0.14–0.67). The authors concluded that for *RAS* wide type LC patients, cetuximab combined with chemotherapy is the best treatment option, and for RC patients, chemotherapy with bevacizumab is preferred [31].

Chemotherapy intensification

The TRIBE phase III trial compared two chemotherapy regimens: FOLFOXIRI with bevacizumab to FOLFIRI with bevacizumab in the first-line palliative treatment of colorectal cancer (n = 508). Based on the result of an interaction test it was suggested, that the greater benefit from more intense chemotherapy is obtained by patients with RC [24].

Resectable liver metastases

It is unknown whether the location of the primary tumour in patients after resection of liver metastases has an impact on the prognosis. The results of the published studies are contradictory, but the majority suggest that RC might be a negative prognostic factor [32–36].

Stage I–III colorectal cancer

Data concerning the location of the primary tumour of colorectal cancer in patients at IV stage disease have led to further retrospective analyses, this time in lower

stages of the disease [37–42]. In the majority of studies, though not in all, it was shown that RC is also an unfavorable prognostic factor for patients with stage III disease because of significantly shorter disease-free survival and a lower 5-year overall survival rate. No such associations were found for stages I–II. In one study, patients with stage II and RC had even better prognosis [38]. An Australian analysis of 9509 patients with locally advanced colorectal cancer (stages I–III) confirmed these observations. RC was associated with a significantly higher 5-year survival of patients at stage II disease (HR = 0.85; 95% CI: 0.75–0.98, p = 0.02) and significantly lower 5-year survival in stage III disease (HR = 1.13; 95% CI: 1.01—1.26, p = 0.032) [42]. Another meta-analysis involving 581 542 patients and 37 studies evaluated the effects of tumour sidedness on outcomes in early disease. Patients with RC and stage II had better OS (HR = 0.89; 95%CI: 0.86–0.92), whereas RC patients with stage III had worse OS (HR = 1.12; 95% CI: 1.04–1.20) [43].

All stages

A meta-analysis of 66 studies including 1 437 846 patients in all stages of disease showed that LC was associated with a significantly reduced risk of death compared to RC (HR = 0.82, 95% CI: 0.79–0.84, p < 0.001). This effect was greater in disseminated disease [44].

Real-world data

The real-world data according to the first-line treatment of metastatic colorectal cancer come from two retrospective multicenter studies. The Italian study involved 351 *RAS* wide type patients treated between 2010 and 2016. LC patients had better OS than RC patients (HR = 0.74; 95% CI: 0.55–0.99, p = 0.049). More favorable OS outcomes were observed for LC, but not RC patients treated with anti-EGFR compared with those treated with anti-VEGF therapy (median OS: 40.7 *vs.* 27.8 months; HR = 0.59; 95% CI: 0.41–0.86; p = 0.005). On the contrary, the efficacy of bevacizumab containing regimens was independent of tumour location [45]. The American study involved 1312 *KRAS* wide-type patients treated in 2013–2017. The prognostic role of primary tumour location was substantiated, but the predictive role for treatment with cetuximab *vs.* bevacizumab was not confirmed [46]. Additionally, in unselected *RAS* patients participating in Portuguese observational study, bevacizumab produced better PFS than cetuximab in RC patients, although this subgroup was very small (n = 58) (HR = 0.52; 95% CI: 0.29–0.93; p = 0.025) [47].

Conclusions

The results of the presented studies indicate that RC is associated with worse prognosis in metastatic CRC, and it seems to be also an unfavorable prognostic factor in patients with stage III. Most of the data show a significant benefit from the anti-EGFR therapy in the first-line palliative treatment in patients with LC. In LC, an anti-EGFR antibody in combination with chemotherapy is more effective than chemotherapy alone and probably also more effective than chemotherapy in combination with anti-VEGF treatment. In RC, the benefit from adding an anti-EGFR antibody to chemotherapy is uncertain. However, it should be emphasized that this conclusion is drawn from retrospective subgroup analyses and should be treated with caution.

There is less data concerning bevacizumab treatment in the context of primary tumour location. It seems that the effectiveness of bevacizumab does not depend on cancer primary location, but available data are contradictory. However, the large CAGB/SWOG80405 study suggests in the first-line palliative treatment of RC higher activity of bevacizumab than cetuximab, both combined with chemotherapy.

Moreover, in RC an intensification of the chemotherapy with the use of FOLFOXIRI plus bevacizumab might be considered.

The diversity of CRC cases with different locations of the primary tumour is important and requires further studies assessing molecular profiles. It remains an open question whether it has a value for clinical practice. It should be remembered that data referring to a predictive value of primary tumour location for molecular treatment is not very reliable. The most consistent data indicate a negative prognostic value of the right-sided location of the primary tumour in stage IV and III diseases and confirm the benefit from anti-EGFR treatment in left-sided cancer.

It seems, however, too early to consider the location of the primary tumour as a factor influencing of treatment decisions. It is still unclear, whether the primary tumour location should be considered as an independent prognostic or predictive factor, or we should rather look for specific genetic and molecular characteristics responsible for demonstrated and potential differences.

Conflict of interest

Piotr Potemski — Roche lecture advisory and clinical fees; Merck lecture fees.

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