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Lower Gastrointestinal Cancers (AB Benson, Section Editor)

Right Versus Left Colon Cancer: Resectable and Metastatic Disease

Michele Ghidini[1]
Fausto Petrelli, MD[2,*]
Gianluca Tomasello[1]

Address
[1]Oncology Unit, Oncology Department, ASST of Cremona, Hospital of Cremona, Viale Concordia 1, 26100, Cremona, Italy
[*,2]Oncology Unit, ASST Bergamo Ovest, Piazzale Ospedale 1, 24047, Treviglio, Italy
Email: faupe@libero.it

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Opinion statement

Colorectal cancer does not represent a single anatomic entity and side of origin has a key impact on prognosis and response to different systemic therapies. Compared to tumours arising in left colon, right colorectal cancers rely on the activation of different molecular pathways (e.g. *BRAF* mutation and MSI status). From a clinical point of view, this results in a different response to anti-EGFR agents. Current guidelines suggest the use of cetuximab or panitumumab in *RAS* wild-type disease and left colon cancer especially for cytoreduction/conversion purposes, since the expected benefit in right colon cancer is absent or clinically modest. The prognostic role of microbiota in colorectal cancer disease deserves more clarification before being considered in common clinical practice. Screening policies could also be affected by these new acquisitions. At the moment, sidedness should be considered as a strong prognostic variable and a surrogate predictor of different activity of anti-EGFR agents in the metastatic setting. Its role in early stages of resected disease is still uncertain.

Introduction

Advancements in diagnosis and cure of colorectal cancer (CRC) have been enriched in advanced disease by molecular predictors of response (e.g. *RAS* and *BRAF* mutational status) to anti-EGFR agents in advanced disease. They are both predictors of efficacy and prognostic factors for survival. Colorectal cancers harbouring these mutations are associated with a poor prognosis both in early and in advanced stages [1–3]. The refinement of knowledge of CRC in terms of molecular biology has now permitted to split the anatomic continuity of large bowel into two separate entities: the right and the left counterparts. Conventionally, tumours proximal to the

splenic flexure are defined as right-sided because the proximal two-thirds of the transverse colon arises embryologically from the midgut, and only the distal portion arises from the hindgut. Tumour side is an independent prognostic factor in patients with early and metastatic CRC: left-sided primaries, located at or distal to splenic flexure, have improved outcomes [4••] A large systematic review and meta-analysis including 66 studies enrolling more than 1,400,000 patients showed that left side was associated with a significantly reduced risk of death and this was independent of stage, race, adjuvant chemotherapy, year/number of participants and quality of included studies. In addition, sidedness also represents a powerful predictor of benefit from anti-EGFR therapies in patients with *RAS* wild-type metastatic CRC [4••]. Specifically, right-sided tumours derive, at best, very limited survival benefit with the addition of cetuximab or panitumumab to chemotherapy [5•].

Aim of this work is to review all the different aspects of biology, clinical behaviour and treatment of right and left CRCs.

Biology of right vs left colorectal cancer

Molecular characterization (Fig. 1)

Right (RCC) and left colon cancers (LCC) harbour different tumourigenic pathways possibly related to diverse epigenetic changes, dissimilar luminal content and distinct microbiota. These differences are present in all steps of carcinogenesis, from pre-malignant lesions to metastatic disease [6].

RCCs are more common in women, are associated with Lynch syndrome and generally dependent on mitogen-activated protein kinase (MAPK) and/or phospoinositide 3-kinase (PI3K) signalling [6, 7]. RCCs show a higher prevalence of microsatellite instability (MSI-H), and CpG island methylation; moreover, driver mutations (such as *KRAS* and *BRAF* mutations) are more common on the right side because of a selective pressure for an increased mutational

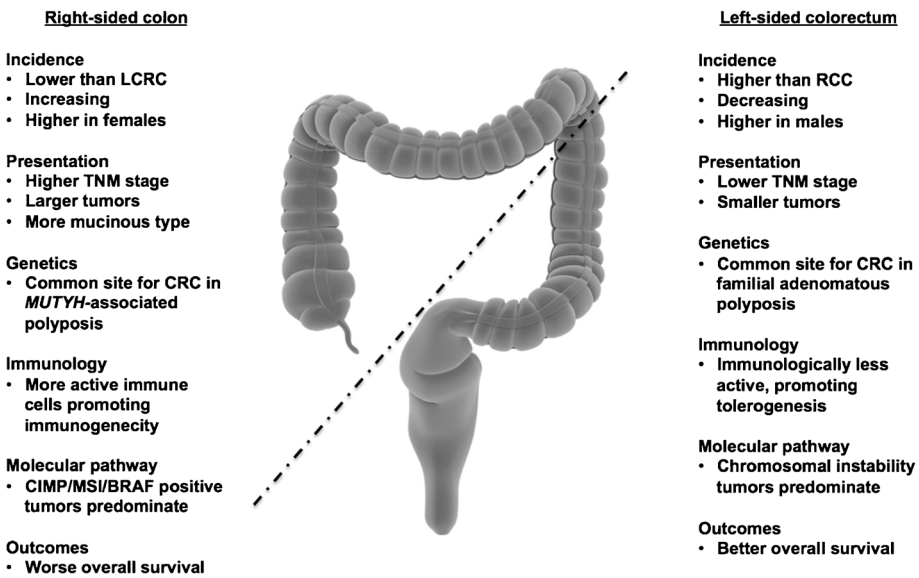

Fig. 1. Different clinicopathological behaviours of right and left colon cancer. Reprinted from *European Journal of Surgical Oncology*, 41(3), Lee GH, Malietzis G, Askari A, Bernardo D, Al-Hassi HO, Clark SK, "Is right-sided colon cancer different to left-sided colorectal cancer?—a systematic review," pages 300–308, ©2015, with permission from Elsevier

burden [7]. On the contrary, LCC is more frequent in men, associated with familial adenomatous polyposis syndrome and mainly dependent on receptor tyrosine kinase (RTK) activity, such as epidermal growth factor receptor (EGFR) signalling [6]. The mutational burden is lower as compared to RCC, with the more frequent gene mutations being those involving *APC*, *p53* and *NRAS* genes [7]. As far as the mainly pathogenic process is related to EGFR pathway activation, LCC benefit from anti-EGFR treatment, whereas RCC genetic alterations are associated with resistance to cetuximab and panitumumab [7]. In a recent molecular profiling of 10,570 CRCs, the average tumour mutational load (TML) was higher in RCC (24.5 mutations/megabase) compared to LCC (5.5 mutations/megabase) and rectal cancers (RC, 5.9 mutations/megabase), with differences not reaching statistical significance. Moreover, a continuous decrease in the prevalence of microsatellite repair-deficient tumours (MMRd) was shown moving from RCC to LCC and RC, with a parallel increase of MSI-H cancers (22.3% for RCC, 4.6% for LCC and 0.7 for RC, $p < 0.05$ for LCC vs RC; $p < 0.001$ for RCC vs LCC and RCC vs RC). RC harboured a lower mutation rate of both *PIK3CA* and *PTEN* genes compared to colon cancers (CC). Since alterations in these genes have been associated with anti-EGFR resistance, RC may have higher responses to EGFR blockade. RCs were also associated with significantly higher rates of type I topoisomerase (TOPO1) expression compared to CC, with possible enhanced sensitivity to irinotecan ($p < 0.01$ for RCC vs RC and $p < 0.001$ for LCC vs RC). Her2/neu amplification analysis with chromogenic in situ hybridization (CISH) reported a higher rate for RC (5.4%) than for CC (1.3 and 2.8%, respectively, for RCC and LCC; $p = 0.03$ for RC vs RCC) [8].

Despite the reported molecular differences between RCC, LCC and RC and the identification of four different consensus molecular subtypes (CMS1, CMS2, CMS 3 and CMS 4) of CC with prognostic and predictive significance (Table 1) [9•], the right/left classification is not exhaustive in recapitulating variations in tumour biology. In fact, in a cohort analysis of 1876 patients with CC and RC, a classification by tumour location rather than sidedness was proposed [10]. In this analysis, transverse tumours had mutational profiles

Table 1. Consensus molecular subtypes in CRC

	CMS 1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
Frequency	14%	37%	13%	23%
Molecular features	MSI and CIMP high, *BRAF* mutated, immune infiltration and activation	SCNA high, *WNT* and *MYC* activation	Mixed MSI status, SCNA and CIMP low, *KRAS* mutated	SCNA high, *TGFβ* and angiogenesis activation
Prognosis	Worse OS after relapse	Longer OS after relapse	–	Worse RFS and OS

CIMP CpG island methylator phenotype, *CMS* consensus molecular subtype, *MSI* microsatellite instability, *OS* overall survival, *RFS* relapse-free survival, *SCNA* somatic copy number alterations

dissimilar from right sided ($p < 0.0001$) but not left sided ($p = 0.87$), suggesting a potential benefit given by anti-EGFR treatment in this cohort of tumours. Moreover, descending and splenic flexure had significantly higher rates of *PIK3CA* mutations than recto-sigmoid and RC ($p = 0.0009$) and a higher proportion of mucinous histology (24 vs 14% for sigmoid, 12% for recto-sigmoid junction and 9% for RC, $p = 0.0005$), resembling a "right-sided behaviour". Therefore, the sigmoid-rectal region and the transversal regions appeared as distinct entities, indifferently from sidedness [10].

Approach in resectable disease

Microbiota (Table 2)

Microbiota, together with tumour microenvironment (immune and stromal cells) and cancer location plays an important role in the multi-molecular characterization of the disease [6]. The intestinal microbiome is altered in CRC tissue and nearby mucosa, with enrichment of several strains such as *Fusobacterium*, *Selenomonas* and *Peptostreptococcus* (Table 1) [11•]. *Fusobacterium*, in particular, has a role in CRC carcinogenesis, and in a retrospective analysis of 1102 CC and RC, the proportion of tumours harbouring enrichment with *Fusobacterium* increased from RC (2.5%) to cecal cancers (11%; $p < 0.0001$) [12]. *Fusobacterium* seems to act by downregulating T cell-mediated antitumour immune responses, promoting tumour progression and being associated with shorter survival (CRC-specific mortality with low vs *Fusobacterium*-high were respectively 1.25 and 1.58, $p = 0.020$). Moreover, its amount was associated with MSI-H status in the multivariate analysis, independent of *CIMP* and *BRAF* mutation status (multivariate odds ratio 5.22; 95% CI 2.86–9.55) [13]. Recent evidence showed the effects of manipulation of the CRC-associated microbiota by using oral supplementation of *Bifidobacterium lactis* and *Lactobacillus acidophilus*. This intervention brought to a reduction of *Fusobacterium*, *Selenomonas* and *Peptostreptococcus* and a parallel increase in the amount of butyrate-producing bacteria (such as *Faecalibacterium* and *Clostridiales* spp.), whose tumour-suppressive properties have been reported (Tab.2) [11•].

Table 2. Microbiota strains associated with CRC promotion or suppression

Strains associated with CRC growth and progression	Protective strains with tumour-suppressive properties
Fusobacterium nucleatum	*Faecalibacterium*
Selenomonas	*Clostridiales* spp.
Peptostreptococcus	*Bifidobacterium lactis*
	Lactobacillus acidophilus
	Roseburia
	Eubacterium
	Lachnospira

Prevention

Estrogens also seem to play a role in the distribution of CRC. In fact, there is a higher incidence of RCC in women. Estrogen receptors are mainly represented in RCC and the reduced level of estrogens occurring with aging promotes the development of proximal cancers [8].

CRCs harbouring *PIK3CA* mutations have a reduced risk of recurrence if treated with aspirin as prevention (HR 0.11; $p = 0.027$) [14], a higher CRC-specific survival (HR 0.18; $p < 0.001$) and increased OS (HR 0.54; $p = 0.01$) [15]. Among all CRCs, descending and splenic flexure tumours have the higher rates of *PIK3CA* mutation [10]. On the contrary, the general use of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, coxibs, ibuprofen, naproxen, piroxicam and indomethacin was associated with a greater but not significant risk reduction of RCC with respect to distal tumours ($p = 0.06$) [16].

Role of endoscopy and limitations of screening

Colonoscopy is mandatory in the screening process in case of positive faecal occult blood tests [17]. In a big cohort of asymptomatic patients with positive test, both adenomas and adenocarcinomas were considered. The majority of neoplasms were detected in the LCC (66%). Interestingly, a tendency towards a shift from distal to proximal lesions was registered, with a 37% rate of proximal neoplasms in patients older than 60 years as compared with 29% in those between 50 and 59 years [17]. Patients with history of at least one distal advanced adenoma had an increased risk of development of proximal neoplasms (OR 1.63). In contrast with distal sigmoidoscopy, colonoscopy allowed the detection of proximal adenomas and was associated with a reduced risk of death from CRC. In particular, risk reduction was higher from distal compared to proximal CRC (OR 0.24 vs 0.58) [18]. Colonoscopy may be not effective in case of inadequate bowel preparation or presence of serrated adenoma which often occurs in the right part of the organ [19]. A direct consequence is the development of interval cancers, occurring in the time between the initial colonoscopy and the subsequent follow-up examination. Interval cancers were more common in the proximal colon and hepatic flexure ($p < 0.0001$) and in patients with 60 years or older, possibly due to higher difficulties in performing the exam in older patients and reaching the right colon [20].

Laterality in stage I–III disease

Tumour sidedness has been evaluated in early stage CRC for the possible prognostic and predictive role of response to adjuvant chemotherapy. In a retrospective Canadian series of stage I–III CRC patients, no difference in OS (HR 1.00) and cancer-specific survival (HR 1.00) was registered comparing RCC and LCC. The same result was confirmed when the analysis was limited to stage III disease [21]. In a retrospective analysis of patients enrolled in the PETACC3 adjuvant trial, stage II cancers had higher RFS when proximal rather than distal tumours were considered (HR 0.65; $p = 0.01$), whereas no difference was seen in stage III cancers (HR 1.03; $p = 0.7$) [22]. The higher RFS in proximal stage II CRC is probably related to the higher amount of MSI tumours with this laterality [22]. In a post-hoc analysis of the PETACC 8 phase III trial, no difference was seen in terms of disease-free survival (DFS) (HR 1.00; $p = 0.98$; however, RCC

had shorter OS (HR 1.25; $p = 0.03$) and survival after relapse (HR 1.54; $p = 0.0001$) when sidedness was considered. Right-sided CRC with *RAS* mutations had a better DFS (HR 0.80; $p = 0.046$), whereas a shorter DFS was seen when *RAS* and *BRAF* wild-type disease was considered (HR 1.39; $p = 0.04$) [23].

Overall, although the prognostic and predictive role of primary tumour sidedness in advanced CRC disease is widely recognized, the same may not hold true for localized disease [24].

Approach in metastatic disease

Comparison of the genomic profiles of localized, recurrent and metastatic CRC underlines important differences in intratumoural heterogeneity and mutational burden. This variability between tumours at different stages may at least partially explain the dissimilar impact of genetic mutations in different disease conditions. As an example, BRAF-mutated localized CRC is generally associated with a favourable prognosis, whereas mutated and advanced tumours have a peculiar and ominous prognosis [24]. BRAF is mutated in 7–10% of metastatic CRCs (mCRCs) with V600E being the most frequent mutation and non-V600E mutations accounting for 22% among all BRAF mutations [25, 26]. Non-V600E-mutated metastatic CRCs (mCRCs) have a longer OS with respect to V600 mCRCs [26]. BRAF codon 594 is the most frequent non-V600E BRAF mutation [27]. Together with BRAF codon 596, it was detected mostly in rectal and non-mucinous disease, with no peritoneal spread and microsatellite stable [28].

The recurrence pattern has been shown to vary according to the primary site, with a higher recurrence rate for RC (21%) compared to RCC (14%) and LCC (16%). This was reported in a retrospective cohort analysis of data from the FACS trial [29]. RC had principally lung relapses; RCC often experience multisite recurrences. RC seemed to benefit more from follow-up, because the proportion of treatable recurrences was higher in RC primary (9%) as compared to to LCC (6%) and RCC (3%), $p = 0.003$ [29].

A recent meta-analysis of 1,437,846 CRC patients confirmed the prognostic role of tumour laterality in all stages of disease. In fact, LCC had a significant reduction in the risk of death as compared to RCC (HR 0.82; $p < 0.001$). LCC resulted in a better outcome independently of stage, race and type of adjuvant chemotherapy [4••].

Two different meta-analyses considered the available randomized first-line studies in the metastatic CRC setting and reported similar results [5•]. The analysis of six randomized trials by Arnold et al. compared chemotherapy plus anti-EGFR antibody (experimental arm) versus chemotherapy or chemotherapy and bevacizumab (control arm). Authors underlined the significantly worse prognosis owned by RCC with reduced OS (HR 2.03 and 1.38 for control and experimental arm, respectively), shorter PFS (HR 1.59 and 1.25) and reduced objective response rate (ORR), with odds ratios (OR) of 0.38 and 0.56. LCC had a significant benefit from anti-EGFR treatment (HR 0.75 and 0.78 for OS and PFS), whereas the same was not true for RCC (HR 1.12 both for OS and PFS). ORR was higher in LCC patients treated with anti-EGFR (OR 2.12) than in RCC patients (1.47). Holch et al. observed a worse OS for RCC compared to LCC (HR 1.56, $p < 0.0001$). Primary tumour location was predictive of improved

survival in *RAS* wild-type LCC (HR for OS in LCC 0.69; $p < 0.0001$) and not in RCC (HR for OS 0.96; $p = 0.802$) when chemotherapy plus anti-EGFR and chemotherapy only were compared as first-line treatments. Moreover, LCC *RAS* wild-type patients had greater benefit from chemotherapy plus anti-EGFR versus chemotherapy and anti-VEGF (HR 0.71; $p = 0.0003$), while the benefit in RCC was poor and mainly associated with bevacizumab-based treatment (HR 1.3; $p = 0.081$) [30]. A retrospective analysis of the CRYSTAL and FIRE-3 confirmed the previous data: in the *RAS* wild-type population, a better OS was registered in case of LCC and treatment with anti-EGFR agent over to comparators (chemotherapy and chemotherapy plus bevacizumab) [31].

Primary tumour location acts as a prognostic factor even in the second-line therapy of CRC. Indeed, in a post-hoc analysis of the FIRE-3 study, second-line therapy had greater efficacy in LCC with both significantly longer progression free survival (PFS2) and overall survival (OS2) after a first event of progressive disease. Moreover, differences in PFS2 and OS2 between study arms (and in favour of an anti-EGFR-based treatment) were evident in patients with LCC but not with RCC [32].

Considering the prognostic and predictive relevance of tumour sidedness in advanced CRC, primary location has become a mainstay of the treatment algorithm for advanced CRC. In particular, usefulness of anti-EGFR treatment in RCC associated with worse prognosis is under debate and may lead to more aggressive approaches including triplet chemotherapy and bevacizumab. On the contrary, LCC benefit from anti-EGFR therapy is much clearer and such patients should receive a chemo doublet in association with the biological agent as a first choice [33].

Future directions

In metastatic setting, major clinical guidelines currently suggest against the use of anti-EGFR agents in RCC. In these patients, doublet or triplet chemotherapy backbones with or without bevacizumab are the preferred choices. However, a major unanswered clinical question is the relative benefit of starting with bevacizumab versus an anti-EGFR agent as the initial biologic agent to be added to chemotherapy for RAS and BRAF wild-type metastatic RCC especially in case of patients presenting with severe symptoms due to a high tumoural burden. In such a clinical scenario, obtaining a quick and deep clinical response is crucial and can positively affect quality of life. In these specific situations, the use of an anti-EGFR agents could still have a role.

Moreover, adding a biological treatment targeting EGFR to triplet chemotherapy regimens in all wild-type RCC has not been completely elucidated and randomized clinical trials investigating such combinations are currently ongoing.

Finally, randomized phase III trials of adjuvant therapy in early stages specifically stratifying patients based on primary tumour sidedness are currently lacking. According to the worse overall prognosis generally associated with right cancers, more aggressive treatment strategies (i.e. more intensive chemotherapy regimens) guided by thorough molecular profile analyses could potentially lead to better outcomes.

Summary

Colorectal cancer is a very heterogeneous disease. It has now been clearly demonstrated that tumours arising in the left or right side of the organ harbour different clinical and biologic characteristics and portend different prognosis and response to treatments with biological agents. Indeed, right-sided tumours show a higher frequency of BRAF mutation, are more likely to have genome-wide hypermethylation via the CIMP and MSI and more often occur in patients with Lynch syndrome) Conversely, left-sided tumours are characterized by chromosomal instability and a gene expression profiles involving the activation of EGFR pathway. Based on these assumptions, treatment of metastatic disease is deeply changing becoming more and more tailored and effective.

However, many questions are still unanswered. Among these, the role of gut microbiota in determining prognosis and susceptibility to biological and immunological therapies and the impact of more specific adjuvant strategies deserve more extensive evaluation. Hopefully, in the next future clinical trials will integrate clinical and biological information in order to provide more opportunities for increasingly personalized therapies.

Compliance with Ethical Standards

Conflict of Interest
Michele Ghidini, Fausto Petrelli, and Gianluca Tomasello declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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