European Journal of Cancer 84 (2017) 69–80

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Understanding the role of primary tumour localisation in colorectal cancer treatment and outcomes

Sebastian Stintzing [a,*], Sabine Tejpar [b], Peter Gibbs [c], Lars Thiebach [d], Heinz-Josef Lenz [e]

[a] *Department of Medicine III, University Hospital, LMU Munich, Germany*
[b] *Molecular Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium*
[c] *Systems Biology and Personalised Medicine, The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia*
[d] *Roche Pharma AG, Grenzach-Wyhlen, Germany*
[e] *USC Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA*

Received 6 April 2017; received in revised form 6 July 2017; accepted 11 July 2017
Available online 5 August 2017

KEYWORDS
Colorectal carcinoma;
Hindgut;
Midgut;
Predictive;
Prognostic;
Colon;
Metastatic

Abstract Metastatic colorectal carcinoma (mCRC) is a heterogeneous disease with differing outcomes and clinical responses and poor prognosis. CRCs can be characterised by their primary tumour location within the colon. The left-sided colon, derived from the hindgut, includes the distal third of the transverse colon, splenic flexure, descending colon, sigmoid colon and rectum. The right-sided colon, derived from the midgut, includes the proximal two-thirds of the transverse colon, ascending colon and caecum. Sometimes, the rectum is described separately, despite originating from the hindgut, and in many clinical series, the left-sided colon includes only tumours within and distal to the splenic flexure. Differences in the microbiome, clinical characteristics and chromosomal and molecular characteristics have been reported between the right and left side of the colon, regardless of how this is defined. There is now strong evidence from clinical studies in patients with mCRC for the prognostic effect of primary tumour location. The impact of primary colonic tumour location on response to treatment is now under investigation in a large number of clinical studies in patients with mCRC.

In this review, we summarise the microbiome, clinical, chromosomal and molecular differences associated with the primary location of CRC. We present an overview of the proven

* *Corresponding author*: Sebastian Stintzing, Department of Medicine III, University Hospital, LMU Munich, Marchioninistrasse 15, 81377 Munich, Germany. Fax: +49 89 4400 75256.
E-mail addresses: sebastian.stintzing@med.uni-muenchen.de (S. Stintzing), sabine.tejpar@uzleuven.be (S. Tejpar), gibbs.p@wehi.EDU.AU (P. Gibbs), lars.thiebach@roche.com (L. Thiebach), LENZ@med.usc.edu (H.-J. Lenz).

http://dx.doi.org/10.1016/j.ejca.2017.07.016

prognostic impact of primary tumour location for patients with mCRC and discuss emerging data for the predictive impact of primary tumour location on clinical outcome.

1. Introduction

In Europe, colorectal carcinoma (CRC) is the second most commonly diagnosed cancer and a leading cause of death [1,2]. Metastatic CRC (mCRC) is a heterogeneous disease with differing outcomes and clinical responses. Over the past 20 years, the clinical outcome for these patients has greatly improved because of the expansion in available systemic therapies and ablative techniques, in addition to improved diagnosis and referral for surgery [3]. However, prognosis for mCRC patients remains poor [3]. Clinical studies, to date, have reported a median overall survival (OS) of approximately 24–30 months, achieved with the aid of multiple lines of treatment followed by best supportive care (BSC) [3].

CRCs can be characterised by their primary tumour location within the colon and rectum [4]. Historically, publications have defined CRCs within three compartments of the gut: distal colon, proximal colon and rectum [4–6]. Right-sided colon carcinomas (RCCs) are located within the colon derived from the embryologic midgut, which encompasses the proximal two-thirds of the transverse colon, ascending colon and caecum (Fig. 1). Left-sided colon carcinomas (LCCs) lie within the colon derived from the embryologic hindgut, which includes the distal third of the transverse colon, splenic flexure, descending colon, sigmoid colon and rectum (Fig. 1). It should be noted that the rectum is sometimes described separately although it embryonically belongs to the hindgut. Most clinical series have used a slightly different definition, with any tumour proximal to the splenic flexure considered a right-sided primary and any tumour from the splenic flexure and distally (including the rectum) considered a left-sided primary. With this definition, at least 63% of patients with CRC have LCC [7].

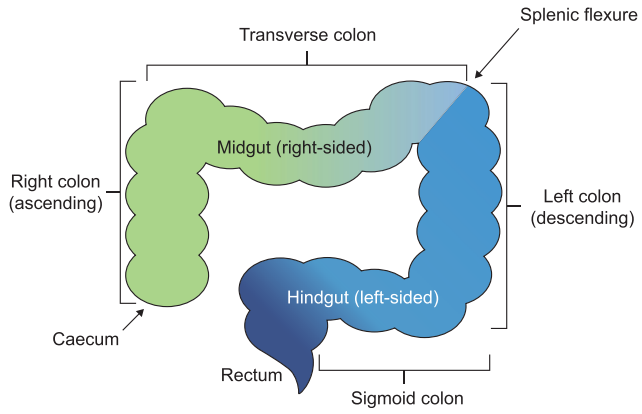

Fig. 1. Schematic diagram of the most commonly used definition of left- and right-sided regions of the colon and rectum.

Prognostic biomarkers predict a likely disease outcome, independent of the treatment received. Strong evidence for the prognostic effect of primary tumour location is available from clinical studies in patients with mCRC [8–13]. Predictive biomarkers may identify patients who are most likely to benefit from a certain treatment. Clinical studies in patients with mCRC are now evaluating the impact of primary colonic tumour location on response to treatment, with a particular focus on biologics [12–17].

Here, we present an overview of the microbiome and molecular differences associated with the primary location of CRC, and we discuss the prognostic and predictive impact of primary tumour location on clinical outcome for these patients.

2. Embryology of the midgut and hindgut

During gastrulation, the right (midgut) and left (hindgut) side of the gut develop from the endoderm and extend along the length of the embryo from the buccopharyngeal membrane to the cloacal membrane [18]. The midgut gives rise to the duodenum distal to the ampulla, the entire small bowel, the caecum, appendix, ascending colon and the proximal two-thirds of the transverse colon [19].

The distal third of the transverse colon, splenic flexure, descending colon and sigmoid rectum and the upper part of the anal canal originate from the hindgut [19]. The most distal portion of the hindgut enters into the posterior region of the cloaca, called the primitive anorectal canal, from which the anal region is derived.

Because both the right and left side of the colon derive from the endoderm [18], embryology does not appear to be the major source of the differences observed in the prognosis of CRC. Distinct gene expression differences, reflecting the midgut and hindgut differences, have been reported between the right and left side of the normal colon, as described later in this article [11,20–22].

3. Microbiome differences between the normal gut and CRC

Limited data are available on the differences of the microbiome within healthy colon tissue, and there are currently no large analyses published on the distinct differences between the transverse and descending colon.

However, an increasing microbial richness from the proximal colon to the rectum has been reported [23]. The microbiome is believed to play an important part in the formation of CRC. Bacterial phylotypes are known to vary depending on the primary tumour location (Table 1) [23–25]: RCCs have a relatively higher abundance of *Prevotella*, *Pyramido-bacterium*, *Selenomonas and Peptostreptococcus* than LCC, which have a higher prevalence of *Fusobacterium*, *Escherichia–Shigella* and *Leptotrichia* compared with RCC [23]. A significantly higher incidence of *Escherichia coli* phylogroup B2 has been detected in mucosal biopsies from patients with RCC compared to those with LCC [24], and a higher risk of *Helicobacter pylori* infection was reported in patients with LCC compared to those with RCC [25]. A lower abundance of Gram-positive, fibre-fermenting clostridia and an increased prevalence of Gram-negative, pro-inflammatory bacteria (i.e. *E. coli* phylogroup B2) has been reported in patients with CRC compared with controls [24,26].

Dense bacterial aggregates, or biofilms, are located within the normal gut and are associated with decreased E-cadherin, enhanced interleukin-6 (IL-6) and signal transducer and activator of transcription 3 (STAT3) activation and increased epithelial cell proliferation [27]. Biofilms can invade the mucus layer of the colon and may be pathogenic when they make direct contact with the mucosal epithelial cells. Invasive poly-microbial bacterial biofilms have been detected on the majority of RCCs, but on only a small percentage of LCC [27].

It remains unclear whether the changed mucosa following the development of CRC attracts different bacteria or if different bacteria have an ability to destroy the mucosa, which then leads to CRC. Both mechanisms have been postulated. *Prevotella*, *Pyramido-bacterium*, *Selenomonas* and *Peptostreptococcus* were identified in relatively higher abundance in proximal tumours compared with distal tumours [23]. Conversely, *Fusobacterium*, *Escherichia-Shigella* and *Leptotrichia* were relatively abundant in distal colorectal tumours compared with proximal tumours [23]. Recently published data show that CRC-associated bacterial clusters are differentially correlated with mucosal gene expression profiles [28]. Some clusters are partly associated with the expression of pro-inflammatory genes in the mucosa, which may result in CRC in future [28].

Table 1
Microbiome differences between RCC and LCC.

RCC	LCC
• Higher abundance of *Prevotella*, *Pyramido-bacterium*, *Selenomonas* and *Peptostreptococcus* [23]	• Higher prevalence of *Fusobacterium*, *Escherichia-Shigella* and *Leptotrichia* [23]
• Higher incidence of *Escherichia coli* phylogroup B2 [24]	• Higher risk of *Helicobacter pylori* infection [25]

LCC, left-sided colon carcinoma; RCC, right-sided colon carcinoma.

Table 2
Chromosomal and molecular characteristics of RCC and LCC.

RCC	LCC
• High MSI and CIMP [9,11]	• Chromosomal aberrations
• Hypermutation state	◦ Deletion of 8p, 17p (including *TP53*), 18p (including *SMAD4*), gain of chromosome 7, 8q (including *MYC*), 20q, loss of 18q [33]
• *KRAS* mutations [9,11]	• Aneuploidy [50]
• *BRAF* mutations [9,11]	• Frequently mutated genes: [33]
• *TGFβR2* mutations [33]	◦ *TP53*
• *PI3KCA* mutations [33]	◦ *APC*
	◦ *KRAS*
	• Overexpression:
	◦ EGFR and HER2 gain [22,36]
	◦ High EGFR ligand expression (EREG and AREG expression) [22,35]
	◦ High VEGF-1 mRNA expression [38]
	◦ COX-2 [39]
• Distribution of CMS subtypes [20]	• Distribution of CMS subtypes [20]
◦ CMS1 – 31%	◦ CMS1 – 7%
◦ CMS2 – 26%	◦ CMS2 – 56%
◦ CMS3 – 19%	◦ CMS3 – 10%
◦ CMS4 – 24%	◦ CMS4 – 27%

AREG, amphiregulin; CIMP, CpG island methylator phenotype; CMS, consensus molecular subtype; EGFR, epidermal growth factor receptor; EREG, epiregulin; LCC, left-sided colon carcinoma; MSI, microsatellite instability; RCC, right-sided colon carcinoma; VEGF-1, vascular endothelial growth factor 1.

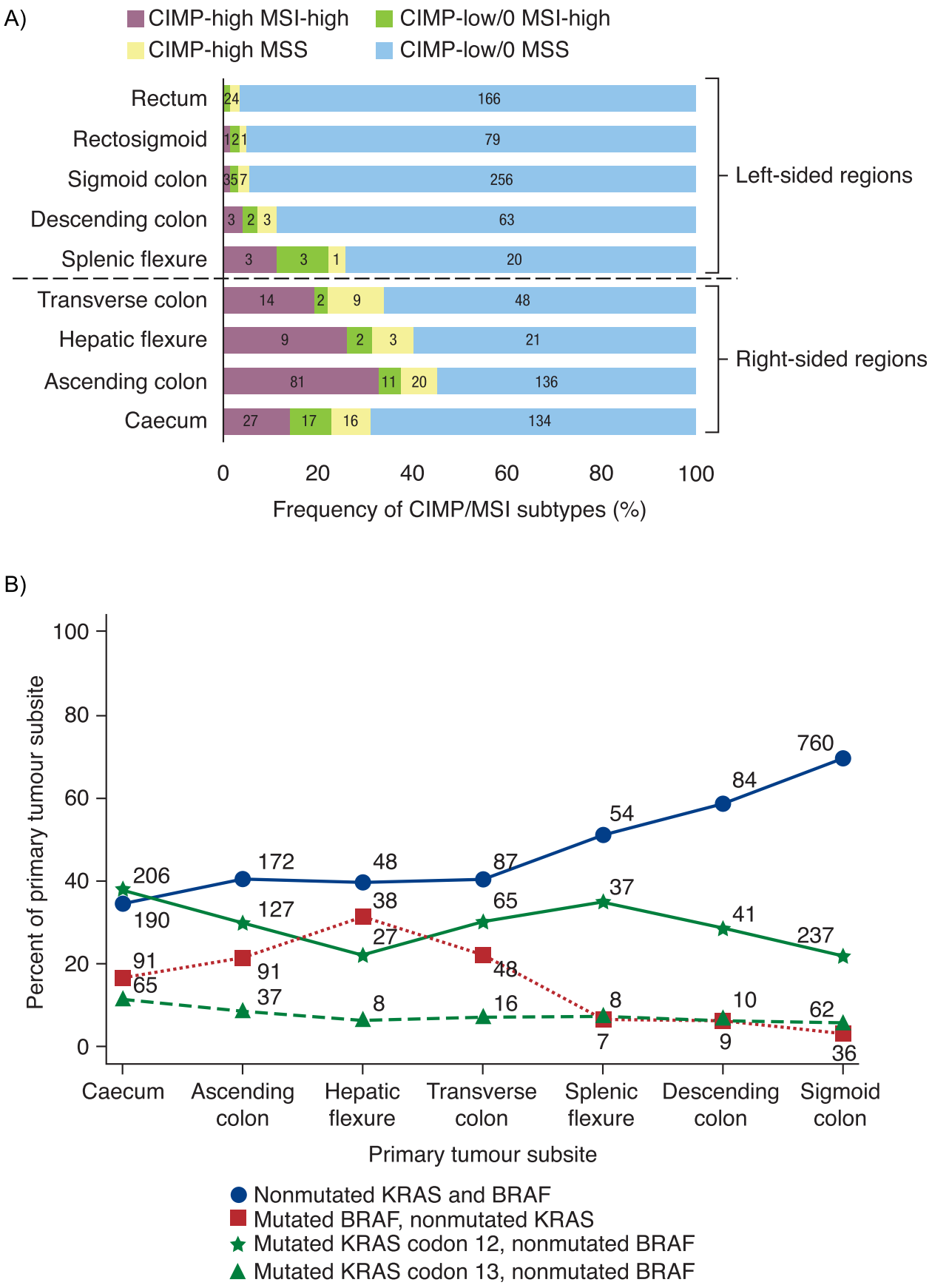

Fig. 2. A) Molecular characteristics of CRC [32] [Reproduced from *Gut* 2012, 'Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal versus distal colorectum', Yamauchi M et al, 61, 847–54,

4. Differences in clinical characteristics according to primary tumour location

A similar or greater proportion of patients with RCC are female, and the median age of patients with RCC at diagnosis is higher compared to patients with LCC [7,8,11]. RCCs are more likely to have high-grade histology and a more advanced tumour stage at initial presentation compared with LCC [7,11,29]. A low-fibre diet, smoking and alcohol excess tend to be associated with LCC [30].

Metastatic spread also differs depending on the primary location of the CRC. RCC more often metastasise to the peritoneum, and a greater proportion of LCC will metastasise to liver and lung [22].

5. Chromosomal and molecular differences according to primary tumour location

A number of chromosomal and molecular differences have been reported between RCC and LCC (Table 2). Chromosomal instability has been detected in approximately 75% of LCC and 30% of RCC [30].

Hypermutation is more prevalent in RCC compared with LCC [22]. RCC have been shown to be associated with an increase in *RAS* and phosphoinositide 3-kinase pathway mutations [31], CpG island methylator phenotype (CIMP)–high and microsatellite instability–high subtypes (Fig. 2A) and *BRAF* mutations (Fig. 2B) [22,32]. The frequency of *KRAS*/*BRAF* mutations has been noted to progressively decrease from the caecum to sigmoid colon (Fig. 2B) [11]. A higher expression of *TGFβR2* mutations also occurs within the RCC compared with the LCC [33].

Mutations in the *APC*, *KRAS*, *SMAD4* and *TP53* genes occur more often in LCC compared with RCC [34]. In addition to the increased chromosomal instability of LCC, these tumours have also been associated with more frequent overexpression of the epidermal growth factor receptor (EGFR) ligands, epiregulin (EREG) and amphiregulin (AREG) and amplification of EGFR and human epidermal growth factor receptor 2 (HER2) [22,35,36]. High AREG expression is inversely associated with *BRAF* mutation and CIMP-high status [35]. Hypermethylation and suppression of EREG and AREG expressions have been demonstrated to be strongly associated with RCC and CIMP-high status [37].

The predominant angiogenic factor, vascular endothelial growth factor (VEGF-1), plays a key role in the progression of CRC. The expression of VEGF-1 has been reported to be significantly higher in LCC compared with RCC [38]. Similarly, a more frequent expression of cyclooxygenase-2 (COX-2), which also has a role in angiogenesis, was identified in LCC compared with RCC [39].

The CRC Subtyping Consortium has defined four molecular subtypes of CRC (consensus molecular subtypes [CMS] 1–4), based on six published gene expression–based CRC subtyping algorithms and the reported differences in clinical, chromosomal and molecular characteristics between the primary tumour locations [20]. RCC are predominantly CMS1 (microsatellite instability and strong immune activation) and LCC are mostly CMS2 (canonical) (Table 2) [37].

6. Prognostic effects of primary tumour location on clinical outcome

The different clinical and biological profiles of RCC and LCC suggested that primary tumour location might have a potential impact on the prognosis of these patients and strong evidence is now available to confirm this (Table 3) [8–13]. Although tumour localisation is not included within the European Society for Medical Oncology consensus guidelines for the treatment of patients with mCRC, it is mentioned in the current National Comprehensive Cancer Network (NCCN) guidelines [3,40].

The prognostic effect of primary tumour localisation on clinical outcome was first reported in 1990 [4]. In a randomised phase III study (FIRE-1), patients with RCC had a significantly shorter progression-free survival (PFS) and OS compared with those who had LCC [15] (Table 3). This study was limited, however, by its small sample size. Further conclusive evidence was provided by multivariable analysis of a prospective pharmacogenetic study (PROVETTA) and two randomised phase III studies (AVF2107g and NO16966) of over 2000 patients with previously untreated mCRC: superior OS and PFS were observed in patients with LCC compared with RCC across all three studies [8]. RCC was therefore confirmed as a negative prognostic variable. A stepwise improvement in OS from the RCC to LCC has been demonstrated by subgroup analysis of OS and time-to-recurrence (TTR) by primary tumour location (Fig. 3) [11]. Caecal tumours had the lowest TTR and OS, and sigmoid colonic tumours had the highest TTR and OS.

Recently, a meta-analysis of 66 clinical studies has been published, comparing the OS of RCC versus LCC

copyright 2017 with permission from BMJ Publishing Group Ltd.] and B) frequency of molecular alterations, according to primary tumour location [11] [Reproduced from *Clin Cancer Res* 2015, 'Analysis of molecular markers by anatomic tumor site in Stage III colon carcinomas from adjuvant chemotherapy trial NCCTG N0147 (Alliance)' Sinicrope FA et al, 21(23), 5294-5304, copyright 2017 with permission from AACR]. CIMP, CpG island methylator phenotype; CRC, colorectal carcinoma; MSI, microsatellite instability; MSS, microsatellite stability.

Table 3
Summary of the prognostic impact of CRC location on clinical outcomes.

Study details	Regimens	Median PFS (RCC versus LCC, months) HR (95% CI), P value	Median OS (RCC versus LCC, months) HR (95% CI), P value
Prospective, pharmacogenetics study			
PROVETTA[a] [8] (n = 200)	FOLFIRI + BEV	9.9 versus 12.1 0.52 (0.36–0.75), <0.001[a]	24.8 versus 42.0 0.44 (0.28–0.70), <0.001[a]
PROVETTA[a]: non-mucinous/*BRAF* WT subgroup [8] (n = 155)	FOLFIRI + BEV	10.0 versus 13.0 0.54 (0.34–0.84), 0.01[a]	28.8 versus 47.6 0.52 (0.30–0.93), 0.02[a]
Retrospective studies			
Chinese 2-center study [17] (n = 110)	CT + CET	5.6 versus 9.1 ND, 0.244	25.1 versus 28.9 ND, 0.512
Chinese 2-centre study [17] (n = 117)	CT	5.7 versus 6.2 ND, 0.160	19.8 versus 20.1 ND, 0.593
Taiwanese single-centre case–control study [51] (n = 121)	FOLFOX or FOLFIRI + CET or BEV	5.8 versus 11.8 ND, <0.001[a]	15.7 versus 27.7 ND, 0.008[a]
Randomised, phase II studies			
AIO KRK-0104 [42] (n = 146)	CET + CAPIRI or CET + CAPOX	5.2 versus 7.8 0.67 (0.47–0.95), 0.02	14.8 versus 26.3 0.63 (0.43–0.92), 0.016
AIO KRK-0104: *KRAS* codon 12/13 WT [42] (n = 95)	CET + CAPIRI or CET + CAPOX	4.6 versus 8.4 0.54 (0.34–0.85), 0.007[a]	13.0 versus 29.0 0.42 (0.25–0.67), <0.001[a]
AIO KRK-0104: *KRAS* codon 12/13 MT [42] (n = 51)	CET + CAPIRI or CET + CAPOX	7.5 versus 5.8 1.01 (0.56–1.82), 0.96	18.9 versus 19.7 1.3 (0.68–2.34), 0.46
PEAK[b] [14] (n = 65)	Pmab + FOLFOX	10.3 versus 14.6 ND	22.5 versus 43.4 ND
PEAK[b] [14] (n = 66)	BEV + FOLFOX	12.6 versus 11.5 ND	23.3 versus 32.0 ND
Randomised, phase III studies			
FIRE-1 [15] (n = 423)	FUFIRI or mIROX	6.0 versus 8.2 0.75 (0.59–0.87), 0.024[a]	13.6 versus 21.8 0.65 (0.50–0.84), 0.001[a]
FIRE-1 [15] (n = 209)	mIROX	6.0 versus 7.8 0.84 (0.59–1.21), 0.35	14.0 versus 20.4 0.74 (0.51–1.08), 0.12
FIRE-1 [15] (n = 214)	FUFIRI	6.0 versus 8.7 0.66 (0.46–0.94), 0.02[a]	12.5 versus 25.0 0.55 (0.39–0.79), 0.001[a]
AVF2017g[c] [8] (n = 559)	CT ± BEV	7.1 versus 8.5 0.68 (0.55–0.83), <0.001[a]	14.6 versus 20.4 0.55 (0.43–0.70), <0.001[a]
AVF2017g[c] [8] (n = 277)	CT + BEV	8.7 versus 11.1 0.62 (0.45–0.85), 0.01[a]	15.9 versus 24.2 0.49 (0.34–0.70), <0.001[a]
AVF2017g[c] [8] (n = 282)	CT	5.4 versus 8.0 0.72 (0.55–0.96), 0.02[a]	13.6 versus 18.0 0.62 (0.44–0.86), 0.01[a]
NCIC CO.17[d]: re-analysis [48] (n = 199)	BSC	ND 1.07 (0.79–1.44), 0.67	ND 0.96 (0.70–1.31), 0.78
NO16966[e] [8] (n = 1268)	FOLFOX4 or XELOX or FOLFOX4 + BEV or XELOX + BEV	7.6 versus 8.9 0.90 (0.79–1.03), 0.12	18.0 versus 23.0 0.71 (0.62–0.82), <0.001[a]
NO16966[e] [8] (n = 441)	FOLFOX4 + BEV or XELOX + BEV	8.6 versus 10.0 0.95 (0.76–1.19), 0.64	20.6 versus 24.7 0.78 (0.61–0.99), 0.04[a]
NO16966[e] [8] (n = 827)	FOLFOX4 or XELOX	7.0 versus 8.3 0.87 (0.74–1.03), 0.10	17.0 versus 22.0 0.67 (0.57–0.80), <0.001[a]
CALGB/SWOG 80405[f]: *KRAS* WT [12] (n = 1025)	CET + CT or BEV + CT	8.9 versus 11.5 1.25 (1.08–1.46), 0.002	19.4 versus 34.2 1.56 (1.32–1.84), <0.0001
CALGB/SWOG 80405[f]: *KRAS* MT [12] (n = 213)	CET + CT or BEV + CT	ND	23.1 versus 30.3 1.28 (0.95–1.73), <0.0001
PRIME[g] [14] (n = 182)	Pmab + FOLFOX	8.9 versus 12.9	22.5 versus 32.5
PRIME[g] [14] (n = 180)	FOLFOX	7.3 versus 9.3	21.5 versus 23.6
FIRE-3[h]: *RAS* exon 2 WT [16] (n = 195)	CET + FOLFIRI	7.6 versus 10.7 2.0 (1.36–2.93), <0.001[a]	18.3 versus 38.3 2.84 (1.86–4.33), <0.001[a]
FIRE-3[h]: *RAS* exon 2 WT [16] (n = 199)	BEV + FOLFIRI	9.0 versus 10.7 1.38 (0.99–1.94), 0.06	23.0 versus 28.0 1.48 (1.02–2.16), 0.04
CRYSTAL[i]: *RAS* WT [16] (n = 175)	FOLFIRI + CET	8.1 versus 12.0 1.77 (1.08–2.91), 0.02	18.5 versus 28.7 1.93 (1.24–2.99), 0.003
CRYSTAL[i]: *RAS* WT [16] (n = 189)	FOLFIRI	7.1 versus 8.9 1.54 (0.96–2.46), 0.07	15.0 versus 21.7 1.35 (0.93–1.97), 0.11

Table 3 (*continued*)

Study details	Regimens	Median PFS (RCC versus LCC, months) HR (95% CI), P value	Median OS (RCC versus LCC, months) HR (95% CI), P value
Registry			
Australian TRACC registry [13] (n = 926)	CT ± BEV	7.6 versus 10.2 (rectum 10.3) ND, <0.0001[a]	18.2 versus 23.6 (rectum 26.2) ND, 0.0007[a]

Clinicaltrials.gov identifiers: [a]NCT01363739; [b]NCT00819780; [c]NCT00109070; [d]NCT00079066; [e]NCT00069095; [f]NCT00265850; [g]NCT00364013; [h]NCT00433927; [i]NCT00154102.

BEV, bevacizumab; BSC, best supportive care; CAPIRI, capecitabine, irinotecan; CAPOX, capecitabine, oxaliplatin; CET, cetuximab; CI, confidence interval; CT, chemotherapy; FOLFOX, bolus 5-fluorouracil/leucovorin/oxaliplatin; FOLFIRI, bolus 5-fluorouracil/leucovorin/irinotecan; FUFIRI, infusional 5-fluorouracil/leucovorin/irinotecan; HR, hazard ratio; LCC, left-sided colon carcinoma; mIROX, irinotecan, oxaliplatin; MT, mutated; ND, not determined (not published in primary source cited); OS, overall survival; PFS, progression-free survival; Pmab, panitumumab; RCC, right-sided colon carcinoma; WT, wild-type; XELOX, capecitabine, oxaliplatin.

[a] Statistically significantly different (P<0.05).

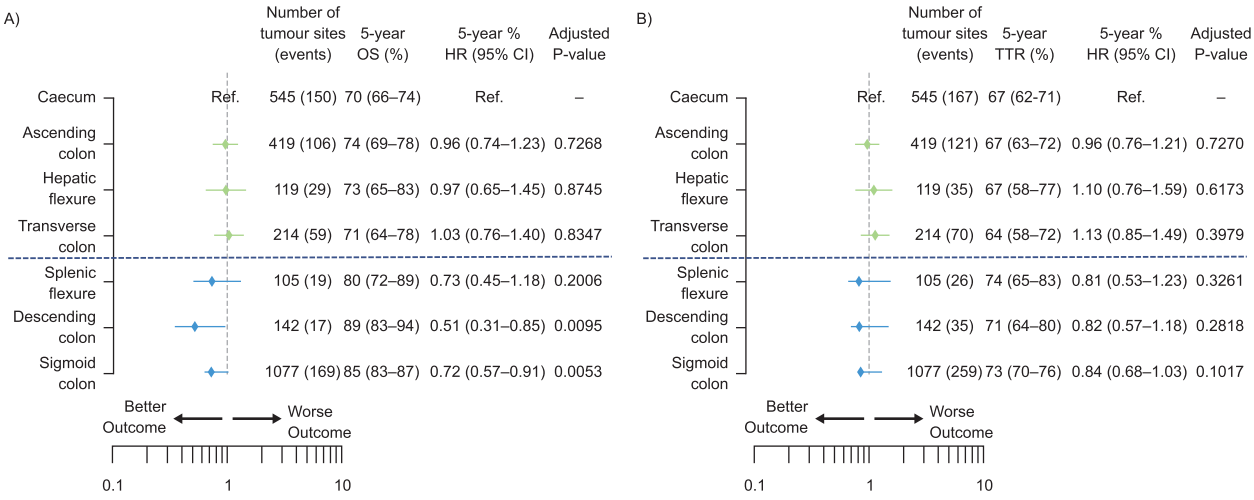

Fig. 3. Clinical outcome of patients with stage III CRC according to tumour localisation: A) overall survival and B) time-to-recurrence [11] [Reproduced from *Clin Cancer Res* 2015, 'Analysis of molecular markers by anatomic tumor site in Stage III colon carcinomas from adjuvant chemotherapy trial NCCTG N0147 (Alliance)' Sinicrope FA et al, 21(23), 5294-5304, copyright 2017 with permission from AACR]. CI, confidence intervals; CRC, colorectal carcinoma; HR, hazard ratio; OS, overall survival; Ref., reference group; TTR, time-to-response.

in over 1.4 million patients with early and advanced CRC [41]. A pooled hazard ratio of 0.82 (P<0.001) was reported in favour of LCC. Patients with LCC had a 20% reduction in the risk of death compared with RCC, independent of ethnicity, disease stage and type of study. This meta-analysis concluded that primary tumour location should be established as a key criterion for confirming OS outcomes in all stages of CRC.

Several studies have investigated the contribution of mutational status (i.e. *KRAS* and *BRAF*) and key marker expression (i.e. HER2 and EGFR) to the impact of primary tumour location on prognosis [11,12,35,42]. In patients with *KRAS* codon 12/13 wild-type (WT) CRC, LCC were associated with a significantly longer PFS and OS compared with RCC [42]. No impact of primary tumour location on clinical outcomes was observed in patients with *KRAS*-mutated (MT) mCRC in this study. In the North Central Cancer Treatment Group (NCCTG) N0147 (Alliance) study, however, *KRAS*-MT LCC was associated with poorer OS compared with *KRAS*-MT RCC [11]. *BRAF* mutations have been shown to be associated with poorer outcomes for patients with mCRC than *BRAF* WT, and these are more prevalent in RCC than LCC [11]. The current international guidelines for the management of patients with mCRC recognise the prognostic impact of mutational status and recommend that patients are tested for *RAS* and *BRAF* mutation status before establishing a first-line treatment regimen [3,40].

However, *RAS* and *BRAF* mutational status are not the only prognostic factors for patients with mCRC. In a multivariant analysis of two randomised phase III studies (CRYSTAL and FIRE-3), LCC and RCC were highly prognostic for PFS and OS even when patients with *BRAF* mutation were excluded [16]. In subgroup analysis from two randomised phase III studies (FIRE-3

and TRIBE), *IL-6* genetic variants were identified as a prognostic factor for patients with mCRC treated with first-line bevacizumab-based chemotherapy, depending on primary tumour location [43].

To summarise, the primary tumour location is a known prognostic factor for patients with CRC [8–13]. A meta-analysis from prospective and retrospective clinical studies reporting OS data for LCC and RCC mCRC concluded that patients with RCC had poorer prognosis than those with LCC [41]. This appears to be independent of the mutational spectrum within these tumours [12,16].

7. Predictive effects of primary tumour location on clinical outcome

Given the differential expression of EGFR and of EGFR ligands, and the differing incidence of *KRAS* mutations between RCC and LCC, several studies have investigated the predictive effect of primary tumour location on clinical outcomes from treatment with EGFR and VEGF inhibitors in patients with CRC [12–17] (Table 4).

Post-hoc analysis of clinical studies suggests that although anti-EGFR therapy provides clinical benefit to patients with *RAS* WT mCRC, this benefit is not relevant for patients with RCC [12,16,44]. In a subgroup analysis by tumour location from the CALGB/SWOG 80405 study, prolonged OS and PFS were observed in patients with LCC treated with either cetuximab or bevacizumab plus 5-fluorouracil/leucovorin/irinotecan (FOLFIRI) or 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX), however outcomes were poorer in patients with RCC who were treated with cetuximab plus FOLFIRI or FOLFOX [12]. In the FIRE-3 and CRYSTAL randomised phase III studies of patients with *RAS* WT CRC, differential treatment effects were observed between primary tumour locations [16]. Patients who received cetuximab plus FOLFIRI in the CRYSTAL study had significantly improved outcomes compared with those who received FOLFIRI alone. This benefit was greater in patients with LCC compared with those with RCC [16]. In FIRE-3, patients with LCC who received cetuximab plus FOLFIRI as first-line therapy had a significantly longer OS than those who received bevacizumab plus FOLFIRI [16]. No significant difference in clinical outcomes was observed between these treatment groups for patients with RCC. This may be driven by LCC having a higher EGFR expression than RCC, differences in EGFR ligand expression or other as yet unidentified factors [22]. The NCCN guidelines recommend the use of anti-EGFR substances for the treatment of *RAS* WT LCC only [40].

Similar data have been presented for the use of panitumumab in first-line mCRC [14]. A retrospective analysis of the PRIME study showed a significant survival benefit for patients with LCC treated with FOLFOX plus panitumumab when compared with FOLFOX alone. In contrast, no benefit was associated with FOLFOX plus panitumumab in patients with RCC. Since this is in accordance with the cetuximab data, it appears to be a class effect. A meta-analysis comparing clinical outcome data from multiple clinical studies according to primary tumour location has already been published [45].

In the prospective PROVETTA clinical study of patients with CRC who received bevacizumab plus chemotherapy, VEGF expression was similar across primary tumour locations [8]. Efficacy results from the PROVETTA, AVF2107g and NO16966 studies confirmed that first-line bevacizumab in combination with chemotherapy improves clinical outcomes for patients with CRC, irrespective of primary tumour location [8]. Several other clinical studies have also provided evidence that tumour location does not appear to be predictive of benefit from bevacizumab treatment in patients with CRC [12,13,46,47].

Limited data are currently available on the predictive impact of primary tumour location on clinical outcome following second-line or later treatment (Table 5). In a reanalysis of the phase III NCIC CO-17 study of patients with *KRAS* WT mCRC who had failed standard chemotherapy, those with LCC who received cetuximab experienced a significantly improved PFS compared with those treated with BSC [48]. This clinical benefit was not observed in patients with RCC. Similarly, in preliminary efficacy data from another phase III study (Study 20050181), where patients with mCRC received second-line panitumumab plus FOLFIRI, improved clinical outcomes were observed in patients with LCC compared with RCC [14]. Although these findings suggest that tumour location may strongly predict clinical benefit with cetuximab or panitumumab, these studies were limited by their low sample size and a lack of stratification by *BRAF* status in some studies. Retrospective analysis from the phase III FIRE-3 study of patients with *KRAS* WT mCRC reported a significantly greater efficacy of second-line therapy in patients with LCC compared with RCC [44]. This difference was more evident for patients with LCC who received second-line cetuximab compared with those who received second-line bevacizumab. These observations indicate that efficacy of second-line therapy is associated with primary tumour location.

HER2/neu has been identified as a predictive biomarker in mCRC [36]. HER2/neu-amplifications have been shown to be more prevalent in LCC than in RCC. This suggests that patients with LCC may benefit more from a HER2-directed therapy, including agents such as trastuzumab [36]. A recent study has reported similar clinical outcomes for patients with HER2-amplified or HER2-non-amplified *RAS*/*BRAF* WT CRC on first-line therapy without anti-EGFR antibodies [49]. Patients with HER2-amplified *RAS*/*BRAF*

Table 4
Summary of the predictive impact of CRC location on clinical outcomes following first-line therapy.

Study details	PFS by treatment arm (months) HR (95% CI), P value		OS by treatment arm (months) HR (95% CI), P value	
	RCC	LCC	RCC	LCC
Retrospective study				
Chinese 2-centre study [17] (n = 227)	CT (5.7) versus CT + CET (5.6) ND, 0.904	CT (6.2) versus CT + CET (9.1) ND, 0.002[a]	CT (19.8) versus CT + CET (25.1) ND, 0.553	CT (20.1) versus CT + CET (28.9) ND, 0.036[a]
Randomised, phase II study				
PEAK[a] [14] (n = 133)	Pmab + FOLFOX (10.3) versus BEV + FOLFOX (12.6) 0.88 (0.39–2.02), ND	Pmab + FOLFOX (14.6) versus BEV + FOLFOX (11.5) 0.67 (0.44–1.02), ND	Pmab + FOLFOX (22.5) versus BEV + FOLFOX (23.3) 0.63 (0.26–1.54), ND	Pmab + FOLFOX (43.4) versus BEV + FOLFOX (32.0) 0.77 (0.46–1.28), ND
Randomised, phase III studies				
FIRE-1 [15] (n = 423)	FUFIRI (6.0) versus mIROX (6.0) 0.94 (0.60–1.489), 0.79	FUFIRI (8.7) versus mIROX (7.8) 1.17 (0.94–1.46), 0.17	FUFIRI (12.5) versus mIROX (14.5) 0.90 (0.57–1.43), 0.65	FUFIRI (25.0) versus mIROX (20.4) 1.17 (0.93–1.47), 0.19
CALGB/SWOG 8040[b]: *KRAS* WT [12] (n = 1137)	CET (7.7) versus BEV (9.5) ND, ND 'similar to OS'	CET (12.0) versus BEV (11.1) ND, ND 'similar to OS'	CET (16.4) versus BEV (24.5) ND, 0.03[a] (CET versus BEV superiority log rank)	CET (37.5) versus BEV (32.1) ND, 0.04[a] (CET versus BEV superiority log rank)
PRIME[c] [14] (n = 362)	Pmab + FOLFOX (8.9) versus FOLFOX (7.3) 0.71 (0.4–1.27), ND	Pmab + FOLFOX (12.9) versus FOLFOX (9.3) 0.69 (0.54–0.88), ND	Pmab + FOLFOX (22.5) versus FOLFOX (21.5) 0.94 (0.53–1.67), ND	Pmab + FOLFOX (32.5) versus FOLFOX (23.6) 0.67 (0.56–0.86), ND
FIRE-3[d]: *RAS* exon 2 WT [16] (n = 394)	FOLFIRI + CET (7.6) versus FOLFIRI + BEV (9.0) 1.44 (0.92–2.26), 0.11	FOLFIRI + CET (10.7) versus FOLFIRI + BEV (10.7) 0.90 (0.71–1.14), 0.38	FOLFIRI + CET (18.3) versus FOLFIRI + BEV (23.0) 1.31 (0.81–2.11), 0.28	FOLFIRI + CET (38.3) versus FOLFIRI + BEV (28.0) 0.63 (0.48–0.85), 0.002
CRYSTAL[e]: *RAS* WT [16] (n = 364)	FOLFIRI + CET (8.1) versus FOLFIRI (7.1) 0.87 (0.47–1.62), 0.66	FOLFIRI + CET (12.0) versus FOLFIRI (8.9) 0.50 (0.34–0.72), <0.001	FOLFIRI + CET (18.5) versus FOLFIRI (15.0) 1.08 (0.65–1.81), 0.76	FOLFIRI + CET (28.7) versus FOLFIRI (21.7) 0.65 (0.50–0.86), 0.002
Registry				
TRACC Australian Registry [13] (n = 926)	CT (4.9) versus CT + BEV (8.54) 0.46 (0.36–0.60), <0.001[a]	CT (7.5; rectum: 7.1) versus CT + BEV (10.5; rectum 11.3) 0.71 (0.56–0.91) (rectum 0.64 [0.50–0.84]), 0.006[a] (rectum 0.001[a])	ND ND	ND ND

Clinicaltrials.gov identifiers: [a]NCT00819780; [b]NCT00265850; [c]NCT00364013; [d]NCT00433927; [e]NCT00154102.
BEV, bevacizumab; CET, cetuximab; CI, confidence interval; CT, chemotherapy; FOLFOX, bolus 5-fluorouracil/leucovorin/oxaliplatin; FOLFIRI, bolus 5-fluorouracil/leucovorin/irinotecan; FUFIRI, infusional 5-fluorouracil/leucovorin/irinotecan; HR, hazard ratio; LCC, left-sided colon carcinoma; mIROX, irinotecan plus oxaliplatin; ND, not determined (not published in primary source cited); OS, overall survival; PFS, progression-free survival; Pmab, panitumumab; RCC, right-sided colon carcinoma.
[a] Statistically significantly different (P<0.05).

Table 5
Summary of the predictive impact of CRC location on clinical outcomes following second-line therapy.

Study details	PFS by treatment arm (months) HR (95% CI), P value		OS by treatment arm (months) HR (95% CI), P value	
	RCC	LCC	RCC	LCC
Retrospective study				
Chinese 2-centre study [17] (n = 189)	CT (4.2) versus CT + CET (3.3) ND, 0.761	CT (3.5) versus CT + CET (4.9) ND, 0.064	CT (13.0) versus CT + CET (13.4) ND, 0.652	CT (12.4) versus CT + CET (17.1) ND, 0.047[a]
Randomised, phase III studies				
NCIC CO.17[a]: re-analysis [48] (n = 399)	CET (1.8) versus BSC (1.8) 0.93 (0.66–1.29), 0.64	CET (3.6) versus BSC (1.8) 0.53 (0.41–0.69), <0.0001[a]	CET (4.8) versus BSC (4.5) 1.00 (0.70–1.43), 1.00	CET (6.8) versus BSC (4.2) 0.60 (0.46–0.80), 0.0003[a]
20050181[b] [14] (n = 335)	Pmab + FOLFIRI (6.8) versus FOLFIRI (3.7) 0.62 (0.34–1.13), ND	Pmab + FOLFIRI (8.0) versus FOLFIRI (6.6) 0.89 (0.69–1.13), ND	Pmab + FOLFIRI (11.9) versus FOLFIRI (10.9) 0.84 (0.46–1.54), ND	Pmab + FOLFIRI (20.1) versus FOLFIRI (16.9) 0.97 (0.76–1.26), ND
FIRE-3[c]: *RAS* exon 2 WT [44] (n = 411)	FOLFIRI + CET (4.0) versus FOLFIRI + BEV (3.3) 1.09 (0.62–1.90)	FOLFIRI + CET (7.3) versus FOLFIRI + BEV (5.3) 0.61 (0.44–0.84), 0.002		

Clinicaltrials.gov identifiers: [a]NCT00819780; [b]NCT00079066; [c]NCT00433927.
BSC, best supportive care; CET, cetuximab; CI, confidence interval; FOLFIRI, bolus 5-fluorouracil/leucovorin/irinotecan; HR, hazard ratio; LCC, left-sided colon carcinoma; ND, not determined (not published in primary source cited); OS, overall survival; PFS, progression-free survival; Pmab, panitumumab; RCC, right-sided colon carcinoma.
[a] Statistically significantly different (P<0.05).

WT CRC who received anti-EGFR antibodies after first-line therapy had a significantly shorter PFS compared to those with HER2-non-amplified CRC. HER2 amplification, therefore, appears to be a predictive biomarker for reduced benefit from anti-EGFR antibody therapy and potential benefit from HER2-targeted therapy (i.e. trastuzumab and lapatinib).

Primary tumour location appears, therefore, to have a predictive effect on first- [12,14,16] and second-line [14,44,48] anti-EGFR treatment and treatment in the chemo-refractory setting [48]. Primary tumour location does not appear to be predictive of clinical benefit from anti-VEGF treatment [8,12,13,46,47].

8. Conclusions

Distinct subsets of mCRC can be defined based on the location of the primary tumour. Patients with RCC and LCC differ in their microbiome, clinical characteristics, molecular profiling, clinical outcome and response to treatment. The driver(s) and reason(s) for these differences remain unknown.

Based on current knowledge, and until the use of anti-EGFR antibodies has been defined for each molecular subgroup of mCRC, we suggest that patients with *RAS* WT RCC may benefit more from initial treatment with bevacizumab in combination with chemotherapy and those with LCC should receive first-line treatment with anti-EGFR therapies and chemotherapy. Currently, data on *RAS*-MT LCC versus RCC are limited; therefore, the prognostic and predictive value of the primary tumour site within the *RAS* MT population still requires evaluation. In addition, further investigations are required to determine if the primary tumour location and type of chemotherapy backbone used (i.e. oxaliplatin-based [XELOX or FOLFOX] or irinotecan-based [FOLFIRI or single-agent irinotecan]) are associated with different efficacies. Primary tumour location should not only be a critical stratification factor for clinical trials but should also be considered for the translational workup of clinical trials and the retrospective analyses of prognostic and predictive markers.

Conflict of interest statement

SS has received honoraria and travel expenses and serves as an advisor for Amgen, Bayer, Lilly, Merck KGaA, Roche, Sanofi and Sirtex. ST has received honoraria from Amgen, Bayer, BMS, Eli Lilly, Merck Serono, MSD, Sanofi and Roche. PG has received research funding from Amgen, Bayer, Merck, Roche, Servier and Sirtex. LT is an employee of Roche Pharma AG. HJL has received honoraria and travel expenses and has served as an advisor for Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Merck KGaA and Roche.

Acknowledgements

Medical writing support was provided by Physicians World Europe GmbH, Mannheim, Germany and was financially supported by Roche Pharma AG, Grenzach-Wyhlen, Germany. The authors directed and are fully

responsible for all content and editorial decisions. All authors contributed to the writing and review of this manuscript and approved the final version.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359–86.

[2] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49(6):1374–403.

[3] Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27(8):1386–422.

[4] Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med 1990;113(10):779–88.

[5] Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. J Surg Oncol 2004;88(4):261–6.

[6] Iacopetta B. Are there two sides to colorectal cancer? Int J Cancer 2002;101(5):403–8.

[7] Hemminki K, Santi I, Weires M, Thomsen H, Sundquist J, Bermejo JL. Tumor location and patient characteristics of colon and rectal adenocarcinomas in relation to survival and TNM classes. BMC Cancer 2010;10:688.

[8] Loupakis F, Yang D, Yau L, Feng S, Cremolini C, Zhang W, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst 2015;107(3).

[9] Nitsche U, Stogbauer F, Spath C, Haller B, Wilhelm D, Friess H, et al. Right sided colon cancer as a distinct histopathological subtype with reduced prognosis. Dig Surg 2016;33(2):157–63.

[10] Price TJ, Beeke C, Ullah S, Padbury R, Maddern G, Roder D, et al. Does the primary site of colorectal cancer impact outcomes for patients with metastatic disease? Cancer 2015;121(6):830–5.

[11] Sinicrope FA, Mahoney MR, Yoon HH, Smyrk TC, Thibodeau SN, Goldberg RM, et al. Analysis of molecular markers by anatomic tumor site in stage III colon carcinomas from adjuvant chemotherapy trial NCCTG N0147 (alliance). Clin Cancer Res 2015;21(23):5294–304.

[12] Venook A, Niedzwiecki D, Innocenti F, Fruth B, Greene C, O'Neil B, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol 2016;34(Suppl.; abstr 3504).

[13] Wong HL, Lee B, Field K, Lomax A, Tacey M, Shapiro J, et al. Impact of primary tumor site on bevacizumab efficacy in metastatic colorectal cancer. Clin Colorectal Cancer 2016;15(2):e9–15.

[14] Boeckx N, Toler A, Op de Beeck K, Kafatos G, Deschoolmeester V, Rolfo C, et al. Primary tumor sidedness impacts on prognosis and treatment outcome: results from three randomized studies of panitumumab plus chemotherapy versus chemotherapy or chemotherapy plus bevacizumab in 1st and 2nd line RAS/BRAF WT mCRC. Ann Oncol 2016;27(Suppl. 6):vi15–42.

[15] Modest DP, Schulz C, von Weikersthal LF, Quietzsch D, von Einem JC, Schalhorn A, et al. Outcome of patients with metastatic colorectal cancer depends on the primary tumor site (midgut vs. hindgut): analysis of the FIRE1-trial (FuFIRI or mIROX as first-line treatment). Anticancer Drugs 2014;25(2):212–8.

[16] Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol 2016 Oct 10. http://dx.doi.org/10.1001/jamaoncol.2016.3797 [Epub ahead of print].

[17] Wang F, Bai L, Liu TS, Yu YY, He MM, Liu KY, et al. Right-sided colon cancer and left-sided colorectal cancers respond differently to cetuximab. Chin J Cancer 2015;34(9):384–93.

[18] Hill MA. Embryology gastrointestinal tract development. 2016.

[19] Sadler TW. Langman's medical embryology. 2014.

[20] Guinney J, Dienstmann R, Wang X, de Reynies A, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21(11):1350–6.

[21] Kawazoe Y, Sekimoto T, Araki M, Takagi K, Araki K, Yamamura K. Region-specific gastrointestinal Hox code during murine embryonal gut development. Dev Growth Differ 2002;44(1):77–84.

[22] Missiaglia E, Jacobs B, D'Ario G, Di Narzo AF, Soneson C, Budinska E, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol 2014;25(10):1995–2001.

[23] Gao Z, Guo B, Gao R, Zhu Q, Qin H. Microbiota disbiosis is associated with colorectal cancer. Front Microbiol 2015;6:20.

[24] Kohoutova D, Smajs D, Moravkova P, Cyrany J, Moravkova M, Forstlova M, et al. Escherichia coli strains of phylogenetic group B2 and D and bacteriocin production are associated with advanced colorectal neoplasia. BMC Infect Dis 2014;14:733.

[25] Zhang Y, Hoffmeister M, Weck MN, Chang-Claude J, Brenner H. *Helicobacter pylori* infection and colorectal cancer risk: evidence from a large population-based case-control study in Germany. Am J Epidemiol 2012;175(5):441–50.

[26] Ahn J, Sinha R, Pei Z, Dominianni C, Wu J, Shi J, et al. Human gut microbiome and risk for colorectal cancer. J Natl Cancer Inst 2013;105(24):1907–11.

[27] Dejea CM, Wick EC, Hechenbleikner EM, White JR, Mark Welch JL, Rossetti BJ, et al. Microbiota organization is a distinct feature of proximal colorectal cancers. Proc Natl Acad Sci USA 2014;111(51):18321–6.

[28] Flemer B, Lynch DB, Brown JM, Jeffery IB, Ryan FJ, Claesson MJ, et al. Tumour-associated and non-tumour-associated microbiota in colorectal cancer. Gut 2017;66(4):633–43.

[29] Weiss JM, Pfau PR, O'Connor ES, King J, LoConte N, Kennedy G, et al. Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results–medicare data. J Clin Oncol 2011;29(33):4401–9.

[30] Shen H, Yang J, Huang Q, Jiang MJ, Tan YN, Fu JF, et al. Different treatment strategies and molecular features between right-sided and left-sided colon cancers. World J Gastroenterol 2015;21(21):6470–8.

[31] Lan YT, Jen-Kou L, Lin CH, Yang SH, Lin CC, Wang HS, et al. Mutations in the RAS and PI3K pathways are associated with metastatic location in colorectal cancers. J Surg Oncol 2015;111(7):905–10.

[32] Yamauchi M, Morikawa T, Kuchiba A, Imamura Y, Qian ZR, Nishihara R, et al. Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal versus distal colorectum. Gut 2012;61(6):847–54.

[33] Mouradov D, Sloggett C, Jorissen RN, Love CG, Li S, Burgess AW, et al. Colorectal cancer cell lines are representative models of the main molecular subtypes of primary cancer. Cancer Res 2014;74(12):3238–47.

[34] Rowan A, Halford S, Gaasenbeek M, Kemp Z, Sieber O, Volikos E, et al. Refining molecular analysis in the pathways of colorectal carcinogenesis. Clin Gastroenterol Hepatol 2005;3(11):1115–23.

[35] Lee MS, McGuffey EJ, Morris JS, Manyam G, Baladandayuthapani V, Wei W, et al. Association of CpG island

methylator phenotype and EREG/AREG methylation and expression in colorectal cancer. Br J Cancer 2016;114(12):1352–61.

[36] Mayer B, Zoller M, Singer T, Magosch S, Joka M, Werner J. Targeted therapy using trastuzumab will overcome chemotherapeutic failure in liver metastasis of colorectal cancer. Eur Surg Res 2015.

[37] Lee MSA SM, Morris J, Jiang Z-Q, Manyam GC, Menter D, Broom BM, et al. Association of primary (1°) site and molecular features with progression-free survival (PFS) and overall survival (OS) of metastatic colorectal cancer (mCRC) after anti-epidermal growth factor receptor (αEGFR) therapy. J Clin Oncol 2016;34.

[38] Bendardaf R, Buhmeida A, Hilska M, Laato M, Syrjanen S, Syrjanen K, et al. VEGF-1 expression in colorectal cancer is associated with disease localization, stage, and long-term disease-specific survival. Anticancer Res 2008;28(6B):3865–70.

[39] Nasir A, Kaiser HE, Boulware D, Hakam A, Zhao H, Yeatman T, et al. Cyclooxygenase-2 expression in right- and left-sided colon cancer: a rationale for optimization of cyclooxygenase-2 inhibitor therapy. Clin Colorectal Cancer 2004;3(4):243–7.

[40] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Colon cancer. 2017. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.

[41] Petrelli F, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dallera P, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. JAMA Oncol 2016.

[42] von Einem JC, Heinemann V, von Weikersthal LF, Vehling-Kaiser U, Stauch M, Hass HG, et al. Left-sided primary tumors are associated with favorable prognosis in patients with KRAS codon 12/13 wild-type metastatic colorectal cancer treated with cetuximab plus chemotherapy: an analysis of the AIO KRK-0104 trial. J Cancer Res Clin Oncol 2014;140(9):1607–14.

[43] Matsusaka S, Hanna DL, Cao S, Zhang W, Yang D, Ning Y, et al. Prognostic impact of IL6 genetic variants in patients with metastatic colorectal cancer treated with bevacizumab-based chemotherapy. Clin Cancer Res 2016;22(13):3218–26.

[44] Modest DP, Stintzing S, Fischer von Weikersthal L, Decker T, Kiani A, Vehlong-Kaiser U, et al. Primary tumor location and efficacy of second-line therapy after initial treatment with FOLFIRI in combination with cetuximab or bevacizumab in patients with metastatic colorectal cancer- FIRE-3 (AIOKRK0306). J Clin Oncol 2017;35(Suppl.).

[45] Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. Eur J Cancer 2017;70:87–98.

[46] Houts AC, Ogale S, Sommer N, Walker MS. Treatment patterns and outcomes in patients with KRAS wild type (WT) metastatic colorectal cancer (mCRC) treated in first line with bevacizumab (B) or cetuximab (C) containing regimens. J Clin Oncol 2016;34.

[47] Lenz H, Lee F, Yau L, Koh H, Knost K, Mitchell E, et al. MAVERICC, a phase 2 study of mFOLFOX6bevacizumab (BV) vs FOLFIRIBV with biomarker stratification as firstline (1L) chemotherapy (CT) in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol 2016;34(Suppl. 4S; abstr 493).

[48] Brule SY, Jonker DJ, Karapetis CS, O'Callaghan CJ, Moore MJ, Wong R, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. Eur J Cancer 2015;51(11):1405–14.

[49] Raghav KPS, Overman Micheal J, Yu R, Meric-Bernstam F, Menter D, Kee BK, et al. HER2 amplification as a negative predictive biomarker for anti-epidermal growth factor receptor antibody therapy in metastatic colorectal cancer. J Clin Oncol 2016;34.

[50] Sugai T, Habano W, Nakamura S, Sato H, Uesugi N, Takahashi H, et al. Genetic alterations in DNA diploid, aneuploid and multiploid colorectal carcinomas identified by the crypt isolation technique. Int J Cancer 2000;88(4):614–9.

[51] Lu HJ, Lin JK, Chen WS, Jiang JK, Yang SH, Lan YT, et al. Primary tumor location is an important predictive factor for wild-type KRAS metastatic colon cancer treated with cetuximab as front-line bio-therapy. Asia Pac J Clin Oncol 2016;12(3):207–15.