

REVIEW ARTICLE

Differences in clinical features and oncologic outcomes between metastatic right and left colon cancer

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Summary

Approximately 20% to 25% of patients with colorectal cancer (CRC) have distant organ metastasis at the time of initial diagnosis. The primary tumor location has been suggested as a prognostic factor for patients with metastatic CRC. In recent years, the distinction between right colon cancer (RCC) and left colon cancer (LCC) has been brought into focus due to their different outcomes, prognoses, and clinical responses to chemotherapy. In this article we aimed to review the underlying differences between metastatic RCC and LCC in terms of epidemiology, clinical features, and oncologic outcomes. The outcomes of patients with left-sided tumors were better than those of patients with right-sided tumors in terms of overall survival (OS) and objective response rate (ORR) after treatment with chemotherapy + panitumumab in the

PRIME and 20050181 trials. The outcomes of patients with LCC were better than those of patients with RCC in terms of OS, progression-free survival (PFS) and ORR after treatment with FOLFIRI + cetuximab in the CRYSTAL and CALGB 80405 trials. In the FIRE-3 trial, the OS and PFS, but not the ORR, of patients with LCC were superior to those of patients with RCC. LCC and RCC exhibit distinctive clinical features and epidemiology. However, we must further investigate the impact of these distinctive features and how they influence the differential oncologic outcomes.

Key words: antineoplastic agents, colonic neoplasms, neoplasm metastasis, survival rate

Introduction

Approximately 20% to 25% of patients with colorectal cancer (CRC) have distant organ metastasis at the time of initial diagnosis [1]. Multimodal treatment approaches including chemotherapy, surgery, and radiation therapy are essential for the treatment for metastatic CRC (mCRC) [2]. There are various prognostic factors for mCRC such as the extent of organ metastasis, number of organ metastases, performance status, and use of combination chemotherapy [3]. In addition, the primary tumor location has been suggested as a prognostic

factor [4]. In recent years, the distinction between right colon cancer (RCC) and left colon cancer (LCC) has been brought into focus due to their different outcomes, prognoses, and clinical responses to chemotherapy.

CRC can be characterized by the primary tumor location within the colon [5,6]. It has long been appreciated that developmental and physiological differences exist between anatomic segments of the colorectum and that CRC occurs at distinct frequencies at different subsites [7]. The proximal colon

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and distal colon have different embryologic origins; the distal duodenum to the proximal two-thirds of the transverse colon is derived from the midgut, whereas the distal third of the transverse colon to the upper two-thirds of the anorectal canal is derived from the hindgut [8]. In addition, these segments have different physiological functions. The capacity to absorb water and electrolytes differs between the proximal colon and the distal colon. The main site of water absorption is the proximal colon, whereas the main function of the distal colon is to facilitate the passage of bowel contents.

To date, several studies have shown that primary tumor sidedness may be a prognostic factor and predictive of the therapeutic response to anti-EGFR agents in patients with mCRC. The *ad hoc* analysis of the CALGB/SWOG 80405 trial showed better overall survival (OS) in patients with *KRAS* wild-type (wt) metastatic LCC [9]. Similar trials, including the CRYSTAL and FIRE-3 trials, showed that the outcomes were superior for patients with left-sided tumors than for those with right-sided tumors [10].

Clinical trials, including the VICTOR and QUASAR2 trials, in the adjuvant setting showed that RCC was associated with poorer OS but not recurrence-free survival (RFS), which did not differ between right and left-sided tumors [11]. This discrepancy between OS and RFS is a result of the worse survival after recurrence of patients with right-sided tumors than of patients with left-sided tumors.

The hypothesis of our study was that there are identifiable reasons for the poorer prognosis of patients with right-sided tumors. We aimed to review the underlying differences between metastatic RCC and LCC in terms of epidemiology, clinical features, and oncologic outcomes.

Epidemiology

Historically, the incidence of LCC has been higher than that of RCC. The influence of gender and age on the subsite distribution of CRC was first reported 46 years ago [12] and has since been confirmed by many others. One study that enrolled approximately 10,000 patients with CRC in Florida showed a progressive decrease in the age group of affected patients moving from the cecum to the rectum [13]. Another population-based study of 57,847 patients showed that the incidence of RCC increases with age [14]. Regarding non-metastatic CRC, patients with RCC are more likely to be female than those with LCC.

Interestingly, one study investigated gender and segment regarding the normal colorectum-

specific susceptibility to DNA methylation at the *hMLH1* and *MGMT* promoters [15]. Normal colorectal mucosa from males showed no consistent methylation patterns at either promoter, but there were striking age- and colon segment-specific differences in the female subgroup. The prevalence of *hMLH1* and *MGMT* methylation increased significantly with age, particularly in the right colon, and the percentage of alleles with *hMLH1* methylation showed an age-related increase. Concomitant methylation of both promoters was also significantly more common in the right colon of women [15].

Clinical features

A number of studies have shown that patients with RCC are predominantly female and older than those with LCC [16,17]. In addition, proximal colon cancer (PCC) lesions are larger, more advanced, mucinous, predominantly of signet ring histology, and more commonly poorly differentiated than distal colon cancer (DCC) lesions [17].

Environmental risk factors

CRC is associated with environmental risk factors such as obesity, diabetes, and meat consumption [18]. In general, a Western diet involves higher intake of red and processed meats, added sugar, and refined grains. Numerous studies have suggested that this dietary pattern is strongly associated with CRC [19,20]. A recent study reported the associations between Western and prudent dietary scores and tumor location and molecular subtype. Western dietary patterns are associated with an increased risk of CRC, particularly distal colon and rectal tumors. A Western diet is also more strongly associated with tumors that are *KRAS* wt or *BRAF* wt, have a negative or low CpG island methylator phenotype, or exhibit microsatellite stability. In contrast, prudent dietary patterns are associated with a lower risk of CRC that does not vary according to anatomic subsite or molecular subtype [21].

Serrated adenoma/polyp

Diagnostic methods for both types of colon cancer do not differ. However, the importance of sessile serrated adenoma/polyp (SSA/P) might affect the interval of surveillance colonoscopies. In general, serrated lesions may be the precursor to approximately one-third of all CRCs [22]. Hyperplastic polyps account for approximately 30% of all colon polyps and comprise the majority (greater than 70%) of serrated polyps [23,24]. Hyperplastic polyps (HPs) are usually small (1-5 mm), sessile,

and most frequently distributed in the distal colon [25,26]. SSA/Ps have been reported to be present in 4% to 9% of all patients undergoing a screening colonoscopy and comprise up to 4% to 23% of all serrated lesions [23]. SSA/Ps are slightly larger than HPs (more than 50% are larger than 5 mm), flat and preferentially located in the proximal colon [23,25,26] (Figure 1). SSA/Ps tend to occur more frequently in females [23,25]. SSA/Ps progress through what is currently called the serrated carcinogenesis pathway and frequently show the *BRAF*^{V600E} activating mutation with infrequent *KRAS* mutations. The characteristic serrated phenotype results from abnormal cellular proliferation driven by constitutive activation of the MAPK pathway [27], which can be activated by mutations in *BRAF* and *RAS*.

The association of serrated polyps with cancer risk has been confirmed by studies showing that proximal and large serrated polyps are associated with synchronous neoplasia at screening colonoscopy and with the interval at which neoplasia is discovered at follow-up colonoscopy [28,29]. O'Brien et al. [30] showed overlapping molecular features of carcinomas arising from serrated lesions in a study comparing residual serrated adenoma with adjacent invasive adenocarcinoma ("serrated carcinoma"); in some cases, both the serrated adenoma and the adenocarcinoma had high microsatellite instability (MSI) with identical loss of *MLH1* by immunohistochemistry, whereas other cases presented as MSI negative in both the cancer and ser-

rated polyp. Several independent investigators reported that the detection of serrated polyps 10 mm or larger at screening colonoscopy is associated with an increased risk of synchronous carcinoma or high-grade adenoma elsewhere in the colon [28,30]. Histology corresponding to SSA, proximal location, and the presence of cytologic dysplasia are additional factors associated with a higher risk of CRC [31].

Current screening guidelines for CRC are based on the risk stratification of conventional adenomas. Patients with conventional adenomas are stratified based on polyp number, size, and grade of dysplasia, as well as the presence of significant villous architecture in the polyps. However, recommendations have only recently been established for serrated lesions [22,31]. The consensus update on CRC by the US Multi-Society Task Force [31] recommends that sessile serrated polyps 10 mm or larger and those with cytologic dysplasia be treated as high-risk adenoma with 3-year surveillance intervals. In addition, the consensus update recommends that serrated polyps smaller than 10 mm without cytologic dysplasia be managed as low-risk adenoma with 3-year surveillance intervals.

Microbiota

CRC has multiple leading causes, one of which is the gut microbiota (Figure 1). One study suggested that the gut microbiota may influence both

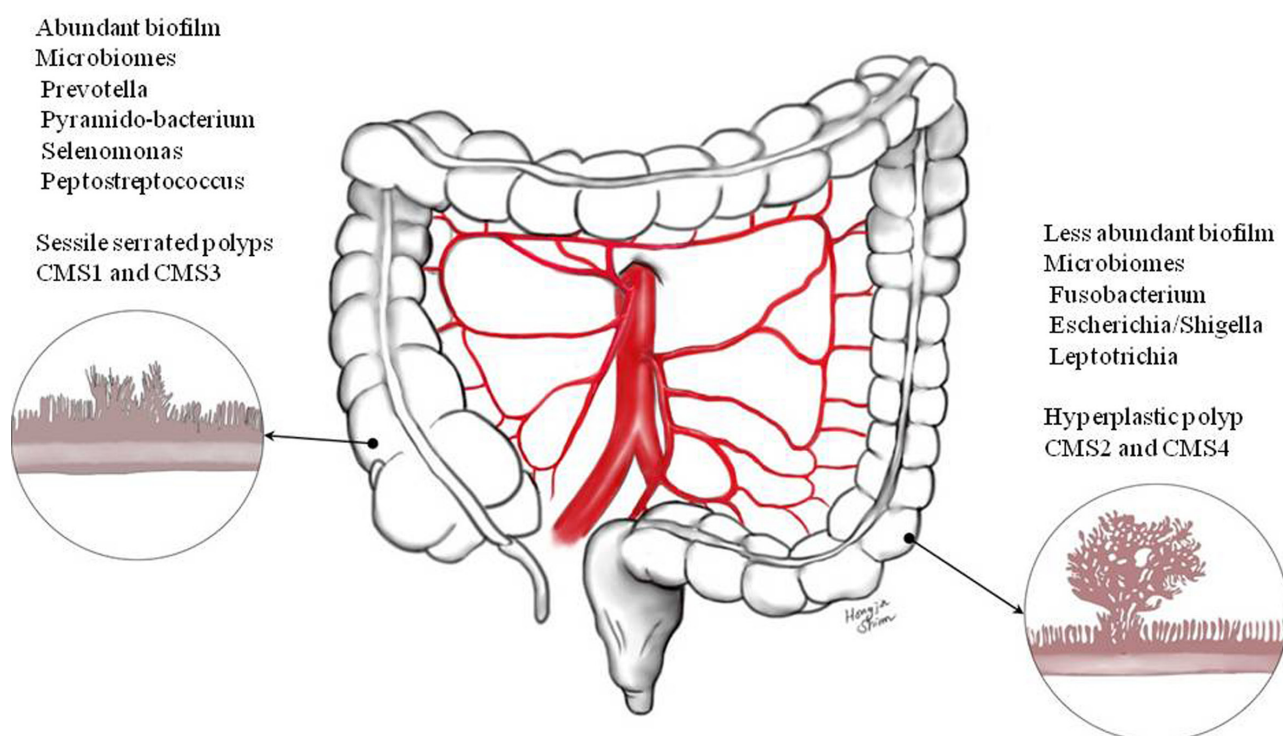


Figure 1. Differences in the microbiomes and molecular phenotypes between proximal and distal colon cancers.

the initiating events of carcinogenesis and carcinogenic progression.

An emerging concept pertaining to the role of microbiota in CRC initiation is that both the microbiota composition and their complex community structures, such as bacterial biofilms, are important.

Prevotella, *Pyramido-bacterium*, *Selenomonas*, and *Peptostreptococcus* were identified at relatively higher abundance in RCC than in LCC. Conversely, *Fusobacterium*, *Escherichia/Shigella*, and *Leptotrichia* were relatively abundant in LCC compared to RCC [32]. Bacterial biofilms were recently shown to be a feature in nearly 100% of RCCs [33]. However, why bacteria preferentially form biofilms on RCC is not fully understood.

Contribution of bile salts in the colon

The concentration of bile salts is different between the proximal and distal colon. The concentration of bile salts is high in the proximal colon, and one theory states that bile acid metabolic profiles selectively increase the risk of PCC [34]. In addition, bile acid metabolism is associated with intestinal microbiota, mainly in the 7 α -hydroxylation process in which cholic acid is converted into deoxycholic acid and chenodeoxycholic acid is converted to lithocholic acid, and it is also linked to colon carcinogenesis. These transformation steps increase the hydrophilicity of secondary bile acids [35]. Deoxycholic acid damages intestinal tract mucosa and contributes to an increase in reactive oxygen species, which damage DNA and thereby generate genomic instability, benefiting tumor growth; this chain of events could be key in the effect of bile acids on colon carcinogenesis [36]. Secondary bile acids may also influence CRC by supporting apoptosis-resistant cells or by interacting with important secondary messengers in pathways that are activated in CRC [37].

Molecular pathways

CRC has variable genetic signatures and develops through at least three major pathways, including chromosomal instability (CIN), MSI, and the methylator phenotype.

Members of the Colorectal Cancer Subtyping Consortium decided to combine their genomic datasets comprising 4151 samples to generate consensus molecular subtypes (CMSs) by applying unsupervised clustering techniques [38]. This process established four CMSs that were classified by 5 categories. Each category has a specific molecular feature. CMS1 and CMS3 were associated with RCC, whilst CMS2 and CMS4 were associated

with LCC (Figure 1). Unfortunately, this CMS classification system was not therapeutically aimed. However, it facilitated a better understanding of the broad biological groups of CRC.

Oncologic outcomes

Chemotherapy for patients with stage IV CRC differs between RCC and LCC. Currently, the preferred treatment option for patients with RAS wt/*BRAF* wt (all wt) tumors is double-agent chemotherapy plus an EGFR antibody. FOLFOXIRI plus bevacizumab is a potential option for selected patients [39] based on evidence from both individual trial findings (CRYSTAL (NC00154102) [40], PRIME (NCT00364013) [41], PEAK (NCT00819780) [42], FIRE-3 (NCT00433927) [43,44], CALGB 80405 (NCT00265850) [45], and 20050181 (NCT00339183) [46]) and present prognostic and predictive analyses using pooled data [39]. This finding indicates that a distinction is needed in treatment decision-making for patients with right- or left-sided tumors. Therefore, chemotherapy + an EGFR antibody is highly recommended for patients with left-sided RAS wt (*BRAF* wt) tumors, while FOLFOXIRI + Avastin is recommended for patients with right-sided RAS wt tumors.

Primary tumor location is a known prognostic factor for patients with CRC, and the prognosis of patients with RCC or LCC differs according to stage. Previous studies suggested that patients with RCC have a slightly better prognosis for stage II colon cancer but a slightly worse prognosis for stage III disease, likely associated with the higher prevalence of MSI-high tumors, which have a good prognosis, among stage II RCCs [47,48]. Moreover, analysis of prospective clinical trials of patients with stage III CRC who received adjuvant chemotherapy also demonstrated inferior DFS of those with RCC [49]. Primary tumor location seems to influence the outcome of adjuvant therapy and survival after treatment with palliative chemotherapy or targeted therapy in patients with stage IV disease. A recent retrospective study of the impact of tumor location on clinical outcome in patients with chemotherapy-refractory *K-RAS* wt mCRC from the NCICCTG CO.17 trial [50] showed that the addition of cetuximab to best supportive care significantly benefitted patients with left-sided tumors, not those with right-sided tumors, in terms of PFS, with a significant interaction between tumor location and treatment effect. Six randomized trials [(CRYSTAL (NC00154102), PRIME (NCT00364013), PEAK (NCT00819780), FIRE-3 (NCT00433927), CALGB 80405 (NCT00265850), and 20050181 (NCT00339183)] have been performed to investi-

gate the prognostic and predictive effects of tumor side on OS, PFS and ORR in patients with RAS wt mCRC who have received first-line or second-line chemotherapy with or without EGFR-targeted monoclonal antibodies.

The trials using panitumumab were the PRIME, PEAK, and 20050181 trials. The prognostic HRs for OS in the chemotherapy + panitumumab arm according to primary tumor location (right sided vs. left sided) were 1.58 (1.92-2.45), 2.68 (1.31-5.46) and 2.01 (1.29-2.13) for the PRIME, PEAK and 20050181 trials, respectively. The outcomes (OS and ORR) of patients with left-sided tumors were better than those of patients with right-sided

tumors after treatment with chemotherapy + panitumumab in the PRIME and 20050181 trials. The treatment outcome in terms of OS was the same in the PEAK trial (Table 1).

The trials using cetuximab were the CRYSTAL, FIRE-3 and CALGB 80405. The prognostic HRs for OS in the chemotherapy + cetuximab arm according to primary tumor location (right sided vs. left sided) were 1.93 (1.24-2.99), 2.84 (1.86-4.33) and 1.82 (1.27-2.56) for the CRYSTAL, FIRE-3 and CALGB 80405 trials, respectively. The outcomes (OS, PFS, and ORR) of patients with LCC were better than those of patients with RCC after treatment with FOLFIRI + cetuximab in the CRYSTAL and

Table 1. Six randomized trials (PRIME, PEAK, 20050181, CRYSTAL, FIRE-3 and CALGB 80405) that added an EGFR antibody (panitumumab or cetuximab) to chemotherapy in patients with RAS wt colorectal cancer

<i>Prognostic results for panitumumab trial patients (RAS wt) according to treatment regimen</i>						
<i>Parameters</i>	<i>PRIME</i>		<i>PEAK</i>		<i>20050181</i>	
	<i>FOLFOX + panitumumab</i>		<i>FOLFOX + panitumumab</i>		<i>FOLFOX + panitumumab</i>	
	<i>Right-sided tumors (n=39)</i>	<i>Left-sided tumors (n=169)</i>	<i>Right-sided tumors (n=22)</i>	<i>Left-sided tumors (n=53)</i>	<i>Right-sided tumors (n=31)</i>	<i>Left-sided tumors (n=150)</i>
OS						
Median (months)	11.1	30.3	17.5	43.4	10.3	20.1
HR (95% CI)	1.58 (1.02-2.45)		2.68 (1.31-5.46)		2.01 (1.29-2.13)	
p value	0.04		0.007		0.002	
PFS						
Median (months)	7.5	12.9	8.7	14.6	4.8	8.0
HR (95% CI)	1.20 (0.79-1.81)		1.61 (0.83-3.12)		1.40 (0.92-2.13)	
p value	0.40		0.16		0.12	
ORR						
Rate (%)	42.1	67.9	63.6	64.2	13.3	49.7
Odds ratio (95% CI)	0.34 (0.18-0.65)		0.98 (0.44-2.17)		0.16 (0.05-0.46)	
p value	<0.001		0.96		<0.001	
<i>Prognostic results for cetuximab trial patients (RAS wt) according to treatment regimen</i>						
<i>Parameters</i>	<i>CRYSTAL</i>		<i>FIRE-3</i>		<i>CALGB 80405</i>	
	<i>FOLFIRI + cetuximab</i>		<i>FOLFIRI + cetuximab</i>		<i>FOLFIRI/FOLFOX + cetuximab</i>	
	<i>Right-sided tumors (n=33)</i>	<i>Left-sided tumors (n=142)</i>	<i>Right-sided tumors (n=38)</i>	<i>Left-sided tumors (n=157)</i>	<i>Right-sided tumors (n=71)</i>	<i>Left-sided tumors (n=173)</i>
OS						
Median (months)	18.5	28.7	18.3	38.3	13.6	39.3
HR (95% CI)	1.93 (1.24-2.99)		2.84 (1.86-4.33)		1.82 (1.27-2.56)	
p value	0.003		<0.001		<0.001	
PFS						
Median (months)	8.1	12.0	7.6	10.7	7.5	12.7
HR (95% CI)	1.77 (1.08-2.91)		2.00 (1.36-2.93)		1.64 (1.19-2.22)	
p value	0.02		<0.001		0.002	
ORR						
Rate (%)	42.4	72.5	52.6	68.8	42.3	69.4
Odds ratio (95% CI)	0.28 (0.13-0.61)		0.51 (0.25-1.03)		0.32 (0.20-0.53)	
p value	0.001		0.06		<0.001	

CALGB 80405 trials. In the FIRE-3 trial, OS and PFS, not ORR, were superior for patients with LCC than for those with RCC.

Outcome differences stem from both primary tumor location and the molecular profile. Recently, in patients with *K-RAS* wt mCRC receiving anti-EGFR therapy, the molecular characteristics that are considered typical of RCC more frequently overlapped with CMS1 (MSI immune), whereas CMS3 and CMS4 were recurrent in LCC [51]. The study also showed a correlation between the different investigated molecular characteristics and the survival results, thus confirming a consistent link between molecular features and clinical outcome.

Conclusions

RCC and LCC show distinct clinical features and epidemiology. However, we must further investigate the impact of these distinctive features and how they influence the differential oncologic outcomes. Further well-designed studies are necessary to identify the causative association

between primary tumor location and oncologic outcomes.

Contributions

KMK, YWK, BRK and HYK conceived the study concept and participated in the study design, data extraction, statistical analysis, and manuscript drafting and editing. HJS participated in the study design and manuscript editing. All authors read and approved the final manuscript.

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Conflict of interests

The authors declare no conflict of interests.

References

- Kim IY, Kim BR, Kim HS, Kim YW. Differences in clinical features between laparoscopy and open resection for primary tumor in patients with stage IV colorectal cancer. *Onco Targets Ther* 2015;8:3441-8.
- Wan Kim Y. Surgical treatment for colorectal cancer in octogenarians and nonagenarians. *J BUON* 2017;22:578-85.
- Kim YW. Ileal perforation following cetuximab and FOLFIRI chemotherapy in a patient with ascending colon cancer with peritoneal carcinomatosis. *J BUON* 2017;22:804-5.
- Kim YW, Kim IY. The Role of Surgery for Asymptomatic Primary Tumors in Unresectable Stage IV Colorectal Cancer. *Ann Coloproctol* 2013;29:44-54.
- Pappas AV, Lagoudianakis EE, Dallianoudis IG et al. Differences in colorectal cancer patterns between right and left sided colorectal cancer lesions. *J BUON* 2010;15:509-13.
- Tentes AA, Korakianitis OS, Kakolyris S et al. Differences between right- and left-sided colon carcinomas. *J BUON* 2010;15:285-9.
- Jensen OM. Different age and sex relationship for cancer of subsites of the large bowel. *Br J Cancer* 1984;50:825-9.
- Mik M, Berut M, Dziki L, Trzcinski R, Dziki A. Right- and left-sided colon cancer - clinical and pathological differences of the disease entity in one organ. *Arch Med Sci* 2017;13:157-62.
- Enzinger PC, Burtness BA, Niedzwiecki D et al. CALGB 80403 (Alliance)/E1206: A Randomized Phase II Study of Three Chemotherapy Regimens Plus Cetuximab in Metastatic Esophageal and Gastroesophageal Junction Cancers. *J Clin Oncol* 2016;34:2736-42.
- Tejpar S, Stintzing S, Ciardiello 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* 2017;3:194-201.
- Kerr DJ, Domingo E, Kerr R. Is sidedness prognostically important across all stages of colorectal cancer? *Lancet Oncol* 2016;17:1480-2.
- de Jong UW, Day NE, Muir CS et al. The distribution of cancer within the large bowel. *Int J Cancer* 1972;10:463-77.
- Gonzalez EC, Roetzheim RG, Ferrante JM, Campbell R. Predictors of proximal vs. distal colorectal cancers. *Dis Colon Rectum* 2001;44:251-8.
- Yang J, Du XL, Li ST et al. Characteristics of Differently Located Colorectal Cancers Support Proximal and Distal Classification: A Population-Based Study of 57,847 Patients. *PLoS One* 2016;11:e0167540.
- Menigatti M, Truninger K, Gebbers JO, Marbet U, Marra G, Schar P. Normal colorectal mucosa exhibits sex- and segment-specific susceptibility to DNA methylation at the hMLH1 and MGMT promoters. *Oncogene* 2009;28:899-909.

16. Nawa T, Kato J, Kawamoto H et al. Differences between right- and left-sided colon cancer in patient characteristics, cancer morphology and histology. *J Gastroenterol Hepatol* 2008;23:418-23.
17. Sinicrope FA, Shi Q, Smyrk TC et al. Molecular markers identify subtypes of stage III colon cancer associated with patient outcomes. *Gastroenterology* 2015;148:88-99.
18. Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer* 2006;119:2657-64.
19. Magalhaes B, Peleteiro B, Lunet N. Dietary patterns and colorectal cancer: systematic review and meta-analysis. *Eur J Cancer Prev* 2012;21:15-23.
20. Wu K, Hu FB, Fuchs C, Rimm EB, Willett WC, Giovannucci E. Dietary patterns and risk of colon cancer and adenoma in a cohort of men (United States). *Cancer Causes Control* 2004;15:853-62.
21. Mehta RS, Song M, Nishihara R et al. Dietary Patterns and Risk of Colorectal Cancer: Analysis by Tumor Location and Molecular Subtypes. *Gastroenterology* 2017;152:1944-53.
22. Rex DK, Ahnen DJ, Baron JA et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol* 2012;107:1315-29; quiz 4, 30.
23. Spring KJ, Zhao ZZ, Karamatic R et al. High prevalence of sessile serrated adenomas with BRAF mutations: a prospective study of patients undergoing colonoscopy. *Gastroenterology* 2006;131:1400-7.
24. Carr NJ, Mahajan H, Tan KL, Hawkins NJ, Ward RL. Serrated and non-serrated polyps of the colorectum: their prevalence in an unselected case series and correlation of BRAF mutation analysis with the diagnosis of sessile serrated adenoma. *J Clin Pathol* 2009;62:516-8.
25. Bettington M, Walker N, Rosty C et al. Critical appraisal of the diagnosis of the sessile serrated adenoma. *Am J Surg Pathol* 2014;38:158-66.
26. Torlakovic E, Skovlund E, Snover DC, Torlakovic G, Nesland JM. Morphologic reappraisal of serrated colorectal polyps. *Am J Surg Pathol* 2003;27:65-81.
27. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology* 2010;138:2088-100.
28. Schreiner MA, Weiss DG, Lieberman DA. Proximal and large hyperplastic and nondysplastic serrated polyps detected by colonoscopy are associated with neoplasia. *Gastroenterology* 2010;139:1497-502.
29. Hiraoka S, Kato J, Fujiki S et al. The presence of large serrated polyps increases risk for colorectal cancer. *Gastroenterology* 2010;139:1503-10, 10 e1-3.
30. O'Brien MJ, Yang S, Mack C et al. Comparison of microsatellite instability, CpG island methylation phenotype, BRAF and KRAS status in serrated polyps and traditional adenomas indicates separate pathways to distinct colorectal carcinoma end points. *Am J Surg Pathol* 2006;30:1491-501.
31. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2012;143:844-57.
32. Gao R, Kong C, Huang L et al. Mucosa-associated microbiota signature in colorectal cancer. *Eur J Clin Microbiol Infect Dis* 2017;36:2073-83.
33. Dejea CM, Wick EC, Hechenbleikner EM et al. Microbiota organization is a distinct feature of proximal colorectal cancers. *Proc Natl Acad Sci U S A* 2014;111:18321-6.
34. McMichael AJ, Potter JD. Host factors in carcinogenesis: certain bile-acid metabolic profiles that selectively increase the risk of proximal colon cancer. *J Natl Cancer Inst* 1985;75:185-91.
35. de Giorgio R, Blandizzi C. Targeting enteric neuroplasticity: diet and bugs as new key factors. *Gastroenterology* 2010;138:1663-6.
36. Rubin DC, Shaker A, Levin MS. Chronic intestinal inflammation: inflammatory bowel disease and colitis-associated colon cancer. *Front Immunol* 2012;3:107.
37. Radley S, Davis AE, Imray CH et al. Biliary bile acid profiles in familial adenomatous polyposis. *Br J Surg* 1992;79:89-90.
38. Guinney J, Dienstmann R, Wang X et al. The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015;21:1350-6.
39. Arnold D, Lueza B, Douillard JY et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol* 2017;28:1713-29.
40. Van Cutsem E, Kohne CH, Hitre E et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408-17.
41. Douillard JY, Siena S, Cassidy J et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697-705.
42. Schwartzberg LS, Rivera F, Karthaus M et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. *J Clin Oncol* 2014;32:2240-7.
43. Heinemann V, von Weikersthal LF, Decker T et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1065-75.
44. Stintzing S, Modest DP, Rossius L et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. *Lancet Oncol* 2016;17:1426-34.
45. CALGB/SWOG C80405: A phase III trial of FOLFIRI or FOLFOX with bevacizumab or cetuximab or both for untreated metastatic adenocarcinoma of the colon or rectum. *Clin Adv Hematol Oncol* 2006;4:452-3.

46. Peeters M, Price TJ, Cervantes A et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 2010;28:4706-13.
47. Benedix F, Kube R, Meyer F et al. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. *Dis Colon Rectum* 2010;53:57-64.
48. Weiss JM, Pfau PR, O'Connor ES 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;29:4401-9.
49. Sinicrope FA, Mahoney MR, Smyrk TC et al. Prognostic impact of deficient DNA mismatch repair in patients with stage III colon cancer from a randomized trial of FOLFOX-based adjuvant chemotherapy. *J Clin Oncol* 2013;31:3664-72.
50. Brule SY, Jonker DJ, Karapetis CS 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;51:1405-14.
51. Lee MS, McGuffey EJ, Morris JS et al. Association of CpG island methylator phenotype and EREG/AREG methylation and expression in colorectal cancer. *Br J Cancer* 2016;114:1352-61.