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TOPIC HIGHLIGHT

2015 Advances in Colorectal Cancer

Different treatment strategies and molecular features between right-sided and left-sided colon cancers

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Abstract

The colon is derived from the embryological midgut and hindgut separately, with the right colon and left colon having different features with regards to both anatomical and physiological characteristics. Cancers located in the right and left colon are referred to as right colon cancer (RCC) and left colon cancer (LCC), respectively, based on their apparent anatomical positions. Increasing evidence supports the notion that not only are there differences in treatment strategies when dealing with RCC and LCC, but molecular features also vary between them, not to mention the distinguishing clinical manifestations. Disease-free survival after radical surgery of both RCC and LCC are similar. In the treatment of RCC, the benefit gained from adjuvant FOLFIRI chemotherapy is superior, or at least similar, to LCC, but inferior to LCC if FOLFOX regimen is applied. On the other hand, metastatic LCC exhibits longer survival than that of RCC in a palliative chemotherapy setting. For KRAS wild-type cancers, LCC benefits more from cetuximab treatment than RCC. Moreover, advanced LCC shows a higher sensitivity to bevacizumab treatment in comparison with advanced RCC. Significant varieties exist at the molecular level between RCC and LCC, which may serve as the cause of all apparent differences. With respect to carcinogenesis mechanisms, RCC is associated with known gene types, such as MMR, KRAS, BRAF, and miRNA-31, while LCC is associated with CIN, p53, NRAS, miRNA-146a, miRNA-147b, and miRNA-1288. Regarding protein expression, RCC is related to GNAS, NQO1, telomerase activity, P-PDH, and annexin A10, while LCC is related to Topo I, TS, and EGFR. In addition, separated pathways dominate progression

to relapse in RCC and LCC. Therefore, RCC and LCC should be regarded as two heterogeneous entities, with this heterogeneity being used to stratify patients in order for them to have the optimal, current, and novel therapeutic strategies in clinical practice. Additional research is needed to uncover further differences between RCC and LCC.

Key words: Colon cancer; Right; Left; Survival; Molecular

Core tip: The colon is derived from the embryological midgut and hindgut separately, with the right colon and left colon having different features with regards to anatomical and physiological characteristics. Based on the location, colon cancers are referred to as either right colon cancer (RCC) or left colon cancer (LCC), respectively, with both having distinct clinical manifestations. Increasing evidence supports the notion that differences exist in terms of sensitivity to adjuvant, palliative, and targeted treatments between RCC and LCC. In further analysis, significant varieties exist at the molecular level between RCC and LCC. Therefore, RCC and LCC should be regarded as two heterogeneous entities. Clinically, this heterogeneity is highly beneficial in therapeutic decision-making.

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INTRODUCTION

The colon is derived from the embryological midgut and hindgut, separately. They are joined together at the joint of the proximal two-thirds and distal one-third of the transverse colon. From an anatomical perspective, blood supplies, innervations, lymphatic drainages, and lumen environments are among the differences between the right and left colons. Correspondingly, numerous varieties present in right colon cancer (RCC) and left colon cancer (LCC). Colon cancers are more commonly found on the left side. However, a continuous right-shift in the site of primary colon cancer is observed as a result from the increasing proportion of RCC occurrence in recent years. The incidence of RCC is associated with a number of risk factors, for example female gender, old age, previous cancer history, and insulin resistance, while LCC is related to individuals with a low fiber diet, heavy smokers, and alcoholics. Small and flat neoplastic lesions located in the right colon are more likely to be missed during colonoscopy screening[1]. In comparison with LCC, RCC has a prevalence toward being poorly-differentiated in nature, commonly in the form of the mucinous histology type, a more advanced disease, and often metastasized to the lymph node or peritoneal region rather than the liver or lung, which are the organs usually affected when left colon cancer metastasis is involved. Other than that, RCC has a higher rate of co-morbidities such as anemia, intestinal perforation, and obstruction, which are also the presenting clinical symptoms of RCC. However, comparison of survival between RCC and LCC is undefined. Therefore, published articles were reviewed here in order to compare their treatment sensitivities to various therapies, and distinct genetic profiles were tracked to explain the origin of apparent differences (Table 1).

Table 1 Differences regarding survival, treatment, and molecular levels between right and left colon cancer.

	RCC	LCC	
Survival			
5-yr OS in 1990s	56.3%	59.7%	$P < 0.01$
in 2000s	67%	71%	$P < 0.01$
5-yr DFS in 2010	73%	74%	$P > 0.05$
in 2014	88.6%	89.4%	$P > 0.05$
Median OS (mo)	18.2%	29.4%	$P < 0.001$
Dominant treatment - Adjuvant	FOLFIRI	FOLFOX	
Palliative	Anti-EGFR therapy	Anti-angiogenesis	
Molecular levels			
Carcinogenesis mechanisms	MMR, KRAS, BRAF, miRNA-31	CIN (p53), NRAS; miRNA-146a, 147b, 1288	
Protein expressions	GNAS, NQO1, Telomerase, p-PDH	ANXA10, Topo I, TS, EGFR	
Relapse pathways	Cell cycle control genes, high WNT signaling	Stromal expression, low WNT signaling	
Prognostic biomarkers	CDX2, ITGA3	NOX4	

RCC: Right colon cancer; LCC: Left colon cancer.

PROGNOSIS AND TREATMENT STRATEGIES

Radical surgery

Surgery resection is generally recognized as the most effective treatment for colon cancer. Survival rates after going through radical surgery were found to be similar between stage Ⅰ-Ⅲ RCC and LCC. The 5-year disease-free survival (DFS) rates were 73% for RCC and 74% for LCC according to Benedix *et al*[2] in 2010, while Moritani *et al*[3] reported 88.6% for RCC and 89.4% for LCC in 2014. In further subgroup analysis, at stage Ⅰ disease, RCC patients presented with a better 5-year DFS than LCC patients (100% *vs* 95.2%, $P = 0.034$). However, there was no significant difference in survival for stage Ⅱ or Ⅲ patients. In Benedix's study, the 5-year DFS rates were reported

to be 79% for RCC and 78% for LCC at stage Ⅱ disease, and 59% for RCC and 58% for LCC at stage Ⅲ disease. However, the data from Moritani's study were 79.4% for RCC and 84.7% for LCC at stage Ⅱ-Ⅲ disease (P = 0.152). The differences in overall survival (OS) between colon cancers varied over time. Studies in the 1980s showed similar OS between RCC and LCC[4,5]. Later, in the 1990s, published studies reported that differences emerged in 5-year OS rates of RCC and LCC; namely 56.3% *vs* 59.7% (P < 0.01)[5]. These numbers improved to 67% and 71% (P < 0.01) in the 2000s[2]. This variation trend may be attributed to the development of adjuvant and palliative chemotherapies in the treatment of colon cancer.

ADJUVANT CHEMOTHERAPY

Survival benefit from adjuvant chemotherapy for colon cancer patients is influenced by two factors: how far the cancer has spread and where the tumor is located. In a review study by Weiss *et al*[6], 23578 stage Ⅱ colon cancer patients received curative surgery through Surveillance, Epidemiology, and End Results (SEER)-Medicare data. Adjuvant chemotherapy was performed in 18% of patients with RCC and 22% with LCC. No OS benefit was observed for RCC (HR = 0.97; P = 0.64) or LCC (HR = 0.97; P = 0.68). For stage Ⅱ disease, adjuvant chemotherapy did not improve overall survival for either RCC or LCC. Among 17,148 cases of stage Ⅲ disease, 5-year OS benefit from chemotherapy was observed for both RCC (HR = 0.64; P < 0.001) and LCC (HR = 0.61; P < 0.001). For stage Ⅲ disease, adjuvant chemotherapy could reduce death risks by 36% and 39% for RCC and LCC, respectively.

Different responses to specific adjuvant chemotherapy regimens were further analyzed. Elsaleh *et al*[7] reported that in the stage Ⅲ colorectal cancer population, the adjuvant chemotherapy regimen consisted of fluorouracil and levamisole and was performed in 39% of 260 RCC cases and 22% of 396 LCC or rectal cancer cases. Compared with those who did not receive adjuvant chemotherapy, striking survival benefits were seen for RCC patients who received the therapy (HR = 0.37; P < 0.0001), yet LCC or rectal cancer patients did not share this result (HR = 0.77; P = 0.081). Fluorouracil exhibited a greater benefit in stage Ⅲ RCC patients than in those with LCC. That being said, the result would be more convincing if DFS was compared and consistent with the discovery of stage Ⅲ RCC patients who had a better response to fluorouracil.

Based on 3045 colon cancer patients who received FOLFIRI adjuvant chemotherapy, Missiaglia *et al*[8] found DFS was similar for patients with RCC and LCC on the whole (HR = 0.98; P = 0.89). In further subgroup analysis, DFS was still similar in stage Ⅲ disease, but RCC patients showed longer DFS when filtered for stage Ⅱ disease. Therefore, the benefit from the FOLFIRI regimen was similar for stage Ⅲ RCC and LCC patients, but for the stage Ⅱ disease population, RCC patients had greater benefit than LCC patients after receiving FOLFIRI therapy. Concerning survival after relapse, RCC patients had poorer outcome than those with LCC (HR = 1.97; P < 0.01) on the whole. Stage Ⅱ and Ⅲ disease showed similar results. It is evident that survival after relapse was influenced by later palliative therapies.

As for FOLFOX adjuvant chemotherapy setting, Sinicrope *et al*[9] analyzed resected stage Ⅲ colon cancer patients in the N0147 trial. The results indicated that DFS was longer for patients with LCC than RCC (HR = 0.82; P < 0.001). In a subgroup of proficient mismatch repair cancers, DFS was inferior for patients with RCC compared to LCC (HR = 1.26; P = 0.0047), while in a subgroup of deficient mismatch repair cancers, favorable DFS was observed in RCC patients, but not LCC patients (P < 0.01). In short, survival benefit from FOLFOX was greater for patients with LCC on the whole, yet was differed by genotype.

Furthermore, Yoon *et al*[10] found that RCC was significantly associated with a shorter DFS compared with LCC when patients with BRAF-wild-type stage Ⅲ disease received adjuvant FOLFOX +/- cetuximab. But in another study with a similar aim[11], no difference was observed concerning time to recurrence (TTR) between the RCC and LCC groups (HR = 0.86; P = 0.164). In the RCC subgroup, KRAS status did not significantly affect either TTR (HR = 1.29; P = 0.96) or DFS (HR = 0.89; P > 0.05). On the contrary, in the LCC subgroup, TTR and DFS were poorer in KRAS mutation cancers, with an increased risk of relapse (HR = 1.96; P < 0.0001) for KRAS codon 12 mutations and the results showing a borderline significance for codon 13 mutations (HR = 1.59; P = 0.051).

Palliative chemotherapy

For stage Ⅳ colon cancer patients receiving palliative therapy, survival is differentiated by tumor site. Price *et al*[12] found that survival was inferior for RCC patients when basic supportive care was given. For patients who received active therapies, RCC patients had a median OS of 18.2 mo, while LCC patients had 29.4 mo (P < 0.001). The amount of patients who received first-line chemotherapy and the proportion of single drug or combination chemotherapy used were similar between RCC and LCC. Notably, the use of second-, third-, or fourth-line therapy was higher in LCC patients[5]. Evidently, LCC patients had better survival than RCC. The median OS for the entire group of RCC patients *vs* LCC patients was 9.6 mo and 20.3 mo, respectively (P < 0.001). Furthermore, RCC had more negative prognostic factors, which included poorly-differentiated, advanced stage, invasive histology type, and these factors contributed to the disappointing outcomes of the RCC patients. As a result, tumor site was found to be an independent prognostic predictor for stage Ⅳ colon cancer[13].

Modest *et al*[14] examined 423 metastatic colorectal

cancer (MCC) patients who received chemotherapy with FuFIRI or mIROX in their efforts to elucidate the different response to specific palliative chemotherapies. Tumors of a midgut origin were associated with inferior outcome compared with those of a hindgut origin, with an objective response rate of 37% *vs* 43% (P = 0.34), respectively. Moreover, median progression-free survival (PFS) was 6.0 mo *vs* 8.2 mo (P = 0.024), and median OS was 13.6 mo *vs* 21.8 mo (P = 0.001). RCC patients showed a significant inferior outcome when treated with FOLFIRI, with a median PFS of 6.0 mo *vs* 8.7 mo (P = 0.02) and a median OS of 12.5 mo *vs* 25.0 mo (P = 0.001). The results indicated that FuFIRI therapy was able to delay disease progression in LCC patients. However, there was no significant difference in the response between RCC and LCC in the mIROX arm, with a median PFS of 6.0 mo *vs* 7.8 mo (P = 0.35) and a median OS of 14.0 mo *vs* 22.4 mo (P = 0.12). Benefit from the mIROX arm was similar for both RCC and LCC patients. Undeniably, FOLFOX regimen plays an important role in the treatment of MCC patients. The lack of data concerning different responses to FOLFOX based on primary tumor location is frustrating, and has restricted its potential.

Anti-EGFR therapy

The majority of clinical experience with anti-EGFR therapy in MCC has been conducted with the monoclonal antibody cetuximab. Clinical data suggest that cetuximab could improve survival of patients with RAS wild-type tumors, which are also affected by tumor location. von Einem *et al*[15] investigated first-line therapy of MCC with cetuximab combined with chemotherapy. The results indicated that LCC patients had a significantly longer outcome, with a median PFS of 7.7 mo *vs* 5.2 mo (HR = 0.67, P = 0.02) and a median OS of 23.6 *vs* 14.8 mo (HR = 0.63, P = 0.016) compared to RCC patients. As a whole, RCC patients gained fewer benefits from cetuximab.

Further analysis showed *KRAS* status influenced the impact of tumor location. The impact of tumor location was not evident in patients with KRAS mutation tumors according to PFS (HR = 1.01, P = 0.96) and OS (HR = 1.3, P = 0.46) results. On the contrary, a prominent effect was present in the KRAS wild-type population, as indicated by PFS (HR = 0.54, P = 0.007) and OS (HR = 0.42, P < 0.001). Brulé *et al*[16] studied patients with chemotherapy refractory and KRAS wild-type MCC. Among the patients who received best supportive care, tumor location (right *vs* left) was not prognostic for PFS (HR = 1.07; P = 0.67) or OS (HR = 0.96, P = 0.78), while among homogeneous patients who received cetuximab, a much greater PFS was observed for LCC than RCC (P = 0.002). They concluded that, in refractory MCC, tumor location was a strong predictor of PFS benefit from cetuximab therapy. Missiaglia *et al*[17] also confirmed that cetuximab-treated *KRAS* wild-type LCC patients had prolonged PFS and a 2-fold higher response rate than RCC patients. It is widely reported that LCC patients benefit more from cetuximab therapy.

Anti-angiogenic therapy

Anti-angiogenic therapy is an anti-cancer strategy that targets the new vessels that grow to provide oxygen and nutrients to actively proliferating tumor cells. Anti-angiogenic therapy could improve patient survival from advanced colon cancer, in which the benefit differs by tumor location. Boisen *et al*[18] analyzed the data of metastatic CRC patients who received CapeOX +/- bevacizumab as standard first-line therapy. Patients treated with CapeOX + bevacizumab with primary tumors located in the sigmoid colon and rectum had a significantly better outcome than patients with primary tumors located anywhere between the cecum to the descending colon, with results showing PFS (9.3 *vs* 7.2 mo, HR = 0.68) and OS (23.5 *vs* 13.0 mo, HR = 0.47). The difference was affirmed by using the method of multivariate analysis adjusted for other potentially prognostic factors. Notably, in the case of patients who received CapeOX only, there was no association found between primary tumor location and outcome. The availability of tumor location as a predictor of bevacizumab should be further investigated in randomized clinical trials. Volz *et al*[19] studied single-nucleotide polymorphisms (SNPs) in genes related to early pericyte maturation in order to predict the efficacy of bevacizumab in metastatic CRC patients who received the first-line treatment regimen of FOLFIRI and bevacizumab. Among RCC patients, PFS was longer for RGS5 (rs1056515) T/T type than G/Tor G/G type (P = 0.012). Among LCC patients, PFS was longest in *CSPG4* (rs1127648) T/T type (PFS, 13.5 mo), then C/C type (PFS, 11.4 mo), and then C/T type (PFS, 10.6 mo) (P = 0.029). The study result also indicated that response rate (RR) was associated with *RALBP1* (rs329007), in which RR was highest in A/A type (68%), then A/G type (53%), and then G/G type (33%) (P = 0.008). It was concluded that bevacizumab exhibited a greater benefit in LLC patients, but this differs by distinct genotype.

GENOTYPE (MOLECULAR FEATURES)

There are epidemiological, morphological, and molecular differences between normal mucosa, as is the case with the situation with right and left colon as well. A study which applied cDNA microarray technology showed that more than 1000 genes are expressed differentially in right *vs* left colon, with 165 genes showing > 2-fold differences and 49 genes showing > 3-fold differences[20]. Colon cancers arising from the right and left colon of animal models had distinct phenotypes even when they had the same human clonal origin, with higher expressions of MMP2, p53, and beta-catenin in RCC than LCC[21]. Tumors

originating from the right and left colon showed obvious divergent in gene expression profiles. Most colon cancers develop in the course of polypus-adenoma-adenocarcinoma, in which a variety of genes take part. Among all the genes being studied, some play a role in carcinogenesis, others are used for early diagnosis, while still others are capable of predicting efficacy or prognosis. Differences in genotype according to location are summarized in this review.

Chromosome instability

Chromosome instability (CIN) results from abnormal structure or number of chromosomes, which then leads to a series of genetic changes, such as loss of heterozygosity, which involves the activation of oncogenes and inactivation of tumor-suppressor genes. Known as the first major carcinogenesis mechanism of colon cancer, CIN differs by primary tumor location. The CIN pathway contributes about 75% of LCC and 30% of RCC. In addition, CIN tumors are easy to be identified in LCC. Therefore, relatively speaking, CIN plays an important role in LCC occurrence and development. *p53* is the most studied tumor suppressor gene. In *p53* gene mutation cancers, p53 protein has a prolonged half-life period, allowing it to be detected by immunohistochemistry in cancer tissues. *p53* mutation type is more common in LCC than RCC (45% *vs* 34%). In subgroup of stage T3N0 colon cancer, Gervaz *et al*[22] found overexpression of p53 protein in 60% of LCC *vs* 16% of RCC. This result implied that tumor location was more influential in stage Ⅱ disease. CIN has been recognized as an independent factor of poor survival in colon cancer patients. An increased risk of death was documented in patients with tumors of *p53* gene mutation or protein overexpression, especially in LCC patients. Overexpression of p53 protein was also an independent factor of poor survival, with 5-year OS rates of 78% in p53 negative tumors *vs* 63% in p53 positive tumors.

Microsatellite instability

Microsatellite instability (MSI) is an outcome from somatic inactivation of the DNA mismatch repair genes by hypermethylation of their promoter, leading to secondary widespread mutation of short repetitive DNA sequences (namely microsatellites), lack of DNA repair function, and accumulation of abnormal genes. Known as the second major carcinogenesis mechanism of colon cancer, MSI has a prevalence of 12%-20% in sporadic CRC. By analyzing 245 patients with stage Ⅱ/Ⅲ CRCs, Shin *et al*[23] found that MSI cancers were more commonly located in the right colon (90.0% *vs* 19.1%; $P < 0.0001$). In the N0147 trial, which included stage Ⅲ colon cancers[9], MSI tumors predominantly occurred in the right colon (21% *vs* 2.8%). Approximately 30%-50% of RCC presented as MSI phenotype, with a much lower proportion of LCC showing MSI phenotype. Many studies have indicated that most MSI tumors originate from the right colon. However, Carethers *et al*[24] reported that, among RCC African American patients, the condition of MSI was absent. Although MSI appeared to be a common phenotype, patients with MSI cancers had better survival rates than those with microsatellite stable cancers. If both factors of mismatch repair status and tumor location were taken into consideration, survival was longest in RCC patients with MSI and shortest in RCC patients with MSS. Several studies have confirmed the notion that patients with MSI status gained no benefit from 5-Fu based adjuvant chemotherapy; in fact the regimen was even harmful for them[25,26]. Therefore, with that in mind, clinical oncologists should assess and stratify patients accordingly by mismatch repair status, especially those with RCC, before treatment strategies are decided and applied.

CpG island methylator phenotype

CpG Island Methylator Phenotype (CIMP) results from the hypermethylation of cytosine at CpG islands in gene promoter, which further leads to tumor suppressor gene silencing and carcinogenesis. CIMP shows an incidence of 16.7%-27.8% in colon cancer. Barault *et al*[27] observed a poor 5-year OS in microsatellite stable colon cancer patients with CIMP *vs* CIMP negative. CIMP was significantly-associated with RCC ($P = 0.011$). Furthermore, in a meta-analysis conducted by Juo *et al*[28], CIMP was independently-associated with a significantly worse prognosis in CRC patients (HR = 1.7; $P = 0.0005$). CIMP was more prevalent in RCC and was also associated with BRAF mutation and MSI tumors[29,30]. Aside from CpG islands, genome-wide methylation analysis demonstrated that differential methylation state was based on colon location. DNA methylation presented more often in RCC than LCC[31]. Furthermore, PRAC gene hypermethylation mainly occurs in RCC, while CDX2 hypermethylation is more commonly found in LCC[32]. Interestingly, Olsen *et al*'s meta-analysis (which identified 52 relevant articles) indicated that loss of CDX2 expression was probably correlated to CIMP and right-sided tumor location.

RAS

The RAS-RAF-MAPK signal pathway has been the subject of intense research scrutiny, leading to the development of pharmacologic inhibitors for the treatment of cancer, in which EGFR and its downstream component regulate key cellular events that drive the progression of many neoplasms. EGFR expression status is related to the efficacy of cetuximab. RAS (*i.e.*, KRAS, NRAS) is a key downstream effector of EGFR, which is mutationally activated and/or overexpressed in many colon cancers. Patients with *KRAS* mutation colon cancer greatly benefit from cetuximab treatment. KRAS mutation was found to be associated with poor prognosis (HR = 1.44)[33]. Incidence of KRAS

mutation was reported to be 23.5%-42.5% in sporadic CRC[34,35]. RCC had a higher frequency of KRAS mutation than LCC (57.3% *vs* 40.4%; $P < 0.0001$)[36] and KRAS mutation was significantly associated with RCC (OR = 2.05; $P < 0.01$)[37]. The status of KRAS mutation also differs by tumor location[10,38]. Rates of mutation in codon 12 and 13 were 34% and 12% in RCC, respectively, but lower in LCC, which was 28% and 6%, respectively. Compared to colon cancer patients with KRAS wild-type, survival was inferior for patients with codon 12 mutation cancer (HR = 1.30; $P = 0.0001$), but there are contradicting results with regards to codon 13 mutation. Imamura *et al*[39] indicated that KRAS codon 13 mutated patients were not significantly associated with a successful prognosis. Yoon *et al*[10] pointed out that KRAS mutation in codon 13 was associated with inferior survival in patients with resected colon cancer (HR = 1.36, $P = 0.0248$), whereas Blons *et al*[11] found that the survival of patients with *KRAS* codon 13 mutation differs by tumor location, with LCC having an inferior outcome ($P < 0.05$) when compared to RCC outcome (without statistical significance). Among stage Ⅲ colon cancer patients who received adjuvant FOLFOX +/- cetuximab therapy, the *KRAS* genotype did not affect TTR and DFS in RCC patients, but affected TTR and DFS in LCC patients, with a significantly increased risk of relapse for KRAS codon 12 mutation (HR = 1.96, $P < 0.0001$) and codon 13 mutation, with borderline significance (HR = 1.59, $P = 0.051$). Shen *et al*[40] used direct sequencing to analyze mutation status for 676 cases from the East Asian colorectal cancer population. The results showed that RCC had a higher PIK3CA mutation ($P < 0.001$), while LCC and rectal cancer shared a higher NRAS mutation ($P = 0.010$).

BRAF

BRAF is another component in the RAS-RAF-MAPK signal pathway, with a reported incidence of 2.5%-20% in CRC[41,42]. RCC took up 95% of BRAF mutation cancers, but only 48% in *BRAF* wild type cancers. On the other hand, the incidence of BRAF mutation was 18.4%-22.4% in RCC and 1.3%-7.8% in LCC and rectal cancer[38]. Many studies have indicated that BRAF mutation was associated with RCC (OR = 6.74, $P < 0.01$)[37,42,43]. Notably, Yamauchi *et al*[44] described a linear correlation between BRAF mutation and tumor location, with BRAF mutation incidence gradually decreasing from nearly 40% to less than 2.3% ($P < 0.0001$) as the tumor location shifted from the ascending colon to the rectum. Eklöf *et al*[45] meta-analysis echoed this result, with *BRAF* mutation mainly occurring in RCC (OR = 5.22; $P < 0.001$) and being associated with a poor prognosis (HR = 2.09). A close relationship was observed between *BRAF* mutation and MSI, with the incidence of *BRAF* mutation being 5% in mismatch repair stable CRCs, but increased to 51.8% in MSI CRCs. On the other hand, incidence of MSI was 76% in BRAF mutation cancers, while merely 9.5%-16% in BRAF wild type cancers ($P < 0.001$). Overall, a tumor with BRAF mutation status is more likely to be right-sided, have a poor outcome, and have a MSI condition.

MicroRNAs

MicroRNAs (miRNAs) constitute a class of small non-coding RNA molecules that function as post-transcriptional gene regulators, either as oncogenes or tumor suppressors. MiRNAs could be over-expressed or under-expressed in colon cancers. By analyzing 760 miRNAs in 29 colon cancers tissues, Nosho *et al*[46] found miRNA-31 had a higher expression in RCC ($P < 0.0001$) and was associated with KRAS and BRAF mutation. Moreover, patients with higher miRNA-31 had higher cancer-specific mortality (HR = 2.06, $P = 0.0008$), which was consistent with the characteristics of RCC. Omrane *et al*[47] found that miRNA-146a and miRNA-147b expression was significantly higher in LCC compared to RCC after investigating 25 colon cancer specimens. The result implied that these two miRNAs, especially miRNA-146a, appeared to be markers for LCC. In a large cohort study of 122 CRC patients[48], Gopalan *et al*[48] discovered that although the expression of miRNA-1288 was reduced or absent in 76% of patients, it was higher in LCC and rectal cancers than RCC ($P = 0.013$). Based on the aforementioned studies, an apparent conclusion can be drawn that various miRNAs have different expressions.

Other genes

Genes express differently based on the alteration of tumor location. For instance, a number of genes and proteins are expressed predominantly in RCC. By conducting a study which involved investigating the tumor locations and genetic profiles of 580 cases, Maus *et al*[49] found that gene expression of ERCC1 was significantly higher in RCC than LCC in KRAS wild-type colon cancers. Fecteau *et al*[50] found GNAS mutation arose in 2.3% of 428 colon tumors assayed, which all presented in the right colon ($P < 0.007$). Freriksen *et al*[51] studied single-nucleotide polymorphisms (SNPs) of the NADPH gene in 1457 CRC patients and 1457 age- and gender-matched controls. The result was that, for the SNP rs1800566 group, a significant association between the CT genotype and RCC was detected (OR = 1.60). By assessing the telomerase activity from samples of 49 CRC patients, Ayiomamitis *et al*[52] found colon cancers had significantly more telomerase than rectal cancers, and RCC expressed significantly higher telomerase than LCC. Analysis performed on 104 samples of surgically-resected CRCs indicated that expression of critical gate enzyme p-PDH tended to be higher in RCC than in left-sided CRC ($P = 0.0883$). PODXL, an anti-adhesive transmembrane sialomucin, is associated with an aggressive tumor phenotype and poor prognosis. Associations of PODXL expression and

tumor location with other clinicopathological variables were explored in 849 consecutive CRC patients[53]. High expression was strongly associated with the right colon ($P < 0.001$). Furthermore, RCC was more poorly differentiated ($P < 0.0001$) and showed higher PODXL expression ($P < 0.001$). High PODXL expression was significantly associated with a higher risk of cancer-specific death in both RCC and LCC. ANXA10 has recently been identified as a marker of sessile serrated adenomas/polyps of the colorectum. By immunohistochemistry analysis of ANXA10 expression status in 168 MSI CRCs, Kim *et al*[54] found 17% of tumors exhibited positive ANXA10. Most of them were located in the right colon (96%; $P < 0.001$), as well as being significantly associated with CIMP phenotype ($P < 0.001$). Several other genes and proteins are predominantly expressed in LCC. For example, topoisomerase I (Topo I) and thymidylate synthase (TS) are essential enzymes for the replication, transcription, and repair of DNA. Azzoni *et al*[55] assessed Topo I and TS expression in 112 consecutive CRCs and discovered that there was an increase in the expression of both, mostly in distal cancers (including LCC and rectal cancers), as well as being associated with the CIN pathway. Missiaglia *et al*[8] assessed gene expression and DNA copy number profiles in 1,404 samples of colon cancer. They found that not only was EGFR or HER2 more often amplified in RCC, but also that epiregulin was more frequently overexpressed in RCC.

There is growing evidence to show that RCC and LCC follow different pathways to relapse[56]. Using microarray data from 102 RCC cases and 95 LCC cases, Bauer *et al*[56] found different pathways dominate progression to relapse in RCC and LCC. RCC with high relapsing risk exhibited elevation in both the expression of cell cycle control genes and Wnt signaling. In comparison, relapse-prone LCC showed elevated expression of genes which promote stromal expansion and reduced expression of tumor suppressor genes responsible for initiating Wnt signaling. In addition, single gene prognostic biomarkers were found separately for RCC and LCC. In LCC with low expression levels of NADPH oxidase 4 (NOX4), the 5-year relapse-free survival probability was 0.89, and in tumors with elevated NOX4 expression the probability was 0.51. RCC with elevated expression levels of caudal type homeobox 2 (CDX2) had a 5-year relapse-free survival probability of 0.88, and those with low CDX2 expression had a corresponding probability of 0.39. Notably, both NOX4 and CDX2 were much less prognostic on the opposite sides. Another study showed that in stage Ⅱ disease, NOX4 was identified to be highly predictive of relapse in LCC, whereas integrin alpha 3 beta 1 (ITGA3) is predictive of relapse in RCC.

CONCLUSION

In conclusion, disease-free survival after radical surgery was similar between resected RCC and LCC. Benefits from adjuvant chemotherapy for colon cancer patients is influenced by both stage and tumor location. Although survival improvement is non-significant for stage Ⅲ disease, it is significant for stage Ⅱ disease. Longer survival is exhibited in metastatic LCC than RCC after palliative chemotherapies. For KRAS wild-type cancers, LCC benefited more from cetuximab treatment than RCC. Advanced LCC also showed superior response to bevacizumab in comparison to advanced RCC. Moreover, significant varieties exist at the molecular level between RCC and LCC, which may be the reason behind all these apparent differences. In regards to carcinogenesis mechanisms, RCC was associated with MMR, KRAS, BRAF, and miRNA-31, while LCC was associated with CIN, p53, NRAS, miRNA-146a, miRNA-147b, and miRNA-1288. In the case of protein expression, RCC was related to GNAS, NQO1, telomerase activity, P-PDH, and annexin A10, while LCC was related to Topo I, TS and EGFR. In addition, distinct pathways dominate progression to relapse in RCC and LCC. Therefore, RCC and LCC should be regarded as two heterogeneous entities and that this heterogeneity should be used to stratify patients in order for them to have the most optimal, current, and novel therapeutic strategies in clinical practice. Additional research is needed to uncover further differences between RCC and LCC.

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