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

Shen H *et al.* Right-sided and left-sided colon cancers

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**Abstract**

Derives from embryological midgut and hindgut separately, right colon and left colon have different features in both anatomical and physiological characteristics. Cancers located at right and left colon are merely referred as right colon cancer (RCC) and left colon cancer (LCC) respectively, based on their apparent anatomical positions. Increasing evidences support the notion that not only there are differences in the treatment strategies when dealing with RCC and LCC but also molecular features are varied between them, not to mention the distinguishing clinical manifestations. Disease free survivals 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 to the least, similar to LCC, however somehow inferior to LCC if FOLFOX regimen is being applied. On the other hand, metastatic LCC exhibits longer survival than that of RCC in palliative chemotherapies 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. Moreover, significant varieties exist at 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 associated with namely 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 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 and that this heterogeneity should be used to stratify patients for them to have the optimal, current and novel therapeutic strategies in clinical practice. Additional research is needed to uncover the further differences between RCC and LCC.

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

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**Core tip**: Derives from embryological midgut and hindgut separately, right colon and left colon have different features in anatomical and physiological characteristics. Based on the location, colon cancers are merely referred as right colon cancer (RCC) and left colon cancer (LCC) respectively and both have distinct clinical manifestations. Increasing evidences support the notion that differences exist in sensitivities to adjuvant, palliative and targeted treatments between RCC and LCC. In further analysis, significant varieties exist at molecular level between RCC and LCC. Therefore, RCC and LCC should be regarded as two heterogeneous entities and clinically this heterogeneity is highly beneficial in therapeutic decision-making.

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**INTRODUCTION**

Colon derives from embryological midgut and hindgut respectively. They are joined together at the joint of proximal two-thirds and distal one-third of transverse colon. From the anatomical perspective, blood supplies, innervations, lymphatic drainages and lumen environments are among the differences that right colon and left colon shared. 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 the primary colon cancer is observed in which is 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, old age, previous cancer history or insulin resistance, while LCC is related to individuals with low fiber diet, heavy smokers and alcoholics. Small and flat neoplastic lesions located at right colon are more likely to be missed during colonoscopy screening[[1](#_ENREF_1)]. In comparison with LCC, RCC has a prevalence to be poorly differentiated in nature, commonly in the form of mucinous histology type, a more advanced disease and often metastasizes to lymph node or peritoneal region rather than 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 comorbidities such as anemia, intestinal perforation and obstruction, of which are 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).

**PROGNOSIS AND TREATMENT STRATEGIES**

***Radical surgery***

Surgery resection is generally recognized as the most effective treatment for colon cancer. Survivals 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 reported by Benedix *et al*[[2](#_ENREF_2)]in 2010, while Moritani *et al*[[3](#_ENREF_3)] reported 88.6% for RCC and 89.4% for LCC in 2014. In further subgroup analysis, at stage I disease RCC patients presented a better 5-year DFS than LCC patients (100% *vs* 95.2%, *P* = 0.034). However, there was no significant difference in survival for stages II and 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, while 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 stages II-III disease (*P* = 0.152). The differences in overall survival (OS) between colon cancers vary as times changes. Studies in 1980s showed similar OS between RCC and LCC[[4](#_ENREF_4),[5](#_ENREF_5)]. Later in 1990s, published studies reported that differences emerged in 5-year OS rates of RCC and LCC, of which were 56.3% *vs* 59.7% (*P* < 0.01)[[5](#_ENREF_5)], and the numbers improved to 67% and 71%(*P* < 0.01) in the 2000s[[2](#_ENREF_2)]. The variation trend may be attributed to the development of adjuvant and palliative chemotherapies in battling 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 study, Weiss et al reviewed 23578 stage II colon cancer patients who received curative surgery through Surveillance, Epidemiology, and End Results (SEER)-Medicare data[[6](#_ENREF_6)]. Adjuvant chemotherapy was performed in 18% of patients with RCC and 22 % with LCC. No benefit of OS was observed for RCC (HR = 0.97; *P* = 0.64) and LCC (HR = 0.97; *P* = 0.68). For stage II disease, adjuvant chemotherapy did not improve overall survival for either RCC or LCC. Among 17148 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 response to specific adjuvant chemotherapy regimen was further analyzed. Elsaleh *et al*[[7](#_ENREF_7)] reported that in the stage III colorectal cancer population, adjuvant chemotherapy regimen consisted of fluorouracil and Levamisole 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 the result (HR = 0.77; *P* = 0.081). Fluorouracil exhibited greater benefit in stage III RCC patients than that 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 had a better response to fluorouracil.

Based on 3045 colon cancer patients who received FOLFIRI adjuvant chemotherapy, Missiaglia *et al*[[8](#_ENREF_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, benefit from 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 received 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 stage 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](#_ENREF_9)] analyzed resected stage III colon cancer patients in the N0147 trial. The result indicated that DFS was longer for patients with LCC than RCC (HR = 0.82; *P* < 0.001). In subgroup of proficient mismatch repair cancers, DFS was inferior for patients with RCC compared to LCC (HR = 1.26; *P* = 0.0047) while in subgroup of deficient mismatch repair cancers, favorable DFS was observed in RCC patients than 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 found that RCC was significantly associated with shorter DFS compared with LCC when patients with BRAF-wild-type stage III disease received adjuvant FOLFOX +/- cetuximab[[10](#_ENREF_10)]. But in another study with similar aim [[11](#_ENREF_11)], surprisingly, no difference was found for time to recurrence (TTR) between RCC and LCC group (HR = 0.86; *P* = 0.164). In RCC subgroup, KRAS status did not significantly affect both TTR (HR = 1.29; *P* = 0.96) and DFS (HR = 0.89; *P* > 0.05). On the contrary, in 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 result showed a borderline significance for codon 13 mutations (HR = 1.59; *P* = 0.051).

***Palliative chemotherapy***

For stage IV colon cancer patients who received palliative therapies, survival would be differed by tumor site. Price *et al*[[12](#_ENREF_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 29.4 mo for LCC patients (*P* < 0.001). The amount of patients 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](#_ENREF_13)]. Evidently, LCC patients had better survival than RCC. Median OS for the entire group of RCC patients *vs* LCC patients was 9.6 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](#_ENREF_14)].

Modest *et al*[[14](#_ENREF_15)] 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 chemotherapy. Tumors of midgut origin were associated with inferior outcome compared with hindgut origin, with an objective response rate of 37% *vs* 43% (*P* = 0.34), respectively. Moreover median progression-free survival (PFS) was 6.0 *vs* 8.2 months (*P* = 0.024), and median OS of 13.6 *vs* 21.8 mo (*P* = 0.001). RCC patients showed a significant inferior outcome when treated with FOLFIRI, with median PFS of 6.0 *vs* 8.7 mo (*P* = 0.02) and median OS of 12.5 *vs* 25.0 months (*P* = 0.001). The result indicated that FOLFIRI therapy was able to delay disease progression in LCC patients. However, there were no significant difference in the response between RCC and LCC in the mIROX arm, with median PFS of 6.0 *vs* 7.8 mo (*P* = 0.35) and median OS of 14.0 *vs* 22.4 mo (*P* = 0.12). Benefit from 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 in revealing different response to FOLFOX based on primary tumor location is frustrating and has restricted its potential.

***Anti-EGFR therapy***

The majority of the clinical experience with anti-EGFR therapy in MCC has been conducted with the monoclonal antibody cetuximab. Clinical data suggested that cetuximab could improve survival of patients with RAS wild-type tumors, which in fact, are also affected by tumor location. Einem *et al*[[15](#_ENREF_16)] investigated first-line therapy of MCC with cetuximab combined with chemotherapy. The result indicated that LCC patients had significantly longer outcome, with median PFS of 7.7 *vs* 5.2 mo (HR = 0.67, *P* = 0.02), and median OS of 23.6 *vs* 14.8 mo (HR = 0.63, *P* = 0.016) as compared to RCC patients. As a whole, RCC patients gained lesser benefit 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, prominent effect was presented in the KRAS wild-type population, as indicated by PFS (HR = 0.54, *P* = 0.007) and OS (HR = 0.42, *P* < 0.001). Brule *et al*[[16](#_ENREF_17)] studied patients with chemotherapy refractory and KRAS wild-type MCC. Among 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](#_ENREF_18)] also confirmed that cetuximab treated KRAS wild-type LCC patients had prolonged PFS and a 2-fold higher in 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 survival of advanced colon cancer, in which the benefit differs by tumor location. Boison *et al*[[18](#_ENREF_19)] 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 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. Moreover the availability of tumor location as a predictor of bevacizumab should be further investigated in randomized clinical trials. Volz *et al*[[19](#_ENREF_20)] studied the single-nucleotide polymorphisms (SNPs) in genes that related to early pericyte maturation in order to predict the efficacy of bevacizumab in metastatic CRC patients who received 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). While among LCC patients, PFS was longest in CSPG4 (rs1127648) T/T type (PFS 13.5months), then C/C type (PFS 11.4 mo), and lastly C/T type (PFS 10.6months) (*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 G/G type (33%) (*P* = 0.008), concluded that bevacizumab exhibited greater benefit in LLC patients but differs by distinct genotype.

**GENOTYPE (MOLECULAR FEATURES)**

There are epidemiological, morphological and molecular differences between normal mucosa, further onwards the claim could be applied on the situation with right and left colon as well. A study which applied cDNA microarray technology showed that more than 1000 genes expressed differentially in right *vs* left colon, with 165 genes showing > 2-fold and 49 genes showing > 3-fold differences[[20](#_ENREF_21)]. Colon cancers arose from right colon 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](#_ENREF_22)]. Tumors originated from right and left colon showed obvious divergent in gene expression profile. 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, and some are used for early diagnosis, while others are capable of predicting efficacy or prognosis. Differences of genotype according to location are summarized in this review.

***Chromosome instability***

Chromosome instability (CIN) is resulted from abnormal structure or number of chromosome, 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. 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. Besides, p53 is the most studied tumor suppressor gene. In p53 gene mutation cancers, p53 protein has a prolonged half-life period, therefore it can be detected by immunohistochemistry in cancer tissues. p53 mutation type takes up a higher proportion in LCC than RCC (45% *vs* 34%). While in subgroup of stage T3N0 colon cancer, Gervaz et al found overexpression of p53 protein in 60% of LCC *vs* 16% of RCC[[22](#_ENREF_23)]. The 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 with LCC patients. On the other hand, overexpression of p53 protein was also an independent factor of poor survival, with 5-year OS rates of 78% in p53 negative *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, leads 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 found MSI cancers more commonly located at the right colon (90.0% *vs* 19.1%; *P* < 0.0001)[[23](#_ENREF_24)]. In the N0147 trial which included stage III colon cancers[[9](#_ENREF_9)], MSI tumors predominantly occurred in right colon (21% *vs* 2.8%). Approximately 30%-50% of RCC presented as MSI phenotype, and much lesser proportion of LCC showed MSI phenotype. Many studies indicated that most MSI tumors originated from right colon. However, Carethers *et al*[[24](#_ENREF_25)]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 longer survival 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, oppositely, shortest in RCC patients with MSS. Several studies confirmed the notion that patients with MSI status gained no benefit from 5-Fu based adjuvant chemotherapy, worse, the regimen was even harmful for them[[25](#_ENREF_26),[26](#_ENREF_27)]. Therefore with that in mind, clinically oncologists should assess and stratify the patients accordingly by mismatch repair status, especially those with RCC, before treatment strategies are being decided and applied.

***CpG island methylator phenotype***

CpG Island Methylator Phenotype (CIMP), results from 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](#_ENREF_28)] observed a worse 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](#_ENREF_28)] CIMP was independently associated with significantly worse prognosis in CRC patients (HR = 1.7; *P* = 0.0005) CIMP was more prevalent in RCC, and it was also associated with BRAF mutation and MSI tumors[[29](#_ENREF_30),[30](#_ENREF_31)]. Aside from CpG islands, genome-wide methylation analysis demonstrated differential methylation state was based on colon location. DNA methylation presented more often in RCC than LCC[[31](#_ENREF_32)]. Furthermore, PRAC gene hypermethylation mainly occurrs in RCC while CDX2 hypermethylation is more commonly found in LCC[[32](#_ENREF_33)]. Interestingly, Olsen *et al*’s meta-analysis which identified 52 articles indicated that loss of CDX2 expression was probably correlated to CIMP and right-sided tumor location.

***RAS***

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. The EGFR expression status is related to efficacy of cetuximab. RAS (*i.e.*, KRAS, NRAS) is a key downstream effector of the EGFR, which is mutationally activated and/or overexpressed in many colon cancers. Patients with KRAS mutation colon cancer benefit much from cetuximab treatment. Elaborately, KRAS mutation was found to be associated with poor prognosis (HR = 1.44)[[33](#_ENREF_34)]. Incidence of KRAS mutation was reported to be 23.5%-42.5% in sporadic CRC[[34](#_ENREF_35), [35](#_ENREF_36)]. Besides, RCC had a higher frequency of KRAS mutation than LCC (57.3% *vs* 40.4%; *P* < 0.0001)[[36](#_ENREF_37)] and KRAS mutation was significantly associated with RCC (OR = 2.05; *P* < 0.01)[[37](#_ENREF_38)]. The status of KRAS mutation was also differs by tumor location[[10](#_ENREF_10),[38](#_ENREF_39)]. Rates of mutation in codon 12 and 13 were 34% and 12% in RCC respectively, but lower in LCC, which are 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 were contradicting results in regards to codon 13 mutation. Imamura *et al*[[39](#_ENREF_40)] indicated that KRAS codon 13 mutated patients were not significantly associated with prognosis. Yooh *et al*[[10](#_ENREF_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](#_ENREF_11)] found that the survival of patients with KRAS codon 13 mutation differs by tumor location in which LCC had inferior outcome (*P* < 0.05) but better outcome was seen in RCC (without statistically significance). Among stage III colon cancer patients who received adjuvant FOLFOX +/- cetuximab therapy, KRAS genotype did not affect TTR and DFS in RCC patients, but affected TTR and DFS in LCC patients, with a significant 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 East Asian colorectal cancer population. The result showed that RCC appeared 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 RAS-RAF-MAPK signal pathway, with a reported incidence of 2.5%-20% in CRC[41,42]. RCC took up of 95% in 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, while 1.3%-7.8% in all of LCC and rectal cancer[[38](#_ENREF_39)]. Many studies indicated that BRAF mutation was associated with RCC (OR = 6.74, *P* < 0.01)[[37](#_ENREF_38), 42,43]. Notably, Kalady *et al*[44]even described a linear correlation between BRAF mutation and tumor location, BRAF mutation incidence gradually decreased from nearly 40% to less than 2.3% (*P* < 0.0001) as the tumor location shift from ascending colon to rectum. Furthermore Eklof’s meta-analysis echoed that BRAF mutation mainly occurred in RCC (OR = 5.22; *P* < 0.001) and was associated with poor prognosis (HR = 2.09)[45]. Other than that close relationship was observed between BRAF mutation and MSI with the incidence of BRAF mutation was 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). In a nutshell, tumor with BRAF mutation status is more likely to be right-sided, has a poor outcome and with MSI condition.

***MicroRNAs***

MicroRNAs (miRNAs) constitute a class of small non-coding RNA molecules, functioning as post-transcriptional gene regulators, either as oncogenes or tumor suppressors. MiRNAs could be overexpressed or underexpressed in colon cancers. By analyzing 760 miRNAs in 29 colon cancers tissues, Nosho et al found miRNA-31 had a higher expression in RCC (*P* < 0.0001)[46] 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), in which was consistent with the characteristics of RCC. Omrane *et al*[47] found that miRNA-146a and miRNA-147b expressions were 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 which 122 CRC patients included[48], Gopalan *et al*[48] discovered that although the expression of miRNA-1288 was reduced or absent in 76% of the patients, yet in comparison, it was higher in LCC and rectal cancers, than RCC (*P* = 0.013). Based on the studies above, 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 express predominantly in RCC. By conducting a study which involved investigating the tumor locations and genetic profiles of 580 cases, Martin *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, all presented in the RCC (*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 for SNP rs1800566 group, a significant association between the CT genotype and RCC was detected (OR = 1.60). By assessing 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). Besides, 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 strongly associated with 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 associated significantly with 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 found 17% of tumors exhibiting positive ANXA10[[54](#_ENREF_54)]. Most of them were located at the right colon (96%; *P* < 0.001) as well as significantly associated with CIMP phenotype (*P* < 0.001). Several other genes and proteins predominantly express 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](#_ENREF_55)] assessed Topo I and TS expression in 112 consecutive CRCs discovered that there was an increase in both expressions, which were mostly found in distal cancers(including LCC and rectal cancers), as well as associated with CIN pathway. Missiaglia *et al*[[8](#_ENREF_8)] assesed gene expression and DNA copy number profiles in 1404 samples of colon cancer. In their discovery, not only EGFR or HER2 was more often amplified in RCC, but also epiregulin was more frequently overexpressed in RCC.

There is growing evidence show that RCC and LCC follow different pathways to relapse[[5](#_ENREF_56)6]. Using microarray data from 102 RCC cases and 95 LCC cases, Bauer *et al*[5](#_ENREF_56)6] found different pathways dominate progression to relapse in RCC and LCC. RCC with high relapsing risk exhibited elevation in both expression of cell cycle control genes and Wnt signaling. On the contrary, relapse-prone LCC show elevated expression of genes which promote stromal expansion and reduced expression of tumor suppressor genes that are 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 while 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 survivals after radical surgery were similar between resected RCC and LCC. Benefit 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 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 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 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 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 for them to have the optimal, current and novel therapeutic strategies in clinical practice. Additional research is needed to uncover the further differences between RCC and LCC.

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**Table 1 Differences regarding survival, treatment and molecular levels between right colon cancer 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 (months) | 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-1469, 1476, 1288 |  |
| Protein expressions | GNAS, NQO1, Tolemerase, p-PDH | ANXA10, TopoI, TS, EGFR |  |
| Replase 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.