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The impact of tumor location on the biological and oncological differences of colon cancer: Multi-institutional propensity score-matched study

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ABSTRACT

Background: Several studies have reported some differences between right-sided and left-sided colon cancer. The aim was to analyze the differences in clinical and pathological features, recurrence, and prognostic impact of tumor location in patients with tumors truly located in the right and left side of the colon.

Patients: The study included 6790 stage I-III colon cancer patients who underwent curative resection. Patient characteristics were balanced using propensity score matching.

Results: Recurrence rates of stage I and II patients with left-sided colon cancer were higher than those in the right-sided group, indicating that recurrence free survival of left-sided colon cancer patients was significantly shorter than that of the right-sided patients. In stage III patients that experienced recurrence, cancer specific survival after recurrence of the right-sided colon cancer patients was significantly shorter than that of the left-sided patients ($P = 0.003$).

Conclusions: In stage I-II patients, left-sided colon cancer was a significant risk factor for recurrence free survival, however, in stage III patients, right-sided colon cancer was a significant risk factor for after recurrence cancer specific survival.

Introduction

Several studies have reported some differences between right-sided and left-sided colon cancer regarding epidemiology, clinical presentation, pathology, and genetic mutations.[1,2] The majority of studies have shown poor prognostic outcomes in right-sided compared to left-sided colon cancer.[2–4] Ishihara, one of the members of the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer (see Acknowledgments), reported that right-sided colon cancer (RCC) had a significantly worse prognosis compared with left-sided colon cancer (LCC) for stage II-III patients.[5] In contrast, Waedchkow et al. reported that the prognosis of localized RCC is better compared to LCC for stage I-III colon cancer.[6] Based on these results, the influence of tumor location on survival outcomes remains unclear in colon cancer.

Based on embryology, the segment extending from the cecum to the proximal two thirds of the transverse colon originates from the midgut. The segment containing the distal third of the transverse colon to the upper anal canal is derived from the hindgut.[7,8] The boundary line is said to be a Cannnon ring, which was distinguished by evaluation with motor function and nervous distribution.[9,10] It is difficult to precisely divide the transverse colon into the right and left side. In order to avoid this ambiguity, we excluded transverse colon patients from our study.

The aim of our study was to analyze the differences in clinical and pathological features, recurrence, and prognostic impact of tumor location in patients with tumors truly located in the right or left side of the colon. Additionally, we sought to determine whether

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this relationship is consistent across tumor stage.

Methods

Our multicenter retrospective study included patients with stage I-III colon cancer who had curative resection from January 1997 to December 2008. These patients were collected from the databases of 23 institutions belonging to the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer (see Acknowledgments).

Patients at these institutions were treated according to the guidelines[11]

The study included 10,801 eligible stage I-III colon cancer patients who underwent R0 resection. D3 dissection was defined as extensive lymph node dissection when the lymph nodes, up to the origin of the feeding artery from the superior mesenteric artery or those at the origin of the inferior mesenteric artery, were dissected.[12] This study protocol was approved by the local ethics committee of each institution. Patients who underwent neoadjuvant chemotherapy or chemoradiation before the procedure were excluded. Pathologic TNM class and stage were determined by the classification of the American Joint Committee on Cancer.[13]

Analysis

The location of the primary tumor was definded as either the right-sided colon (cecum and ascending colon) to hepatic flexure or the left-sided colon (descending colon and sigmoid colon) from splenic flexure to the height of the promontrium.

Recurrence-free survival (RFS), in days, was tabulated from the date of curative resection surgery to the date of first detection of a probable recurrence. The sites of recurrence were determined according to findings of disease on x-ray, abdominal ultrasound, colonoscopy, CT, MRI, or PET/CT. Every institute observes the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines, and all patients had follow-up after curative resection according to the guidelines.[12] The standard follow-up protocol was as follows: measurement of a serum tumor marker every 3 months and chest and abdominal computed tomography every 6 months for the first 3 years with colonoscopy every 1–2 years. If recurrence is suspected and it is not clear by CT etc, MRI and PET examination are often done[12]. Although neoadjuvant chemotherapy and therapy after recurrence, such as indications of chemotherapy and metastasis resection, was not unified, treatment was done according to the guidelines. The following data were assessed: gender, age, CEA, carbohydrate antigen 19–9 (CA19-9), pathology, tumor size, T classification, number of removed lymph nodes, number of metastatic lymph nodes, lymphatic invasion, venous invasion, stage classification, grade of lymph node dissection, and adjuvant chemotherapy. Cancer-specific survival (CSS) was defined as the period between the date of treatment and the date of colon cancer death or the date of last known follow-up. Cancer specific survival after recurrence (CSSAR), for patients with recurrence only, was defined as the period between the date of recurrence recognition and the date of colon cancer death or the date of last known follow-up. The last follow-up date was November 2016 for surviving patients.

Statistical methods

Patients in both locations were matched using a 1:1 propensity score matching method (PSM) without replacement, and clinical outcomes were analyzed. Twelve covariates were used to compute propensity scores, including age, gender, tumor marker, pathology, T classification, number of removed lymph nodes, number of metastatic lymph nodes, lymphatic invasion, venous invasion, stage classification, grade of lymph node dissection, and adjuvant chemotherapy. Comparisons of cancer characteristics between the LCC and RCC cohorts were made using Student's t, Wilcoxon Rank-Sum, and chi-square tests. The Kaplan-Meier method and log-rank test were used for univariable analysis of RFS, CSS, and CSSAR. Cox Proportional Hazards Regression was used for univariable analysis as well. P-values <0.05 were considered statistically significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC).

Results

The total number of patients eligible for inclusion was 10,801.1176 patients were excluded due to missing clinical or pathologic information. Therefore, 9625 patients were included in the analysis (RCC; $n = 3,734$, LCC; $n = 5891$). Table 1 shows the colon cancer characteristics before and after PSM. Before PSM, Table 1 shows that patients with RCC were older, more often female, had more advanced tumor stage, increased tumor size and more poorly differentiated tumors than the patients with LCC (all $P < 0.01$). Patients with RCC had a higher mean number of lymph nodes removed during surgery (25.9 vs. 18.4, $P < 0.01$), and higher mean number of lymph nodes with metastasis (positive lymph nodes) (1.33 vs. 1.16, $P = 0.09$). There were statistically significant differences in RCC vs. LCC for all patient characteristics except for CEA, venous invasion, and adjuvant chemotherapy.

After PSM (Table 1), 6790 patients were included in the analysis. The mean age of patients with RCC was 67.5 (±standard deviation (SD) of 11.0) years compared to 67.4 (±SD of 10.2) years for patients with LCC in our cohort. There were no statistically significant differences between patients with RCC and LCC (Table 1), except mean tumor size, which was slightly larger in RCC than LCC (4.5 ± 2.4 vs. 4.4 ± 2.8 cm, $P = 0.041$).

Recurrence

After PSM, the overall 5-year recurrence rate was 14.6% (95% CI 13.4–15.9) for RCC and 15.4% (95% CI 14.2–16.7) for LCC ($P = 0.52$). As seen in Table 2, 5-year Recurrence rates for stage I-II patients were higher in LCC than RCC (Both $P < 0.05$), while recurrence rates for stage III patients were similar ($P = 0.27$). Equivalently, RFS among stage I-II LCC patients was significantly shorter than RCC (Stage I; $P = 0.02$, Stage II; $P = 0.02$) (Fig. 1a and b). There were no significant differences in stage III patients, indicating similar RFS between RCC and LCC patients (Fig. 1c).

Recurrence site

Liver metasitases and local/anastomosis recurrence in the LCC group were significantly higher than in the RCC group for stage I and II patients, respectively ($P = 0.02$, $P = 0.01$) (Table 3). Peritoneal dissemination in the RCC group was significantly higher than in patients with LCC in stages III ($P < 0.01$) (Table 3). Rates of recurrence were not different between RCC and LCC for any other site.

CSS and CSSAR

There were no significant differences in CSS for patients of any stage after surgery (Table 4). Overall, 988 patients experienced a recurrence, 486 in the RCC group and 502 in the LCC group. Median follow-up after recurrence was 3.6 years for the RCC group and 4.1 for LCC ($p = 0.037$). There was no significant difference in the use of

Table 1
Colon character characteristics.

	Unmatched Cohort					Matched Cohort				
	Left Colon (N = 5891)		Right Colon (N = 3734)		p-value	Left Colon (N = 3395)		Right Colon (N = 3395)		p-value
	Mean	*SD*	*Mean*	*SD*		*Mean*	*SD*	*Mean*	*SD*	
Age, in years	65.0	10.7	68.1	11.0	<**.0001**	67.4	10.2	67.5	11.0	0.3808
Size, in cm	4.0	2.5	4.7	3.0	<**.0001**	4.4	2.8	4.5	2.4	**0.0413**
Follow up years (Median, Q1-Q3)	6.1	2.9–6.2	5.9	2.9–6.1	**0.0030**	6.0	2.9–6.2	6.0	2.9–6.1	0.9233
	N	*%*	*N*	*%*		*N*	*%*	*N*	*%*	
Sex										
Female	2432	41.3	1806	48.4	<**.0001**	1597	47.0	1577	46.5	0.6266
Male	3459	58.7	1928	51.6		1798	53.0	1818	53.5	
pT Category										
T1	1071	18.2	506	13.6	<**.0001**	488	14.4	494	14.6	0.7939
T2	821	13.9	546	14.6		531	15.6	501	14.8	
T3	2960	50.2	1977	52.9		1771	52.2	1788	52.7	
T4	1039	17.6	705	18.9		605	17.8	612	18.0	
pN Category										
N0	3733	63.4	2323	62.2	**0.0145**	2160	63.6	2136	62.9	0.8163
N1	1634	27.7	1012	27.1		899	26.5	921	27.1	
N2/N3	524	8.9	399	10.7		336	9.9	338	10.0	
Histologic Type										
Well Differentiated	3018	51.2	1715	45.9	<**.0001**	1681	49.5	1651	48.6	0.7662
Moderately Differentiated	2689	45.6	1629	43.6		1535	45.2	1561	46.0	
Other	184	3.1	390	10.4		179	5.3	183	5.4	
Lymph Node Dissection										
D1	375	6.4	188	5.0	<**.0001**	177	5.2	180	5.3	0.9798
D2	1889	32.1	884	23.7		855	25.2	850	25.0	
D3	3627	61.6	2662	71.3		2363	69.6	2365	69.7	
Stage										
I	1534	26.0	863	23.1	**0.0051**	837	24.7	819	24.1	0.7927
II	2198	37.3	1458	39.0		1322	38.9	1315	38.7	
III	2159	36.6	1413	37.8		1236	36.4	1261	37.1	
Adjuvant Chemotherapy										
No	3331	56.5	2143	57.4	0.1996	1934	57.0	1959	57.7	0.8095
Yes	1468	24.9	842	22.5		802	23.6	974	28.7	
Unknown	1092	18.5	719	19.3		659	19.4	642	18.9	

chemotherapy between groups overall (50.4% vs. 47.1%, p = 0.35), or at any stage in these patients (all p > 0.10). CSSAR was similar for stage I and II patients (Table 4), however, CSSAR was shorter in the RCC group than the LCC group (HR = 1.35, 95% CI 1.11–1.66, P = 0.003) (Table 4 and Fig. 2). The 5-year CSSAR rate for stage III patients with LCC was 38.3%, while the rate for stage III RCC patients was 27.8%.

Discussion

Data on prognosis of RCC versus LCC is currently controversial. One reason is that most studies included total transverse colon in the right-sided colon group. Based on embryology, the segment extending from the cecum to the proximal two thirds of the transverse colon originates from the midgut and is perfused by the superior mesenteric artery. The segment containing the distal third of the transverse colon to the upper anal canal is derived from the hindgut and is served by the inferior mesenteric artery.[7,8,14]

We believe that the total transverse colon is composed of both the right and left-sided colon, and it is difficult to differentiate between the right-sided and the left-sided colon. Therfore, we believe that separating the site-specific survival outcomes will be beneficial for guiding future research and study. This is the first article where tumor characteristics, recurrence, and survival were

Table 2
5-Year recurrence and mortality rates by stage.

	Left Colon		Right Colon		p-value
	Rate (%)	*95% CI*	*Rate (%)*	*95% CI*	
Stage I	N = 837		N = 819		
Recurrence	2.6	1.7–4.0	0.8	0.4–1.8	**0.0233**
Overall Mortality	5.5	4.1–7.4	3.1	2.1–4.6	**0.0171**
Cancer Specific Mortality	1.0	0.5–2.0	0.1	0.1–0.9	0.3095
Stage II	N = 1322		N = 1315		
Recurrence	13.5	11.6–15.5	10.1	8.5–11.9	**0.0231**
Overall Mortality	11.7	10.0–13.7	9.1	7.6–10.9	0.0584
Cancer Specific Mortality	6.1	4.9–7.7	4.0	3.0–5.3	0.1669
Stage III	N = 1236		N = 1261		
Recurrence	26.1	23.7–28.8	28.0	25.6–30.7	0.2701
Overall Mortality	18.6	16.5–21.1	21.1	18.9–23.6	0.3387
Cancer Specific Mortality	13.4	11.5–15.6	17.3	15.2–19.6	0.0724

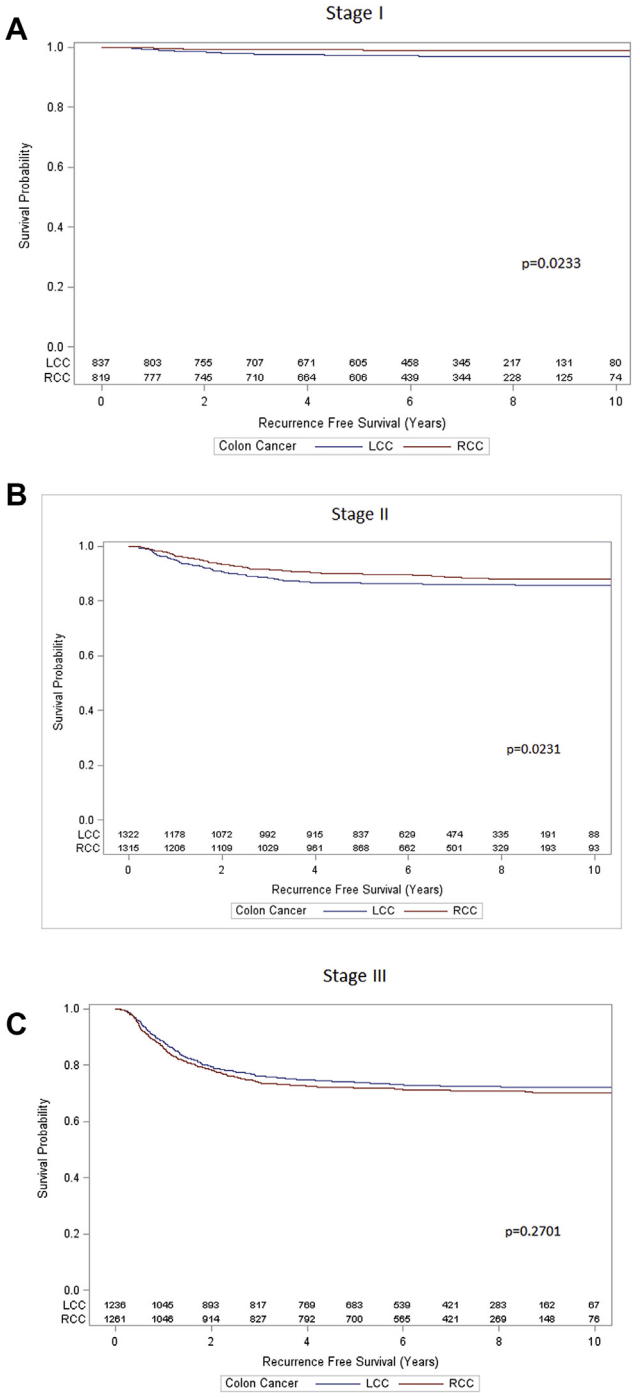

Fig. 1. (**a**). Recurrence-Free Survival among stage I patients, LCC vs. RCC. (**b**). Recurrence-Free Survival among stage II patients, LCC vs. RCC. (**c**). Recurrence-Free Survival among stage III patients, LCC vs. RCC.

compared between RCC and LCC, excluding tranverse colon from the RCC group.

Several studies have suggested that patients with RCC have worse prognosis than those with LCC. Our results, however, have demonstrated no difference in CSS between RCC and LCC, within each stage. Muguid et al. reported no significant difference in CSS between RCC and LCC for stage I,[15] which agrees with our results.

Additionally, our study shows that the recurrence rate in patients with LCC is higher than that of RCC in stage I and II patients.

Table 3
5-Year recurrence rates by site and stage.

	Left Colon		Right Colon		p-value
	Rate (%)	*95% CI*	*Rate (%)*	*95% CI*	
Stage I	N = 837		N = 819		
Liver	1.9	1.2–3.2	0.5	0.8–1.4	**0.0189**
Lung	0.3	0.1–1.1	0.1	0.1–0.9	0.9694
Peritoneal	0.0	0–0	0.0	0–0	–
Lymph Nodes	0.0	0–0	0.2	0.1–1.3	0.3118
Anasto/Local	0.0	0–0	0.0	0–0	–
Other	0.4	0.1–1.3	0.2	0.1–1.1	0.3245
Stage II	N = 1322		N = 1315		
Liver	6.7	5.4–8.3	5.0	3.9–6.4	0.2515
Lung	4.0	3.3–5.4	3.9	2.9–5.2	0.7230
Peritoneal	1.2	0.7–2.1	1.3	0.8–2.2	0.7807
Lymph Nodes	0.9	0.5–1.7	0.8	0.4–1.6	0.8823
Anasto/Local	2.0	1.4–3.1	0.8	0.4–1.5	**0.0106**
Other	1.2	0.7–2.1	1.3	0.7–2.0	0.7842
Stage III	N = 1236		N = 1261		
Liver	13.3	11.4–15.5	11.5	9.8–13.6	0.3296
Lung	8.2	6.7–10.1	9.0	7.4–10.9	0.5557
Peritoneal	3.7	2.7–5.0	8.4	6.9–10.3	<**.0001**
Lymph Nodes	4.1	3.0–5.6	5.5	4.3–7.1	0.1322
Anasto/Local	3.4	2.4–4.8	2.0	1.3–3.1	0.0730
Other	2.3	1.5–3.4	2.1	1.4–3.2	0.8479

The liver recurrence rate in patiets with stage I LCC was higher than those with RCC (Table 3). LCC patients had a higher overall recurrence rate for stage 2 disease (Table 2), which is primarily due to an increased rate of local recurrences. This may be due to proximity to the rectum, which has high recurrence rates.

Cancer-specific survival after recurrence (CSSAR)

In the current study, stage I and II patients with LCC have shorter RFS than RCC patients, but similar CSSAR (Table 4). LCC patients have a higher rate of liver recurrence in stage I. Many of the institutions are actively performing R0 surgery for liver metastasis, which may improve the survival of those patients after recurrence.

We also found that stage III RCC patients had shorter CSSAR than those with LCC (HR = 1.35, 95% CI 1.11–1.66, P = 0.003). One possible explanation for this difference is that peritoneal dissemination was observed more frequently for the patients with RCC in stage III (Table 3). RCC patients are less likely to develop stenosis symptoms,[3] and at the time of diagnosis the tumor diameter was larger than that of the LCC group (Table 1). This may be the reason why peritoneal dissemination recurrence is more common in RCC. Several studies have reported that peritoneal dissemination is more difficult to treat, compared to liver or lung metastasis,[16,17] potentially explaining the poor prognosis for CSSAR in RCC.

Table 4
Univariable Survival in the Matched Cohort, RCC vs. LCC.

	Cox PH Regression			
	HR	95% CI		p-value
Recurrence-Free Survival				
Stage I	0.42	0.19	0.91	**0.0279**
Stage II	0.77	0.61	0.96	**0.0235**
Stage III	1.09	0.93	1.27	0.2708
Cancer Specific Survival				
Stage I	0.57	0.19	1.70	0.3158
Stage II	0.80	0.58	1.10	0.1678
Stage III	1.19	0.98	1.45	0.0735
After Recurrence Cancer Specific Survival				
Stage I	0.68	0.18	2.58	0.5742
Stage II	1.01	0.71	1.44	0.9432
Stage III	1.35	1.11	1.66	**0.0032**

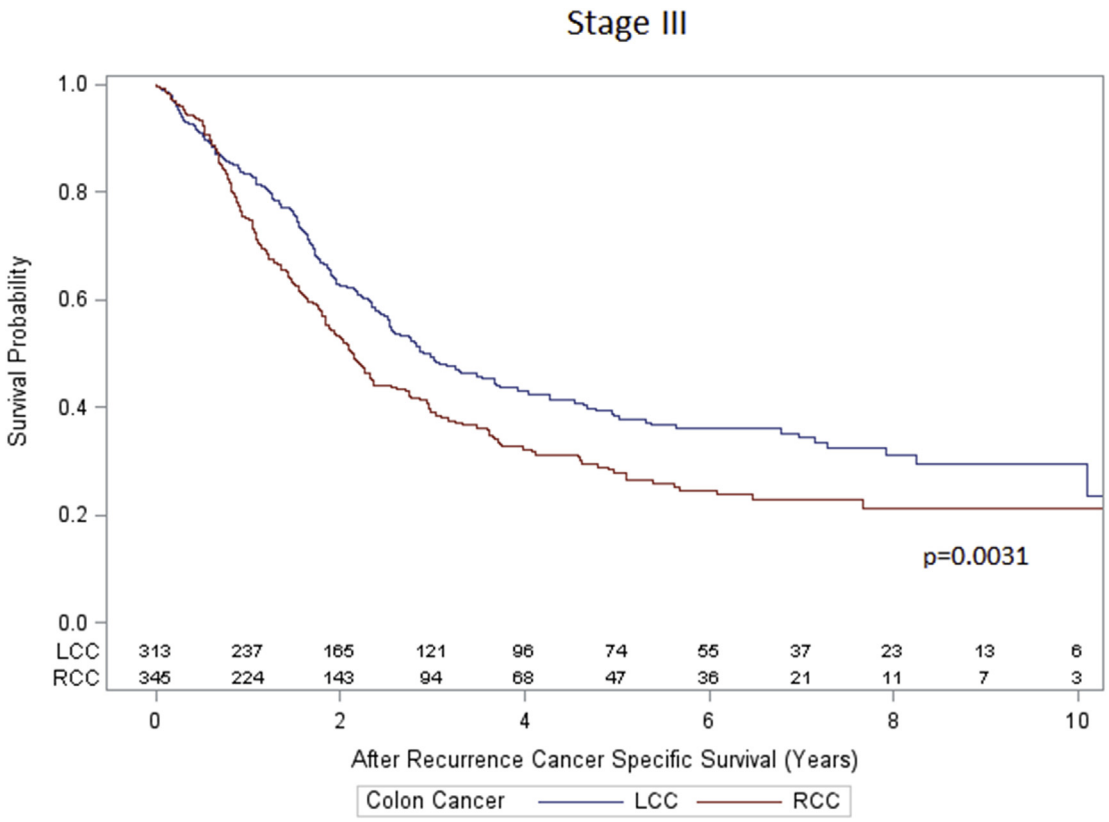

Fig. 2. Cancer-Specific Survival After Recurrence among stage III patients, LCC vs. RCC.

Postoperative adjuvant chemotherapy has been shown to prolong recurrence free survival in some stage II and stage III patients.[18,19] It is reasonable to consider adjuvant chemotherapy as an important factor affecting the risk of recurrence and death.[20] However, this study showed no significant differences in the rate of adjuvant chemotherapy between RCC and LCC groups in PSM. This may be due to the various adjuvant chemotherapy regimens. Since this was a multi-institutional retrospective study the postoperative therapy was not standardized. In order to reduce such bias, prospective studies that set a unified protocol for post-recurrence therapy are necessary.

Tumors arising on the right and left side of the colon seem to follow different molecular pathways of oncogenesis.[21] As a result, many studies have been conducted to search for theoretical genetic backgrounds of various lesions.

These studies show that patients with RCC were more commonly characterized by Microsatellite instability (MIS)-high, CpG island methylation (CIMP)-high, and BRAF mutations.[22,23] Coversely, patients with LCC were found to frequently have p53, APC and KRAS mutations.[24]

MIS and BRAF mutations have been reported to be associated with less frequent liver metastasis and more frequent peritoneal dissemination, respectively.[22] This may explain the differences in recurrences rates in Table 3. Further research for the mutations of BRAF, which has been reported as a poor prognostic factor in stageIV CRC, suggests these mutations are more frequent in RCC patients.[25]

Several studies have found that patients with microsatellite instability-positive (MSI-H) tumors have a better overall prognosis and that MSI status is a favorable independent predictor of survival.[26,27] It has been reported that of the different genetic mechanisms, MSI contributes to carcinogenesis in RCC and LCC.[2] The frequency of MSI was different between right- and left-sided colon cancers and also differed between tumor stages.[2] Additionally, Jernvall et al. estimated that the rate of MSI-high in stage II RCC is more frequent compared to stage III RCC.[28] They also reported that the survival advantage associated with MSI-high status was limited to patients with RCC.[28,29] Gervaz et al. suggested that stage II RCC patients had lower mortality compared to patients with LCC,[30] while stage III RCC patients had higher mortality than those with LCC.[31] These studies, which reported the association between recurrence site, MSI status and primary tumor location, support our results that the CSSAR in satge III with RCC patients were worse compared to LCC. Moreover, analyses of prospective clinical trials of patients with stage III CRC who received adjuvant chemotherapy demonstrated shorter disease-free survival in those with RCC.[32]

Therefore, genome-wide analysis might reveal that gene expression patterns are different according to tumor locations and stages. RCC and LCC have remarkably different underlying biologic characteristics. Our findings could be useful for identifying more powerful prognostic indicatiors and improving postoperative treatment and surveillance.

The microbiome has been reported to play an important part in the formation of CRC. A number of chromosomal and molecular differences have been investigated between RCC and LCC.[33] This review summarized the microbiome, clinical, chromosomal and molecular differences associated with the primary location of CRC.[33] Patients with RCC and LCC differ in their microbiome, clinical characteristics, molecular profiling, clinical outcomes and response to treatment. Little is known about reason for these differences.[33,34]

Limitations

While our study was the largest to examine recurrence rates,

CSS, and CSSAR in stage I–III colon cancer patients following curative resection, there are potential limitations of our study that should be considered. First, since this was a multi-institutional retrospective study, therapy after recurrence, such as indications of chemotherapy and metastasis resection, was not standardized. Second, detailed information of chemotherapy was unclear. Adjuvant chemotherapy was given in 3893 (57%) patients. There were 1301(19%) patients in which there were missing details regarding chemotherapy regimens (Table 1). Of those with known regimens, most received infusional 5-fluorouracil or a 5-fluorouracil prodrug. The remaining known regimens included hepatic infusion, oxaliplatin-based regimens, irinotecan-based regimens, and others. This study contained cases during the research period when anti-EGFR therapy was not yet used, which might have inserted some bias in oncological outcomes. Third, this study lacks individual information regarding MSI and other molecular biology such as KRAS and BRAF mutations. Prospective studies with unified policies in postoperative follow-up are needed. In addition, genetic analysis data is also required.

Conclusion

By excluding transverse colon cancer, it was possible to compare biological and oncological differences between RCC and LCC more precisely. Previous studies have reported an increase in mortality for RCC compared LCC. Our findings, however, have shown that RFS in stage I and II LCC patients was significantly shorter than RCC. After recurrence, compared to LCC, RCC was a significant risk factor for CSSAR in stage III patients. We suggest that a major reason for this inconsistent relationship between RFS, CSSAR, tumor location, and stage is due to biologic characteristics, particularly MSI status.

For future clinical trials in colon cancer, we propose that detailed information on tumor location (right-sided, transverse, and left-sided colon) should be included in order to deepen the understanding of genomic colon cancer onset mechanisms. Our results may provide a better understanding of the biological and the oncological differences between RCC and LCC, and might allow for personalized therapy based on biologic characteristics.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amjsurg.2018.07.005.

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