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Comparison of oncological outcomes of right-sided colon cancer versus left-sided colon cancer after curative resection

Which side is better outcome?

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Abstract

Propose: There are embryological origins, anatomical, histological, genetic, and immunological differences between right-sided colon cancer (RCC) and left-sided colon cancer (LCC). Many studies have sought to determine the survival and prognosis according to tumor location. This study aimed to analyze outcomes between RCC and LCC.

Material and method: Between January 2000 and December 2012, data on 414 patients who underwent curative resection for RCC and LCC were retrieved from a retrospective database. Propensity score matching (1:1) was performed and RCC was identified in 207 and LCC in 207 patients.

Results: On average, RCC exhibited a more advanced N stage, increased tumor size, more frequently poorly differentiated tumors, more harvested lymph nodes, and more positivity of lymphovascular invasion than LCC. With a median follow-up of 66.7 months, the 5-year overall survival (OS) rates for RCC and LCC were 82.1% and 88.7%, respectively, ($P < .05$). The 5-year disease-free survival (DFS) rates were 81.4% (RCC) and 88.3% (LCC; $P < .05$). In stage III cancers, the DFS rates were 61.1% (RCC) and 81.9% (LCC; $P < .05$), while the OS rates were 65.6% (RCC) and 78.6% (LCC; $P = .056$).

Conclusion: On the basis of present data, LCC exhibited better survival outcomes than RCC after curative resection. Especially in stage III, LCC showed better oncologic outcomes. Proper specialized treatment related to the location of colon cancer is needed.

Abbreviations: AJCC = American Joint Committee on Cancer, ASA = American society of anesthesiologists, BMI = body mass index, CEA = carinoembryonic antigen, CT = computed tomography, DFS = disease-free survival, LCC = left-sided colon cancer, MSI = microsatellite instability, OS = overall survival, PET = positron emission tomography, RCC = right-sided colon cancer, TNM = tumor node metastasis.

Keywords: colonic neoplasms, location, outcome

1. Introduction

Colorectal cancer is one of the most common cancers in the world,[1] and it is the fourth most common cancer among both men and women in Asian countries (1998–2007).[2] In Korea, colorectal cancer is the third most common cancer in general, the second most common cancer among men, and the third most common cancer among women.[3] The mainstay treatment of colon cancer is surgical resection. The surgeries performed for colon cancer, according to location of tumor, are right hemicolectomy, extended right hemicolectomy, left hemicolectomy, and anterior resection. There is evidence that right-sided colon cancer (RCC) is different from left-sided colon cancer (LCC) and rectal cancer. There are embryological origins, as well as anatomical, histological, genetic, and immunological differences between RCC and LCC.[4,5] During embryological development, the right-sided colon (cecum, ascending colon, and proximal two-thirds of the transverse colon) arises from the midgut, while the left-sided colon (distal one-third of the transverse colon, descending colon, and sigmoid colon) arises from the hindgut. The characteristics of RCC are associated with iron deficiency anemia, advanced stage, and old age.[6] Furthermore, RCC tends to involve bulky, exophytic, polypoid lesions growing into the colon lumen. In contrast, the characteristics of LCC tend to involve infiltrating, constricting lesions encircling the colorectal lumen and causing obstruction.[6] It has been shown that patients with RCC are older and more often female, and the disease is associated with advanced tumor stages, increased tumor size, more frequent poorly differentiated tumors, and different molecular biological tumor patterns.[7–9] For the reasons described above, many studies have reported that oncologic

Editor: Won Sup Lee.

Funding/support: This work was supported by the Soonchunhyang University Research Fund.

The statistics of this manuscript, including propensity matching score and internal validation, have been contributed by Bora Lee, a statistician belong to the department of Biostatistics, Clinical Trial Center, Soonchunhyang University Hospital, Bucheon.

Ethical approval was not necessary, as this analysis was based on a retrospective review.

The authors declare no conflict of interest in this work.

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Medicine (2017) 96:42(e8241)

Received: 30 April 2017 / Received in final form: 22 August 2017 / Accepted: 15 September 2017

http://dx.doi.org/10.1097/MD.0000000000008241

outcomes of colon cancer are different according to the location of tumor. Most studies have reported poorer oncologic outcomes in patients with RCC compared with patients with LCC.[9–13] However, recent studies have reported that the prognosis of localized RCC is better than that of LCC.[14,15] The present study aimed to analyze clinicopathological findings and oncologic outcomes between RCC and LCC after curative resection.

2. Materials and methods

Between January 2000 and December 2012, 563 patients who underwent curative surgery for right-sided and left-sided colon adenocarcinomas were identified from a retrospective database. Patients with stage IV disease were excluded from the present study, as were patients with metachronous and synchronous cancer. All data on clinical and pathological features were reviewed retrospectively. RCC was defined as location of the tumor, including the cecum/appendix, ascending colon, hepatic flexure, and proximal transverse colon (proximal two-thirds of the transverse colon). LCC was defined as location of the tumor, including the distal transverse colon (distal one-third of the transverse colon), splenic flexure, descending colon, and sigmoid colon. Rectosigmoid colon cancer and rectal cancer were excluded in the present study. All patients underwent colonoscopy, biopsy, and staging scans [chest, abdomen, and pelvis computed tomography (CT) scans], and occasionally, positron emission tomography (PET) scans were performed. All patients underwent curative resection. Adjuvant chemotherapy was carried out with 5-fluorouracil and a leucovorin-based regimen [6 cycles of monthly bolus intravenous administration of 5-fluorouracil (400–425 mg/m^2/day) and leucovorin (20 mg/m^2/day) days 1–5]. The reasons for not performing postoperative adjuvant chemotherapy included advanced age, patient refusal, and the side effects of adjuvant chemotherapy. Patients received close follow-up and were included in a database until July 2016 or their death if this occurred before July 2016. Disease-free survival (DFS) was defined as extending from the date of surgery to the date of the detection of recurrence, the last follow-up, or death. Patients in the 2 groups were compared with respect to patient demographics, peri- and postoperative morbidity, and pathological and oncologic outcomes.

2.1. Statistical analysis

All statistical analyses were performed using SAS Version 9.1.3 (SAS Institute Inc., Cary, NC) and SPSS software, Version 24.0 (SPSS, Chicago, IL). Categorical variables were analyzed using the χ^2 or Fisher exact test, and continuous variables were analyzed using the Student *t* test/Mann–Whitney *U* rank test. Cumulative-incidence methods were used to estimate the rate of cancer recurrence. Overall survival (OS) and DFS were analyzed using the Kaplan–Meier method, and a comparison was performed using the log-rank test. In the results, *P* values less than .05 were considered statistically significant. The differences in OS and DFS were assessed using the log-rank test.

Propensity score matching was performed (1:1 matching method). Propensity score matching was performed for the original 563 patients, a 1:1 matching method stratified into 2 groups, as follows (total 418 patients): Group I included 207 patients with RCC who underwent curative resection, and Group II included 207 patients with LCC who underwent curative resection.

Internal validation was performed by the bootstrap method using the new datasets created by random drawing from the sample with replacement. In each of the new data sets (n = 1000), the Cox proportional hazard model about the OS and DFS was repeated.

Analyses were performed using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-roject.org/).

3. Results

3.1. Patient characteristics

Patient characteristics were analyzed through a comparison of Group I and Group II (Table 1). Mean age, sex ratio, height,

Table 1

Patient characteristics (n = 414).

	Right side colon (n = 207) (%)	Left side colon (n = 207) (%)	*P*
Age [mean ± SD,(range)], y	62.9 ± 12.5 (36–85)	62.1 ± 11.4 (33–84)	.334
Sex, n (%)			1.000
Male	109 (52.7%)	109 (52.7%)	
Female	98 (47.3%)	98 (47.3%)	
Weight mean ± SD, (range), kg	59.6 ± 9.7 (38.6–91.7)	60.4 ± 10.3 (38.9–105.8)	.495
Height [mean ± SD, (range)], cm	159.1 ± 9.2 (137.5–185.8)	160.0 ± 9.2 (131.0–180.4)	.961
BMI [mean ± SD, (range)], kg/m^2	23.5 ± 3.3 (16.9–33.7)	23.5 ± 2.9 (15.3–34.5)	.207
ASA score, n (%)			.765
1	76 (36.7%)	80 (38.6%)	
2	125 (60.4%)	119 (57.5%)	
3	6 (2.9%)	8 (3.9%)	
Initial CEA	5.4 ± 8.1 (0.19–113.41)	5.9 ± 10.8 (0.30–70.92)	.152
Tumor location			NS
Right side			
Cecum	7 (3.4%)		
Ascending colon	140 (67.6%)		
Hepatic flexure colon	7 (3.4%)		
Proximal transverse colon	53 (25.6%)		
Left side			
Distal transverse colon		7 (3.4%)	
Splenic flexure colon		2 (1.0%)	
Descending colon		24 (11.6%)	
Sigmoid colon		174 (84.0%)	

Table 2

Postoperative pathologic outcomes.

	Right side colon (n=207) (%)	Left side colon (n=207) (%)	*P*
pTNM stage, no. (%) 0	4 (1.9%)	5 (2.4%)	.138
I	39 (18.8%)	53 (25.6%)	
IIa	88 (42.5%)	80 (38.6%)	
IIb	3 (1.4%)	4 (1.9%)	
IIc	2 (1.0%)	2 (1.0%)	
IIIa	7 (3.4%)	11 (5.3%)	
IIIb	41 (19.8%)	44 (21.3%)	
IIIc	23 (11.1%)	8 (3.9%)	
pT stage, no. (%)			.354
Tis	4 (1.9%)	5 (2.4%)	
1	27 (13.0%)	41 (19.8%)	
2	20 (9.7%)	23 (9.9%)	
3	140 (67.6%)	128 (11.1%)	
4a	13 (6.3%)	7 (3.4%)	
4b	3 (1.4%)	3 (1.4%)	
pN stage, no. (%)			.019
0	136 (65.7%)	144 (69.6%)	
1a	20 (9.7%)	22 (10.6%)	
1b	19 (9.2%)	24 (11.6%)	
2a	10 (4.8%)	12 (5.8%)	
2b	22 (10.6%)	5 (2.4%)	
Grade of differentiation, no. (%)			<.005
Well	40 (19.3%)	44 (21.3%)	
Moderate	118 (57.0%)	152 (73.4%)	
Poorly	28 (13.5%)	9 (4.3%)	
Mucinous	19 (9.2%)	2 (1.0%)	
Signet ring cell	2 (1.0%)	0 (0.0%)	
Harvested no. of lymph nodes, (mean±SD, range), (No.)	30.3±17.2 (1–94)	16.3±11.1 (1–72)	<.005
Lymphovascular invasion			.022
−	127 (61.4%)	149 (71.9%)	
+	80 (38.6%)	58 (28.1%)	
Perineural invasion			.138
−	176 (85.0%)	186 (89.9%)	
+	31 (15.0%)	21 (10.1%)	
PRM, (mean±SD, range), cm	14.7±9.4 (2.8–58.0)	9.2±4.9 (1.5–28.0)	<.005
DRM, (mean±SD, range), cm	15.9±9.5 (0.5–59.0)	6.1±4.9 (1.0–54.0)	<.005
Mass size	5.6±3.1 (0.5–15.0)	4.4±2.3 (0.7–10.0)	.008

weight, body mass index (BMI), and ASA scores, as well as initial CEA, did not significantly differ between the 2 groups. The distribution of RCC was 3.4% cecum (n=7), 67.6% ascending colon (n=140), 3.4% hepatic flexure colon (n=7), and 25.6% proximal transverse colon (n=53). The distribution of LCC was 3.4% distal transverse colon (n=7), 1.0% splenic flexure colon (n=2), 11.6% descending colon (n=24), and 84.0% sigmoid colon (n=174).

3.2. Pathological results

The tumor–node–metastasis (TNM) stage, pT stage, pN stage, and pM stage were classified according to the American Joint Committee on Cancer (AJCC, 7th edition). In the distribution of TNM stage, the N stage was significantly different between the 2 groups except the T stage. The histological grades of differentiation significantly differed between the 2 groups ($P=.019$). Group II had more patients with a moderate differentiation of cancer (n=152, 73.4% in Group II vs n=118, 57.0% in Group I; $P<.005$). The mean numbers of harvested lymph nodes were 30.3±17.2 in Group I and 16.3±11.1 in Group II ($P<.005$). The mean proximal resection margins in Groups I and II were 14.7±9.4 and 9.2±4.9 cm, respectively ($P<.005$). The mean distal resection margins were 15.9±9.5 and 6.1±4.9 cm, respectively ($P<.005$). The mean specimen mass sizes were 5.6±3.1 cm in Group I and 4.4±2.3 cm in Group II ($P=.008$). The lymphovascular invasion rates were 38.6% in Group I and 28.1% in Group II ($P=.022$). The perineural invasion rates were 15.0% in Group I and 10.1% in Group II ($P=.138$; Table 2).

3.3. Oncologic outcomes

With a median follow-up of 66.7 months, the 5-year DFS rates were 81.4% in Group I and 88.3% in Group II ($P=.031$). The 5-year OS rates were 82.1% in Group I and 88.7% in Group II ($P=.012$; Fig. 1). For stage I, the 5-year DFS rates were 97.7% in Group I and 100.0% in Group II ($P=.17$). The 5-year OS rates were 95.2% in Group I and 98.9% in Group II ($P=.66$). For stage II, the 5-year DFS rates were 89.3% in Group I and 84.6% in Group II ($P=.564$). The 5-year OS rates were 87.4% in Group I and 87.9% in Group II ($P=.633$; Fig. 2). For stage III, the 5-year DFS rates were 61.1% in Group I and 81.9% in Group II ($P=.008$). The 5-year OS rates were 65.6% in Group I and 78.6% in Group II ($P=.056$; Fig. 3.).

3.4. Univariate and multivariate analysis of prognostic factors

Old age (≥70 years), tumor location (right side), large tumor size (≥5 cm), T3-4 stage, node-positive stage (N1-2), histological

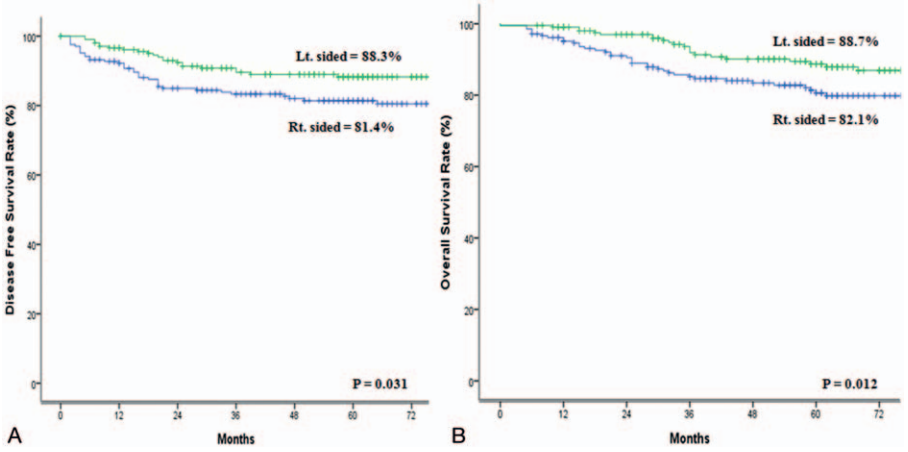

Figure 1. Five-year disease-free survival rate (A) and 5-year overall survival rate (B) of right-sided colon cancer and left-sided colon cancer after curative surgery.

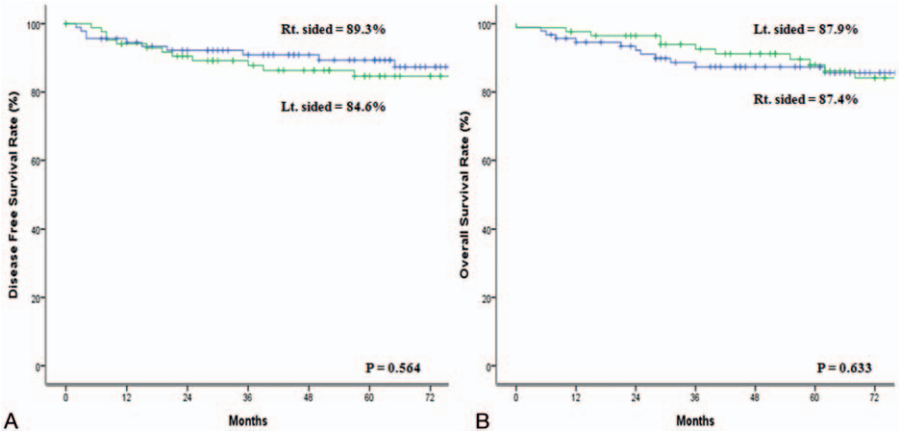

Figure 2. Five-year disease-free survival rate (A) and 5-year overall survival rate (B) of right-sided colon cancer and left-sided colon cancer after curative surgery at Stage II.

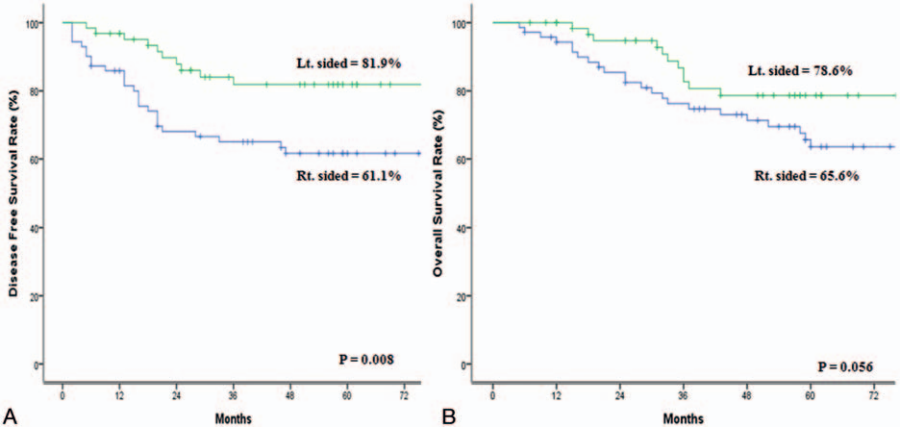

Figure 3. Five-year disease-free survival rate (A) and 5-year overall survival rate (B) of right-sided colon cancer and left-sided colon cancer after curative surgery at Stage III.

grade, and lymphovascular invasion were analyzed as poor prognostic factors for the OS rate after surgery in univariate analysis (Table 3.). The old age (≥70 years), T3-4 stage, and node-positive stage (N1-2) were analyzed as a poor prognostic factor for the OS rate after surgery in multivariate analysis. In addition, tumor location (right side), large tumor size (≥5 cm), T3-4 stage, node-positive stage (N1-2), histological grade, lymphovascular invasion, and perineural invasion were analyzed as prognostic factors for the DFS rate after surgery in univariate analysis. The T3-4, node-positive stage (N1-2), and histological

Table 3

Univariate and multivariate analysis for prognostic factor of overall survival after surgery for colon cancer.

	Univariate analysis			Multivariate analysis		
Factors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age, y (<70 vs ≥70)	2.19	1.31–3.55	.003	2.07	1.25–3.41	.005
Sex (Male vs Female)	0.94	0.82–0.94	.821			
BMI (<25 vs ≥25)	0.64	0.36–1.14	.118			
Tumor location (Rt. side vs Lt. side)	0.52	0.31–0.87	.011	0.71	0.41–1.24	.229
Tumor size, cm (<5 vs ≥5)	2.76	1.61–4.72	<.05	1.48	0.83–2.67	.186
T stage (T1-2 vs T3-4)	8.48	2.67–27.07	<.05	4.12	1.20–14.08	.024
N stage (N0 vs N1–2)	2.94	1.79–4.84	<.05	2.09	1.23–3.54	.006
Number of harvested lymph node (<12 vs ≥12)	1.24	0.68–2.24	.477			
Histological grade (Well-mod. vs others)	3.02	1.76–5.18	<.05	1.64	0.91–2.94	.097
Lymphovascular invasion (present vs absent)	2.56	1.56–4.21	<.05	1.37	0.80–2.35	.249
Perineural invasion (present vs absent)	1.78	0.95–3.33	.092			

CI = confidence interval, HR = hazard ratio.

Table 4

Univariate and multivariate analysis for prognostic factor of disease-free survival after surgery for colon cancer.

	Univariate analysis			Multivariate analysis		
Factors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age, y (<70 vs ≥70)	1.36	0.80–2.31	.258			
Sex (Male vs female)	1.31	0.79–2.19	.296			
BMI (<25 vs ≥25)	0.84	0.48–1.48	.545			
Tumor location (Rt. side vs Lt. side)	0.56	0.33–0.96	.031	0.84	0.48–1.47	.544
Tumor size, cm (<5 vs ≥5)	3.28	2.04–5.28	<.05	1.72	0.92–3.24	.088
T stage (T1-2 vs T3-4)	12.8	3.12–52.34	<.05	5.69	1.30–24.94	.021
N stage (N0 vs N1-2)	3.67	2.18–6.20	<.05	2.31	1.32–4.05	.003
Number of harvested lymphnode (<12 vs ≥12)	1.35	0.71–2.54	.345			
Histological grade (Well-mod. vs others)	3.59	2.09–6.16	<.05	1.77	0.98–3.22	.045
Lymphovascular invasion (present vs absent)	2.71	1.73–4.25	<.05	1.33	0.76–2.36	.320
Perineural invasion (present vs absent)	2.32	1.27–4.22	.011	1.29	0.69–2.40	.428

CI = confidence interval, HR = hazard ratio.

grade were analyzed as prognostic factors for the DFS rate after surgery in multivariate analysis (Table 4).

3.5. Internal validation

Stability in the result of Cox PH analyses for OS and DFS was assessed over the 1000 bootstrap samples. In the case of OS, age, T stage, and N stage were selected in all 1000 bootstrap samples and BMI, tumor size, histologic grade, and lymphovasulcar invasion were selected in 13.4%, 11.5%, 17.9%, and 24.3% of the cases, respectively, and there left out of the model, including the tumor location that was the primary factor in this study. In the case of DFS, T stage, N stage, and histologic grade were selected in all 1000 bootstrap samples and tumor size, lymphovascular invasion, and perineural invasion were selected in 28.9%, 10.8, and 37.7% of the cases, respectively, and therefore left out of the model including the tumor location as the above reason.

4. Discussion

Colon cancer has different clinicopathological features and genetic differences between the right side and the left side. Many studies have reported that patients with RCC are older and more often female; moreover, they have more advanced tumor stages, increased tumor size, more often poorly differentiated tumors, and different molecular biological tumor patterns.[7–9] In addition, MSI-high cancer has been reported to be more frequent in RCC than in LCC.[16,17] The incidence rate of LCC is higher than that of RCC, and the most recent figures reported by the American Cancer Society confirm a higher proportion of LCC (51%) compared with RCC (42%) in the United States.[18] In the present study, LCC (n = 345, 61.3%) was higher than RCC (n = 218, 38.7%) in the same period (2000–2012). In the present study, the mean age and sex ratio were not significantly different between Group I and Group II. The mean ages were 62.9 years (RCC) and 62.1 years (LCC; $P = .334$). One previous study reported that the median age at diagnosis was greater for RCC than for LCC. In this study, the median age was 71 to 74 years for RCC group versus 66 to 71 years for LCC group; thus, RCC patients were older than LCC patients.[7] Another study reported that RCC is more common in patients older than 60 years of age compared with LCC.[19] In present study, the distribution of gender was relatively equal ($P = 1.000$). A nationwide Danish cohort study was reported that a significantly higher proportion of RCC (56.8%) than LCC (46%) patients were women ($P < .0001$).[13]

Several studies have reported that LCC more often represents an early-stage disease compared with RCC, and these results have affected the disparity in prognoses according to the location of tumors.[20,21] Similarly, several studies have reported that RCC tends to exhibit a more advanced stage compared with LCC.[12,13,22] In the present study, although there were not significant differences between the 2 groups, especially, stage IIIc was more often found in RCC (11.1%) than in LCC (3.9%; $P = .138$). The distribution of the T stage was not significantly different between the 2 groups ($P = .354$). However, distribution of the N stage was significantly different between the 2 groups ($P = .019$), especially N2b (right side, 10.6% vs left side, 2.4%). In addition, RCC is more poorly differentiated (13.5% vs 4.3%), mucinous (9.2% vs 1.0%), and likely to exhibit signet ring cells (1.0% vs 0%) compared with LCC in histological grade ($P < .005$). Previous studies reported that higher proportions of poorly differentiated cancers were noted in RCCs more frequently than in LCCs.[8,12,23]

Mik et al[24] reported that the total number of harvested lymph nodes was higher in the RCC group than in the LCC group (11.7 ± 6 vs 8.3 ± 5; $P = .0001$). The lymph node ratio was higher in the LCC group (0.45 ± 0.28 vs 0.30 ± 0.25; $P = .0063$).[24] A recent

Table 5

Survival rate of right-sided colon cancer versus left-sided colon cancer in systemic review.

Ref.	Country	Study type	Article, n	Prognosis	HR	CI
Yahagi et al [28]	Japan	PRIAMA	16	Rt.< Lt.	1.14	1.06–1.22
Lee et al [29]	UK	PRIAMA	13	Rt.<Lt.		
Hansen et al [4]	Denmark	PRIAMA	17	Rt.<Lt.	1.12	1.018–1.226
Petrelli et al [30]	Italy	PRIAMA	66	Rt.<Lt.	0.82	0.79–0.84

CI = confidence interval, HR = hazard ratio, PRIAMA = preferred reporting items for systematic reviews and meta-analysis.

study reported that RCC patients exhibited more lymph nodes (18.7 vs 16.3) compared with LCC patients, and RCC patients were more likely to have ≥12 modes ($P<.001$), whereas RCC showed lower rates of node positivity ($P<.001$).[25] The reasons for these node-status differences were field of surgery and differences in the immune response and molecular features between RCC and LCC.[26,27] The field of resection in right hemicolectomy is wider compared with that of left hemicolectomy or anterior resection. Anatomically, the right-sided colon mesentery may contain a more complex lymphatic system, leading to an enhanced immune response and an increased number of lymph nodes examined for RCC.[26] In the present study, the total number of harvested lymph nodes was higher in Group I than in Group II (30.3 ± 17.2 vs 16.3 ± 11.1; $P<.005$). Moreover, the rate of node positivity in Group I was higher than that in Group II (34.3% vs 30.4%; $P=.019$). For these reasons, in accordance with previous studies, RCC was associated with poorer oncologic outcomes compared with LCC in this research. Indeed, previous studies have reported poorer oncologic outcomes in patients with RCC compared with patients with LCC [4,28–30] (Table 5). The 5-year OS rate was 82.1% in Group I and 88.7% in Group II ($P=.012$). In more detail, at stage I and II, there were no significant differences between the 2 groups, although the oncologic outcomes for RCC were low compared with those associated with LCC. In stage III, there were significant differences between the 2 groups (DFS: 61.1% vs 81.9%, $P=.008$; OS, 65.6% vs 78.6%, $P=.056$).

In present study, the T3-4 stage and node-positive stage (N1-2) were analyzed as prognostic factors for the OS and DFS rate after surgery in multivariate analysis. Of course, tumor location (right side/left side) is not an independent prognostic factor for the OS and DFS rate after surgical treatment in colon cancer. In present study, it was also not analyzed as an independent prognostic factor in multivariate analysis. However, as shown in multivariate analysis in present study, advanced T stage, node positivity, and poor histological grade were an independent prognostic factor for oncologic outcomes. The RCC trend to have more advanced T stage, node positivity, and poor histological grade than the LCC.[7,8] Therefore, the prognosis of RCC is expected to be worse compared with LCC, relatively. In the present study, it was also analyzed that the RCC trend to have more advanced node positivity (N2a-b; 15.4% vs 8.2, $P=.019$) and poor histological grade (poorly/mucinous; 21.7% vs 5.3%, $P<.005$) than the LCC. The present study has several limitations, including its retrospective study, significant selection biases, small sample size, and single center study. Nevertheless, the present study has shown results similar to those of previous studies.[4,28–30] The present study has tried to minimize such bias. All patients in the present study are Koreans and all surgeries were performed in 1 hospital. Propensity score matching and internal validation was performed. The present study was a comparison between the 2 groups in these patients, and several factors affecting results were no significant difference between the 2 groups.

In conclusion, RCC was associated with more advanced stage, increased tumor size, more often poorly differentiated tumors, more harvested lymph nodes, and more node positivity than LCC in the present study. On the basis of present data, LCC has better survival outcome compared with RCC after curative resection (especially for stage III). More large-scaled studies are needed and proper specialized treatment related to the location of colon cancer is needed.

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