

Tumor Sidedness Could be a Prognostic Factor in Patients with Stage II Colon Cancer

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Abstract

Background : The search for high-risk factors in stage II colon cancer (CC) is ongoing and several high-risk factors for stage II CC have been identified; however, the effects of tumor sidedness on prognosis is not clear. This study aims to determine whether tumor sidedness could be identified as another high-risk factor for stage II CC.

Methods : We retrospectively analyzed 189 patients with stage II CC, following consecutive curative resection surgery performed between 2008 and 2014. We compared clinicopathological findings and long-term outcomes between the patients with right colonic cancer (RCC) and patients with left colonic cancer (LCC). Prognostic factors for survival were determined using univariate and Cox proportional regression analyses.

Results : A total of 72 patients were diagnosed with RCC and 117 patients were diagnosed with LCC. Patients with RCC were significantly older ($p < 0.001$) than those with LCC, and the number of harvested lymph nodes (HLNs) was greater in the RCC group (RCC: 25 vs. LCC: 19; $p = 0.003$). The overall survival (OS) was notably worse in the RCC group than the OS in the LCC group (5 year survival rate—RCC: 81.3% vs. LCC: 90.4%; $p = 0.025$), whereas no significant difference was observed in disease-free survival (5 year survival rate—RCC: 74.8% vs. LCC: 83.4%; $p = 0.065$). Cox proportional regression analysis showed that tumor sidedness (hazard ratio (HR): 3.78, 95% confidence interval (CI): 1.61–8.85, $p = 0.022$), gender (HR: 3.27, 95% CI: 1.27–8.47, $p = 0.014$), and the number of HLNs (HR: 4.58, 95% CI: 1.95–10.74, $p < 0.001$) were independent prognostic factors for OS.

Conclusion : Patients with a right-sided primary tumor location have more negative prognostic factors and worse long-term outcomes than those with a left-sided primary tumor location in stage II CC.

Background

Colorectal cancer (CRC) is a major health problem worldwide. CRC is the third most common cancer in the world and the second highest cause of cancer-related death[1, 2]. Recently, several molecular and genetic mechanisms of CRC carcinogenesis have been identified[3, 4]. It has also been reported that the oncological features differ between colon cancer (CC) and rectal cancer[5]. In stage II CC, there are several high-risk factors, according to the guidelines of the National Comprehensive Cancer Network, the European Society for Medical Oncology, and the Japanese Society for Cancer of the Colon and Rectum (JSCCR)[6–8]. These include bowel obstruction, perforation, poorly differentiated histology, lymphovascular invasion, perineural invasion, pT4, low number of harvested lymph nodes (HLNs; <12), and unclear resection margins. However, these risk factors vary by region, and there is still no rigorous evidence. The search for other prognostic factors in stage II CC is ongoing. For decades, carcinogenetic differences between right colonic cancer (RCC) and left colonic cancer (LCC) have been suggested[9, 10]. Also, there have been reports of differences in clinical, pathological, molecular, and biological features, according to the tumor sidedness, and there has been much debate about the impact of tumor location

on prognosis[9, 11, 12]. Nevertheless, few reports have evaluated tumor sidedness as a risk factor of stage II CC, because many of these reports target advanced stage cancers, including metastatic CRC, to analyze the differences in chemotherapy effects. In these advanced stage and metastatic CRCs, molecular and biological differences are considered when selecting a chemotherapy regimen[13, 14]. Meanwhile, investigations into the effects of adjuvant chemotherapy on stage II CRC have not yet been concluded; the main problem being that the high-risk factors have not been identified. Therefore, the current challenges are to identify the high-risk factors and evaluate the benefits of adjuvant chemotherapy. Previous studies of adjuvant chemotherapy for stage II CRC were designed to identify survival benefits, with the focus mainly on high-risk patients[15, 16]. The problem, however, is that most of the previous studies of stage II CRC have not evaluated tumor sidedness. In this study, we hypothesize that differences in tumor sidedness define the prognosis of stage II CC. This study aims to determine the influence of tumor sidedness on the long-term outcomes and prognosis for stage II CC.

Method

Patients

Subjects for the study were selected from patients with CRC at the Department of Surgery, Saiseikai Yokohamashi Nanbu Hospital, between January 2008 and December 2014. The inclusion criteria were as follows: (1) patients with stage II colonic adenocarcinoma without rectal cancer, based on the Union for International Cancer Control's (UICC) TNM classification (seventh edition); (2) patients had undergone surgery with R0 resection; and (3) patients without synchronous or metachronous malignancy. The selected patients were divided into two groups, based on tumor location (the RCC and LCC groups). RCC was defined as a tumor arising from the cecum, ascending colon, or transverse colon. LCC was defined as a tumor arising from the descending colon, sigmoid colon, or recto-sigmoid colon.

Surgical procedure and follow-up

The procedures were performed by colorectal surgeons (with the patients under general anesthesia) and involved a complete mesocolic excision. The method of surgical approach (open surgery or laparoscopic surgery) was determined in each case, depending on the patient's medical history and tumor progression. Laparoscopic surgery was performed using five trocars. Adequate resection margins were determined according to JSCCR guidelines, and D2 or D3 lymphadenectomies were performed in all cases[8]. All patients were followed up regularly at our institution, including carcinoembryonic acid (CEA) and cancer antigen 19 – 9 assays every 3 to 6 months, and computed tomography every 6 to 12 months. A colonoscopy was performed annually, for at least 5 years. Adjuvant chemotherapy was offered to all high-risk stage II patients having at least one high-risk factor, according to the JSCCR Guidelines for the Treatment of Colorectal Cancer. Treatment was started after pathological evaluation of the tumor specimen, which was performed within 8 weeks of surgery, under informed consent. In adjuvant chemotherapy, oral 5-fluorouracil prodrug (capecitabine) was taken by the patient for 6 months following the operation.

Evaluation of surgical outcomes and prognostic factors for survival

We retrospectively compared patient characteristics, including age, gender, and pathological findings, between the RCC group and the LCC group. Tumor histology was described using the World Health Organization classification[17]. Pathological staging was performed according to the UICC's TNM classification. The surgeries were organized by procedure type, and the data included the extent of lymph node dissection, the number of HLNs, duration of surgery, volume of blood loss, postoperative stay, and complications. Postoperative complications were described using the Clavien–Dindo classification; grade II or higher was considered a major complication in this study[18]. Postoperative results included pathological findings, recurrence rate, overall survival (OS), and disease-free survival (DFS).

Statistical analysis

Statistical analysis included the Student's t-test, which compares the mean of a continuous variable with a parametric distribution, and the Mann–Whitney U test, for variables with nonparametric distributions. The chi-square test or Fisher's exact test were used to compare proportions. Survival was estimated by the Kaplan–Meier method, and the group data were compared using the log-rank test. Prognostic factors for survival were determined using univariate and Cox proportional regression analyses. All tests were two-tailed and P-values < 0.05 were considered to be significant.

Results

Demographic and clinicopathological characteristics, and surgical outcomes

A total of 1,398 CRC patients underwent resective surgery at our hospital between January 2008 and December 2014. Of those, 189 patients with stage II CC were extracted, based on the inclusion criteria; 72 were diagnosed with RCC and 117 were diagnosed with LCC. Demographic and clinicopathological characteristics are summarized in Table 1. Patients with RCC were significantly older ($p < 0.001$) than the LCC patients, and the number of HLNs was significantly higher in the RCC group (RCC: 25 vs. LCC: 19; $p = 0.003$). Gender, serum CEA level, tumor diameter, histological type, the incidence of preoperative obstruction and tumor perforation, and the other pathological data did not differ between the two groups. There was no significant difference in the incidence of postoperative complications (Clavien–Dindo classification \geq II) between the two groups ($p = 0.08$). A total of 27 patients (14.3%) received adjuvant chemotherapy, and there was no difference in the rate of adjuvant chemotherapy between the two groups (RCC: 12.5% vs. LCC: 19.4%; $p = 0.40$).

Table 1
Patients' characteristics in the RCC and LCC groups

	RCC (n = 72)	LCC (n = 117)	P-value
Age (years) ^a	75 (40–91)	71 (44–89)	< 0.001
Gender			
Male/Female	29/43	62/55	0.10
Tumor location ^b			
C/A/T	13/46/13	-	-
D/S/RS	-	12/71/34	-
Serum CEA level (ng/ml) ^a	3.8 (0.6–260.0)	4.4 (0.8–87.1)	0.62
Tumor diameter (mm) ^a	45 (15–130)	50 (10–150)	0.96
Histological type			
Differentiated	64	113	0.061
Poorly differentiated	8	4	
Obstruction			
Yes/No	4/68	8/109	1.0
Tumor perforation			
Yes/No	1/71	2/115	1.0
pT stage			
pT3/pT4	13/59	15/102	0.40
Lymphovascular invasion			
Absent/present	15/57	38/79	0.097

^a median (range)

^b C: cecum, A: ascending colon, T: transverse colon, D: descending colon,
S: sigmoid colon, RS: rectosigmoid colon

^c C-D classification: Clavien-Dindo classification

RCC, right colonic cancer; LCC, left colonic cancer

	RCC (n = 72)	LCC (n = 117)	P-value
Perineural invasion			
Absent/present	59/13	15/102	0.40
Number of harvested ^a Lymph nodes	25 (2–53)	19 (2–49)	0.003
Approach			
Open/Laparoscope	43/29	79/38	0.35
Extent of lymphadenectomy			
D3/D2	57/15	87/30	0.49
Major complications (C-D classification \geq II) ^c			
Yes/No	23/49	23/94	0.08
Adjuvant chemotherapy			
Yes/No	8/64	19/98	0.40
^a median (range)			
^b C: cecum, A: ascending colon, T: transverse colon, D: descending colon, S: sigmoid colon, RS: rectosigmoid colon			
^c C-D classification: Clavien-Dindo classification			
RCC, right colonic cancer; LCC, left colonic cancer			

Recurrence pattern and post-recurrence therapy between the groups

Recurrence patterns and treatments for recurrence are summarized in Table 2. Ten patients (13.9%) recurred in the RCC group, compared with 14 patients (12.0%) in the LCC group. The recurrence sites were the liver, lungs, peritoneum, and bone. The liver was the most commonly recurring organ in both groups. There was no significant difference between the two groups in recurrence sites ($p = 0.44$). Treatments for recurrence were performed in 90% and 92.9% of cases in the RCC and LCC groups, respectively. Five patients (50%) underwent surgery, and four (40%) received chemotherapy in the RCC group. In the LCC group, eight patients (57.2%) underwent surgery, and five (35.7%) received chemotherapy.

Table 2

Recurrence pattern and post-recurrence therapy between the groups

	RCC (n = 72)	LCC (n = 117)	P-value
Follow-up period (month) ^a	59 (9-121)	60 (12–122)	0.02
Recurrence, n (%)			
Total	10 (13.9)	14 (12.0)	0.82
Recurrence site			0.44
Liver	7 (70.0)	7 (50.0)	
Lung	1 (10.0)	5 (35.8)	
Peritoneal dissemination	2 (20.0)	1 (7.1)	
Bone	0 (0)	1 (7.1)	
Treatments for recurrence, n (%)			1
Surgery	5 (50.0)	8 (57.2)	
Chemotherapy	4 (40.0)	5 (35.7)	
None	1 (10.0)	1 (7.1)	
^a median (range)			
RCC, right colonic cancer; LCC, left colonic cancer			

Long-term outcomes

The survival rates are described in Fig. 1. The OS was significantly lower in the RCC group than in the LCC group (5 year survival rate—RCC: 81.3% vs. LCC: 90.4%; $p = 0.025$), whereas no significant difference was observed in DFS (5 year survival rate—RCC: 74.8% vs. LCC: 83.4%; $p = 0.065$).

Prognostic factors for survival of stage II colon cancer

Tables 3 and 4 show the results of the OS and DFS prognostic factor analysis. Univariate analysis revealed that tumor location, gender, histological type, and number of HLNs were prognostic factors for OS, although no significant difference was observed in age, serum CEA level, tumor diameter, obstruction and tumor perforation, pT stage, lymphovascular invasion, perineural invasion, approach, extent of lymphadenectomy, complications, or adjuvant chemotherapy. Cox proportional regression analysis showed that tumor sidedness (hazard ratio (HR): 3.78, 95% confidence interval (CI): 1.61–8.85, $p = 0.022$), gender (HR: 3.27, 95% CI: 1.27–8.47, $p = 0.014$), and the number of HLNs (HR: 4.58, 95% CI: 1.95–10.74, $p < 0.001$) were independent prognostic factors for OS. In univariate analysis for DFS, gender ($p = 0.0020$)

and the number of HLNs ($p < 0.001$) were prognostic factors, whereas tumor sidedness was not a significant factor ($p = 0.065$). Multivariate analysis showed that both gender (HR: 2.35, 95% CI: 1.14–4.82, $p = 0.020$) and the number of HLNs (HR: 2.84, 95% CI: 1.45–5.56, $p = 0.0022$) were independent prognostic factors for DFS.

Table 3
Univariate analysis of prognostic factors for stage II colon cancer

Variables	n	5 year OS (%)	5 year DFS (%)	P-value (OS/DFS)
Age (year)				
<65/≥65	41/148	94.5/84.8	92.3/76.7	0.062/0.057
Gender				
Male/Female	91/98	80.2/93.3	71.3/88.2	0.0040/0.0020
Tumor sidedness				
Right/Left	72/117	81.3/90.4	74.8/83.4	0.025/0.065
Serum CEA level (ng/ml)				
<5/≥5	113/76	89.3/85.5	80.9/79.0	0.34/0.56
Tumor diameter (mm)				
<50/≥50	96/93	88.9/85.2	82.5/77/9	0.62/0.54
Histological type				
Differentiated	177	87.9	80.5	0.037/0.24
Poorly differentiated	12	75.0	75.0	
Obstruction				
Yes/No	12/177	86.6/91.7	75.0/80.5	0.84/0.33
Tumor perforation				
Yes/No	3/186	66.7/87.3	66.7/80.4	0.37/0.69
pT stage				
pT3/pT4	161/28	87.6/83.7	81.9/69.7	0.46/0.10
Lymphovascular invasion				
Absent/present	53/136	89.8/85.8	86.1/77.8	0.30/0.14
Perineural invasion				
Absent/present	161/28	85.9/96.2	79.9/82.6	0.26/0.78

^a C-D classification: Clavien-Dindo classification

OS, overall survival; DFS, disease free survival

Variables	n	5 year OS (%)	5 year DFS (%)	P-value (OS/DFS)
Number of harvested Lymph nodes				
<12/≥12	38/151	67.3/91.4	55.0/86.0	< 0.001/<0.001
Approach				
Open/Laparoscope	122/67	85.3/90.2	78.1/84.0	0.33/0.30
Extent of lymphadenectomy				
D3/D2	144/45	88.9/80.9	82.2/73/5	0.15/0.39
Major complications (C-D classification ≥ II) ^a				
Yes/No	46/143	80.5/89.0	78.8/80.6	0.36/0.90
Adjuvant chemotherapy				
Yes/No	27/162	83.2/87.7	73.1/81.3	0.84/0.43
^a C-D classification: Clavien-Dindo classification				
OS, overall survival; DFS, disease free survival				

Table 4
Multivariate analysis of prognostic factors for stage II colon cancer

Overall survival				Disease free survival			
Variables	Hazard ratio	95% confidence interval	P-value	Variables	Hazard ratio	95% confidence interval	P-value
Gender				Gender			
Male vs Female	3.27	1.27–8.47	0.014	Male vs Female	2.35	1.14–4.82	0.020
Tumor sidedness							
Right vs Left	3.78	1.61–8.85	0.022				
Histological type							
Poorly differentiated vs differentiated	1.99	0.66–5.98	0.22				
Number of harvested Lymph nodes				Number of harvested Lymph nodes			
<12 vs ≥ 12	4.58	1.95–10.74	< 0.001	<12 vs ≥ 12	2.84	1.45–5.56	0.0022

Discussion

This study investigated the long-term outcomes and prognostic factors for stage II CC, according to the tumor sidedness. It confirmed that tumor sidedness has a major influence on prognosis. The main clinicopathological findings of this study were that stage II RCC was more frequent in more elderly patients and was characterized by a higher number of dissected lymph nodes, when compared with stage II LCC patients. Furthermore, tumor sidedness was an independent prognostic factor for OS, and the number of HLNs and gender were independent factors for both OS and DFS. For decades, there have been many suggestions that tumor location in CC potentially influences prognosis because of clinical and biological differences. Furthermore, it appears that tumors arising in right colonic lesions have different molecular and genetic pathways, when compared with those arising in left colonic lesions[3, 13, 19].

In related studies, it was reported that defective mismatch repair genes, high microsatellite instability (MSI-H), BRAF/KRAS mutations, and CpG island methylator phenotype positive were the notable

characteristics of RCC, whereas LCC was characterized by frequent NRAS and p53 mutations[4, 13, 20–22]. These molecular and genetic features of CC that were due to the tumor location have been associated with prognosis, and the treatment, such as 5-fluorouracil-based chemotherapy or anti-EGFR therapy[19, 23, 24]. Meanwhile, in stage II CC, the efficacy and role of adjuvant chemotherapy is still uncertain[16, 25]. In addition, there is an ongoing debate over which factors are high risk in the prognosis for stage II CC. Although tumor sidedness is not included as a stage II high-risk factor in the current guidelines, attention must be paid to tumor location in view of these molecular biological differences.

Several previous reports have indicated that RCC patients have lower survival rates than those with LCC. For example, Meguid et al. reported the survival analysis of 77,978 colorectal cancer patients, using the Surveillance, Epidemiology, and End Results program database. They found that median survival for RCC was 78 months, compared with 89 months for LCC ($p < 0.001$), indicating poor prognosis for RCC patients[26]. Mejri et al. also reported the prognostic impact of tumor location for stage II/III CC. Two hundred and three patients with stage II/III CC were analyzed, and it was found that 5 year OS was significantly worse in RCC than in LCC (65% vs. 82%, HR: 2.07; 95% CI: 1.05–4.09; $p = 0.03$)[27]. A systemic review and meta-analysis of prognostic survival associated with tumor localization was reported in Italy. Petreli et al. analyzed 66 studies, which included 1,437,846 patients, and revealed that LCC patients had a low risk of death, when compared with RCC (HR: 0.82; 95% CI: 0.79–0.84; $p < 0.01$). This trend was independent of stage, race, adjuvant chemotherapy, and year of study[28]. These findings are compatible with our results.

One notable evaluation factor based on tumor sidedness is the number of HLNs. In stage II CRC, current guidelines suggest that fewer than 12 lymph nodes harvested is considered a high-risk factor[6, 7]. Low lymph node yields may result in positive lymph nodes being missed and increase the risk of understaging[29, 30]. Tsai et al. analyzed 1,167 stage I–III CRC patients and categorized high harvests (≥ 12 lymph nodes) and low harvests (< 12 lymph nodes). They found that patients with low harvests had poorer OS with stages II and III CRC (stage II: $p < 0.0001$; stage III: $p = 0.001$)[31]. In the present study, similar results were obtained, and multivariate analysis showed that the number of lymph nodes was a significantly independent factor for both OS and DFS. Furthermore, the number of HLNs was higher in the RCC group than in the LCC group (23.8 vs. 19.2, $p = 0.003$). Mik et al. also reported that the total number of HLNs was higher in the RCC group (11.7 vs. 8.3 ; $p = 0.0001$), and these results are similar to our own findings[32]. The reason for this was due to the differences in the resected area, depending on the tumor location. The right-sided colon mesentery may anatomically contain a more complex lymphatic system and a larger area of resection, when compared with the left-sided colon[33, 34]. Therefore, the reference value for the number of lymph node dissections may be better considered separately for each tumor location.

In this study, tumor sidedness was not an independent prognostic factor for DFS, although a certain trend was observed ($p = 0.065$). However, tumor sidedness is an independent factor for OS in stage II CC. We speculate that RCC could have a greater potential for malignancy with poor biological behavior, once it has recurred, when compared with LCC. Therefore, our results strongly indicate that RCC should be

considered as a risk factor for stage II CC. In addition, it is necessary to develop multidisciplinary treatment strategies that include tumor sidedness, as well as pathological and genomic factors.

This study has some limitations. First, the small sample size, retrospective design, and single-center setting may limit the generalization of results. Second, this study did not include the status of BRAF/KRAS/NRAS mutations, MSI, sporadic mismatch repair deficiency, germline mutation-prompted Lynch syndrome, or any family history. These genomic and epigenomic characteristics should be considered, in addition to the tumor location. Therefore, it is necessary to conduct randomized controlled trials with a large sample size, including genomic information, at multiple institutions across different countries, to confirm the prognostic factors in stage II CC.

Conclusions

In conclusion, this study revealed that tumor sidedness was an independent prognostic factor for OS in stage II CC. We strongly suggest that tumor sidedness should be considered as a high-risk factor in stage II CC patients, in addition to the traditional factors.

Abbreviations

BRAF: v-raf murine sarcoma viral oncogene homolog B; CC: colon cancer; CI: confidence interval; CEA: carcinoembryonic acid; CRC: colorectal cancer; DFS: disease-free survival; EGFR: epidermal growth factor receptor; HLN: harvested lymph node; HR: Hazard ratio; KRAS: Kirsten rat sarcoma viral oncogene; LCC: left colonic cancer; MSI-H: high microsatellite instability; NRAS: neuroblastoma ras viral oncogene homolog; OS: overall survival; RCC: right colonic cancer

Declarations

Ethics approval and consent to participate

The study was conducted following the ethical guidelines of the Declaration of Helsinki. The protocol of this study was approved by the Ethics Committees of Saiseikai Yokohamashi Nanbu Hospital (Ethical approval number: NANBU-D23).

Consent for publication

All authors read and approved the final manuscript.

Availability of data and materials

Not applicable.

Competing interests

All authors declare no conflict of interest.

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Authors' contributions

All authors contributed equally to this study. Details of contributions by each author are as follows;

Concept and study design were conducted by KI, HM, SH, DI, YM and TF. Data collection and literature search were done by KI, HM, MN. Data analysis and interpretation were done by KI, HM, HT, NY, YR and MM. Interpretation of data was done by investigators. Drafting the article was done by KI and HM. Finally, this article was revised and approved by all investigators.

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Figures

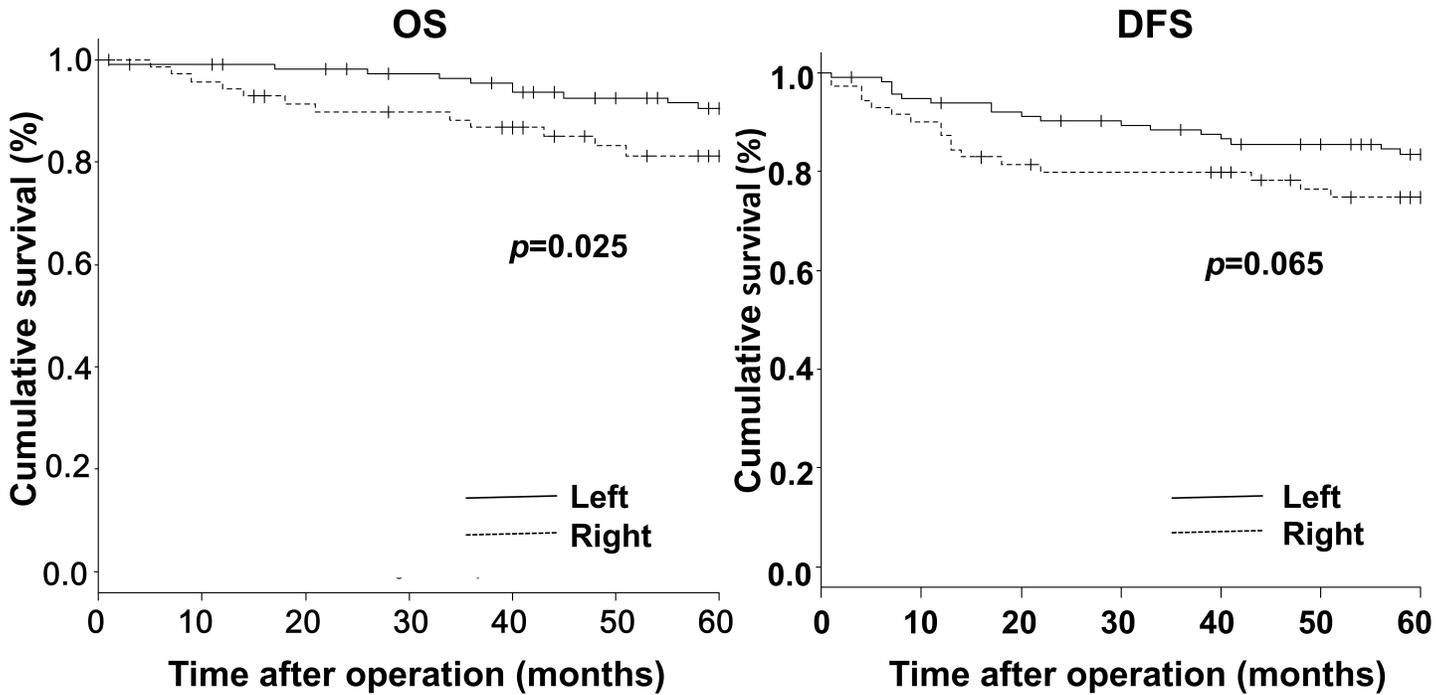


Figure 1

Overall survival and disease-free survival of stage II colon cancer compared with tumor sidedness. The Kaplan-Meier analysis of overall survival and disease-free survival by tumor sidedness. The OS was significantly lower in the RCC group than in the LCC group (5 year survival rate—RCC: 81.3% vs. LCC: 90.4%; $p = 0.025$), whereas no significant difference was observed in DFS (5 year survival rate—RCC: 74.8% vs. LCC: 83.4%; $p = 0.065$).