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# Oncological impact of vascular invasion in colon cancer might differ depending on tumor sidedness

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**Purpose:** Vascular invasion is a well-known independent prognostic factor in colon cancer and tumor sidedness is also being considered a prognostic factor. The aim of this study was to compare the oncological impact of vascular invasion depending on the tumor location in stages I to III colon cancer.

**Methods:** A retrospective analysis was performed using data from patients who underwent curative resection between 2004 and 2015. Patients were divided into right-sided colon cancer (RCC) and left-sided colon cancer (LCC) groups according to the tumor location. Disease-free survival (DFS) and overall survival (OS) were compared between the RCC and LCC groups, depending on the presence of vascular invasion.

**Results:** A total of 793 patients were included, of which 304 (38.3%) had RCC and 489 (61.7%) had LCC. DFS and OS did not differ significantly between the RCC and LCC groups. Vascular invasion was a poor prognostic factor for DFS in both RCC (hazard ratio [HR], 2.291; 95% confidence interval [CI], 1.186–4.425; $p = 0.010$) and LCC (HR, 1.848; 95% CI, 1.139–2.998; $p = 0.011$). Additionally, it was associated with significantly worse OS in the RCC (HR, 3.503; 95% CI, 1.681–7.300; $p < 0.001$), but not in the LCC group (HR, 1.676; 95% CI, 0.885–3.175; $p = 0.109$). Multivariate analysis revealed that vascular invasion was independently poor prognostic factor for OS in the RCC (HR, 3.186; 95% CI, 1.391–7.300; $p = 0.006$).

**Conclusion:** This study demonstrated that RCC with vascular invasion had worse OS than LCC with vascular invasion.

**Keywords:** Colonic neoplasms, Vascular invasion, Survival, Tumor sidedness

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## INTRODUCTION

Colorectal cancer is the second most common cancer and the fourth leading cause of cancer deaths in Korea [1]. Traditional prognostic factors for colon cancer are the TNM stage, lymphatic invasion, vascular invasion, perineural invasion, obstruction, and perforation. Recently, considerable attention has been focused on the tumor sidedness in colon cancer, due to the side-related differences in the molecular pathways of carcinogenesis and oncological outcomes [2–4]. Several studies have shown that right-sided colon cancer (RCC) has a worse oncological outcome than left-sided colon cancer (LCC) [5–7]. Therefore, tumor side in


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colon cancer is now considered to be one of the risk factors.

Lymphovascular invasion is a well-established independent prognostic factor for colorectal cancer [8]. Compared with lymphatic invasion, vascular invasion is more critical for the prediction of recurrence and systemic metastasis, and extramural venous invasion is a more significant prognostic factor than intramural venous invasion [9–11]. However, few studies have examined the impact of vascular invasion depending on the tumor sidedness in colon cancer. Only one study has demonstrated that the severity of vascular invasion differs according to the tumor location in upper urinary tract cancer [12].

Several studies have reported that RCC has a worse long-term oncological outcome than LCC; thus, we hypothesized that the oncological impact of vascular invasion could be different depending on the tumor sidedness in colon cancer, and this may be one of the reasons why RCC shows worse prognosis compared to LCC.

The aim of this study was to evaluate the difference in the oncological impact of vascular invasion according to tumor side in colon cancer.

## MATERIALS AND METHODS

### Patients and data collection

Data from patients with stages I to III colon cancer who underwent curative resection between 2004 and 2015 at Incheon Saint Mary's Hospital, The Catholic University of Korea were retrospectively reviewed. All data were prospectively collected and retrospectively analyzed. The right-sided colon was defined as from the cecum to the transverse colon, and the left-sided colon was defined as from the splenic flexure colon to the rectosigmoid colon above the peritoneal reflection. Pathologic stage classification was based on the 7th American Joint Cancer Committee (AJCC) TNM classification system [13]. Favorable histological grade was defined as well- and moderately-differentiated adenocarcinoma. Poor histological grade was defined as poorly-differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma. We excluded patients with rectal cancer, multiple colon cancers, and hereditary colon cancers including familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer, and those who had undergone palliative surgery. We used the hematoxylin and eosin staining method to detect vascular invasion and only extramural invasion was analyzed in our study.

### Study design and endpoint

The patients were divided into the RCC group and LCC group according to the tumor location. We compared disease-free survival (DFS) and overall survival (OS) to evaluate the oncological outcomes according to the presence of vascular invasion in RCC and LCC, respectively. DFS was calculated from the date of surgery until the date of detection of disease recurrence or the last follow-up. OS was calculated from the date of surgery until the date of death or last follow-up. Subsequently, subgroup analysis was performed, including only the patients with stage III disease.

### Statistical analysis

All statistical analyses were performed with IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using the chi-square or Fisher exact test. DFS and OS rates were calculated using the Kaplan-Meier method, and comparisons were performed using the log-rank test. Multivariate analysis was performed using backward conditional Cox proportional hazards analysis. The $p$ values less than 0.05 were considered significant.

## RESULTS

### Baseline characteristics

A total of 793 patients with stages I to III colon cancer were included in this study. The median follow-up duration was 48 months (interquartile range, 29–65 months). Among these, 397 patients (50.1%) were older than 65 years and 430 patients (54.2%) were male. Surgery was performed via a laparoscopic approach in 738 patients (93.1%) and via a conventional approach in 55 patients (6.9%). Resection of other organs was performed in 109 patients (13.7%). On final pathology, 76 patients (9.6%) had a poor histologic grade tumor. Vascular invasion was observed in 109 (13.7%), lymphatic invasion in 362 (45.6%), and perineural invasion in 291 patients (36.7%). We observed stage I disease in 54 (6.8%), stage II disease in 330 (41.6%), and stage III disease in 409 patients (51.6%) (Table 1).

Of the total 793 patients, 304 (38.3%) were in the RCC group and 489 (61.7%) in the LCC group. Their clinicopathological characteristics are shown according to the tumor location in Table 1. The patients with RCC were more likely to be women (50.7% vs. 42.7%, $p = 0.030$) and older than 65 years (54.9% vs. 47.0%, $p = 0.031$) compared to those with LCC. The rate of surgery via the laparoscopic approach was lower in the RCC group than in the LCC group (90.8% vs. 94.5%, $p = 0.047$). On pathological examination, the rates of lymph node harvest more than 12 (95.7% vs. 88.1%, $p < 0.001$) and poor histological grade (18.8% vs. 3.9%, $p < 0.001$) were higher in the RCC than in the LCC group. There were no significant differences in comorbidity, rates of other organ resection, TNM staging, and the presence of vascular, lymphatic, and perineural invasion according to the tumor location.

**Table 1.** Clinicopathological characteristics according to tumor location

| Variable | Total | RCC group | LCC group | *p* value |
|---|---|---|---|---|
| No. of patients | 793 | 304 | 489 | |
| Age (yr) | | | | 0.031 |
| ≤65 | 396 (49.9) | 137 (45.1) | 259 (53.0) | |
| >65 | 397 (50.1) | 167 (54.9) | 230 (47.0) | |
| Sex | | | | 0.030 |
| Male | 430 (54.2) | 150 (49.3) | 280 (57.3) | |
| Female | 363 (45.8) | 154 (50.7) | 209 (42.7) | |
| Comorbidity | | | | 0.597 |
| No | 421 (53.1) | 165 (54.3) | 256 (52.4) | |
| Yes | 372 (46.9) | 139 (45.7) | 233 (47.6) | |
| Surgical approach | | | | 0.047 |
| Laparoscopic | 738 (93.1) | 276 (90.8) | 462 (94.5) | |
| Conventional | 55 (6.9) | 28 (9.2) | 27 (5.5) | |
| Combined resection | | | | 0.868 |
| No | 684 (86.3) | 263 (86.5) | 421 (86.1) | |
| Yes | 109 (13.7) | 41 (13.5) | 68 (13.9) | |
| LN harvest | | | | <0.001 |
| ≥12 | 722 (91.0) | 291 (95.7) | 431 (88.1) | |
| <12 | 71 (9.0) | 13 (4.3) | 58 (11.9) | |
| Histologic grade | | | | <0.001 |
| Favor | 717 (90.4) | 247 (81.3) | 470 (96.1) | |
| Poor | 76 (9.6) | 57 (18.8) | 19 (3.9) | |
| Vascular invasion | | | | 0.220 |
| No | 684 (86.3) | 268 (88.2) | 416 (85.1) | |
| Yes | 109 (13.7) | 36 (11.8) | 73 (14.9) | |
| Lymphatic invasion | | | | 0.857 |
| No | 431 (54.4) | 164 (53.9) | 267 (54.6) | |
| Yes | 362 (45.6) | 140 (46.1) | 222 (45.4) | |
| Perineural invasion | | | | 0.827 |
| No | 502 (63.3) | 191 (62.8) | 311 (63.6) | |
| Yes | 291 (36.7) | 113 (37.2) | 178 (36.4) | |
| Adjuvant systemic chemotherapy[a)] | | | | 0.075 |
| No | 141 (27.5) | 65 (31.9) | 76 (24.7) | |
| Yes | 371 (72.5) | 139 (68.1) | 232 (75.3) | |
| T stage | | | | 0.408 |
| 1 | 33 (4.2) | 8 (2.6) | 25 (5.1) | |
| 2 | 51 (6.4) | 20 (6.6) | 31 (6.3) | |
| 3 | 558 (70.4) | 217 (71.4) | 341 (69.7) | |
| 4 | 151 (19.0) | 59 (19.4) | 92 (18.8) | |

**Table 1.** Continued

| Variable | Total | RCC group | LCC group | *p* value |
|---|---|---|---|---|
| N stage | | | | 0.214 |
| 0 | 384 (48.4) | 147 (48.4) | 237 (48.5) | |
| 1 | 241 (30.4) | 101 (33.2) | 140 (28.6) | |
| 2 | 168 (21.2) | 56 (18.4) | 112 (22.9) | |
| TNM stage | | | | 0.880 |
| I | 54 (6.8) | 19 (6.3) | 35 (7.2) | |
| II | 330 (41.6) | 128 (42.1) | 202 (41.3) | |
| III | 409 (51.6) | 157 (51.6) | 252 (51.5) | |
| Recurrence | | | | 0.760 |
| No | 640 (80.7) | 247 (81.3) | 393 (80.4) | |
| Yes | 153 (19.3) | 57 (18.8) | 96 (19.6) | |

Values are presented as number (%).
RCC, right-sided colon cancer; LCC, left-sided colon cancer; LN, lymph node.
[a]This variable was analyzed for 512 patients who had data on adjuvant chemotherapy.

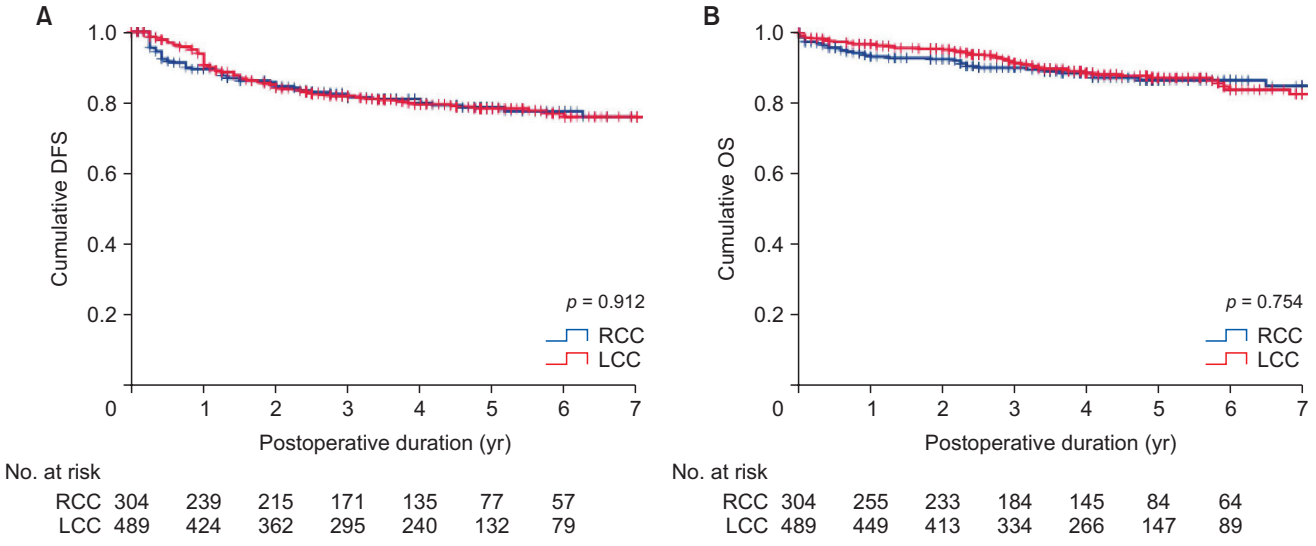


**Fig. 1.** Kaplan-Meier curves according to the tumor sidedness in stage I to III colon cancer. (A) Disease-free survival (DFS). (B) Overall survival (OS). RCC, right-sided colon cancer; LCC, left-sided colon cancer.

## Oncological outcomes according to the tumor location

Local or distant recurrences were observed in 153 patients (19.3%), with no significant difference according to the tumor location. Recurrences were observed in 57 patients (18.8%) in the RCC and 96 (19.6%) in the LCC group ($p = 0.760$). There were no significant differences in DFS and OS between the two groups (Fig. 1). The 3-year DFS rates were 81.2% in the RCC group and 81.6% in the LCC group ($p = 0.912$). The 3-year OS rates were 89.9% in RCC group and 91.3% in the LCC group ($p = 0.754$).

## Oncological impact of vascular invasion according to the tumor location

DFS and OS graphs for RCC and LCC according to the presence of vascular invasion were shown in Fig. 2. The 3-year DFS rates for RCC with and without vascular invasion were 61.6% and 83.5%, respectively (hazard ratio [HR], 2.291; 95% confidence interval [CI], 1.186–4.425; $p = 0.010$), and those for LCC with and without vascular invasion were 72.3% and 83.1%, respectively (HR, 1.848; 95% CI, 1.139–2.998; $p = 0.011$) (Fig. 2A, B).

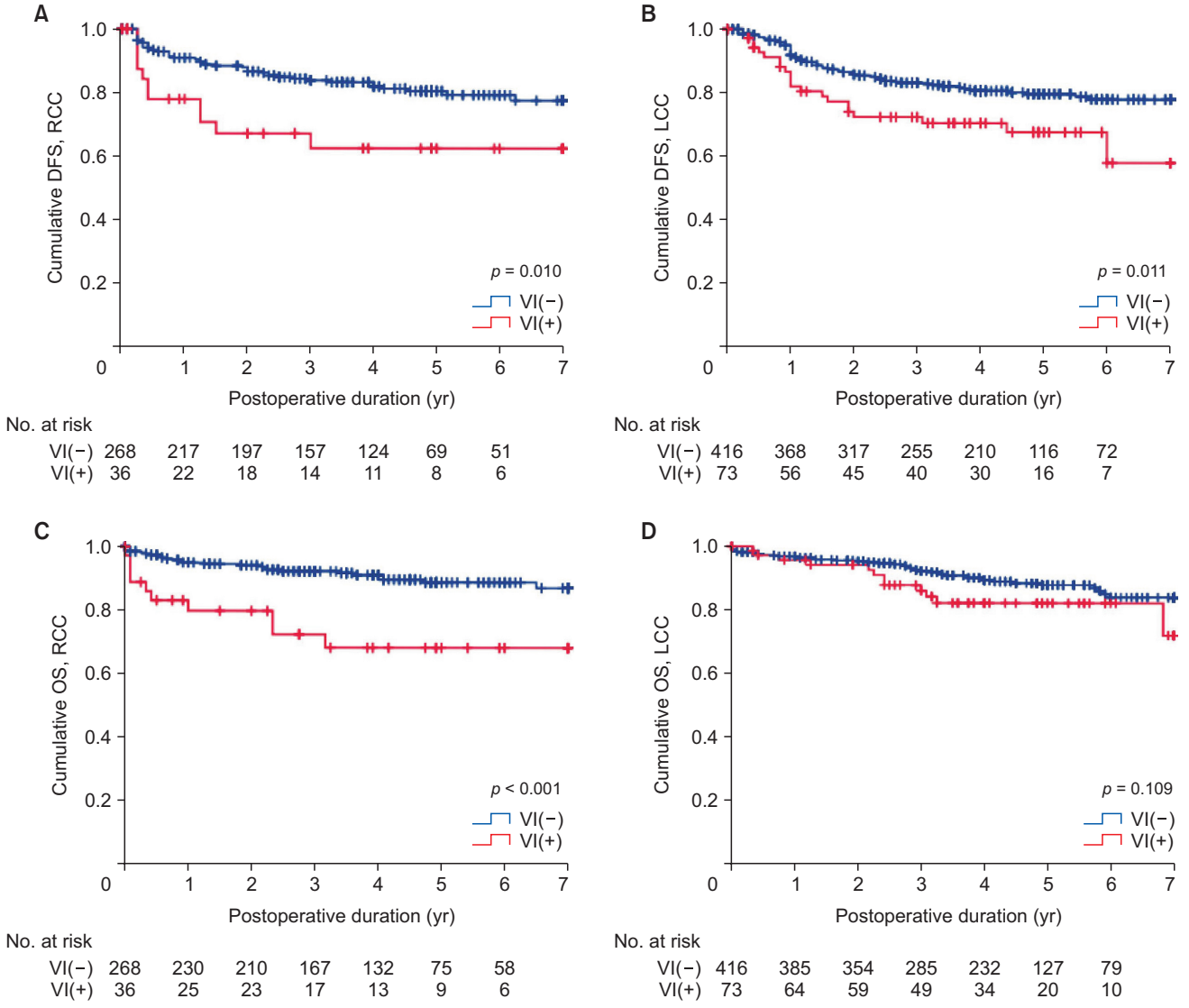


**Fig. 2.** Kaplan-Meier curves according to the presence of vascular invasion (VI) in stage I to III colon cancer. (A) Disease-free survival (DFS) in right-sided colon cancer (RCC). (B) DFS in left-sided colon cancer (LCC). (C) Overall survival (OS) in RCC. (D) OS in LCC.

The 3-year OS rates for RCC with and without vascular invasion were 71.9% and 92.2%, respectively (HR, 3.503; 95% CI, 1.681–7.300; $p < 0.001$). The 3-year OS rates for LCC with and without vascular invasion were 86.0% and 92.2%, respectively (HR, 1.676; 95% CI, 0.885–3.175; $p = 0.109$) (Fig. 2C, D).

The 3-year DFS rates for RCC and LCC with vascular invasion were 61.6% and 72.3%, respectively (HR, 1.285; 95% CI, 0.618–2.671; $p = 0.502$). The 3-year DFS rates for RCC and LCC without vascular invasion were 83.5% and 83.1%, respectively (HR, 1.006; 95% CI, 0.697–1.452; $p = 0.974$).

The 3-year OS rates for RCC and LCC with vascular invasion were 71.9% and 86.0%, respectively (HR, 2.037; 95% CI, 0.878–4.727; $p = 0.097$). The 3-year OS rates for RCC and LCC without vascular invasion were 92.2% and 92.2%, respectively (HR, 0.930; 95% CI, 0.569–1.519; $p = 0.771$).

Multivariate analyses for DFS and OS depending on the tumor sidedness were shown in Tables 2 and 3. Vascular invasion was independently poor prognostic factor for OS in the RCC (HR, 3.186; 95% CI, 1.391–7.300; $p = 0.006$). However, vascular invasion was not included in the multivariate analysis using backward conditional hazard model in the LCC.

## Subgroup analysis of stage III colon cancer

The 3-year DFS rates for stage III RCC and LCC were 73.1% and 76.5%, respectively ($p = 0.539$). The 3-year OS rates for stage III RCC and LCC were 84.2% and 88.8%, respectively ($p = 0.164$).

DFS and OS graphs for stage III RCC and LCC according

**Table 2.** Multivariate analysis for disease-free survival and overall survival in right-sided colon cancer

| Variable | Disease-free survival | | Overall survival | |
|---|---|---|---|---|
| | HR (95% CI) | *p* value | HR (95% CI) | *p* value |
| T stage | | | | |
| 1–3 | Reference | | | |
| 4 | 2.197 (1.201–4.018) | 0.011 | | |
| N stage | | | | |
| 0 | Reference | | Reference | |
| 1 | 2.712 (1.254–5.866) | 0.011 | 4.049 (1.717–9.547) | 0.001 |
| 2 | 2.744 (1.436–5.244) | 0.002 | 4.158 (1.553–11.129) | 0.005 |
| Vascular invasion | | | | |
| No | | | Reference | |
| Yes | | | 3.186 (1.391–7.300) | 0.006 |
| Adjuvant chemotherapy | | | | |
| No | Reference | | Reference | |
| Yes | 0.383 (0.217–0.677) | 0.001 | 0.144 (0.069–0.300) | <0.001 |

HR, hazard ratio; CI, confidence interval.

**Table 3.** Multivariate analysis for disease-free survival and overall survival in left-sided colon cancer

| Variable | Disease-free survival | | Overall survival | |
|---|---|---|---|---|
| | HR (95% CI) | *p* value | HR (95% CI) | *p* value |
| Age (yr) | | | | |
| ≤65 | | | Reference | |
| >65 | | | 2.023 (1.164–3.516) | 0.012 |
| T stage | | | | |
| 1–3 | Reference | | Reference | |
| 4 | 1.914 (1.209–3.030) | 0.006 | 2.118 (1.183–3.792) | 0.012 |
| N stage | | | | |
| 0 | Reference | | | |
| 1 | 1.369 (0.804–2.332) | 0.247 | | |
| 2 | 2.266 (1.365–3.764) | 0.002 | | |
| Differentiation | | | | |
| Well or moderate | Reference | | Reference | |
| Poorly | 2.329 (1.157–4.688) | 0.018 | 4.994 (2.373–10.506) | <0.001 |

HR, hazard ratio; CI, confidence interval.

to the presence of vascular invasion were shown in Fig. 3. The 3-year DFS rates for stage III RCC with and without vascular invasion were 54.9% and 76.7%, respectively (HR 1.939, 95% CI 0.946–3.973; $p = 0.062$). The 3-year DFS rate for stage III LCC did not differ according to the status of vascular invasion (74.6% vs. 76.9%; HR, 1.213; 95% CI, 0.681–2.160; $p = 0.510$) (Fig. 3A, B).

The 3-year OS rates for stage III RCC with and without vascular invasion were 67.8% and 87.7%, respectively (HR, 2.796; 95% CI, 1.244–6.283; $p = 0.009$). The 3-year OS rates for stage III LCC with and without vascular invasion were similar (83.1% vs. 90.3%; HR, 1.435; 95% CI, 0.667–3.008; $p = 0.352$) (Fig. 3C, D).

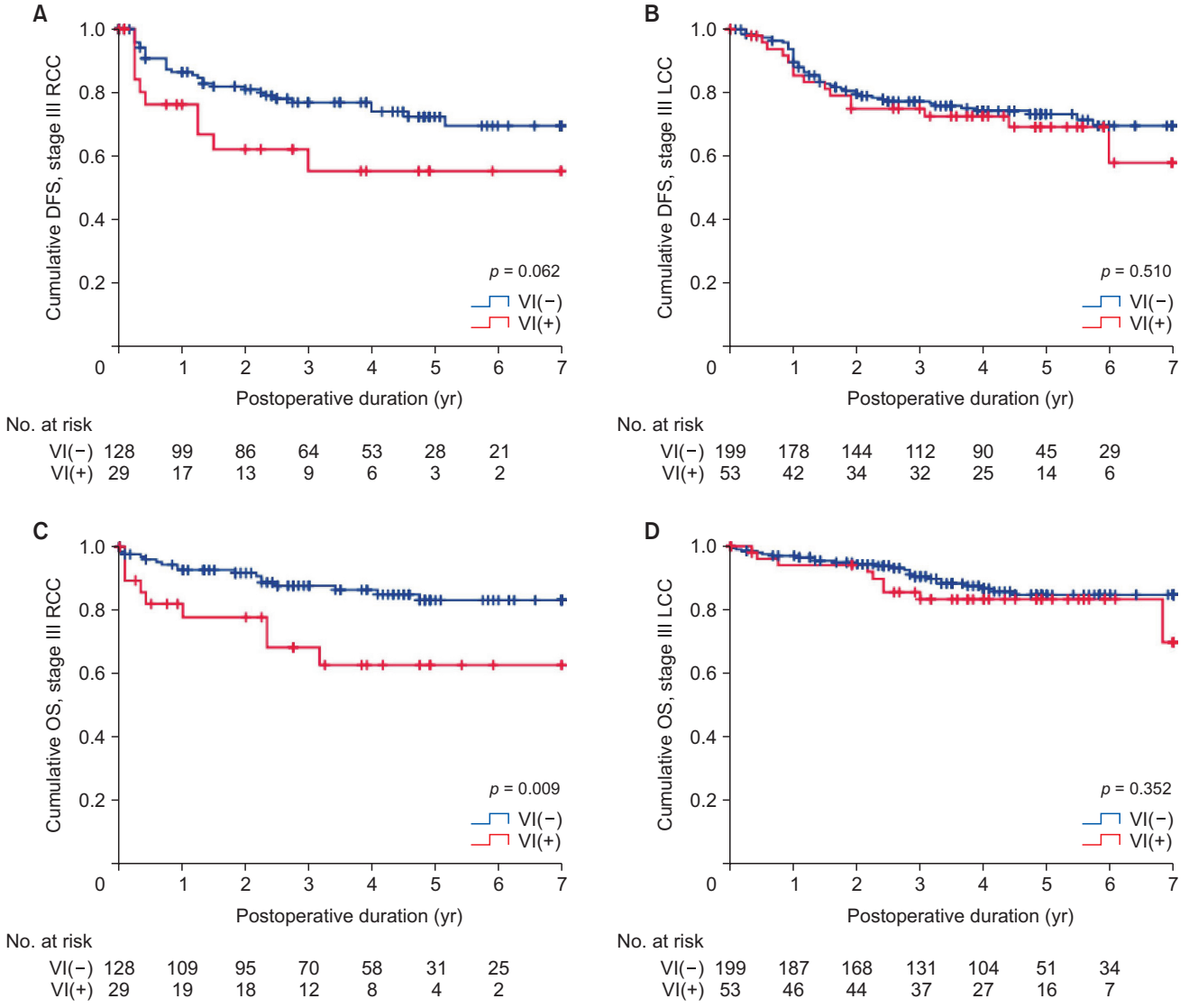


**Fig. 3.** Kaplan-Meier curves according to the presence of vascular invasion (VI) in stage III colon cancer. (A) Disease-free survival (DFS) in stage III right-sided colon cancer (RCC). (B) DFS in stage III left-sided colon cancer (LCC). (C) Overall survival (OS) in stage III RCC. (D) OS in stage III LCC.

## DISCUSSION

In the present study, the presence of vascular invasion was associated with a worse DFS in both RCC and LCC. However, the HR of DFS for vascular invasion was higher in patients with RCC than in those with LCC. Moreover, vascular invasion was a significantly poor prognostic factor for OS in RCC, but not in LCC. In the subgroup analysis, there were no significant differences in DFS and OS between stage III RCC and stage III LCC. However, stage III RCC with vascular invasion showed a significantly worse OS than stage III RCC without vascular invasion, whereas no such difference was detected for LCC. Although, there were no significant differences in DFS according to the presence of vascular invasion in both right- and left-sided stage III colon cancers, we discovered a tendency for negative impact of vascular invasion on DFS in stage III RCC ($p = 0.062$). Otherwise, there was certainly no difference on DFS in stage III LCC ($p = 0.510$).

Colon cancer has different clinical, pathological, and genetic characteristics depending on the tumor sidedness. In general, an advanced stage at the time of diagnosis, a large number of harvested lymph nodes, and poor histologic grade tumors are more commonly observed with RCC than LCC [2,14–18]. Several randomized clinical trials have revealed worse outcomes for metastatic RCC compared to those for metastatic LCC [19–21]. Furthermore, several studies have demonstrated a worse prognosis for nonmetastatic RCC [5–7,22]. However, another study re-

vealed that there was no difference in prognosis according to the tumor location in colon cancer [23]. A study even claimed that the prognosis of nonmetastatic RCC was better than that of LCC [2]. Thus, to date, the evidence regarding the risk of tumor sidedness in nonmetastatic colon cancer remains controversial. In the present study, we did not detect any differences in the long-term oncological outcome between RCC and LCC.

Vascular invasion is traditionally well-known as an independent prognostic factor in colorectal cancer. A study investigating 700 colorectal cancer cases showed that vascular invasion had a significant negative impact on survival rates and increased the possibility of liver metastasis development [24]. Moreover, several studies have reported that vascular invasion is much more closely related to distant metastasis and a worse prognosis than other risk factors [8-10,25]. The location of vascular invasion has also been considered to be a prognostic factor. The invasion of extramural veins, rather than intramural veins, and of large veins, rather than small veins, has been shown to be related to a poor prognosis [24]. We defined only extramural venous invasion as vascular invasion in this study. Vascular invasion also has a poor prognostic impact on rectal cancer. Chand et al. [26] reported that vascular invasion has an independent poor prognostic impact on DFS in stages II and III rectal cancer, and demonstrated that stage II rectal cancer with vascular invasion has similar clinical outcomes to stage III rectal cancer following preoperative chemoradiotherapy.

Similar to the previous study, our study showed the negative impact of vascular invasion on DFS and OS in colon cancer. To the best of our knowledge, this is the first study to compare the oncological impact of vascular invasion according to the sidedness of colon cancer. Interestingly, vascular invasion was found to be associated with worse oncological outcomes in patients with RCC than in those with LCC. This suggests that the impact of vascular invasion might be more aggressive in RCC than in LCC. One reason for this finding may be that the vascular anatomy of the right colon is more complicated and variable than that of the left colon [27,28]. Moreover, manipulation of the tumor and its vasculature during surgery is more frequent for RCC than LCC, and it might result in the dissemination of the tumor cells into the blood and lymphatic circulation [29]. The presence of vascular invasion under these surgical conditions might result in increased dissemination of tumor cells into the vasculature, which could be one of the reasons that explain the poor prognosis of RCC with vascular invasion.

There are several limitations of this study. First, selection bias cannot be denied because of its retrospective nature. Second, this study investigated only single institution patients, and sample size was not large. Consequently, a large-scale multicenter study is needed. Finally, the detection rate of vascular invasion was low (13.7%). Several studies showed that using elastic stain increases the detection rate of vascular invasion compared to the use of hematoxylin and eosin (H&E) staining [30]. On the other hand, we used only H&E staining method, which may have led to low detection rate of vascular invasion in the present study.

In conclusion, our study indicated that oncological impact of vascular invasion could be worse in nonmetastatic RCC than in nonmetastatic LCC. To the best of our knowledge, this is the first study that demonstrated that the presence of vascular invasion could have a variable prognostic impact depending on the tumor sidedness in nonmetastatic colon cancer. A further large-scale investigation is required to clarify the oncological impact of vascular invasion according to the tumor location in colon cancer.

## NOTES

### Ethical statements

The study was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki 2013. The study protocol was approved and monitored by the Institutional Review Board of College of Medicine, The Catholic University of Korea (No. OC19RESI0035) with a waiver for the informed consent.

### Authors' contributions

Conceptualization, Formal analysis, Methodology, Visualization: MSAS, JHB, YSL
Data curation, Investigation: All authors
Writing–original draft: MSAS, JHB
Writing–review & editing: YSL
All authors read and approved the final manuscript.

### Conflict of interest

All authors have no conflicts of interest to declare.

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