Tumor Sidedness Could be a High-risk 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. Tumor sidedness is a high-risk factor in stage II CC patients.

Background

Colorectal cancer (CRC) is a major health problem worldwide. CRC is the third most common cancer and the second highest cause of cancer-related death in the world[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 perforation, obstruction, 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; (2) patients had undergone primary tumor resection with R0; and (3) patients without synchronous or metachronous malignancy. The selected patients were divided into two groups, based on tumor sidedness (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 all procedures were performed by skilled surgeons (with the patients under epidural and general anesthesia). 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 ports and optimal resection margins and extent of lymph node dissection were determined according to JSCCR guidelines in all cases[8]. All patients were followed up regularly at our institution, including carcinoembryonic acid (CEA) and cancer antigen 19-9 assays every, computed tomography, and colonoscopy. 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 colectomy, 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 at diagnosis, gender, tumor-marker level, high-risk factors, surgical outcomes and pathological findings, between the RCC group and the LCC group. All data were collected from patients' medical records. Tumor histology was determined by using the World Health Organization classification system[17]. Postoperative complications were classified

according to the Clavien–Dindo classification system; grade II or higher was defined as a complication in this study[18]. Long-term outcomes between the groups were evaluated by recurrence rate, overall survival (OS), and disease-free survival (DFS).

Statistical analysis

Quantitative data were analyzed by Student's t-test or Mann–Whitney U test. Categorized data were analyzed by the chi-squared test. Fisher's exact test were used for low numbers. Survival analyses was estimated by the Kaplan–Meier method, and compared by the log-rank test. Univariate and Cox proportional regression analyses were used to analyze prognostic factor. A *p*-value <0.05 was considered to be statistically significant.

Results

Demographic and clinicopathological characteristics, and surgical outcomes

A total of 1,398 CRC patients underwent colorectomy for CRC 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 patients were classified into RCC group and 117 patients were classified into LCC groups. 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. The incidence of postoperative complications were similar 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%; $p = 0.40$).

Recurrence and post-recurrence therapy between the groups

Recurrence patterns and type of post-recurrence therapy 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.

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 sidedness, gender, histological type, and number of HLNs were prognostic factors for OS. In contrast, 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.

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]. In metastatic CRC, these molecular and genetic features of CRC by 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 CRC patients, using the large population 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 CRC patients. They revealed that LCC patients had a low mortality compared with RCC (HR: 0.82; 95% CI: 0.79–0.84; $p < 0.01$). This trend was independent of tumor staging, race, present or absent of adjuvant chemotherapy, and year of research[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, as a result, increase the risk of stage migration[29,30]. Tsai et al. grouped 1,167 CRC patients by number of HLNs and reported that patients with low harvests (<12) 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, its retrospective nature, and single-institution 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.

List Of 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

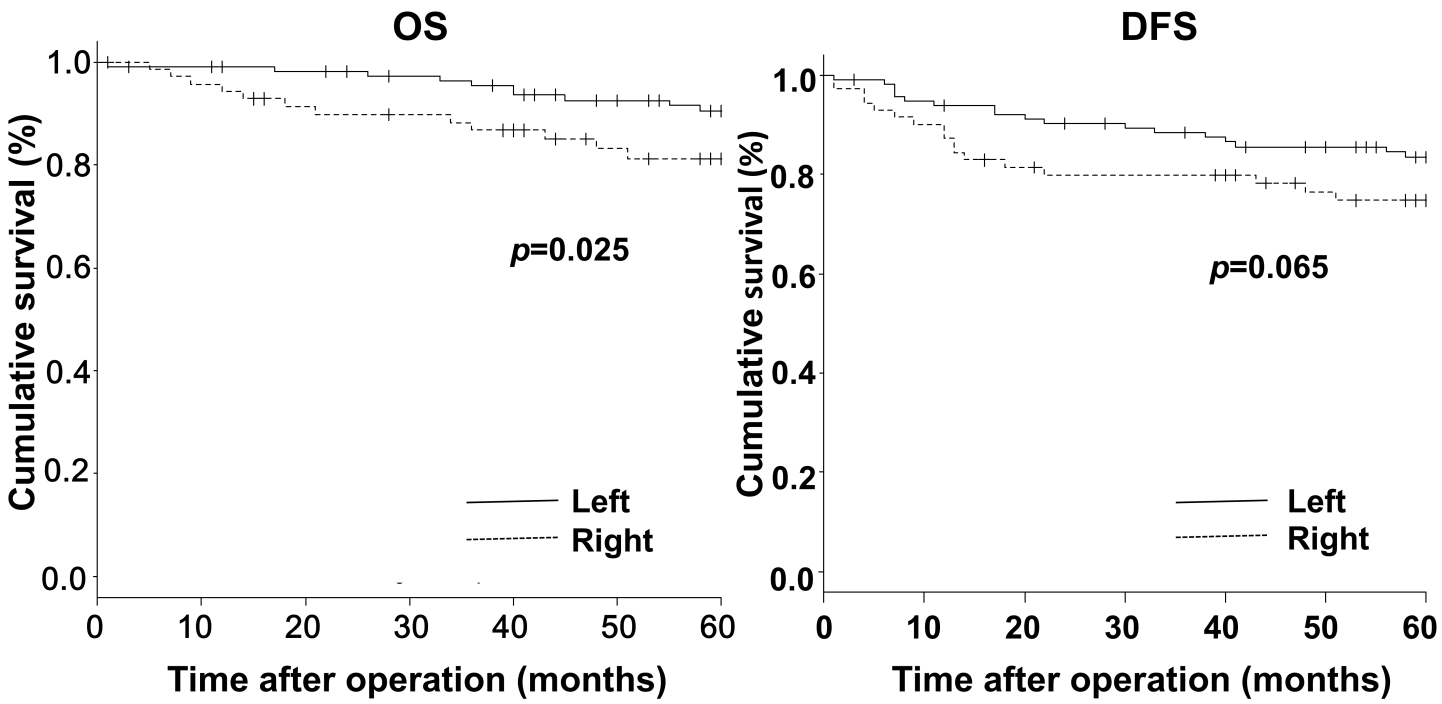

Figure 1

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).