The impacts of primary tumor location on risk factors for recurrence in patients with advanced stage II colon cancer undergoing curative resection

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Abstract

Purpose

It has been reported that colon tumors show different characteristics according to the location of the primary tumor (left vs. right side). The aim of this study was to identify and compare clinicopathological risk factors for colon cancer recurrence based on primary tumor location, specifically, the right versus left colon.

Methods

A total of 235 patients with stage II colon cancer (including rectosigmoid cancer) who underwent curative resection with D2 or above lymph node dissection in multiple acute hospitals were analyzed retrospectively to compare clinicopathological risk factors and prognosis for recurrence of tumors originating in the right or left colon. Multivariate analysis of overall survival (OS) and recurrence-free survival (RFS) were modeled using the Cox-hazard model.

Results

For right-sided tumors, multivariate analysis revealed that no independent risk factors were associated with recurrence. In contrast, the risk factors associated with recurrence in left-sided tumors were perineural invasion and venous invasion. The 5-year overall survival rates and recurrence-free survival rates for patients with right and left side-originating tumors were comparable (OS: 93.0% and 93.3%, RFS: 93.0% and 88.3%, respectively).

Conclusion

Different clinicopathological risk factors for recurrence were identified in patients with right- vs. left-sided stage II colon cancer.

Introduction

It has been reported that despite the right and left sides of the colon constituting the same organ, they have distinct characteristics.[1] These distinctions, thought to be associated with genetic and molecular differences, have certain implications for postoperative follow-up and adjuvant chemotherapy planning. Retrospective subgroup analysis of large clinical trials investigating RAS-positive stage IV unresectable colon cancer demonstrated that the patients in the right-sided group showed worse prognosis than those in the left-sided group.[2–4] Conversely, no consensus has yet been reached regarding differences in prognosis between the right- and left-side of the colon in patients with resectable colon cancer.[5–7]

For patients who have resected stage II colon cancer, adjuvant chemotherapy is not considered as standard therapy. However, according to major groups such as the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO), adjuvant chemotherapy could be considered for patients with “high risk” clinicopathological features, after discussing the risks and benefits.[8] If right- and left-sided colon cancer have different clinicopathological risk factors for recurrence, appropriate adjuvant chemotherapy and follow-up plans should be considered separately for each group. Therefore, the aim of this study was to compare postoperative prognosis and independent clinicopathological risk factors for recurrence between right- and left-sided stage II colon cancer.

Methods

Patients

The ethics review boards of Hirosaki University and the qualifying medical facilities approved the study protocol. This study adhered to the principles of the Declaration of Helsinki. All patients provided informed consent to have their chart data used for research purposes.

We retrospectively reviewed 240 patients with stage II colon cancer (including rectosigmoid) aged 75 years or younger who were treated between 1994 and 2003 at any of the following qualifying facilities: Hirosaki University Hospital, Aomori Municipal Hospital, Akita City Hospital, Odate City Hospital, Hakodate City Hospital, Yamagata Prefectural Kahoku Hospital, Hirosaki Hospital, Misawa City Hospital, Shichinohe Hospital, and Nohegi Hospital. Patients who had genetic diseases such as familial adenomatous polyposis, multiple synchronous large bowel carcinomas, an Eastern Cooperative Oncology Group performance status score of 2 or higher, positive cytology or metastases to other organs, or who received neoadjuvant chemotherapy or radiotherapy were excluded from this study. Patients were classified based on the primary tumor location. Tumors between the cecum and splenic flexure were considered right-sided in origin, while tumors between the descending colon and rectosigmoid colon were considered left-sided in origin. Staging and exact primary tumor locations were defined according to the American Joint Committee on Cancer tumor-node-metastasis (TNM) criteria 8th edition.[9]

Of the 240 patients with stage II colon cancer (including rectosigmoid) who underwent open radical curative surgical resection with D2 and D3 lymph node dissection, we excluded 5 cases due to inadequate pathological description. Therefore, a total of 235 patients were enrolled in this study. According to the Japanese Classification of Colorectal Carcinoma, regional lymph nodes were categorized into three groups based on location.[10] D1 included pericolic lymph nodes close to the bowel wall, D3 included the main lymph nodes at the orifice of the feeding artery, and D2 included intermediate nodes along the feeding arteries between the D1 and D3 nodes. Based on the preference of the physicians, 190 of the 235 patients received oral 5-fluorouracil (5-FU) at 200 or 300 mg per day for 1 year as adjuvant chemotherapy.

Patient information was extracted from the electronic medical chart system in each hospital. M.K. extracted the patients' data and A.O. double-checked it to prevent misclassification. The pathological slides of the enrolled patients were obtained, and a retrospective histopathological reevaluation was performed by two board-certified Japanese pathologists according to the criteria of the TMN 8th edition.

Surveillance

In accordance with the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines,[11] patients were followed up until 5-years after surgery, recurrence, or death, whichever came first. The patients were evaluated with routine physical examinations, measurement of serum tumor markers such as carcinoembryonic antigen and carbohydrate 19-9 (every 3 months during the first 3 years after the surgery and once every 6 months from the fourth year onward), thoracoabdominal computed tomography scans (every 6 months), and colonoscopy (1 and 3 years after the surgery).

Designs and outcomes

The following clinicopathological parameters were analyzed to determine if they represented independent risk factors for recurrence: tumor depth, histology, number of dissected LNs, lymphatic invasion, venous invasion, budding,[12] perineural invasion (PNI)[13], Extramural cancer deposit[14], chemotherapy. Overall survival (OS) and recurrence-free survival (RFS) were also analyzed. Patient survival was confirmed in outpatient clinic visits or by telephone call.

Statistical Analyses

The chi-squared test was used for categorical univariate analysis. Survival analyses were performed using the Kaplan–Meier method, and between-group differences were assessed with the log-rank test. Hazard Ratios were estimated using Cox proportional hazards model. The backward method was used to select retained factors ($p < 0.1$) during multivariate analysis. All statistical tests were two-tailed, and p -values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software version 22 (IBM Corp., Armonk, NY, USA).

Results

A total of 235 patients were enrolled in this study. The median follow-up period was 1836 days (40 – 2534 days). Among the 235 patients, 22 (9.4%) experienced recurrence (right-sided: 8 [36.4%]; left-sided: 14 [63.6%]). The median time until disease recurrence was 662.5 days (range: 158 – 1524 days). Five-year RFS in the right- and left-sided groups was 93.0% and 88.3%, respectively, while five-year OS rates were 93.0% and 93.3%, respectively (Figure 1, Table. 1) There was no significant difference in OS or RFS between the two groups.

Table 2 shows the clinicopathological characteristics of the patients enrolled in this study. Patients with right-sided colon cancer accounted for 48.9% (115/235) of the entire cohort.

Table 1
Five-year recurrence-free and overall survival rates according to tumor location.

		Right side (n=115)	Left side (n=120)	Total
Stage II (n=235)	5y-OS	93.0% (107/115)	93.3% (112/120)	93.2% (219/235)
	5y-RFS	93.0% (107/115)	88.3% (108/120)	91.5% (215/235)

Table 2
Demographic and clinico-pathological characteristics of patients with stage II colon cancer

		Total	Right	Left	p value	No. of recurrences
No. of patients		235	115	120		22
Age	Median (range)	64 (27-75)	65 (32-75)	62 (27-75)		
Sex	Male	130	60	70	Male/Female	7
	Female	105	55	50	0.34	15
Tumor location	Cecum		18			2
	Ascending		61			6
	Transverse (right 1/2)		36			0
	Transverse (left 1/3)			0		0
	Descending			14		3
	Sigmoid			68		7
	Rectosigmoid			38		4
Pathological T stage	pT3 (SS/A)	167	75	92	pT3/pT4a-4b	10
	pT4a (SE)	65	38	27	0.053	11
	pT4b (SI/AI)	3	2	1		1
Histological differentiation	Well differentiated adenocarcinoma	152	66	86	tub1-2/por,muc	12
	Moderately differentiated adenocarcinoma	64	36	28	0.08	9
	Poorly differentiated adenocarcinoma	10	7	3		0
	Mucinous adenocarcinoma	9	6	3		1
Lymphatic invasion	ly0	15	7	8	ly0-1/ly2-3	0
	ly1	124	54	70	0.062	10
	ly2	70	37	33		8
	ly3	26	17	9		4

		Total	Right	Left	<i>p</i> value	No. of recurrences
Venous invasion	v0	94	47	47	v0-1/v2-3 0.13	4
	v1	106	55	51		10
	v2	33	12	21		8
	v3	2	1	1		0
Budding	Grade 1	133	62	71	Grade 1-2/Grade 3 0.41	7
	Grade 2	82	41	41		8
	Grade 3	20	12	8		7
Perineural invasion (PNI)	PN0	172	88	84	PN0/PN1 0.26	10
	PN1	63	27	36		12
Chemotherapy	Performed	180	91	89	Performed/NA 0.36	18
	N/A	55	24	31		4

Table 3 shows the risk factors for recurrence in right-sided stage II colon cancer patients. Multivariate analysis identified no independent recurrence risk factor on the right side.

Table 3
Risk factors of recurrence for right-side stage II colon cancer.

		No. of cases	Recurrence rate	Univariate analysis	Multivariate analysis	Exp (95%CI)
Tumor depth	T3 (SS)	75	3 (4.0%)	0.088	0.088	
	T4a+T4b (SE/SI)	40	5 (12.5%)			
Histology	tub1-tub2	102	8 (7.8%)	0.295		
	Others	13	0 (0%)			
No of dissected LNs	Under 12	30	2 (6.7%)	0.942		
	Over 12	85	6 (7.1%)			
Ly invasion	ly0+1	61	4 (6.6%)	0.858		
	ly2+3	54	4 (7.4%)			
Venous invasion	v0+1	102	8 (7.8%)	0.295		
	v2+3	13	0 (0%)			
Budding	Grade 1	62	2 (3.2%)	0.089	0.089	
	Grade 2+3	53	6 (11.3%)			
PN invasion	PN0	88	5 (5.7%)	0.332		
	PN1	27	3 (11.1%)			
Chemotherapy	Performed	91	7 (7.7%)	0.546		
	N/A	24	1 (4.2%)			

Table 4 shows the risk factors for recurrence in left-sided stage II colon cancer patients. Multivariate analysis identified venous invasion (v0+1 vs v2+3: HR, 6.99; 95%CI, 2.01-24.39; p=0.002) perineural invasion (PN0 vs PN1: HR, 4.01; 95%CI, 1.15-13.99; p=0.002) were selected on the left side.

Table 4
Risk factors of recurrence for left-side stage II colon cancer.

		No. of cases	Recurrence	Monovariate analysis	Multivariate analysis	Exp (95%CI)
Tumor depth	T3 (SS)	92	7 (7.6%)	0.012	0.062	
	T4a+T4b (SE/SI)	28	7 (25.0%)			
Histology	tub1-tub2	114	13 (11.4%)	0.695		
	Others	6	1 (16.7%)			
No of dissected LNs	Under 12	48	5 (10.4%)	0.728		
	Over 12	72	9 (12.5%)			
Ly invasion	ly0+1	78	6 (7.7%)	0.065	0.188	
	ly2+3	42	8 (19.0%)			
Venous invasion	v0+1	98	6 (6.1%)	0.001	0.002	6.99 (2.01-24.39)
	v2+3	22	8 (36.4%)			
Budding	Grade 1	71	5 (7.0%)	0.057	0.409	
	Grade 2+3	49	9 (18.4%)			
PN invasion	PN0	84	5 (6.0%)	0.003	0.029	4.01 (1.15-13.99)
	PN1	26	9 (34.6%)			
Chemotherapy	Performed	89	11 (12.4%)	0.689		
	N/A	31	3 (9.7%)			

Discussion And Conclusions

In this study, multivariate analysis identified different independent risk factors for tumor recurrence depending on the location of the original tumor. We also found that there was no significant difference in 5-year OS or RFS between patients with right- vs. left-sided stage II colon cancer after curative resection.

Different independent risk factors for recurrence were identified by multivariate analysis between right- and left-sided stage II colon cancer patients. When the tumor is located on the right side of the colon, no independent risk factor was selected, whereas venous invasion and PNI were selected on the left which suggest the difference in prognosis factors between the right and left colon. Although both the right- and

left-side of the colon constitute the same organ, their origins are entirely different. The right-side of the colon arises from the midgut and is vascularized by the superior mesenteric artery (SMA). In contrast, the left-sided colon is derived from the hindgut and is vascularized by the inferior mesenteric artery (IMA). From this embryological perspective, it is reasonable to expect that not only the expression of molecular subtypes but also independent risk factors for recurrence are different between right- and left-sided colon cancer patients.

Our study also showed that there was no significant difference in 5-year RFS or OS rates between patients with right- vs. left-sided stage II colon cancer. The influence of the primary tumor location was found to be consistent with previously reported studies of metastatic unresectable colon cancer.[2–4] However, the impact of the primary tumor location on the prognosis of resectable colon cancer is still unclear, and a consensus has not yet been reached.[5–7] We propose that these discrepancies arise from the association between tumor location and expression of biological molecular subtypes. Supporting this, it has been reported that BRAF and RAS mutations are more common in patients with right-sided colon cancer compared to those with left-sided colon cancer.[15] One randomized clinical trial in Europe demonstrated that among patients with stage III colon cancer with a RAS or BRAF mutant phenotype, disease-free survival (DFS) was better in the right- vs. the left-sided group. In contrast, the European study also showed that in those who were wild-type for RAS and BRAF, DFS was better in the left- vs. the right-sided group.[16] Hence, molecular subtypes seem to have a major impact on prognosis and are influenced by the location of the tumor. In addition, clinicopathological parameters such as budding[12], EX[14], venous invasion, and perineural invasion[13] are also known to have an impact on prognosis. We hypothesize that these factors also have some connection with both molecular subtype and tumor location. To achieve a consensus on the impact of tumor location on the prognosis of resectable colon cancer, we should consider not only the location of the primary tumor, but also the molecular subtype and clinicopathological parameters.

According to the guidelines of major groups such as ASCO,[8] NCCN,[17] and ESMO,[18] adjuvant chemotherapy is not considered as standard of care for patients with stage II colon cancer and is used only in patients with high-risk clinicopathological features, regardless of the primary tumor location. Our study demonstrated that these high-risk clinicopathological features depend on the primary tumor location, suggesting that adjuvant chemotherapy for patients with stage II colon cancer should be considered separately for patients with right- vs. left-sided tumors.

This study has some limitations. First, the patients in this study were treated in the 1990s and 2000s. Thus, patients received oral 5-FU as adjuvant chemotherapy according to the assigned physicians' preference, despite oxaliplatin-based regimens currently being considered the standard regimen. Second, this study had a retrospective observational design, which may have resulted in misclassification of data or selection bias.

Different independent risk factors for recurrence were identified in right- and left-sided stage II colon cancer, although there was no significant difference in the 5-year postoperative prognosis between

patients with right- and left-sided stage II colon cancer after curative resection. The right - and left-sided colon should be regarded as different organs, and high-risk clinicopathological features of stage II colon cancer should be assessed separately for each side. These findings could have an impact on indications for adjuvant chemotherapy and therapeutic regimens for patients with stage II colon cancer. Further prospective studies that assess risk factors for recurrence in the right- and left-sided groups, including evaluation of patients receiving modern adjuvant chemotherapy, are warranted.

Declarations

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Disclosure

Conflict of Interest: The authors declare no conflict of interest.

Author contribution: All authors are in agreement with the content of the article.

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Figures

Figure 1

Five-year RFS and OS comparing right- and left-sided group.