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The Incidence of Metachronous Colorectal Cancer after Surgical Resection of Left and Right Sides Colon

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ABSTRACT

Background : The increase in the amount of secondary bile acids into the colon has been reported as a cause of the increased incidence of colorectal cancer in rats. After completing digestion, bile acids are reclaimed in the terminal ileum by ileal bile acid transporter. We have hypothesized that resection of the terminal ileum increases the risk of metachronous colorectal cancer. Therefore, to assess this hypothesis, the present study compared the incidence of metachronous colorectal cancer in patients who had undergone resection of the right side or the left side of the colon.

Methods : From January 2005 through December 2012, the medical records of 141 patients with colorectal cancer who had undergone curative resection (R0) at our hospital were reviewed. The final participants were patients who had undergone colon resection on the left side (L group, 92 patients) or on the right side (R group, 44 patients). This retrospective study compared the incidence of metachronous colorectal cancer in between these groups.

Results : Clinicopathological factors, including sex, pathological type, and disease stage, did not differ significantly between the groups. The overall survival rate for each disease stage was similar between the groups. The L group had a significantly higher rate of metachronous adenoma ($p=0.022$), although the incidence of metachronous cancer was similar between the groups ($p=0.898$).

Conclusion : Resection of the terminal ileum does not increase the risk for metachronous colorectal cancer.

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Key words : metachronous colorectal cancer, colon resection, ileal bile acid transporter, secondary bile acids

INTRODUCTION

The increase in the amount of secondary bile acids in the colon has been reported to increase the incidence of colorectal cancer in rats[1]. A meta-analysis of 20 studies of patients with colorectal cancer has shown increased fecal excretion of a primary bile acid and chenodeoxycholic acid[2]. However, no evidence has been found in humans of a relation between secondary bile acids and colorectal carcinogenesis. Approximately 85% of bile acids released from the duodenum are reabsorbed by the ileal bile acid transporter (IBAT) in the terminal ileum[3]. Therefore, we have hypothesized that if the terminal ileum is resected, the incidence of metachronous colorectal cancer is increased. To test this

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hypothesis, the present study examined the incidence of metachronous colorectal cancer after colorectal resection with or without resection of the terminal ileum.

Materials and Methods

The Ethics Committee of the Nishisaitama Chuo National Hospital Institutional Review Board approved the protocol (approval code : 30-8). Also, the consent for the publication of this article was obtained from the patients included in this study. The medical records of 141 patients with colorectal cancer who had undergone curative resection (R0) at this hospital from January 2005 through December 2012 were reviewed. "Right colon resection" was defined as colon resection that included the resection of the terminal ileum, and "left colon resection" was defined as colorectal resection without the resection of the terminal ileum. Specifically, the right colon resection group (R group) consisted of patients who had undergone ileocecal resection and right hemicolectomy, and the left colon resection group (L group) consisted of patients who had undergone partial resection of transverse colon, left hemicolectomy, sigmoid colectomy, high and low anterior resection, Hartmann's operation, and abdominoperineal resection of the rectum. Excluded from this study were patients with an obstructive colorectal cancer through which a colonoscope could not be passed. The medical records of all patients were reviewed, and the stages of the tumors were classified according to the Japanese Classification of Colorectal Carcinoma[4]. In this guideline, "metachronous cancer" is defined as a secondary colorectal cancer occurring more than 2 months after the index cancer[4]. Because "metachronous colorectal adenoma," was not defined in the guideline, it was defined for the present study as an adenoma longer than 5 mm occurring more than 1 year after surgery for the primary cancer. Finally, the participants of this study were 44 patients (32%) of the R group and 92 patients (68%) of the L group (Fig. 1).

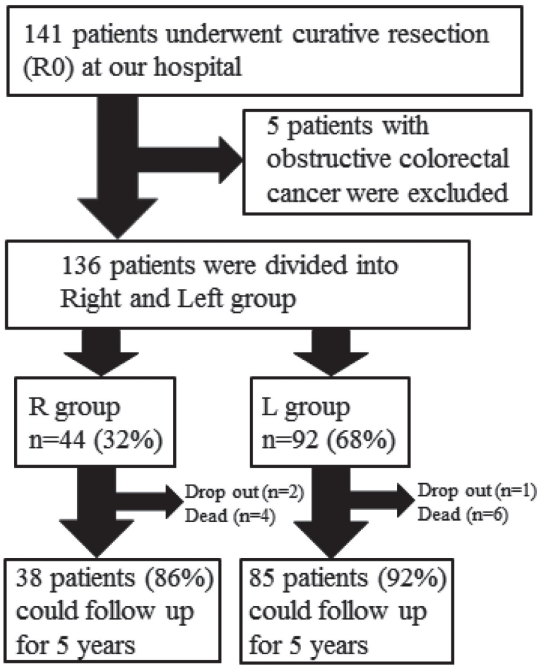

Fig. 1. Flow chart demonstrating study inclusion or exclusion

Follow-up after surgery and postoperative chemotherapy

All patients had been followed up for 5 years, with serum levels of carcinoembryonic antigen and carbohydrate antigen 19-9 measured every 3 months, computed tomography (CT) performed every 6 months, and colonoscopy performed every 12 months. If the patient was found to have any symptom, CT or colonoscopy was performed at that time. If recurrence of cancer was suspected, CT with positron emission tomography was performed. Colorectal polyps larger than 5 mm were removed with endoscopic resection. Patients with stage II or III disease received oral S-1 or capecitabine for 6 months after surgery. Patients with stage IV disease received intensive chemotherapy, including oxaliplatin-based regimens (infusional fluorouracil and folinic acid plus oxaliplatin [FOLFOX], S-1 plus oxaliplatin [SOX], or capecitabine plus oxaliplatin [XELOX]), for 6 months after surgery, depending on their physical status.

Statistical analysis

Continuous variables are expressed as medians and ranges. The Wilcoxon rank sum test was used to compare differences in the continuous variables, and the Chi-square test was used to compare differences in the categorical data. Overall survival after surgery was examined with the Kaplan-Meier method and log-rank analysis. A p-value of less than 0.05 indicated significance. All data were analyzed with the software program SPSS version 24.0 (IBM Japan, Ltd., Tokyo, Japan).

Results

The average observation period after surgery was 58 months in both the L group and the R group.

Comparison of clinicopathological features between L group and R group (Table 1)

The median age of patients was significantly lower in the L group (67 years ; range, 37–88 years) than in the R group (71 years ; range, 54–94 years ; $p=0.040$). However, other clinicopathological factors, including sex, pathological type, and disease stage, did not differ significantly between the groups.

Comparison of overall survival between the L and R groups for each disease stage

The 5-year overall survival rates did not differ significantly between the groups for patients with stage I disease (L group : 30 patients, 100% ; R group, 12 patients, 100%), stage II disease (L group : 27 patients, 89.3% ; R group : 16 patients 93.8% ; $p=0.6009$), or stage III disease (L group : 32 patients, 90.6% ; R group : 15 patients ; 72.7% ; $p=0.1061$) (Fig. 2).

Incidence of metachronous cancer or adenoma or both

The incidence of metachronous cancer did not differ between the R and L groups ($p=0.898$), but the incidence of metachronous adenoma was significantly greater in the L group than in the R group ($p=0.022$) (Table 2).

Details of cases of metachronous colorectal cancer (Table 3)

All cases had good outcomes, except 1 case in which metachronous rectal cancer with multiple liver and lung metastases were found in spite of regular follow-up examinations after surgery. The mean time until the diagnosis of a metachronous colorectal cancer did not differ significantly ($p=0.273$) between the R group (55 months) and the L group (39 months). The number of cases in which metachronous colorectal cancer could be removed with endoscopic resection did not differ significantly between the R group (2 cases, 50%) and the L group (2 cases, 22% ; $p=0.328$).

Discussion

In the present study, the incidence of metachronous colorectal cancer was not significantly greater in the R group, in which the terminal ileum is resected, than in L group. Therefore, with this result our hypothesis, that the incidence of metachronous colorectal cancer increases after resection of the terminal ileum, is not supported. Several earlier studies have had similar results. Studies that have followed up patients for 5 years or 25 years after they have undergone partial ileal bypass surgery for hyperlipidemia have found that the incidence of death caused by colorectal cancer was not decreased[5,6]. Furthermore, a phase 3 trial of elobixibat — a minimally absorbed inhibitor of IBAT which interrupts the enterohepatic circulation of bile acids and up-regulates hepatic bile acid synthesis[7] and has been approved in Japan for the treatment of chronic constipation—found no

Table 1. Comparison of clinicopathological features between the L and R groups

Characteristics	L group ($n=92$)	R group ($n=44$)	p value
Mean age, years*	67 (37–88)	71 (54–94)	0.040
Sex, *n* (%)			
Male	52 (57)	18 (41)	0.108
Female	40 (43)	26 (59)	
Stage			
I, *n* (%)	30 (33)	12 (27)	0.811
II, *n* (%)	27 (29)	16 (37)	
III, *n* (%)	32 (35)	15 (34)	
IV, *n* (%)	3 (3)	1 (2)	
Pathological type of tumor			
Well/moderately differentiated adenocarcinoma, *n* (%)	89 (97)	39 (89)	0.065
Poorly differentiated adenocarcinoma, *n* (%)	1 (1)	3 (6)	
Others, *n* (%)	2 (2)	2 (5)	

*median and ranges

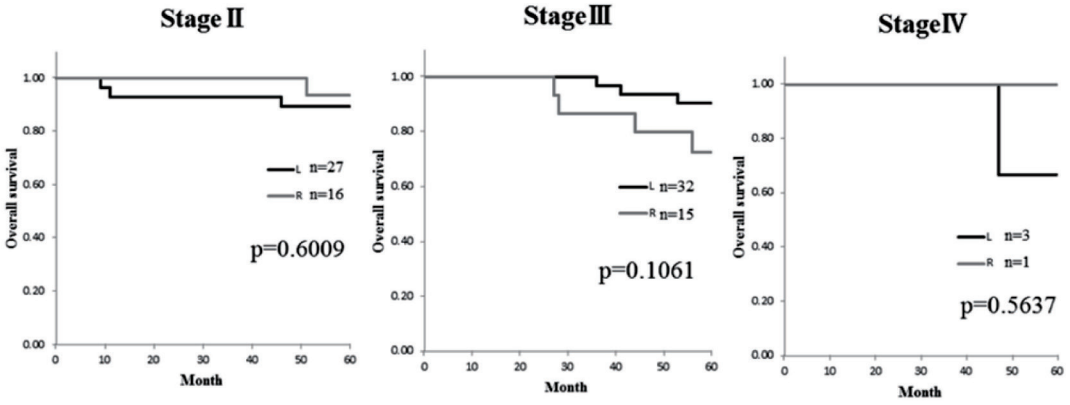

Fig. 2. Comparison of overall survival between the L and R groups in each disease stage

Table 2. Incidence of metachronous cancer or adenoma or both

Type of recurrence	L group (n=92)	R group (n=44)	p value
Metachronous cancer, n (%)	9 (10)	4 (8)	0.898
Advanced cancer, n (%)	7 (8)	2 (4)	0.506
Mucosal cancer, n (%)	2 (2)	2 (4)	0.484
Metachronous adenoma, n (%)	29 (32)	5 (10)	0.022

cases of colorectal cancer during 52 weeks of observation[8]. Therefore, the results of that trial also suggest that increased concentrations of bile acids in the colon are not a risk factor for colorectal carcinogenesis.

A recent meta-analysis of 27 endoscopy-based studies has found that most metachronous colorectal cancers are detected during the first 2 to 3 years after surgery for a primary cancer, after which the incidence substantially decreases[9]. However, these findings are not in accord with our present results. We found that metachronous colorectal cancers were diagnosed more than 36 months after surgery in 7 of 13 patients (54%).

The effect of the location of the first colorectal cancer on the risk of metachronous colorectal cancer is controversial, with various conclusions having been made. The risk of metachronous colorectal cancer has been reported to be increased by a first cancer of the transverse and descending colon[10] and to not be affected by a first cancer's location[11]. Furthermore, several studies have found that a first colon cancer in the proximal colon increases the risk of a metachronous colorectal cancer with standardized incidence ratios of 1.9 to 2.1[12-15]. However, in the present study, we

Table 3. Details of cases of metachronous colorectal cancer

				Primary lesion						Metachronous lesion							
Group	Case	Sex	Age* (years)	Location	TNM stage	Differentiation	Lymphatic invasion	Venous invasion	Adjuvant therapy	Interval of time (months)	Location	TNM stage	Differentiation	Lymphatic invasion	Venous invasion	Treatment	Outcome (months)
R	1	M	56	C	T3N1M0	tub2	2	0	no	87	T	T3N0M0	tub2	1	1	surgery	alive (>60)
	2	F	64	A	T1bN0M0	tub1	0	0	no	69	D	TisN0M0	tub1	0	0	EMR	alive (>60)
	3	M	62	C	T4aN1M0	tub2	1	0	S-1	36	R	T4bN1M1	unknown	unknown	unknown	chemotherapy	dead (47)
	4	M	62	A	T1bN0M0	tub1	0	0	no	29	S	TisN0M0	tub1	0	0	EMR	alive (>60)
L	1	M	71	R	T4aN1M0	tub2	0	0	S-1	46	A	T3N0M0	tub2	0	0	surgery	alive (>60)
	2	F	66	R	T3N0M0	tub1	0	0	no	84	A	T3N0M0	tub2	0	1	surgery	alive (>60)
	3	F	62	S	T3N1M0	tub2	1	0	S-1	31	C	T1bN0M0	tub1	0	0	surgery	alive (>60)
	4	M	82	S	T3N1M0	unknown	1	0	no	14	D	T3N0M0	tub2	0	0	surgery	alive (>60)
	5	M	65	R	T1bN0M0	tub1	0	0	no	6	S	T1bN0M0	tub1	0	0	surgery	alive (>60)
	6	F	84	R	T4bN0M0	tub1	0	0	no	36	C	T1bN0M0	tub1	0	0	surgery	alive (>60)
	7	M	83	D	T3N0M0	tub2	0	0	no	53	S	TisN0M0	tub1	0	0	EMR	alive (>60)
	8	F	62	S	T3N1M0	tub2	1	0	no	45	A	T2N0M0	tub1	0	0	surgery	alive (>60)
	9	M	59	R	T4aN1M0	tub2	1	1	S-1	38	T	TisN0M0	tub1	0	0	EMR	alive (>60)

*Age at first operation ; C, cecum ; A, ascending colon ; T, transverse colon ; D, descending colon ; S, sigmoid colon ; R, rectum ; EMR, emergency room

found that the risk of metachronous cancer was not associated with the location of the primary colorectal cancer.

Most cases of colorectal cancer are sporadic and arise from polyps originating within aberrant crypts. Approximately 10% of such polyps develop into early adenoma, followed by advanced adenoma, and, finally, colorectal cancer. Such progression is broadly categorized as either the adenoma-adenocarcinoma sequence pathway or the serrated pathway[16,17]. Colorectal cancer occurring from the serrated pathway is characterized as a microsatellite instability with a variation of the B-Raf proto-oncogene, serine/threonine kinase gene (BRAF), and most such cancers develop in the ascending colon of elderly patients[18-22]. Such a pathway might be related to our finding that the incidence of metachronous adenoma was significantly higher in the L group than in the R group ($p=0.022$). Colon polyps might have been more likely in patients of the L group because the carcinogenic pathway in most of these patients was the adenoma-adenocarcinoma sequence pathway.

Conclusion

Resection of the terminal ileum does not increase the risk for metachronous colorectal cancer.

Conflict of Interest Statement

Authors have no conflict of interest.

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