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Multiple Colorectal Carcinomas and Colorectal Carcinoma Associated with Extracolonic Malignancies

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Abstract: In this study, we analyzed 149 surgical cases of colorectal cancer between January 1983 and August 1989. Thirteen cases (8.7 per cent) of colorectal primary cancer associated with extracolonic primary malignancy of 14 lesions and 10 cases (6.7 per cent) of multiple primary colorectal cancers were included. Among the 14 lesions of extracolonic primary malignancy, there were 6 gastric carcinomas, 2 endometrial carcinomas, 2 urinary bladder carcinomas, and one each in the esophagus, liver, bile duct and jejunum. The second tumor was not detected preoperatively in 3 of 4 cases of synchronous multiple primary colorectal carcinoma. A curative resection was done in 10 (77 per cent) out of 13 cases of colorectal cancer associated with extracolonic malignancy, while 7 (88 per cent) out of 8 cases of multiple colorectal cancers had a curative resection. Nine patients (69 per cent) with colorectal cancer associated with extracolonic malignancy were disease-free for 2 months to 14 years. Seven patients (88 per cent) with multiple colorectal cancers were disease-free for one to 22 years. We recommend, therefore, that in any patient with colorectal cancer, the entire large bowel should be thoroughly searched for any other primary tumors, by taking the existence of extracolonic tumors into account. A curative resection should be performed, and the follow-up period should be life-long.

Key Words: multiple primary colorectal cancers, associated extracolonic cancer, metachronous cancer, synchronous cancer

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Introduction

Carcinoma of the large bowel is markedly increasing in Japan, and the colon is also the most common site for multiple primary malignant tumors.[1] Because of progress in the diagnosis and improvements in the prognosis of multiple primary malignancies, therapeutic and genetic interest among clinicians and pathologists has increased in recent years.

The present study deals with an analysis of 149 cases of colorectal adenocarcinoma, in an attempt to elucidate the most appropriate diagnostic and therapeutic regimens on multiple primary malignant tumors of the colon and rectum, and extracolonic organs.

Materials and Methods

From January 1, 1983, through August 31, 1989, 149 patients with a histological diagnosis of colorectal primary adenocarcinoma underwent resection at Osaka Teishin Hospital.

For cases of colorectal primary carcinoma associated with extracolonic primary malignancy, the diagnostic criteria according to Warren and Gates[2] were used: 1) Each tumor had to present a definite picture of malignancy; 2) each tumor had to be distinct; and 3) the probability that one was metastatic from the other had to be excluded. Also, we used the criteria according to Kaibara et al. for multiple primary colorectal cancers[3]: 1) Every tumor had a definite picture of malignancy; 2) each tumor was surrounded by intact tissue; and 3) the tumor was clearly separated from the margins of previous anastomoses. Cases of carcinoma associated with familial polyposis were excluded.

Synchronous cancer were defined as those diagnosed simultaneously or within an interval of one year. Cancers were considered metachronous when the

Table 1. Frequency of colorectal cancer associated with extracolonic primary malignant tumors, and multiple primary colorectal cancers between January, 1983 and August, 1989

Tumor group	Number of patients (per cent)
Surgical cases of colorectal cancer	149
Single colorectal cancer	128
Colorectal cancer associated with extracolonic primary malignant tumor	13 (8.7)
Synchronous	7 (4.7)
Metachronous { Colorectal cancer preceding / Extracolonic cancer preceding	2 / 4 > 6 (4.0)
Multiple colorectal cancer	10 (6.7)
Synchronous	5[a] (3.4)
Metachronous	5[a] (3.4)

[a]: Included is each case of colorectal cancer associated with extracolonic malignancy

Table 2. Sex and age

	Single colorectal cancer	Colorectal cancer associated with extracolonic malignancy			Multiple colorectal cancer		
		Synchronous	Metachronous		Synchronous	Metachronous	
			Colorectal cancer preceding	Extracolonic cancer preceding			
Male	78	5	1	2	5	3	
Female	50	2	1	2	0	2	
						First cancer	Second cancer
Age at operation (years)	26–86	41–82	53–65	54–68	41–71	32–63	54–64
Average age (years)	57.8	68.0	59[a]	59.3[b]	63.0	45.8	58.2

[a] Average age, second cancer: 62
[b] Average age, first cancer: 53.8

second was diagnosed more than a year after the first. The designations of "first" and "second" primary tumor were chosen according to the size and spread of the cancer.

Results

Among 149 cases of primary colorectal carcinoma, there were 13 cases (8.7 per cent) of colorectal cancer associated with extracolonic primary malignant tumor and 10 cases (6.7 per cent) of colorectal multiple primary malignant tumor (Included are 2 cases of colorectal cancer associated with extracolonic malignancy in this tumor group). A total of 21 patients (14.1 per cent) were involved (Table 1).

As far as the sex ratio is concerned, males predominated over females except in colorectal cancer associated with metachronous extracolonic malignancy. The average age of each tumor group was about 59 years except for colorectal cancer associated with synchronous extracolonic malignancy and in the first cancer of metachronous multiple colorectral cancers. Those who had colorectal cancer associated with synchronous extracolonic malignancy underwent operation at the average age of 68, which was considerably older than the other tumor groups. On the other hand, those who had the first tumor of metachronous multiple colorectal cancer were operated upon, at by far an earlier age than the other tumor groups (Table 2).

The distribution of colorectal carcinoma with extracolonic primary malignancy and multiple colorectal carcinomas disclosed no significant variation, compared with single colorectal carcinoma. Namely, the sigmoid colon and rectum predominated in frequency in each tumor group (Table 3).

There were 14 cancers among the 13 cases of colorectal cancer associated with extracolonic malignancy. The most common site of extracolonic organs is the stomach. Besides the stomach, other organ sites are the uterus, urinary bladder, esophagus, liver, bile duct and jejunum (Table 4).

Table 3. Tumor distribution in colon and rectum (%)

Tumor group		No. of cases	No. of lesions	Appendix	Cecum	Ascending colon	Transverse colon	Descending colon	Sigmoid	Rectum
Single colorectal carcinoma		128		1 (0.8)	3 (2.3)	15 (11.7)	8 (6.3)	5 (3.9)	40 (31.3)	56 (43.7)
Colorectal carcinoma with extracolonic primary malignancy	Synchronous	7	10			2 (20.0)	1 (10.0)		2 (20.0)	5 (50.0)
	Metachronous	6	6				1 (16.7)		2 (33.3)	3 (50.0)
Multiple colorectal carcinomas	Synchronous	5	11			2 (18.2)		1 (9.1)	5 (45.4)	3 (27.3)
	Metachronous	5	14				2 (14.2)	1 (7.1)	3 (21.4)	8 (57.3)

Table 4. Site of extracolonic organs in colorectal cancer associated with extracolonic primary malignancy

Organ	Male	Female	Total
Stomach	4	2	6
Uterine body		2	2
Urinary bladder		2	2
Esophagus	1		1
Liver	1		1
Bile duct	1		1
Jejunum	1		1

Among the 7 cases of synchronous colorectal cancer and extracolonic primary malignant tumor, the second tumors were all detected preoperatively, except for "Patient 4", in which sufficient examinations could not be performed due to an intestinal obstruction. The second cancers of 3 cases of colorectal cancer associated with primary gastric cancer were all asymptomatic, but all were detected by means of gastroscopy or X-ray examination, which is always performed as a routine preoperative examination (Table 5).

The time interval between the first and second tumor in colorectal cancer associated with metachronous extracolonic malignancy ranged from 1.5 to 10.5 years. There was one interesting case in that "Patient 1" developed five primary different carcinomas (sequentially, transverse colonic carcinoma, gastric carcinoma, sigmoid colonic carcinoma, rectal carcinoma and urinary bladder cancer) over a period of 27 years (Table 6).

Table 6. Time interval between the first and second tumor in colorectal cancer associated with metachronous extracolonic malignancy

Patient number	Site of first cancer	Interval (Years)	Site of second cancer
1[a]	Transverse colon	7.0	Stomach
2	Rectum	4.3	Stomach
3	Stomach	5.3	Rectum
4	Bile duct	5.7	Sigmoid colon
5	Liver	1.5	Rectum
6	Uterus	10.5	Sigmoid colon
7	Transverse colon	1.9	Uterus

[a] A patient who developed five primary carcinomas (besides the above, sequentially sigmoid colonic carcinoma, rectal carcinoma, and urinary bladder cancer) over a period of 27 years

Table 5. Time of diagnosis in colorectal cancer associated with synchronous extracolonic primary malignant tumor

Patient number	First tumor	Second tumor	Diagnosis	
			Pre-operative	Peri-operative
1	Rectum	Stomach	○	
2	Ascending colon	Stomach	○	
3	Ascending colon	Stomach	○	
4	Rectum	Sigmoid Jejunum		○
5	Rectum	Urinary bladder	○	
6	Rectum	Urinary bladder	○	
7	Esophagus	Rectum	○	

Table 7. Time of diagnosis in synchronous multiple primary colorectal cancers

Patient number	First tumor	Second tumor	Diagnosis	
			Pre-operative	Peri-operative
1	Descending colon	Sigmoid colon		○
2	Rectum	Sigmoid colon		○
3	Ascending colon	Transverse colon Sigmoid colon		○
4	Sigmoid colon	Rectum	○	

Next, we describe the clinical characteristics of multiple primary colorectal cancers. Concerning the time of diagnosis in synchronous multiple primary colorectal cancer, only one case "Patient 4" had the synchronous second cancer detected preoperatively among the 4 cases. In the other 3 cases, the second tumor was not detected due to a preoperative examination miss. Perioperative diagnosis was made by careful inspection and palpation. For the one case of descending and sigmoid colonic cancer, although double contrast barium study was performed, sigmoid colonic cancer was missed, because the outlines of the long sigmoid colon were folded in a complicated manner, and colonoscopy was unfortunately not performed. In another case, neither barium study nor colonoscopy was made due to high degree stenosis of the advanced rectal carcinoma. In the third mistaken case, a giant ascending colonic cancer shaded a smaller transverse colonic cancer, and no colonoscopy was done, although a barium study was made (Table 7).

In the 4 cases of metachronous multiple primary colorectal cancers, the time interval ranged from 1.1 to 22 years (an average time, 10.9 years) after the first resection (Table 8).

Table 8. Time interval between the first and second tumor in metachronous multiple primary colorectal cancers

Rectum	22 (years)	Sigmoid colon
Descending colon	10.5	Rectum + sigmoid colon
Sigmoid colon	9.9	Rectum
Sigmoid colon	1.1	Transverse colon

A curative resection was done in 10 (77 per cent) out of 13 cases of colorectal cancer associated with extracolonic malignancy, while 7 (88 per cent) out of 8 cases of multiple colorectal cancer had curative resection. Nine patients (69 per cent) with colorectal cancer associated with extracolonic malignancy were alive and doing well for 2 months to 14 years. On the other hand, 7 patients (88 per cent) with multiple colorectal cancers were alive and well for one to 22 years (Table 9).

Discussion

No operation for cancer of the large bowel should be done without a thorough investigation of the whole large bowel; this advice remains as true today as when first suggested in 1972.[4]

Multiple primary malignant tumors (MPMT), and especially those involving the large bowel, are no longer a medical curiosity.[5] They require, in daily practice, important considerations to be taken regarding management.

The incidence of MPMT, which ranges from 0.6 per cent to 36 per cent, in autopsy studies is higher than in clinical studies, probably because some MPMT are silent during life.[6] Lee et al. reviewed 9329 cases from series in the literature of primary colorectal cancer with follow-up: among those, 479 (5.1 per cent) were confirmed as having primary malignant tumors at site other than the colon.[7] Among 308 patients with colorectal cancers, 34 (11.0 per cent) had additional primary carcinomas entirely independent of their colonic lesions.[7] These were similar to our study.

Table 9. Resectability and prognosis (%)

	Colorectal cancer associated with extracolonic malignancy		Multiple colorectal cancers	
	Synchronous	Metachronous	Synchronous	Metachronous
Curative resection	4/7	6/6	3/4	4/4
	Total 10/13 (77)		Total 7/8 (88)	
Prognosis (alive/total)	3/7	6/6	3/4	4/4
	Total 9/13 (69)		Total 7/8 (88)	

Extracolonic primary cancer coexisting with primary colorectal cancer is reported most frequently in the skin, stomach, breast, urinary bladder and prostate.[8] However, among the cases of primary colorectal cancer and associated extracolonic primary malignant tumors, gastric cancer was the most common tumor in this study as in other reports in Japan.[9] Furthermore, it is the most frequently the case that the stages of colorectal cancer and associated gastric cancer would be advanced and early, respectively.[10] We, therefore, make it a rule to perform gastroscopy or X-ray examination against a patient with colorectal cancer, searching for a second asymptomatic early gastric cancer.

Although patients with multiple tumors are uncommon, recognition of such an occurrence is important to avoid attributing symptoms to metastases from a previously diagnosed tumor.

Preoperative diagnosis was difficult, being achieved in only one out of 4 cases of multiple primary colorectal cancers, which was similar to those of Adloff et al..[11] Those patients receiving a barium enema, unfortunately without colonoscopy, were simply poorly assessed.

For those patients with an occlusive primary tumor in whom preoperative colonoscopy is not feasible, new advancements in laser techniques might still present a chance for an accurate preoperative assessment.[11] Nevertheless, simultaneous colorectal primaries remain necessary for intraoperative detection in most cases by means of a careful inspection and palpation,[12] and intraopeative colonoscopy.[13]

For cases of synchronous primary colorectal cancer and associated extracolonic primary cancer, they should both be radically resected at first laparotomy.

In regard to the extent of resection, Fogler and Weiner,[14] have chosen a subtotal colectomy as the procedure of choice for patients affected by synchronous colorectal carcinomas. Fortunately, multiple primary colorectal cancers, however, have a pronounced tendency to occur in the same region of the colon. In fact, 68 per cent of 261 multiple primary colorectal cancers reported by Moertel were confined to the same segment.[15] So we elect to resect each growth curatively and radically but by retaining the normal colon.[11]

The prognosis for the colorectal cancer associated with extracolonic malignancy and multiple primary colorectal cancers was relatively good in this study as far as curative resection was performed. The presence of MPMT does not alter survival rates to any appreciable degree.[6] Even for the quadruple primary cancers, the average length of survival from diagnosis of the first malignancy was 10.9 years.[16] Sequential primary tumors may thus be amenable to curative treatment.[17] The fact that patients with cancer may have a higher susceptibility to cancer does not lessen their chance for cure, and radical treatment is not contraindicated for consecutive primary malignant tumors.[6,17] Because the longer a patient lives, the more predisposed he or she is to the development of one or more additional cancers, it is very important that elederly cancer patients have a continuous follow-up. When tumor symptoms develop in a patient who has been treated for an initial tumor, they must not be assumed to immediately represent metastases. For example, extracolonic primary cancer may occur as long as 17 years before, or 20 years after, the diagnosis of the colorectal cancer.[15] Early diagnosis of the second cancer(s), bases on an awareness of its potential, will substantially increase survival.[6]

Our conclusions are as follows: 1) In any patient with cancer of the colon or rectum, the entire large-bowel should be thoroughly searched for other primary malignant tumors, and extracolonic tumors should be considered as a second primary tumor unless proved to be metastatic. 2) The followup period should be lifelong and include frequent and intensive colorectal examinations for the occurrence of a second primary tumor. 3) Resection should be performed at first laparotomy in a synchronous case, and radical curative surgery should be completed, whether the case is synchronous or metachronous.

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