

Original Article

Clinical Characteristics of Patients with Sporadic Primary Colorectal and Gastric Cancers

Cheng-Ying Chiang^{1,6}

Yung-Sung Yeh¹

Chin-Fan Chen^{1,2}

Cheng-Jen Ma¹

Fang-Ming Chen^{1,3}

Hon-Man Chan^{1,3}

Ming-Feng Hou^{1,3,4}

Che-Jen Huang^{1,3}

Jan-Sing Hsieh^{1,3}

Jaw-Yuan Wang^{1,3,5}

¹Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

²Department of Surgery, Pingtung Hospital,

³Department of Health, Pingtung, Taiwan

⁴Department of Surgery, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

⁵Cancer Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

⁶Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

⁶Department of Surgery, Jannren Hospital, Kaohsiung, Taiwan

Key Words

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Purpose. Patients with colorectal cancer (CRC) are at increased risk of developing cancer at a number of other sites. In this study, we focused on patients with primary CRC and primary gastric cancer (GC), and described our clinical experience with these patients.

Methods. We analyzed 10 patients with synchronous or metachronous primary CRC and primary GC from 1752 patients who underwent surgical treatment for sporadic CRC at the Department of Surgery of Kaohsiung Medical University Hospital from January 1998 to May 2007.

Results. There were ten patients with ages ranging from 53 and 87 years (median, 68 years). Three patients were in the synchronous group with the interval between two cancers being within one year, and seven patients were in the metachronous group with the interval between two cancers ranging from 3 to 16 years. UICC stages of CRC patients were as follows: 2 patients were stage I (20%), 3 patients were stage III (30%), 3 patients were stage IV (30%), and 2 patients were stage IV (20%). The most common major clinical symptoms and signs were hematochezia (4/10) and ileus (4/10). Most patients (9/10) were diagnosed preoperatively by abdominal computed tomography (CT) scan combined with colonoscopic examination. The operative procedures for CRC were as follows: 4 patients received right hemicolectomy, 3 patients received anterior resection, and three patients received subtotal colectomy, abdominoperineal resection, and Hartmann's procedure respectively. All patients were discharged uneventfully without surgical mortality. Mean of follow-up time after CRC operation was about 20.9 months, and median was 12.5 months. To date, nearly all patients (9/10) have survived, and only one patient of UICC stage IV died of terminal disease due to the delayed diagnosis of peritoneal carcinomatosis.

Conclusions. It might be appropriate to arrange colonoscopic examinations for GC-bearing patients if they have hematochezia or ileus, in order to detect synchronous or metachronous CRC. Careful attention should always be paid to the second CRC in treating these GC cancer patients, because early surgical intervention would markedly improve prognosis.

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Correspondence to: Dr. Cheng-Ying Chiang, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan. Tel: +886-7-3121-1101ext.5575

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality in Europe and USA, and approximately 300,000 new cases and 200,000 deaths due to CRC are reported in these areas annually.¹ In Taiwan, CRC is one of the most frequently occurring malignancies and the third major cause of cancer-related death among all cancers (<http://www.doh.gov.tw/statistic/index.htm>; accessed in June 2008). The rapidly increasing rate of CRC in recent years has drawn special attention to this site in terms of synchronous and metachronous malignancies of other organs. Owing to medical advancement, current cancer patients have better survival rates than previously. This leads to cancer patients having increased chances to develop second primary cancer of other organs, and then multiple cancers may occur in an individual. The development of multiple cancers may be due to environmental factors, genetic predisposition, cancer therapy, or immunodeficiency.²

Since synchronous and metachronous CRC is well known clinically, second primary cancer from other sites isn't rare either. Patients with CRC are at increased risk of developing cancer at a number of other sites.² Consequently, it is important to perform pre-operative and post-operative surveillance for CRC-bearing patients. Previous results have shown that gastric cancer (GC) predominates among CRC patients with accompanied with primary cancer of other organs.^{3,4} In this article, we focused on patients with these two gastrointestinal tract cancers and described our clinical experience of CRC patients with synchronous and metachronous primary GC.

Methods

From January 1998 to May 2007, one thousand, seven hundred and fifty-two sporadic CRC patients received surgical treatment at the Department of Surgery of Kaohsiung Medical University Hospital. Among these patients, CRC was accompanied by cancer of other organs in 42 patients (2.40%), either synchronously or metachronously. Finally, 10 patients were subsequently diagnosed as 3 synchronous, as well as 7 metachronous CRC and GC. Inclusion criteria were that each tumor had definite histological di-

agnosis of CRC, and clearly did not have any origin of metastasis from another tumor. Second primary cancers detected within 1 year after the detection of first primary cancers were regarded as synchronous cancers, and intervals between double-primary cancers which were over 1 year were regarded as metachronous cancers. The medical records included the demographic presentation, the clinical presentation, the diagnosis, the treatment procedure and follow-up of these patients respectively. Clinical stage and pathological features of primary tumors were defined according to the criteria of the American Joint Commission on Cancer.⁵

Results

The demographic and the clinical presentation of CRC patients with primary GC are shown in Table 1. There were 3 synchronous and 7 metachronous double-primary cancer (CRC+GC) patients. Of these 10 patients, there were 4 females and 6 males with ages ranging between 53 and 87 years (median, 68 years). The interval between metachronous double-primary cancers ranged from 3 to 16 years. All of the metachronous double-primary cancer patients had primary GC first, and then developed CRC in the following years. The most common sites of CRC were the sigmoid colon (4/10) and ascending colon (4/10). UICC stages of CRC patients were as follows: 2 patients were stage I (20%), 3 patients were stage III (30%), 3 patients were stage IV (30%), and 2 patients were stage IV (20%). In two CRC patients with stage IV, one patient had peritoneal carcinomatosis which was found during operation, and the other one had liver metastasis before operation. The histological types of CRC were as follows: 8 cases were moderately differentiated carcinoma, and 2 cases were poorly differentiated carcinoma. Additionally, all 10 patients were examined for serum carcinoembryonic antigen (CEA) level preoperatively. Only 2 patients, one in the synchronous group and one in the metachronous group, had increased CEA level (over 5 ng/dL). Mean of follow-up time after CRC operation was about 20.9 months, and median was 12.5 months.

Table 2 shows the diagnosis and the treatment

Table 1. Demographic and Clinical Description of Colorectal Cancer Patients Accompanied with Gastric cancer

No.	Age/Gender	Phase	Site of CRC	UICC stage	Histology	Pre-operative CEA level (mg/dL)	Interval (years)	Follow-up time after CRC operation	Total follow-up time
1	65/Female	Synchronous	D-colon	T4N0M1 stage IV	MD	156	Within 1	1 year and 4 months	1 year and 4 months
2	68/Male	Synchronous	Rectum	T3N1M0 stage III	PD	3.45	Within 1	4 years and 6 months	4 years and 6 months
3	87/Male	Synchronous	S-colon	T2N0M0 stage I	MD	4.87	Within 1	1 year and 6 months	1 year and 6 months
4	69/Female	Metachronous	A-colon	T3N0M0 stage II	MD	1.37	12	4 years and 8 months	16 years
5	74/Male	Metachronous	S-colon	T3N0M0 stage II	MD	2.33	5	3 years and 1 month	8 years
6	67/Female	Metachronous	A-colon	T3N1M0 stage III	MD	2.76	10	9 months	10 years
7	76/Male	Metachronous	S-colon	T3N1M1 stage IV	MD	1206	9	9 months	9 years
8	64/Male	Metachronous	S-colon	T2N0M0 stage I	MD	1.77	16	6 months	16 years
9	66/Male	Metachronous	A-colon	T3N0M0 stage II	MD	0.72	12	2 months	12 years
10	53/Female	Metachronous	A-colon	T3N2M0 stage III	PD	0.51	3	2 months	3 years

CRC, Colorectal cancer; A-colon, ascending colon; D-colon, descending colon; S-colon, sigmoid colon; MD, moderately differentiated; PD, poorly differentiated; Interval, interval (years) between diagnosis of first primary and second primary cancers.

Table 2. Diagnosis of Colorectal Cancer and Treatment Procedure for the Two Cancers

No.	Major Symptoms	Preoperative examinations	Operative procedure for colorectal cancer	Operative procedure for gastric cancer	Chemotherapy regimen	Outcome	Cause of death
1	Obstructive ileus	CT	Subtotal colectomy	subtotal gastrectomy + Billroth II reconstruction	5-FU + Irinotecan	Death	Peritoneal carcinomatosis of descending colon cancer
2	Hematochezia	CT, CS	Abdominoperineal resection	radical gastrectomy + Roux-en-Y reconstruction	Tegafur uracil	Alive	Nil
3	Bowel habit change	CT, CS	Anterior resection	subtotal gastrectomy + Billroth II reconstruction	Nil	Alive	Nil
4	Obstructive ileus	CT, CS	Right hemicolectomy	subtotal gastrectomy + Billroth II reconstruction	Nil	Alive	Nil
5	Hematochezia	CT, CS	Anterior resection	radical gastrectomy + Roux-en-Y reconstruction	Nil	Alive	Nil
6	Hematochezia	CT, CS	Right hemicolectomy	subtotal gastrectomy + Billroth II reconstruction	Folfox4	Alive	Nil
7	Obstructive ileus	CT, CS	Hartmann's procedure	subtotal gastrectomy + Billroth II reconstruction	Folfiri + cetuximab	Alive	Nil
8	Hematochezia, bowel habit change	CT, CS	Anterior resection	subtotal gastrectomy + Billroth II reconstruction	Nil	Alive	Nil
9	Abdominal pain	CT, CS	Right hemicolectomy	subtotal gastrectomy + Billroth II reconstruction	Nil	Alive	Nil
10	Obstructive ileus	CT, CS	Right hemicolectomy	radical gastrectomy + Roux-en-Y reconstruction	Capecitabine	Alive	Nil

CT, Computed tomography; CS, colonoscopic examination

procedure of CRC patients with primary GC. The most common major clinical symptoms and signs were hematochezia (4/10) and obstructive ileus (4/10), and others included bowel habit change and

abdominal pain. Most patients (9/10) were diagnosed preoperatively by abdominal computed tomography (CT) scan combined with colonoscopic examination, and one patient was diagnosed by image study only,

due to severe bowel obstruction. The operative procedures for CRC were as follows: 4 patients accepted right hemicolectomy, 3 patients accepted anterior resection, and three patients accepted abdominal perineal resection, subtotal colectomy, and Hartmann's procedure respectively. The operative procedures for GC were for subtotal gastrectomy with Billroth II reconstruction in 7 patients, and radical total gastrectomy with Roux-en-Y esophagojejunostomy in 3 patients respectively. For two left-sided CRC patients with prominent obstruction, more complicated procedures than those without obvious obstruction sign were performed. In this group, one received Hartmann's procedure and the other one received subtotal colectomy due to difficulty in bowel preparation. All patients were discharged uneventfully without surgical mortality. Five of 10 CRC patients of UICC stage III or IV received chemotherapy, and the regimen of chemotherapy is listed in Table 2. To date, nearly all patients (9/10) have survived and have had persistent follow-up at the out-patient department, except for one patient (No.1) of UICC stage IV who died of terminal disease due to the delayed diagnosis of peritoneal carcinomatosis.

Discussion

Due to a remarkable improvement in cancer treatment, many cancer patients survive long after treatment. Accordingly, they are at increased risk of developing second primary cancers in the same or other organs, and may die from this condition. Therefore, it is important to recognize the characteristics of multiple cancers in order to detect the second cancer early enough to treat and cure it. There have been many reported cases of double cancers of the gastrointestinal tract. The incidence of a second primary cancer for CRC is within 1.26-3.3% according to data from previous studies.^{4,6,7} It is also supposed that cancer-bearing patients have increased risk of developing cancers of other organs.⁸ According to data from health and national health insurance annual statistics of the Department of Health of the Executive Yuan of Taiwan, CRC is the third leading cause of death from cancer in Taiwan in these years (1996-2007) (<http://www.doh.gov.tw/statistic/index.htm>; accessed in June 2008).

With the increase in numbers of CRC patients in recent years, some CRC patients may have a history of previous malignancy from other organs, or the possibility of developing secondary cancers of other organs.

Ueno et al stated that when colonic cancer was combined with other cancers, stomach cancer (1.4%) was the most frequently encountered neoplasm, and when rectal cancer was combined with other cancers, stomach cancer (0.6%) was also the most frequently encountered neoplasm.³ Under the above reasoning, we should follow-up on cancer-bearing patients closely, and check the possibility of developing secondary CRC among GC patients, or the possibility of developing secondary GC among CRC patients postoperatively. Ueno et al supported and suggested that CRC patients may accept upper gastrointestinal endoscopic examination before colorectal operation; in addition, they also recommended repeating the procedure at 2-year intervals during the first 5 years after operation.³ In our analysis, we fortunately found 3 synchronous CRC and GC patients, of whom simultaneous operative procedures for CRC and GC were performed smoothly.

It is not only GC patients who have increased risk of association with CRC. Breast malignancy was the second most frequent primary cancer from other sites encountered with CRC by Ueno et al.³ Recently, we have observed CRC patients who had second primary cancers in the order from the stomach, breast, cervix, and ovaries.⁴ Nevertheless, in another earlier research group in Taiwan, the most common second primary cancer in CRC patients was hepatocellular carcinoma,⁹ and this may relate to a gradually decreasing incidence of hepatocellular carcinoma in Taiwan area. These results hint that we also should pay more attention to the colorectal tract in patients with breast cancer, gynecologic cancer, or hepatocellular carcinoma, and particularly in patients with active gastrointestinal symptoms or signs.

In this study, we analyzed ten patients who had synchronous or metachronous primary GC. The reason that the follow-up time is based on the timing of CRC operation is described below. First, all of the metachronous double-primary cancer patients had

primary GC first, and then developed CRC in the following years. Second, we collected data from CRC patients by reviewing their previous history and ongoing follow-up. Another method that could be offered to follow up on the colorectal system of patients with previous malignant history is computed tomographic colonoscopy (CTC). Contrast-enhanced computed tomographic colonoscopy (CTC) is an acceptable tool for the detection of synchronous CRC or advanced adenoma among GC patients.¹⁰ CTC is not only for postoperative surveillance of malignancy, and the diagnostic yield of colorectal polyp was 31.4% in patients with GC.¹⁰

Another tool for postoperative surveillance of GC patients is serum CEA measurement, and for patients with increased serum CEA level after GC operation, possible development of second primary CRC must be suspected. Certainly, we would arrange detailed surveillance for patients with increased CEA, but follow-up of CEA level still has its limited sensitivity and specificity. Between 7 patients with metachronous double-primary cancer in this study, all of them had primary GC first and then developed metachronous CRC in the following years, and only one patient (No.7) had increased CEA level over 5 ng/dL (up to 1206 ng/dL). According to this finding, we should remain wary of possible development of second primary CRC in patients with normal serum CEA level after primary GC operation.

In conclusion, systemic surveillance for second primary cancer is important for cancer-bearing patients, although this cost-effectiveness is still uncertain and remains to be further evaluated. We suggest it might be applicable to arrange an upper gastrointestinal endoscopic examination for CRC-bearing patients before colorectal operation in order to detect synchronous GC. We also suggest that the colorectal tract of patients with previous GC, particularly with active gastrointestinal symptoms or signs, should be evaluated carefully during follow-up to early diagnosis of CRC.

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