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• BRIEF REPORTS •

Clinical features, diagnosis, treatment and prognosis of multiple primary colorectal carcinoma

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Abstract

AIM: To investigate the clinical features, diagnosis, treatment and prognosis of multiple primary colorectal carcinomas (MPCC).

METHODS: A retrospective analysis of 37 patients with MPCC from 1974 to 1998 was carried out.

RESULTS: The incidence of MPCC was 2.74%(37/1 348) in patients with primary colorectal carcinomas, 15 cases of them were patients with synchronous carcinomas (SC) and 22 cases were diagnosed as metachronous carcinomas (MC). Most tumors were located in the right colon and rectum. Fifty-five percent (12/22) of MC were diagnosed within 3 years after tumor resection and 41%(9/22) of MC occurred after 8 years. Radical resections were performed in all patients except for 1 case. The 5-year survival rate of SC was 72.7%(8/11) and that of MC after the first cancer and second cancer was 71.4%(15/21) and 38.9%(7/18), respectively.

CONCLUSION: The results indicate the importance of complete preoperative examination, careful intraoperative exploration and periodic postoperative surveillance. Early diagnosis and radical resection can increase survival rate of MPCC.

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INTRODUCTION

Multiple primary colorectal carcinoma (MPCC) refers to two or more primary colorectal carcinomas detected in a single individual simultaneously or consecutively. It is named synchronous carcinoma (SC) and metachronous carcinoma (MC) respectively. The prognosis of colorectal carcinoma is good compared with other carcinomas of the digestive organs. Along with increasing incidence of colorectal carcinomas and prolonged survival after radical resection, patients with MPCC have increased gradually. Generally, SC does not affect prognosis if it is recognized and treated in time, but if ignored, it may turn into more advanced MC. Therefore, after colorectal cancer surgery, occurrence of metachronous carcinoma is regarded as an serious problem[1]. Due to influence of doctor's recognition degree, missed and error diagnosis or inaccurate treatment appears frequently. The purpose of this review was to discuss the prevalence, preoperative diagnosis, postoperative follow-up and survival, in order to strengthen the acquaintance of MPCC.

MATERIALS AND METHODS

A total of 1 348 cases of primary colorectal carcinomas were treated at the Department of Surgery, Beijing Cancer Hospital from January 1, 1974 to December 31, 1998. MPCC was diagnosed according to the following criteria proposed by Moertel[2]. Each tumor must have a definite pathologic picture of malignancy, metastasis or recurrence from another colorectal cancer was excluded, all cancers detected at the same time or within 6 mo were defined as SC, otherwise as MC, Tumors must be distinctly separated by at least 5 cm of an intact bowel wall from each other. MC must be more than 5 cm away from the normal anastomotic site of index cancer resection. MPCC originated from familial colonic polyposis or ulcerative colitis was excluded[2].

Tumor locations were divided into 3 groups: (1) right colon which included appendix, cecum, ascending colon, hepatic flexure, and transverse colon; (2) left colon which included splenic flexure, descending colon and sigmoid colon; (3) rectum, upper boundary of which was 15 cm from the dentate line. It was considered as lost follow-up if a patient failed to come back to the Outpatient Department or could not be contacted by letter or telephone for more than one year.

Independent *t*-test and χ^2-test were used to compare the factors in different groups. A P value less than or equal to 0.05 was considered statistically significant.

RESULTS

A total of 1 348 patients with colorectal carcinoma were treated during 25 years period. Fifteen cases had 2 SCs and 22 patients had 2(20 cases) or 4(1 case) or 5(1 case) MCs, respectively (Tables 1 and 2). No significant differences were noted among the groups in age and gender. The second MC appeared in 8-240 mo (mean: 68 mo), 55%(12/22) were diagnosed within 36 mo and 41%(9/22) after 96 mo. The interval of other one patient was 45 mo. Two patients had three times of MC, their interval was 15 years (one cancer), 19 years (two cancers) and 12 years (one cancer), 17 years (three cancers) respectively.

The distribution of MC and SC is shown in Table 2. Lesions were located at the adjacent intestinal segment in 6 of SC group (43%). In MC group, 20 patients had 2 lesions, 1 had 4 lesions and the other one had 5 lesions.

The clinical presentation was variable. All the 15 patients in SC group went to see doctors because of symptoms, such as bloody stool, abdominal pain, diarrhea, anemia and abdominal mass. The time of the development symptoms was more than 1 year. Thirteen cases (87%) were diagnosed by barium enema and/or colonoscopy before operation. And 2, 9 and 2 patients were staged as Dukes B, C and D, respectively. Other 2 patients of this group were diagnosed intraoperatively. In MC group,

3 of 22 cases (13.6%) were proved by routine postoperative colonoscopy (2: Dukes A, 1: Dukes B). Twenty-one patients went to see doctor owing to symptoms, 18(86%) were diagnosed preoperatively, 2 were diagnosed intraoperatively, and 1 was diagnosed by postoperative pathology.

Operation was the primary option. In SC group, 14 cases (93%) received radical resection. Among them, 5 cases received subtotal colectomy in combination with rectoileostomy, others received radical resection or combined radical resection of adjacent loop according to the cancer locations. One received by-pass due to severe local spread. In MC group, all the 22 cases with index cancer received radical resection. All secondary or third lesions except one underwent radical resection.

The histological types of all cancers are shown in Table 2. No significant differences were noted between the second cancer and SC with index cancer. There was a significant difference between the third cancer and index cancer.

The 5-year and 10-year survival rates are shown in Table 2. There was no significant difference between SC and index cancer of MC. The 5-year survival rate of the patients with secondary cancer could reach 39% after operation.

Table 1 Age and gender of patients with MPCC

	Group SC	Group MC
Number of patients	15	22
Age(yr)		
mean±SD	47±12	48±12
Range	27-71	30-68
P value		>0.1
Gender		
Male	11(73%)	16(73%)
Female	4(27%)	6(27%)
P value		>0.1

All statistical comparisons were with index cancer of MC by independent *t*-test or χ^2-test.

DISCUSSION

MPCC is not uncommon in clinic. The estimated incidence rates of SC and MC were 2.0-8.1% and 0.6-10.6% respectively[3-10]. Such a significantly different result of these series may be due to several reasons. For example, the definition varied to allow diagnosis of a second carcinoma at a range of 6 mo to 3 years after the diagnosis of the index tumor. The patient number, observation period and follow-up time all could influence the final results. Bulow *et al*.[9] followed up 501 patients younger than 40 years old with colorectal carcinoma for up to 41 years. In the first 10 years, only 12 cases developed MC. Since then, another 32 patients had developed MC in succession. Cali *et al*.[1] reported that the calculated incidence for MC was 0.35 percent per year and the cumulative incidence at 18 years was 6.3 percent according to a group of 5 476 patients. In another larger group of 141 945 patients with histologically confirmed primary colorectal tumors within 14 years (mean follow-up of 4.72 years), 3 402(2.4%) and 1 526(1.1%) cases were diagnosed with SC and MC respectively[8]. In our study, the incidence of MPCC was 2.74%(37/1348). The reported data showed that the occurrence of MPCC had a rising trend[11].

Chen *et al*.[12] reported that there was no difference in age of patients with SC, MC and single colorectal carcinoma. Oya *et al*.[13] found the index lesions of synchronous cases did not differ from single lesions in age, size, differentiation, and location. However the male: female ratio was higher and distant metastasis was more frequent in synchronous cases than in single cases. Welch[14] found that patients with synchronous tumors were older than those with single colon cancers or initial metachronous lesions. Our results showed that patients with SC or MC had similar age, gender, and location.

The time intervals between the diagnosis of index and metachronous cancers varied obviously. Kiefer *et al*. showed that early metachronous cancers (within 2 years) reached 40%[15]. But others[8] considered the "early" MC as an overlooked SC. The interval of MC could reach 41 years after the first tumor. Welch[14] pointed out that the median interval between metachronous tumors was 9 years. The symptom duration was shorter before discovery of the second metachronous tumors. The occurrence of the second MC was 55% within 3 years and 41% after 8 years from index cancer resection in our series. The longest was 20 years. Therefore, early follow-up examination (within 3 years) was very important.

Table 2 Location, types, and survival rate in two groups

	MC			SC
	Index cancer	2nd cancer	3rd cancer	
No. of tumors	22	22	5	30
Location				
Right colon	9(41%)	7(32%)	2(40%)	7(23%)
Left colon	7(32%)	8(36%)	2(40%)	15(50%)
Rectum	6(27%)	7(32%)	1(20%)	8(27%)
P value		>0.1	>0.1	>0.1
Types				
AC	20(91%)	19(86%)	3(60%)	18(64%)
Mucoid AC	2(9)	1(5)		7(25)
Canceration		1(5%)	2(40%)	3(11%)
(Adenoma / Polypus)				
Ring cell C		1(5)		
P value		>0.1	<0.01	>0.05
Survival Rate				
5-yr	71%(15 / 21)	39%(7 / 18)		73%(8 / 11)
10-yr	53%(10 / 19)	19%(3 / 16)		63%(5 / 8)
P value				>0.1

A: Adenoid; C: Carcinoma. All statistical comparisons were with index cancer of MC by independent *t*-test or χ^2-test.

The preoperative detection of SC not only can allow an appropriate surgical strategy to be carried out but also establish a logical policy for follow-up. It is stressed that a second tumor may present in large intestine during follow-up. Barium enema and/or colonoscopy should be given to patients in time. Examinations such as B-ultrasound, CT scan, CEA, fecal occult blood and fecal occult albumin may help to improve diagnosis, especially SC preoperatively. CEA, fecal occult blood and fecal occult albumin test were also used to detect the early stage colorectal cancer during mass screening for asymptomatic or follow-up for high risk populations[16]. However, many results were still unsatisfactory[5,12,17]. Finan *et al*.[5] diagnosed only 42% of 59 SC patients preoperatively. Chen *et al*.[12] reported that 66%(31/47) of SC were omitted during preoperative barium enema (46 patients) and/or colonoscopy (7 patients). But other report[18] showed that the sensitivity of colonoscopy reached 76.7%(56/73) for detecting SC and 82%(14/17) of missed lesions were smaller than 1 cm polyps. In our group, although preoperative diagnostic rate of SC reached 87%, but 85% were Dukes C or D. The reason why multiple lesions could not be identified preoperatively was that the occluded distal lesions made it difficult to detect the proximal lesions. Therefore, we could not be satisfactory for diagnosis of one colorectal cancer and should examine the whole large bowel carefully pre- or postoperatively.

It is important to palpate the whole colon and to check pathological specimens carefully before the end of operation so that misdiagnosis of SC can be avoided. Even now, miss-diagnosis is still existed. Chen's report[12] showed that there were still 13 patients without detection of SC by operative palpation in the 31 preoperative undiagnosed cases. Intraoperative colonoscopy should be advised if necessary. We think that this technique should not be used as a routine one and could be performed early (within 6 mo) after surgery.

It is an effective measure to follow up with barium enema or colonoscopy periodically for diagnosing MC earlier. A previous report[9] showed that surveillance colonoscopy once every three years after surgery, together with a fecal occult blood test, would be an efficient and appropriate way to detect MC. Some nonfamilial colorectal cancers have been reported to have microsatellite instability (MSI)[19-23]. A research[19] indicated the incidence of MC in MSI-positive group was significantly higher than that in MSI-negative. Logical analysis showed that MSI and coexistence of adenoma were significantly independent risk factors for the occurrence of MC. Studies[20,21] showed the analysis of MSI and testing for replication errors at microsatellite loci in tumors might be helpful in predicting the development of MC in sporadic carcinomas of the distal colon and rectum. Others[10,24] discovered the significant risk factor for developing MC was the presence of synchronous adenoma or carcinoma at the initial operation and the subsequent development of recurring metachronous adenomas. Therefore, colorectal cancer patients with MSI-positive and coexistence of adenoma should be given more rigorous surveillance. Togashi[25] monitored 341 colorectal cancer cases with colonoscopy about 4.6 times in 6.2 years after operation. Twenty-two MCs were detected in 19 cases (5.6%), of these 17 MCs (77%) were less than 1 cm, 14 MCs (64%) occurred within 5 years and 71%(10/14) were early stage cancers. In our study, 12 MCs (55%) were diagnosed in 3 years, 3 MCs were discovered by routine colonoscopy (Dukes A: 2 patients, Dukes B: 1 case) and 9 MCs were diagnosed after the development of symptoms (Dukes B, C, D: 3, 2, 4 respectively). These results might prove that colonoscopy was important after surgery. We suggest that regular postoperative colonoscopic examinations should be performed annually during the first 5 years, then once every 3 years.

The treatment of SC or MC is the same as single colorectal carcinoma, with removal of enough intestines and cleaning of local lymph node. It is suggested that subtotal colectomy with rectoileostomy should be performed for patients with far apart SC, combined with multiple adenomatoid polyps or a familial hereditary history if their general condition suits for operation. Fajobi *et al*.[7] recommended that SC in different lymph drainage areas seemed a justifiable indication for subtotal colectomy. Easson *et al*.[26] considered multiple colon cancer was an important factor for performing subtotal colectomy. While subtotal colectomy could eliminate the need for colonoscopic surveillance, however examining the rectum is still required.

Generally speaking, MPCC develops slowly and their prognosis is acceptable. Chen[12] reported that the 5 -year survivals of patients after radical resection for MPCC did not differ from that of patients with single colorectal cancer. The incidence rate was 54%, 60%, and 62% for "single", SC, MC respectively. Other reports[8,27] displayed similar conclusions. Adloff[3] found patients with SC or single lesions had similar 5-year survival, even when classified by Dukes' stage. Rennert *et al*.[8] reported that survival time of patients with the second tumor in the rectum was shorter than that of a single tumor in the same stage and site. Only the stage of the second tumor was found to influence survival time of patients with metachronous tumors. Welch's result[14] was quite worse. The overall uncorrected 5-year survival rate of MPCC was only 21 percent. In our study, there was no significant difference between SC and index cancer of MC in the 5-year or 10-year survival rate. The 5-year survival rate could reach 39% after second cancer resection. We consider early diagnosis with complete preoperative examination; careful intraoperative exploration and periodic postoperative surveillance and radical resection can increase the survival time of patients with MPCC.

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