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Synchronous Colorectal Carcinoma: Clinico-pathological Features and Prognosis

Masatoshi Oya[1], Shuhei Takahashi[1], Takashi Okuyama[1], Masahiko Yamaguchi[1] and Yoshihiko Ueda[2]

Departments of [1]Surgery and [2]Pathology, Koshigaya Hospital, Dokkyo University School of Medicine, Koshigaya, Saitama, Japan

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Objective: The present study was undertaken to clarify the clinical and pathological features of synchronous colorectal carcinomas, to compare prognosis between cases with synchronous carcinomas and those with single carcinomas and to explore prognostic factors of synchronous carcinomas.

Patients and methods: Among 876 surgically resected primary colorectal carcinomas, 42 cases (4.8%) with synchronous carcinomas were identified. Clinical characteristics, routine pathological findings according to the TNM classification and postoperative survival were compared between synchronous cases and single cases. Prognostic factors of synchronous cases were explored using the proportional hazard model.

Results: The index lesions of synchronous cases did not differ from single lesions in age, size, differentiation, location, pT value, pN value, pathological stage, morphology or lymphatic invasion. However, the male:female ratio was higher and distant metastasis was more frequent in synchronous cases than in single cases. Although postoperative survival of synchronous cases was shorter than that of single cases, they were similar in the multivariate proportional hazard model including pathological stage and curability as co-factors. Only pathological stage and curability of the index lesion were significant co-factors of postoperative survival of synchronous cases.

Conclusion: Synchronous carcinomas and single carcinomas were similar in clinical characteristics and routine pathological findings. The prognosis of synchronous cases and that of single cases did not differ if the pathological stages were identical and the resections were curative.

Key words: synchronous colorectal carcinoma – pathology – prognosis

INTRODUCTION

It is well known that patients with primary colorectal carcinomas may have more than one malignant lesion within the colon and rectum at the time of initial presentation (synchronous carcinoma). The reported incidence of synchronous colorectal carcinoma ranged between 2.3 and 12.4% (1,2). Preoperative or intraoperative diagnosis of the presence of synchronous colorectal carcinomas is very important because once they are overlooked, they present as early metachronous carcinomas with advanced stages and usually require re-operation. If synchronous carcinomas are detected intraoperatively, the surgical procedure occasionally needs to be altered.

Although synchronous colorectal carcinoma has been recognized as a significant clinical entity, its clinical and pathological features and its prognosis are still controversial (3–5). The aims of the present study were to clarify clinical and pathological features of synchronous carcinomas, to compare prognosis between synchronous carcinomas and single carcinomas and to explore prognostic factors of synchronous carcinomas.

METHODS

From June 1984 to December 1999, 879 cases of invasive colorectal adenocarcinoma were surgically resected at the Department of Surgery, Koshigaya Hospital, Dokkyo University School of Medicine. After excluding two cases of ulcerative colitis and one case of familial adenomatous polyposis, 876 cases were selected for the study. Patients who were operated for intramucosal carcinoma were not included. Of these, 834 cases were single carcinomas and 42 cases (4.8%) were synchronous carcinomas, in which two or more invasive

For reprints and all correspondence: Masatoshi Oya, present address Department of Surgery, Cancer Institute Hospital, 1–37–1 Kami-Ikebukuro, Toshima-Ku, Tokyo 170-8455, Japan. E-mail: masatoshi.oya@jfcr.or.jp

carcinomas were identified in each case. Cases with one invasive carcinoma and one or more intramucosal carcinomas were included in the single cases. We used the following criteria for multiple colorectal carcinoma: each tumor had to have a definite histological picture of invasive malignancy, be distinctly separated by intact bowel wall and clearly have no metastatic origin from another colorectal tumor (6,7). Carcinomas detected within 1 year after the prior operation were regarded as synchronous carcinomas. Thus, one case in which the concurrent carcinoma was detected at 3 months after the resection of the index lesion was included in the synchronous case.

Tumor locations were divided into three groups: (i) right colon, which included appendix, cecum, ascending colon, hepatic flexure colon and transverse colon; (ii) left colon, which included splenic flexure colon, descending colon and sigmoid colon; and (iii) rectum, which was below the level of the sacral promontrium. The morphology of each lesion was macroscopically classified as elevated or ulcerated. Other pathological diagnosis was based on the TNM classification (8) except for differentiation, which was diagnosed according to the predominant pattern. In synchronous cases, the lesions which were the most advanced pathologically were designated to be the index lesions. When the two or more lesions were in an identical pathological stage, the largest lesion was regarded as the index lesion.

Categorical data and numerical data were compared between groups using the chi-squared test and the Mann–Whitney *U* test, respectively. Postoperative survival was analyzed using both the Kaplan–Meier survival curves with log-rank test and the proportional hazard model. Only patients followed up for at least 6 months or until death were included in the analysis of prognosis; the median follow-up of survivors was 54.1 months.

RESULTS

Characteristics of Synchronous Lesions

A total of 90 synchronous lesions were identified in 42 cases of synchronous carcinomas. The numbers of synchronous carcinomas in each case of synchronous carcinoma were two in 37 cases, three in four cases and four in one case. Synchronous carcinomas were present nearby (within the same segment or adjacent segment) in 29 cases, whereas they were present in two segments apart from each other in 11 cases. In one case having four lesions, synchronous carcinomas were detected both nearby and in segments apart. The combinations of wall penetrations of the index and concurrent lesions were pT1 and pT1 in one case, pT2 or pT3 or pT4 and pT1 in 17 cases and pT2 or pT3 or pT4 and pT2 or pT3 or pT4 in 24 cases.

Comparison Between Synchronous Carcinomas and Single Carcinomas

Synchronous carcinomas were significantly smaller in size than single carcinomas. Synchronous carcinomas were more frequently found in the left colon than single carcinomas. Wall penetrations of synchronous carcinomas were less than those of single carcinomas. Elevated lesions were more common in synchronous carcinomas than in single carcinomas (Table 1).

Table 1. Comparison of pathological findings between synchronous and single carcinomas

	No. of lesions		*P*
	Synchronous	Single	
No. of lesions	90	834	
Size*	40 (20–50)	45 (32–60)	<0.001
Differentiation			
Well	62	507	0.653
Moderate	21	268	
Poor	2	17	
Mucinous	5	34	
Others	0	8	
Location			
Right colon	29	189	0.001
Left colon	39	272	
Rectum	22	373	
Wall penetration			
pT1	22	56	<0.001
pT2	14	108	
pT3	39	428	
pT4	15	242	
Morphology			
Elevated	26	126	0.003
Ulcerated	64	703	
Others	0	5	
Lymphatic invasion			
Present	55	586	0.095
Absent	35	248	
Venous invasion			
Present	31	218	0.118
Absent	59	616	

*Median (interquartile range).

Comparison Between Index Lesions and Concurrent Lesions in Synchronous Cases

Index lesions were larger in size, more frequently moderately differentiated, more deeply penetrated and more often ulcerated in morphology than concurrent lesions (Table 2). Lymphatic invasion was more frequent in index lesions than in concurrent lesions.

Table 2. Comparison of pathological findings between index lesions and concurrent lesions in synchronous carcinomas

	No. of lesions		*P*
	Index lesion	Concurrent lesion	
No. of lesions	42	48	
Size*	50 (40–65)	21 (15–40)	<0.001
Differentiation			
Well	23	39	0.008
Moderate	16	5	
Poor	0	2	
Mucinous	3	2	
Location			
Right colon	14	15	0.292
Rectum	13	9	
Wall penetration			
pT1	1	21	<0.001
pT2	3	11	
pT3	24	15	
pT4	14	1	
Morphology			
Elevated	3	23	<0.001
Ulcerated	39	25	
Lymphatic invasion			
Present	33	22	0.003
Absent	9	26	
Venous invasion			
Present	17	14	0.366
Absent	25	34	

*Median (interquartile range).

Comparison Between Index Lesions of Synchronous Cases and Single Carcinomas

Synchronous carcinomas were more frequently found in males than in females (Table 3). Age at operation did not differ between patients with synchronous carcinomas and those with single carcinomas. Neither size, differentiation, location, pT value, pN value, pathological stage, morphology, nor lymphatic invasion differed significantly between index lesions of synchronous cases and single carcinomas. However, distant metastasis was significantly more common in index lesions of synchronous cases than in single carcinomas. Venous invasion was marginally more frequent in index lesions of synchronous cases than in single carcinomas (Table 3).

Comparison of Prognosis Between Synchronous Cases and Single Cases

Postoperative survival was significantly shorter in synchronous cases than in single cases in univariate analysis (Fig. 1A). However, when only curatively (R0) resected cases were

Table 3. Comparison of clinical characteristics and pathological findings between index lesions of synchronous carcinomas and single carcinomas

	No. of patients		*P*
	Synchronous	Single	
No. of patients	42	834	
Age*	65.3 (58.1–71.8)	63.2 (54.8–71.3)	0.251
Gender (male:female)	33:9	492:342	0.018
Size*	50 (40–65)	45 (32–60)	0.141
Differentiation			
Well	23	507	0.494
Moderate	16	268	
Poor	0	17	
Mucinous	3	34	
Others	0	8	
Location			
Right colon	14	189	0.152
Left colon	15	272	
Rectum	13	373	
Wall penetration			
pT1	1	56	0.194
pT2	3	108	
pT3	24	428	
pT4	14	242	
Lymph node metastasis			
pN0	14	321	0.187
pN1	13	244	
pN2	10	125	
pNx	5	144	
Distant metastasis			
Present	14	140	0.011
Absent	28	694	
Stage			
1	2	75	0.173
2	14	232	
3	10	247	
4	14	154	
Undetermined	2	126	
Morphology			
Elevated	3	126	0.314
Ulcerated	39	703	
Others	0	5	
Lymphatic invasion			
Present	33	586	0.327
Absent	9	248	
Venous invasion			
Present	17	218	0.062
Absent	25	616	

*Median (interquartile range).

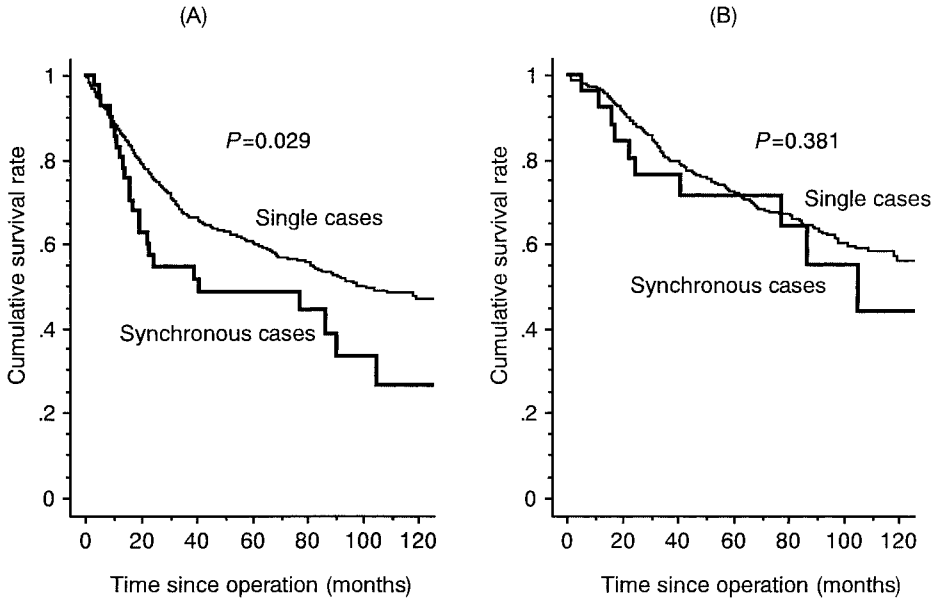

Figure 1. Comparisons of postoperative survival between synchronous and single cases. (A) All cases; (B) curatively resected cases.

analyzed, the difference was not significant (Fig. 1B). In the multivariate proportional hazard model in which pathological stage and curability were included in possible prognostic cofactors, postoperative survival did not differ between synchronous and single cases (Table 4).

Prognostic Factors of Synchronous Cases

In univariate analysis, the postoperative survival of patients having synchronous carcinomas was shorter in those having index lesions with deeper wall penetration (higher pT value), more extensive lymph node metastasis (larger pN value), distant metastasis and consequently more advanced pathological stage. Non-curative (R1 or R2) resection was also associated with relatively short postoperative survival (Table 5). Neither the number of synchronous lesions, distance between the synchronous lesions, nor depth of wall penetration of synchronous lesion significantly affected postoperative survival.

Metachronous Colorectal Carcinoma and Malignancies in Other Organs

Postoperatively, metachronous colorectal carcinoma, which was found at 1 year or more after the operation for the index lesion occurred in 10 cases. However, the incidence of metachronous carcinoma did not significantly differ between synchronous and single cases (Table 6). Malignancies in other organs were pre- or postoperatively associated in 33 cases (3.8%). The incidence of malignancies in other organs also did not differ between synchronous and single cases.

Table 4. Prognostic significance of synchronous carcinoma versus single carcinoma in the multivariate proportional hazard model

	Hazard ratio	95% Confidence interval		*P*
		Lower	Upper	
Synchronous:single	1.157	0.747	1.791	0.513
Pathological stage	1.792	1.461	2.198	<0.001
Curability (R0:R1 or R2)	0.284	0.198	0.408	<0.001

DISCUSSION

The incidence of synchronous colorectal carcinoma in our series was 4.8%, which was similar to that in other reports from Western countries (4,9–11).

We did not analyze lesions treated with endoscopic resection, which was a sufficient treatment for both intramucosal carcinomas and adenomas. Moreover, the pathological criteria for intramucosal carcinoma, especially its discrimination from adenomas with high-grade atypia, was shown to differ between Western and Japanese pathologists (12). Therefore, cases only with intramucosal carcinomas were excluded from the study and cases with one invasive carcinoma and one or more intramucosal carcinomas were regarded as single cases.

In the comparison between synchronous and single cases, the ages of the patients were similar to each other. However, synchronous carcinomas were found more frequently in males than in females; the male:female ratio in synchronous cases was 3.67:1 whereas that in single carcinoma was 1.44:1. Although the male:female ratio of synchronous cases did not differ significantly from that of single cases in other reports, it was marginally larger in Chen and Sheen-Chen's Chinese series (5). The ratio of 2.19:1 in Kaibara et al.'s larger cumulative series (13) was also significantly larger than the male: female ratio in all cases of the Multi-institutional Registry of Large Bowel Cancer in Japan (1.44:1) (14).

In the present study, synchronous carcinomas were found predominantly in the left colon. In most other studies, synchro-

Table 5. Prognostic significance of clinical characteristics and pathological findings in synchronous carcinoma

	Hazard ratio	95% Confidence interval		*P*
		Lower	Upper	
Age	1.007	0.974	1.040	0.699
Gender (male:female)	2.037	0.713	12.945	0.133
Location of the index lesion				
Right colon:rectum	0.511	0.188	1.389	0.188
Left colon:rectum	0.692	0.266	1.808	0.454
Differentiation of the index lesion				
Well:mucinous	0.322	0.087	1.119	0.088
Moderate:mucinous	0.627	0.170	2.320	0.484
Size of the index lesion	1.018	0.996	1.039	0.104
Morphology of the index lesion				
Elevated:ulcerated	0.452	0.061	3.375	0.439
Wall penetration of the index lesion				
pT value	2.513	1.211	5.216	0.013
Lymph node metastasis of the index lesion				
pN value	2.744	1.494	5.040	0.001
Distant metastasis of the index lesion				
M0:M1	0.268	0.115	0.622	0.002
Pathological stage	2.634	1.589	4.366	<0.001
Curability of the index lesion				
R0:R1/2	0.158	0.066	0.379	<0.001
No. of synchronous lesions	1.012	0.412	2.486	0.979
Combination of wall penetration of synchronous carcinomas				
pT2/3/4 + pT2/3/4:pT2/3/4 + pT1	0.634	0.279	1.438	0.275
Distance between the synchronous carcinomas				
Near/adjacent:apart	0.816	0.345	1.930	0.644

Table 6. Metachronous carcinomas and malignancies of other organs

	No. of patients		*P*
	Synchronous	Single	
Metachronous carcinomas			
Present	2	8	0.142
Absent	39	775	
Malignancies in other organs			
Present	2	31	1.000
Absent	39	752	

nous carcinomas were more frequently located in the right colon (4,5,10). However, Finan et al. (9) reported a predominance in the left colon. The left-colon predominance in the present study is probably because concurrent lesions were frequently found in the sigmoid colon in cases of which the index lesion was in the rectum.

Synchronous carcinomas were less advanced pathologically than single carcinomas in a comparison including all the lesions of the synchronous cases in the present study. This results reproduced Passman et al.'s report (4) and was due to the fact that 21 out of 48 concurrent lesions in synchronous cases were pT1 lesions. Because the pathologically most advanced lesion was defined as the index lesion, concurrent lesions of synchronous cases were less advanced than index lesions. Other authors have also reported less advanced pathological stages in concurrent lesions than in index lesions (5,9).

Family history of cancer may be an important factor in the study of synchronous carcinoma. The relationship between family history of cancer and the incidence of synchronous lesion was explored only by Kimura et al., who found no significant correlation between them (3). We were unable to analyze the relationship because the data on family history in the hospital records were insufficient for this purpose in many patients.

The index lesions of synchronous carcinomas were similar to single carcinomas in size, differentiation, location and wall penetration. Therefore, the prediction of the presence of synchronous carcinomas from clinical characteristics or pathological findings is thought to be impossible. Genetic analysis such

as the detection of microsatellite instability (MSI) has been shown to be useful in the prediction of metachronous carcinoma (15). In addition, it has been reported that some synchronous carcinomas are related to MSI and some patients may be those with hereditary non-polyposis colorectal cancer (16–18). MSI of the index lesions, therefore, may be useful in the prediction of synchronous lesions. On the other hand, the examination of histologically normal mucosa may identify a 'field defect,' which is likely to be associated with the development of carcinoma of the whole large bowel (19,20).

Distant metastasis was more frequent in synchronous cases than in single cases. This may be partly due to the relatively frequent venous invasion found in the index lesions of synchronous cases in the present series. In addition, a patient having multiple advanced carcinomas may have a synergistically high risk of distant metastasis. Indeed, eight (33.3%) out of 24 patients having two or more advanced carcinomas (pT2, pT3 or pT4 lesions) had distant metastasis at the time of operation.

With regard to postoperative survival, Kimura et al. reported worse prognosis in synchronous cases than in single cases, although the difference was not significant (3). Other recent studies did not find a significant difference in survival between synchronous cases and single cases (4,5). In the present study, postoperative survival was significantly shorter in synchronous cases than in single cases. This difference is thought to be due mainly to the relatively frequent distant metastasis in synchronous cases. Therefore, when the pathological stage of the index lesion and the curability of resection were adjusted in the multivariate analysis, postoperative survival in synchronous cases was not worse than that in single cases and was mainly dependent on the pathological stage and curability of the index lesions.

In cases with synchronous carcinomas, extensive bowel resection such as total or subtotal colectomy is sometimes necessary (10,11,21). If synchronous lesions are overlooked at the time of surgery for the index lesion, the patient may soon have to undergo repeated surgery for early metachronous carcinoma. Such lesions are inevitably advanced in pathological stages and poor in prognosis. Preoperative total colonoscopy if possible (22,23), cautious intraoperative palpation of the whole colon and careful inspection of the resected specimen should be performed in all patients with colorectal carcinomas in order to detect synchronous carcinomas,

In conclusion, the current study revealed that synchronous carcinoma occurred in 4.8% of patients with colorectal carcinoma. Although synchronous cases were more frequently associated with distant metastasis than single cases, the prognosis of synchronous cases was similar to that of single cases if pathological stages were identical and the resections were curative.

References

1. Welch JP. Multiple colorectal tumors. An appraisal of natural history and therapeutic options. *Am J Surg* 1981;142:274–80.
2. Cunliffe WJ, Hasleton PS, Tweedle DE, Schofield PF. Incidence of synchronous and metachronous colorectal carcinoma. *Br J Surg* 1984;71: 941–3.
3. Kimura T, Iwagaki H, Fuchimoto S, Hizuta A, Orita K. Synchronous colorectal carcinomas. *Hepatogastroenterology* 1994;41:409–12.
4. Passman MA, Pommier RF, Vetto JT. Synchronous colon primaries have the same prognosis as solitary colon cancers. *Dis Colon Rectum* 1996;39: 329–34.
5. Chen HS, Sheen-Chen SM. Synchronous and 'early' metachronous colorectal adenocarcinoma: analysis of prognosis and current trends. *Dis Colon Rectum* 2000;43:1093–9.
6. Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and statistical study. *Am J Cancer* 1932;16:1358–414.
7. Moertel CG, Bargen JA, Dockerty MB. Multiple carcinomas of the large intestine: a review of the literature and a study of 261 cases. *Gastroenterology* 1958;34:85–98.
8. American Joint Committee on Cancer. AJCC Cancer Staging Manual. Philadelphia: Lippincott-Raven 1997.
9. Finan PJ, Ritchie JK, Hawley PR. Synchronous and 'early' metachronous carcinomas of the colon and rectum. *Br J Surg* 1987;74:945–7.
10. Adloff M, Arnaud JP, Bergamaschi R, Schloegel M. Synchronous carcinoma of the colon and rectum: prognostic and therapeutic implications. *Am J Surg* 1989;157:299–302.
11. Slater G, Aufses AH Jr, Szporn A. Synchronous carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1990;171:283–7.
12. Schlemper RJ, Itabashi M, Kato Y, Lewin KJ, Riddell RH, Shimoda T, et al. Differences in the diagnostic criteria used by Japanese and Western pathologists to diagnose colorectal carcinoma. *Cancer* 1998;82:60–9.
13. Kaibara N, Koga S, Jinnai D. Synchronous and metachronous malignancies of the colon and rectum in Japan with special reference to a coexisting early cancer. *Cancer* 1984;54:1870–4.
14. Multi-institutional Registry of Large Bowel Cancer in Japan. Vol. 19. Cases Treated in 1992. Tokyo: Japanese Society for Cancer of the Colon and Rectum 2000.
15. Masubuchi S, Konishi F, Togashi K, Okamoto T, Senba S, Shitoh K, et al. The significance of microsatellite instability in predicting the development of metachronous multiple colorectal carcinomas in patients with nonfamilial colorectal carcinoma. *Cancer* 1999;85:1917–24.
16. Pedroni M, Tamassia MG, Percesepe A, Roncucci L, Benatti P, Lanza G Jr, et al. Microsatellite instability in multiple colorectal tumors. *Int J Cancer* 1999;81:1–5.
17. Abe Y, Masuda H. Genetic alterations of sporadic colorectal cancer with microsatellite instability, especially characteristics of primary multiple colorectal cancers. *J Surg Oncol* 2000;74:249–56.
18. Ueda E, Watanabe T, Umetani N, Ishigami H, Sasaki S, Nagawa H. Microsatellite instability of cancers and concomitant adenomas in synchronous multiple colorectal cancer patients. *J Exp Clin Cancer Res* 2002; 21:149–54.
19. Terpstra OT, van Blankenstein M, Dees J, Eilers GA. Abnormal pattern of cell proliferation in the entire colonic mucosa of patients with colon adenoma or cancer. *Gastroenterology* 1987;92:704–8.
20. Ponz de Leon M, Roncucci L, Di Donato P, Tassi L, Smerieri O, Amorico MG, et al. Pattern of epithelial cell proliferation in colorectal mucosa of normal subjects and of patients with adenomatous polyps or cancer of the large bowel. *Cancer Res* 1988;48:4121–6.
21. Arenas RB, Fichera A, Mhoon D, Michelassi F. Incidence and therapeutic implications of synchronous colonic pathology in colorectal adenocarcinoma. *Surgery* 1997;122:706–9; Discussion 709–10.
22. Pagana TJ, Ledesma EJ, Mittelman A, Nava HR. The use of colonoscopy in the study of synchronous colorectal neoplasms. *Cancer* 1984;53:356–9.
23. Tate JJ, Rawlinson J, Royle GT, Brunton FJ, Taylor I. Pre-operative or postoperative colonic examination for synchronous lesions in colorectal cancer. *Br J Surg* 1988;75:1016–8.