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ORIGINAL ARTICLE

Multiplicity of Advanced T Category–Tumors Is a Risk Factor for Survival in Patients with Colorectal Carcinoma

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Background: Previous studies on synchronous colorectal carcinoma (SCRC) have reported inconsistent results about its clinicopathologic and molecular features and prognostic significance. **Methods:** Forty-six patients with multiple advanced tumors (T2 or higher category) who did not receive neoadjuvant chemotherapy and/or radiotherapy and who are not associated with familial adenomatous polyposis were selected and 99 tumors from them were subjected to clinicopathologic and molecular analysis. Ninety-two cases of solitary colorectal carcinoma (CRC) were selected as a control considering the distributions of types of surgeries performed on patients with SCRC and T categories of individual tumors from SCRC. **Results:** SCRC with multiple advanced tumors was significantly associated with more frequent nodal metastasis (p = .003) and distant metastasis (p = .001) than solitary CRC. *KRAS* mutation, microsatellite instability, and CpG island methylator phenotype statuses were not different between SCRC and solitary CRC groups. In univariate survival analysis, overall and recurrence-free survival were significantly lower in patients with SCRC than in patients with solitary CRC, even after adjusting for the extensiveness of surgical procedure, adjuvant chemotherapy, or staging. Multivariate Cox regression analysis revealed that tumor multiplicity was an independent prognostic factor for overall survival (hazard ratio, 4.618; 95% confidence interval, 2.126 to 10.030; p < .001), but not for recurrence-free survival (p = .151). **Conclusions:** Findings suggested that multiplicity of advanced T category–tumors might be associated with an increased risk of nodal metastasis and a risk factor for poor survival, which raises a concern about the guideline of American Joint Committee on Cancer's tumor-node-metastasis staging that T staging of an index tumor determines T staging of SCRC.

Key Words: Synchronous colorectal carcinoma; Multiple colorectal carcinoma; Clinical outcome; T category

Colorectal carcinoma (CRC) is the third most common cancer in men and the second most common in women. CRC has been reported to occur more commonly in the western countries, but over the past few decades, the incidence of CRC has increased in many Asian countries including South Korea, with about 610,000 Asian patients newly diagnosed in 2012.[1] Synchronous CRC (SCRC) refers to more than one CRC detected in a single patient at the time of diagnosis. Unlike what is expected, little is known about the clinicopathologic features of SCRC. With a handful of previous studies addressing the issue, the only consensus seems to be the male predominance; most of the previous studies reported that SCRC was observed more frequently in men.[2-6] The reported incidence of SCRCs varies from 1.1% to 8.1%,[3,5,7-15] with the narrower range of 3.1% to 3.9% in three large-scale studies performed on a population larger than 10,000 patients.[3,12,13] While some studies concluded that the average age at diagnosis was higher in patients with SCRC than in patients with solitary CRC,[10,13,16] others failed to demonstrate a significant difference between them.[5,12,15,17] Some studies reported that SCRC preferentially affects the distal colon,[5,18-20] but others, including large-scale studies, concluded that the proximal colon was more frequently involved by SCRC.[21,22]

Research has mainly focused on single factors such as microsatellite instability (MSI) for the underlying molecular mechanisms of SCRC. Some studies have reported that MSI-high (MSI-H) phenotype was more common in SCRC than in solitary CRC and the incidence of MSI-H phenotype was upto 30% in SCRC.[23-25] In particular, Nosho *et al*.[26] found that not only MSI-H phenotype but also *BRAF* mutation and CpG island methylator phenotype (CIMP)-high (CIMP-H) phenotype were more common in SCRC than in solitary CRC, suggesting that SCRC may arise through the serrated neoplasia pathway. A similar finding has been reported by Gonzalo *et al*.[27] who found that CIMP-H was more frequent in SCRC than in solitary CRC and

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suggested a close association between tumor multiplicity and CIMP-H phenotype. However, one study reported that MSI occurs only in 10% of SCRCs.[28] Besides MSI, long interspersed nuclear element-1 (LINE-1) hypomethylation in colonic epithelial cells has been suggested to be a possible risk factor for the occurrence of metachronous or SCRC based on finding that LINE-1 methylation of non-neoplastic colonic epithelial cells was lower in SCRC than in solitary CRC.[29] Some studies found that *KRAS* and *TP53* may show discordant mutation statuses between individual tumors of SCRCs,[30,31] but correlations between SCRC and various clinicopathological or molecular parameters still remain unclear.

It seems plausible that a patient with multiple tumors at the time of diagnosis would show poorer prognosis than one with a solitary tumor. Strikingly, this has not been proved with the sufficient level of confidence in CRC, which is the reason that the current TNM staging of CRC does not reflect tumor multiplicity unlike other cancers such as intrahepatic cholangiocarcinoma.[32] In fact, the prognostic effect of tumor multiplicity at the time of diagnosis has been inconsistent among studies; with only a few studies reporting significantly worse prognosis,[26,33] many failed to demonstrate significant differences in survival between patients with solitary CRC and SCRC and some researchers even concluded that SCRC was associated with favorable prognosis.[10,22] Therefore, the current TNM staging guideline for SCRC advises that the lesion with the most advanced pathologic staging is designated to be an index lesion and it is assumed that the survival of the patients with SCRC follows the stage of the index lesions.[5,22] In this scheme, patients with SCRC with the index lesion of pT3 category would show similar survival to those with solitary pT3 CRC.

The purpose of the current study is to address all the inconsistency and to draw clearer conclusion on the prognostic effect of the tumor multiplicity at the time of diagnosis. To do so, we identified a group of patients with SCRCs with advanced T categories, examined their clinicopathologic and molecular features and compared their survival to those with the comparable group of patients with solitary CRC.

MATERIALS AND METHODS

Tissue collection

Two thousand eight hundred thirty-four CRC patients who underwent surgery at Seoul National University Hospital, Seoul, Korea, from January 2007 to December 2010 were reviewed. Among them, 2,701 were solitary CRC patients and 133 were diagnosed as SCRC. From the 133 patients, we excluded patients with familial adenomatous polyposis (FAP) (n = 3) and those who received neoadjuvant chemo- and/or radiotherapy (n = 8). In order to focus on patients with advanced stages, we further excluded patients with intramucosal carcinoma (n = 37) and T1-category lesions (n = 39). As a result, 46 cases with multiple advanced tumors (T2 or higher category) were selected for this study (Fig. 1). Of the 46 patients, 16 underwent extensive surgery including total colectomy and subtotal colectomy, and 30 had a relatively simple procedure (8 cases of anterior resection, 14 cases of ultra-low or low anterior resection, 4 cases of right or left hemicolectomy, and 4 cases of extended right hemicolectomy). Considering the distributions of pT categories of individual tumors and types of surgeries performed on patients with SCRC, we selected 92 cases of solitary CRC with similar distributions of pT categories (Table 1) and types of surgeries (35 cases of anterior resection, 31 cases of low anterior resection, 12 cases of right or left hemicolectomy, and 14 cases of extended right hemicolectomy). However, we could not retrieve patients with solitary CRC who received extensive surgery. This study was approved by the Institutional Review Board (IRB No. 1101-007-345). IRB exempted the informed consent due to the retrospective nature of the study.

Clinicopathologic data

Clinical and histopathologic data from the 46 patients with SCRC (99 tumors) and 92 patients with solitary CRC (92 tumors) were collected through the electronic medical record and a microscopic examination. The parameters of the clinicopathologic data included patient age, sex, overall survival (OS), recurrence-free survival (RFS), tumor location, tumor multiplicity, American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) category, tumor differentiation, lymphovascular invasion, and perineural invasion.

KRAS mutation and MSI analysis

Through histological examination, representative tumor portions were marked and then subjected to manual microdissection. The dissected tissues were collected into microtubes containing lysis buffer and proteinase K and were incubated at 55°C for upto 2 days. DNA from paraffin-embedded tissues was extracted, and polymerase chain reaction was performed. Mutations in *KRAS* codons 12 and 13 were analyzed in each case using direct sequencing. The MSI status of each tumor was determined through the evaluation of five microsatellite markers (BAT25, BAT26, D2S123, D5S346, and D17S250) as standardized by the National Cancer Institute. MSI-H status was defined as when tumor DNA

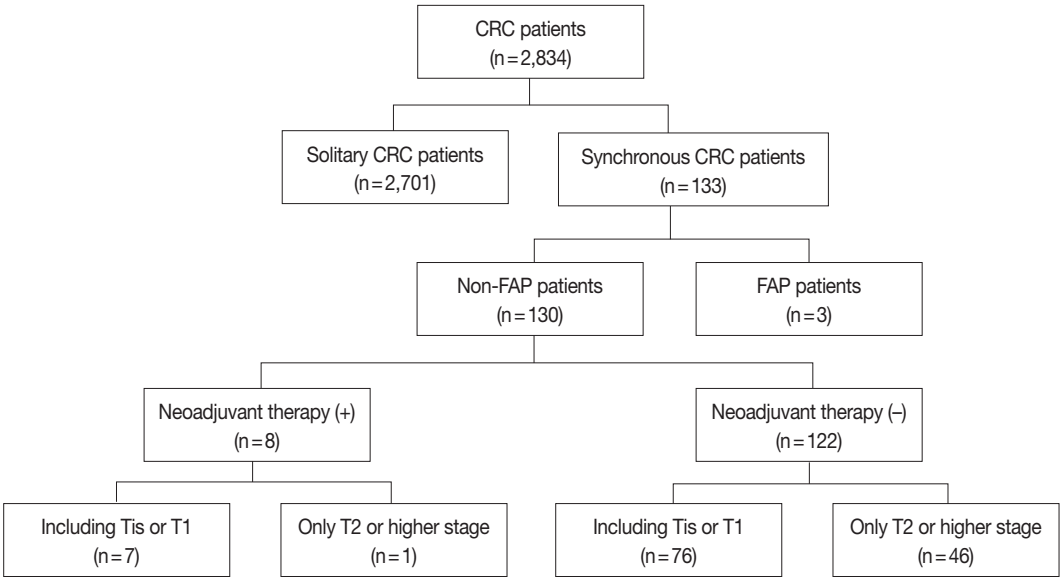

Fig. 1. Schematic diagram for selection of patients with synchronous colorectal cancer (CRC). FAP, familial adenomatous polyposis.

had altered alleles compared to normal DNA in two or more markers. MSI-low status was defined as when tumor DNA had altered allele compared to normal DNA in one marker. Microsatellite-stable was defined as when no altered allele was present in tumor DNA. We performed immunohistochemistry (IHC) for DNA mismatch repair proteins (MLH1 and MSH2) to assess MSI status for tumors that were not evaluated for MSI status using polymerase chain reaction-coupled capillary electrophoresis (50 individual tumors from SCRCs and 3 solitary CRCs). IHC was performed using antibodies against MLH1 (Ventana Medical Systems, Tucson, AZ, USA), MSH2 (Invitrogen, Camarillo, CA, USA) and automated immunostainers (Ventana BenchMark XT for MLH1; Bond-III, Leica Biosystems, Novocastra, Newcastle-upon-Tyne, UK for MSH2).

Analysis of CIMP

The CIMP status of individual tumors was analyzed using a real-time methylation-specific quantitative polymerase chain reaction method (MethyLight) and eight CIMP-specific markers (*CACNA1G*, *CDKN2A*, *CRABP1*, *IGF2*, *MLH1*, *NEUR0G1*, *RUNX3*, and *S0CS1*). We classified CRCs into CIMP-0 (no methylated marker), CIMP-low (1–4 methylated markers), and CIMP-H (5 or more methylated markers).

Statistical analysis

In this study, statistical analysis was performed using SPSS ver. 23 (IBM Corp., Armonk, NY, USA). Comparison between categorical variables was conducted with the chi-square test or Fisher exact test. Survival analysis using OS and RFS data was performed using the Kaplan-Meier method with the log-rank test. Hazard ratios (HRs) were calculated using the Cox proportional hazard model. All variables that were associated with OS with a $p < .10$ were entered into the model. These variables were reduced by backward elimination. All p-values were two-sided and p-values of $< .05$ were considered to be statistically significant.

RESULTS

Clinicopathologic features

The detailed clinicopathologic features are summarized in Table 1 and Fig. 2. SCRC with multiple advanced tumors was associated with more frequent nodal metastasis ($p = .003$) and advanced TNM category ($p = .003$). SCRC exhibited a tendency toward male predominance with marginal significance ($p = .050$). Metachronous metastasis was significantly more frequent in SCRCs with multiple advanced tumors than in solitary CRCs ($p = .001$). However, there were no significant differences in terms of lymphatic and vascular invasion between two groups. In addition, *KRAS* mutation and MSI status did not show any significant difference between the two groups. In CIMP analysis for SCRC, CIMP-H phenotype was observed in four of 46 patients (8.7%), which was quite lower compared with results of previous studies (35% in Nosho *et al.*'s study[26] and 66.6% in Gonzalo *et al.*'s study[27]). However, the frequency of CIMP-H in terms of individual tumors was 5.1% (5 of 99 tumors) which was not different from the frequency of CIMP-H in solitary CRCs (6.5%) of the

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Table 1. Clinicopathologic and molecular characteristics of CRCs according to tumor multiplicity

Variable	Solitary CRCs (92 patients, 92 tumors)	Synchronous CRCs (46 patients, 99 tumors)	p-value
Age (yr)	63.5 (33–82)	66.0 (43–88)	.087
Sex			.050
Male	59 (64.1)	37 (80.4)	
Female	33 (35.9)	9 (19.6)	
Location			.247
Proximal	18 (19.6)	29 (29.3)	
Distal	48 (52.2)	42 (42.4)	
Rectum	26 (28.3)	28 (28.3)	
Gross type			.114
Polypoid	11 (12.0)	22 (22.2)	
Ulcerofungating	61 (66.3)	53 (53.5)	
Ulceroinfiltrative	20 (21.7)	24 (24.2)	
T category			.548
T2	12 (13.0)	18 (18.2)	
T3	73 (79.3)	72 (72.7)	
T4	7 (7.6)	9 (9.1)	
N category			.003
N0	49 (53.3)	12 (26.1)	
N1, N2	43 (46.7)	34 (73.9)	
M category			.001
M0	73 (79.3)	23 (50.0)	
Synchronous M1	7 (7.6)	12 (26.1)	
Metachronous M1	12 (13.0)	11 (23.9)	
Stage			.003
I	9 (9.8)	1 (2.2)	
II	40 (43.5)	11 (23.9)	
III	36 (39.1)	22 (47.8)	
IV	7 (7.6)	12 (26.1)	
Surgery			< .001
Simple	92	30 (65.2)	
Extensive	0	16 (34.8)	
Chemotherapy			1.000
Treated	80 (87.0)	40 (87.0)	
Non-treated	12 (13.0)	6 (13.0)	
Differentiation			.722[a]
Well	9 (9.8)	9 (9.1)	
Moderately	78 (84.8)	87 (87.9)	
Poorly	5 (5.4)	3 (3.0)	
Lymphatic invasion			.068
Absent	73 (79.3)	67 (67.7)	
Present	19 (20.7)	32 (32.3)	
Venous invasion			.086
Absent	86 (93.5)	85 (85.9)	
Present	6 (6.5)	14 (14.1)	
Perineural invasion			.986
Absent	80 (87.0)	86 (86.9)	
Present	12 (13.0)	13 (13.1)	
MSI			0.740[a]
MSS/MSI-low	87 (94.6)	95 (96.0)	
MSI-high	5 (5.4)	4 (4.0)	
KRAS mutation			.908
Wild type	55 (59.8)	60 (60.6)	
Mutant	37 (40.2)	39 (39.4)	
CIMP			.761
CIMP-0, low	86 (93.5)	94 (94.9)	
CIMP-high	6 (6.5)	5 (5.1)	

CRC, colorectal carcinoma; MSI, microsatellite instability; MSS, microsatellite-stable; CIMP, CpG island methylator phenotype.
[a]Fisher exact test.

present study and those of previous Korean CRC studies.[34,35] Nodal and distant metastasis showed significant differences between SCRC and solitary CRC when we restricted comparative analyses to CRC cases with non-extensive surgery or cases with R0 surgery (Table 2).

Prognostic implication of tumor multiplicity in CRCs

In order to examine the prognostic effect of tumor multiplicity per se, we sought to focus on subgroups where compounding variables were adjusted. Firstly, we performed Kaplan-Meier survival analysis on patients who had no metastasis at the time of diagnosis and hence underwent curative surgery (85 patients with solitary CRC and 34 patients with SCRC). As a result, SCRC patients with multiple advanced tumors showed worse OS and RFS than the respective ones of patients with solitary CRC (Fig. 3A, B). Since it cannot be excluded a possibility that the extensiveness of surgery itself might affect the survival of patients with SCRC, survival analysis was conducted in 85 solitary CRC and 22 SCRC patients with exclusion of patients who underwent the extensive surgical procedures such as total colectomy and subtotal colectomy, which revealed significant associations between SCRC and poor OS or RFS (Fig. 3C, D). When we further excluded patients who did not receive adjuvant chemotherapy to adjust for the effect of adjuvant chemotherapy, univariate survival analysis in 36 patients with solitary CRC and 13 patients with SCRC revealed that the prognosis of SCRC with multiple advanced tumors tended to be worse than that of solitary CRC patients (Fig. 3E, F). To validate these results, we selected 24 SCRC cases with an index tumor of T3 category and recruited another independent set of patients with solitary CRC of T3 category (n = 120) on the criteria of R0 surgery and adjuvant chemotherapy. Because SCRC cases were composed of nine N0, seven N1, and eight N2 cases, 45 solitary CRC cases of N0 category, 35 of N1 category, and 40 of N2 category were recruited.

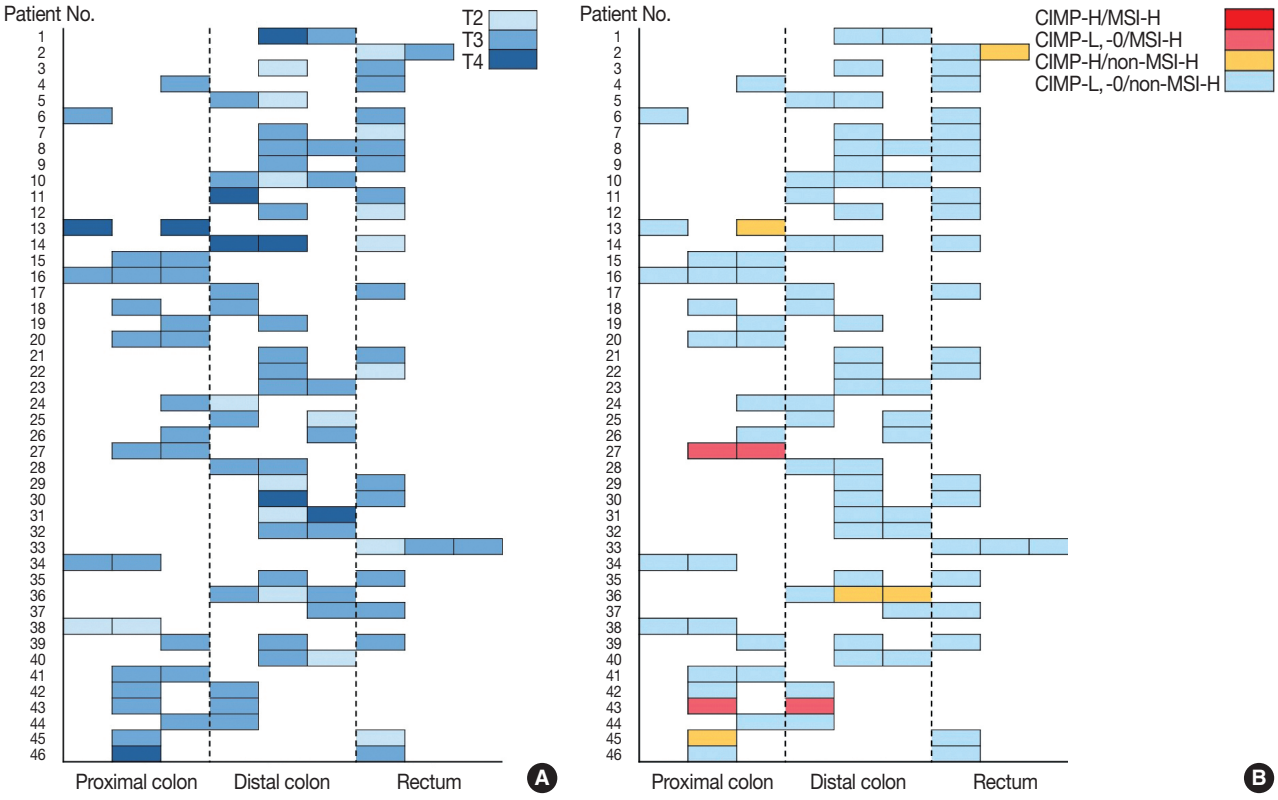

Fig. 2. Distribution of tumor location with specification of T category (A) and molecular features (B) for individual tumors of synchronous colorectal cancer. CIMP, CpG island methylator phenotype; CIMP-H, CIMP-high; CIMP-L, CIMP-low; CIMP-0, no methylated marker; MSI, microsatellite instability; MSI-H, MSI-high.

Kaplan-Meier survival analysis showed that patients with SCRC still had worse OS compared with patients with solitary CRC group that matched T and N category, but not for RFS (Fig. 3G, H). In multivariate Cox regression analysis, tumor multiplicity was found to be an independent prognostic factor for OS (HR, 4.618; 95% confidence interval, 2.126 to 10.030; $p < .001$), but not for RFS ($p = .151$) (Tables 3, 4).

DISCUSSION

In this study, we investigated the clinicopathologic and molecular characteristics of SCRC as well as the prognostic implication of the tumor multiplicity at the time of diagnosis. The reported incidence of SCRC in the literature varies from 1.1% to 8.1%.[3,5,7-15] This variance might be attributable to the difference in the definition of SCRC; whether FAP or intramucosal carcinoma is included or not in the definition of SCRC can make a significant difference.[20] In this study, we excluded SCRC associated with FAP (n = 3). The incidence of SCRC was 4.6% (n = 130) when intramucosal carcinomas were included and 3.2% (n = 91) when excluded, in line with the previous studies. Of these patients (n = 91), we excluded those patients who received neoadjuvant chemo- and/or radiotherapy (n = 6) or T1-category lesion (n = 39). We only selected SCRCs in which all the individual tumors were of pT2 or higher category and resultantly, 46 patients were included in the present study.

The median age at diagnosis of SCRC with multiple advanced tumors was higher than that of solitary CRC, but the difference did not reach a statistical significance in this study. Several studies have reported that the mean age of patients with SCRC is significantly higher than that of patients with solitary CRC.[10,13,16] However, in Oya *et al.*'s study,[5] age difference failed to reach the statistical significance, and Latournerie *et al.*[12] conducted a large-scale study to discover that there was no significant difference. Regarding sex distribution, previous studies reported that SCRC is more common in men,[2-6] but this study confirmed this tendency only with the marginal significance. Previous studies have reported inconsistent results on the sidedness of SCRC. Finan *et al.*[18] reported that SCRC is more common in the distal part of colon, the same with the solitary CRC in general, but Lam *et al.*[22] showed that SCRC more commonly affects the proximal colon than solitary CRC does. In the present study, SCRC showed a ten-

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Table 2. Differences in clinicopathologic characteristics according to subgroup analysis

Variable	Total cases of CRC		CRC cases with R0 resection		CRC cases with non-extensive surgery	
	Solitary CRC (n=92)	SCRC (n=46)	Solitary CRC (n=85)	SCRC (n=34)	Solitary CRC (n=92)	SCRC (n=30)
Age (yr)	63.5 (33–82)	66.0 (43–88)	63.0 (33–82)	66.0 (48–79)	63.5 (33–82)	66.0 (43–88)
p-value	.087		.150		.168	
Sex						
Male	59 (64.1)	37 (80.4)	56 (65.9)	25 (73.5)	59 (64.1)	24 (80.0)
Female	33 (35.9)	9 (19.6)	29 (34.1)	9 (26.5)	33 (35.9)	6 (20.0)
p-value	.050		.419		.106	
T category						
T2	12 (13.0)	18 (18.2)	12 (14.1)	13 (17.8)	12 (13.0)	13 (20.3)
T3	73 (79.3)	72 (72.7)	68 (80.0)	52 (71.2)	73 (79.3)	42 (65.6)
T4	7 (7.6)	9 (9.1)	5 (5.9)	8 (11.0)	7 (7.6)	9 (14.1)
p-value	.548		.374		.154	
N category						
N0	49 (53.3)	12 (26.1)	49 (57.6)	12 (35.3)	49 (53.3)	8 (26.7)
N1, N2	43 (46.7)	34 (73.9)	36 (42.4)	22 (64.7)	43 (46.7)	22 (73.3)
p-value	.003		.028		.011	
M category						
M0	73 (79.3)	23 (50.0)	73 (85.9)	23 (67.6)	73 (79.3)	14 (46.7)
Synchronous M1	7 (7.6)	12 (26.1)	-	-	7 (7.6)	8 (26.7)
Metachronous M1	12 (13.0)	11 (23.9)	12 (14.1)	11 (32.4)	12 (13.0)	8 (26.7)
p-value	.001		.023		.002	
Lymphatic invasion						
Absent	73 (79.3)	67 (67.7)	69 (81.2)	53 (72.6)	73 (79.3)	37 (57.8)
Present	19 (20.7)	32 (32.3)	16 (18.8)	20 (27.4)	19 (20.7)	27 (42.2)
p-value	.068		.200		.004	
Venous invasion						
Absent	86 (93.5)	85 (85.9)	81 (95.3)	65 (89.0)	86 (93.5)	55 (85.9)
Present	6 (6.5)	14 (14.1)	4 (4.7)	8 (11.0)	6 (6.5)	9 (14.1)
p-value	.086		.139		.116	

Values are presented as median (range) or number (%).

dency toward the right colon, but with no statistical significance.

In line with several previous studies which showed that the proportion of advanced stage is higher in SCRC than in solitary CRC,[12,19,20,22] we discovered that SCRC cases tended to be more advanced than solitary cases. Lymphatic and venous invasions tended to be more frequent in individual tumors of SCRC than in solitary CRC. Although our findings indicated that nodal metastasis was significantly more common in SCRC with multiple advanced tumors than in solitary CRC, a concern is that selection of solitary CRC might be biased toward collection of solitary CRC with less frequent nodal metastasis. To exclude such a possibility, we analyzed the frequency of nodal metastasis in 593 cases of solitary T3 CRC. The frequency of N0 was significantly higher in solitary T3 CRC than in SCRC with an index tumor of T3 category (45.5% vs. 26.3%, p = .027). This finding suggests that multiplicity of advanced T category–tumors might be a risk factor for nodal metastasis.

Molecular analysis performed in this study revealed that the prevalence of MSI and *KRAS* mutation in the SCRC were not different from the respective ones of the solitary CRC. Out of the 99 individual tumors from 46 SCRC patients, only four tumors from two patients were MSI-H. The analysis of CIMP status for these tumors showed that these MSI-H tumors were negative for *MLH1* methylation and not CIMP-H, which suggests the possibility that these SCRC patients with multiple MSI-H tumors might be patients with Lynch syndrome. In fact, both of these patients had first-degree relatives with CRC as well as SCRC with MSI-H phenotype, and could be diagnosed as hereditary nonpolyposis colon cancer. However, in previous studies, exploration on MSI status of SCRC showed a higher proportion of MSI-H phenotype in SCRC than in solitary CRC.[23-25] Nosho *et al*.[26] found that SCRC was more likely to be *BRAF*-mutated, CIMP-H and MSI-H, suggesting that MSI-H phenotype in SCRC is likely to be sporadic rather than hereditary. Such a discrepancy between previous studies and the present study might be attributable to the fact that we excluded tumors of Tis or T1 category or the fact

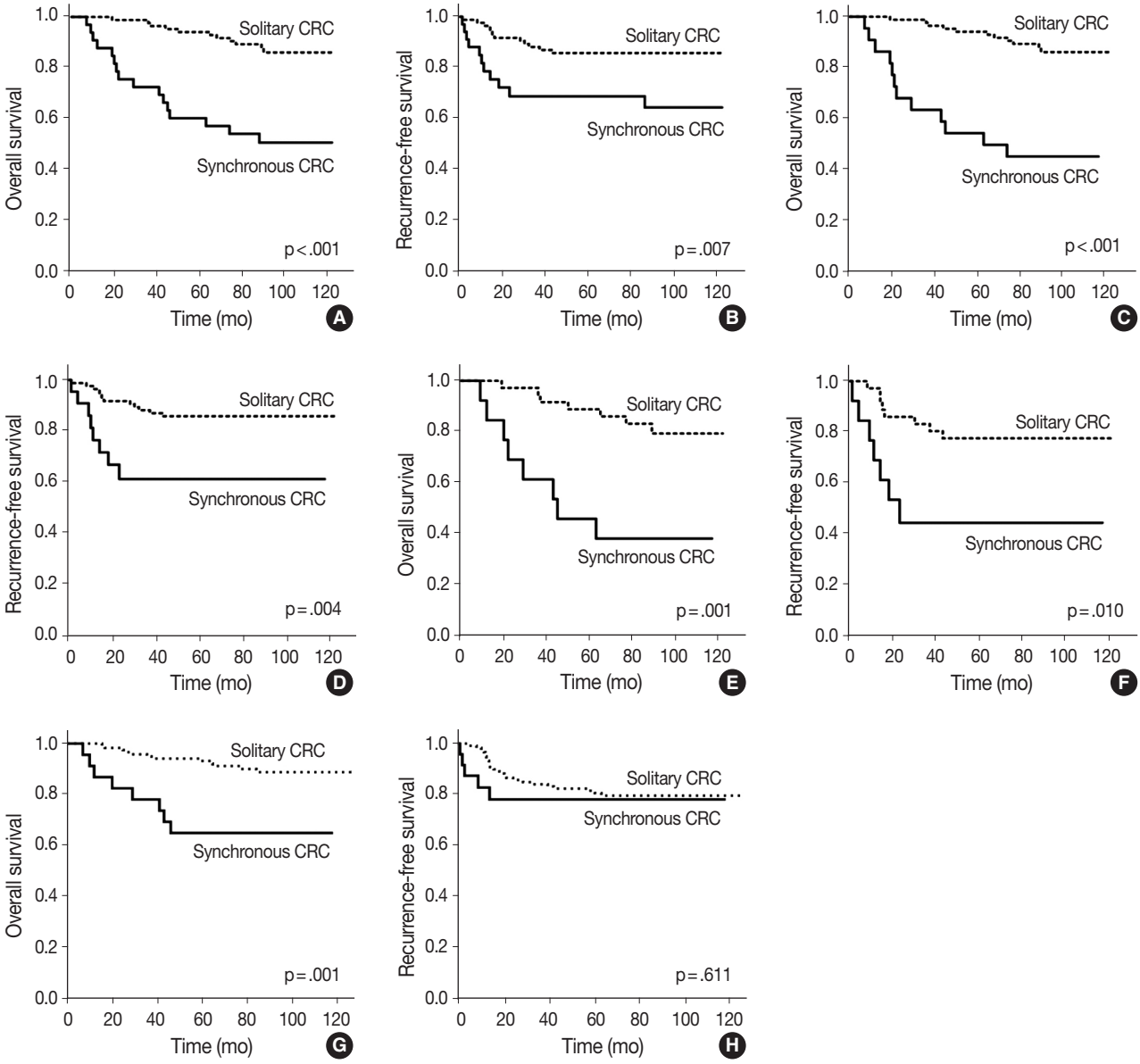

Fig. 3. Kaplan-Meier survival curves for overall survival and recurrence-free survival according to the tumor multiplicity in colorectal cancer (CRC) patients with curative surgery (n=119) (A, B), in CRC patients with curative and non-extensive surgery (85 patients with solitary CRC and 22 patients with synchronous CRC) (C, D), in CRC patients with curative and non-extensive surgery and adjuvant chemotherapy (36 patients with solitary CRC and 13 patients with synchronous CRC) (E, F), and in stage-matched CRC patients with R0 surgery and adjuvant chemotherapy (120 patients with solitary CRC and 24 patients with synchronous CRC) (G, H).

that the frequency of CIMP-H phenotype is lower in CRCs from Korean patients than those from western people.[36]

Most of the previous studies reported that the survival of the patients with SCRC was not significantly different from that of patients with solitary CRC and only depended on the pathologic staging of the index cancer.[22] Even Hu *et al*.[10] suggested that patients with SCRC might have survival benefit. Only a few studies have discovered that patients with SCRC had worse prognosis than that of patients with solitary CRC.[26,33] It should be pointed out that previous studies which reported no difference in survival between SCRC and solitary CRC were conducted on a population of SCRC in which SCRC with Tis or T1 tumor as a non-index tumor comprise approximately 46% and 30% of the study cases, respectively.[16,22] In accordance with the hypothesis that patients with multiple advanced tumors would indeed have more tumor burden, we only selected SCRC cases in which all the individual tumors were of T2 or higher categories. Kaplan-Meier survival analysis showed that SCRC patients with multi-

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Table 3. Univariate and multivariate Cox analysis for overall survival (n=119)

Variable	Univariate		Multivariate	
	HR	p-value	HR	p-value
Age (≥65 yr/<65 yr)	4.088 (1.728–9.673)	.001	4.041 (1.703–9.587)	.002
Sex (male/female)	1.051 (0.472–2.347)	.902	-	-
Multiplicity (synchronous/solitary)	5.075 (2.350–10.960)	<.001	4.618 (2.126–10.030)	<.001
T category (T3, 4/T2)	3.487 (0.473–25.709)	.220	-	-
N category (N1, 2/N0)	3.617 (1.528–8.564)	.003	3.072 (1.291–7.309)	.011
Vascular invasion (present/absent)	2.373 (0.897–6.273)	.082	-	.159
Lymphatic invasion (present/absent)	2.836 (1.326–6.065)	.007	-	.122
Perineural invasion (present/absent)	1.617 (0.612–4.270)	.333	-	-
Tumor location (including right colon/left colon only)	0.907 (0.397–2.072)	.817	-	-
Chemotherapy (treated/not-treated)	1.088 (0.376–3.147)	.876	-	-
Surgery (extensive/simple)	1.837 (0.635–5.314)	.262	-	-
MSI (MSI-H/MSS, MSI-L)	0.045 (0.000–33.308)	.357	-	-
KRAS (mutant/wild type)	2.337 (1.049–5.204)	.038	-	-

HR, hazard ratio; MSI, microsatellite instability; MSI-H, MSI-high; MSS, microsatellite-stable; MSI-L, MSI-low.

Table 4. Univariate and multivariate Cox analysis for recurrence-free survival (n=119)

Variable	Univariate		Multivariate	
	HR	p-value	HR	p-value
Age (≥65 yr/<65 yr)	1.803 (0.791–4.114)	.161	2.163 (0.905–5.171)	.083
Sex (male/female)	1.672 (0.733–3.815)	.222	-	-
Multiplicity (synchronous/solitary)	2.939 (1.294–6.674)	.010	-	.151
T category (T3, 4/T2)	2.993 (0.403–22.224)	.284	-	-
N category (N1, 2/N0)	4.378 (1.623–11.805)	.004	3.943 (1.457–10.670)	.007
Vascular invasion (present/absent)	3.658 (1.440–9.294)	.006	4.114 (1.527–11.081)	.005
Lymphatic invasion (present/absent)	3.096 (1.365–7.025)	.007	-	.225
Perineural invasion (present/absent)	2.417 (0.952–6.136)	.063	-	-
Tumor location (including right colon/left colon only)	1.370 (0.509–3.690)	.534	-	-
Chemotherapy (treated/not-treated)	0.555 (0.130–2.369)	.427	-	-
Surgery (extensive/simple)	1.535 (0.456–5.169)	.489	-	-
MSI (MSI-H/MSS, MSI-L)	0.045 (0.000–63.182)	.401	-	-
KRAS (mutant/wild type)	1.776 (0.768–4.105)	.179	-	-

HR, hazard ratio; MSI, microsatellite instability; MSI-H, MSI-high; MSS, microsatellite-stable; MSI-L, MSI-low.

ple advanced tumors had worse survival than that of patients with solitary CRC. We performed a subgroup analysis in order to adjust for the effect of adjuvant chemotherapy, extensive surgical procedure such as total colectomy or subtotal colectomy, or T and N categories, and discovered that tumor multiplicity was an independent prognostic factor for OS in multivariate analysis. The reason why SCRC patients with multiple advanced tumors pursue worse clinical outcome than patients with solitary CRC is related to the fact that SCRC was associated with more frequent nodal metastasis and metachronous metastasis.

In conclusion, we selected SCRC with all the individual tumors of T2 or higher category and compared various characteristics between SCRC and solitary CRC of similar T category–distribution. We found that SCRC was featured with higher incidence of nodal metastasis and metachronous metastasis and shortened OS time compared with solitary CRC. Based on the finding that multiplicity of advanced T category–tumors was an independent prognostic parameter heralding poor overall survival, the current staging of SCRC with multiple advanced tumors according to the tumor-node-metastasis guideline of AJCC that an index tumor of advanced T category determines the T category of SCRC, is likely to evaluate better than actual prognosis. More studies would be needed to validate this finding and discover the underlying mechanism of it.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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