Prognostic Impact and Clinicopathological Features of Multiple Colorectal Cancers and Extracolorectal Malignancies: A Nationwide Retrospective Study

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Keywords

Multiple primary malignancies · Multiple cancers · Colorectal cancer · Prognosis

Abstract

Introduction: Multiple primary malignancies (MPMs) are likely to develop in patients with colorectal cancer (CRC); however, their prognoses are unclear. This study aims to investigate the prognostic impacts and clinicopathological features of multiple CRCs and extracolorectal malignancies (EMs) with CRC. **Methods:** We retrospectively evaluated a total of 22,628 patients with stage I–III CRC who underwent curative resection at 24 referral institutes in Japan between January 2004 and December 2012. MPMs were classified as synchronous CRCs (SCRCs), metachronous CRCs, synchronous EMs (SEMs), and metachronous EMs. **Results:** The presence of SCRCs (odds ratio 1.54, $p < 0.001$) was independently associated with SEMs in the multivariate analyses. SEMs were the strongest poor prognostic factor for OS (hazard ratio [HR] 2.21, $p < 0.001$) and RFS (HR 1.69, $p < 0.001$) compared with age, sex, and primary T and N factors. The inci-

dence of stomach cancer was the highest in EMs, followed by lung, breast, and prostate cancers. Multiple CRCs were evenly distributed throughout the right-side colon to the rectum. **Discussion/Conclusion:** SEMs were a strong poor prognostic factor for patients with stage I–III CRC. Patients with CRC, particularly those with SCRCs, should be surveyed for SEMs, especially for stomach and lung cancers.

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Introduction

Colorectal cancer (CRC) is the third most common malignant disease worldwide and the second most common cause of cancer mortality [1]. Patients with CRC are likely to develop multiple primary malignancies (MPMs). In fact, patients with CRC have a 1.4–1.7-fold greater risk of developing a second CRC compared with the healthy population [2, 3]. CRC is also likely accompanied by extracolorectal malignancies (EMs). Several hereditary diseases, such as Lynch syndrome or familial adenomatous polyposis, increase the risk of many types of cancers, in-

cluding CRC. However, patients with CRC without these hereditary diseases are also at a high risk for accompaniment by various types of primary malignancies in extra-colorectal organs [4]. The popularization of health screening and the progression of technology for diagnosis and treatment have enabled early detection and appropriate treatment of CRC. Therefore, the number of CRC survivors has increased in recent years. According to the multi-institutional registry of the Japanese Society for Cancer of the Colon and Rectum (JSCCR), the 5-year survival of all Japanese patients with CRC was 72%, which increased to 82% when focusing on patients with stage 0–III CRC who underwent curative resection [5]. Therefore, it is important to consider the effects of MPMs when deciding on a treatment strategy or postoperative surveillance for patients with CRC.

Although several studies have reported about MPMs in patients with CRC, the results have greatly differed owing to differences in the study designs and cohorts [6, 7]. Moreover, the prognostic impact of EMs and multiple CRCs has not been completely investigated. There are few reports regarding the prognoses of patients with CRC with EMs. We previously reported that EMs, particularly synchronous EMs (SEMs), are strongly associated with poor survival [8]; however, whether this result can be generalized remains uncertain because it was a single-center study. Therefore, validation in a Japanese nationwide cohort is necessary. Several studies have reported that multiple CRCs are associated with poor prognoses [9, 10], whereas other studies have reported no difference in prognoses [11, 12]. Therefore, associating multiple CRCs with prognoses remains controversial [13]. According to our previous report [12], patients with synchronous CRCs (SCRCs) had poorer relapse-free survival (RFS) than those with solitary CRCs; in contrast, the presence of SCRCs did not significantly affect overall survival (OS). However, this was a single-center study, the study population was relatively small, and it contained many patients with stage IV SCRCs. Thus, it could not examine the prognostic impact of multiple CRCs.

In turn, OS or RFS has been used for prognostic analyses in many reported clinical studies. The events in these indexes not only include CRC-related deaths but also any other causes of death, including MPM-related deaths [14, 15]. Therefore, it is important to consider the effects of MPMs when evaluating OS or RFS. Unfortunately, the definitions of these endpoints are frequently missing in many studies [14]. This study aimed to investigate the prognostic impacts and clinicopathological features of multiple CRCs and EMs with CRC.

Materials and Methods

Study Population

We retrospectively collected the data from 24 referral hospitals in Japan (see the Acknowledgment section). The study population consisted of 22,628 consecutive patients with pathological stage I–III CRC who had undergone curative resection between January 2004 and December 2012 in each institute. The following patients were excluded from this study: 249 patients who were treated for reasons other than carcinoma, 30 patients with hereditary colorectal disease, such as Lynch syndrome or familial adenomatous polyposis, 91 patients with inflammatory bowel diseases, and 371 patients with inadequate clinicopathological data. Thus, 21,887 patients were included in the analysis (Fig. 1). The onset of multiple CRCs and EMs was defined according to the Japanese Classification of Colorectal, Appendiceal, and Anal carcinoma, 7th edition [16]; multiple CRCs and EMs diagnosed within a year before and after surgery were defined as SCRCs and SEMs. Those diagnosed at >1 year before and after surgery were defined as metachronous CRCs (MCRCs) and metachronous EMs (MEMs). Patients were surveyed according to the JSCCR guidelines [17] for treatment of CRC at least 5 years after surgery by physical examination, tumor marker (carcinoembryonic antigen and carbohydrate antigen 19-9) measurements, CT examination, and colonoscopy. Typically, tumor markers were examined every 3 months, CT was performed every 6 months, and colonoscopy was performed every year. The median follow-up period was 70 months. OS was defined as death for any reason (event cases) or loss to follow-up (censored cases). RFS was defined as recurrence of CRC or death for any reason (event cases) or loss to follow-up (censored cases) as recommended by Punt et al. [14].

The Ethics Committee of the University of Tokyo (No. 2018028NI-[1]) and local ethics committees in each participant institute approved the study protocol. The study was conducted in accordance with the Declaration of Helsinki. Informed consent was replaced by the obligation of information to the participants and the right of participants to opt out due to the study's retrospective nature.

Statistical Analyses

All analyses were performed using JMP Pro 14.2 (SAS Institute Inc., Cary, NC, USA, www.jmp.com). The associations between the clinicopathological background and the presence of SCRCs or SEMs were evaluated using Pearson's χ^2 test as the univariate analysis and logistic regression models as the multivariate analysis. Cumulative survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HRs) for OS and RFS were calculated using univariate and multivariate Cox proportional hazards regression models. All reported *p* values are 2-tailed, and *p* values of <0.05 were considered significant.

Results

Characteristics

The patient flow and incidences of multiple CRCs and EMs are shown in Figure 1. Of the 21,887 patients, 1,884 (8.6%) had multiple CRCs, including 1,221 (5.6%) with SCRCs, and 3,444 (15.7%) had EMs, including 859 (3.9%)

Fig. 1. Patient flow and incidence of multiple CRCs and EMs. CRCs, colorectal cancers; EMs, extracolorectal malignancies; SCRCs, synchronous CRCs; MCRCs, metachronous CRCs; SEMs, synchronous EMs; MEMs, metachronous EMs.

with SEMs. We first analyzed SCRCs and SEMs. As shown in Table 1, patients with SCRCs and SEMs were older ($p < 0.001$), more likely to be male ($p < 0.001$), and more commonly had the colon as the primary CRC site rather than the rectum (SCRCs: $p < 0.001$; SEMs: $p = 0.036$). We also evaluated the association between the presence of SCRCs and SEMs. SEMs were more frequent in patients with SCRCs than in those without SCRCs ($p < 0.001$); similarly, SCRCs were more frequent in patients with SEMs than in those without SEMs ($p < 0.001$).

Risk Factors of SEMs

In the logistic regression analysis, independent factors associated with SEMs included male sex (odds ratio [OR] 1.61, $p < 0.001$), older age (over 70) (OR 1.58, $p < 0.001$), and presence of SCRCs (OR 1.54, $p < 0.001$) (Table 2).

Survival Analyses

The results of the prognostic analyses are shown in Figure 2 and Tables 3 and 4. As shown by the Kaplan-Meier curves (Fig. 2), patients with SEMs had poorer

prognoses in OS ($p < 0.001$) and RFS ($p < 0.001$). Patients with SCRCs also had a poorer prognosis in OS ($p = 0.049$). Figure 3 shows Kaplan-Meier curves of CRC-related and EM-related death. The 5-year overall, CRC-related, and EM-related death rates were 13.5, 7.1, and 2.3%, respectively. In the multivariate analyses (Tables 3, 4), SEMs were an independent risk factor of poor prognosis in OS (HR 2.21, $p < 0.001$) and RFS (HR 1.69, $p < 0.001$). Notably, the impact of SEMs on OS was the strongest factor compared to the others. Conversely, there were no significant differences in OS and RFS with or without SCRCs in the multivariate analyses. A multivariate analysis of OS including the site of SEM is shown in online suppl. Table (see www.karger.com/doi/10.1159/000517271 for all online suppl. material). Among SEMs, stomach and lung cancers were independent risk factors for OS, while breast and prostate cancers were not.

Distribution of EMs

The details of EMs, which combined SEMs and MEMs, are shown in Table 5. Some of the 3,444 patients with EMs

Table 1. Patients' characteristics according to the presence of EMs and multiple CRCs

	SCRCs		<i>p</i> value	SEMs		<i>p</i> value
	(−), <i>n</i> = 20,661	(+), <i>n</i> = 1,284		(−), <i>n</i> = 20,705	(+), <i>n</i> = 956	
Age, median (range), years	67 (14–99)	69 (22–99)	<0.001	67 (14–99)	70 (22–95)	<0.001
Sex, <i>n</i> (%)						
Male	11,908 (58.2)	860 (67.3)	<0.001	11,920 (58.1)	652 (68.7)	<0.001
Female	8,570 (41.8)	418 (32.7)		8,603 (41.9)	297 (31.3)	
Location of primary CRC, <i>n</i> (%)						
Right-side colon	5,919 (28.9)	426 (33.3)	<0.001	5,952 (29.0)	298 (31.4)	0.036
Left-side colon	6,044 (29.5)	404 (31.6)		6,058 (29.5)	298 (31.4)	
Rectum	8,503 (41.5)	448 (35.1)		8,501 (41.4)	353 (37.2)	
Unknown	12 (0.1)	0 (0.0)		12 (0.1)	0 (0.0)	
Histological type, <i>n</i> (%)						
Well/mod	19,050 (93.0)	1,182 (92.5)	0.460	19,084 (93.0)	874 (92.1)	0.299
Others	1,428 (7.0)	96 (7.5)		1,439 (7.0)	75 (7.9)	
T factor, <i>n</i> (%)						
T1–T2	7,377 (36.0)	437 (34.2)	0.176	7,381 (36.0)	341 (35.9)	0.945
T3/T4	13,068 (63.8)	840 (65.7)		13,108 (63.9)	608 (64.1)	
Unknown	36 (0.2)	1 (0.1)		37 (0.2)	0 (0.0)	
N factor, <i>n</i> (%)						
N0	13,250 (64.7)	782 (61.2)	0.012	13,219 (64.4)	631 (66.5)	0.198
N+	7,198 (35.1)	493 (38.6)		7,274 (35.4)	316 (33.3)	
Unknown	30 (0.1)	3 (0.2)		30 (0.1)	2 (0.2)	
Lymphatic invasion, <i>n</i> (%)						
Absent	9,215 (45.0)	614 (48.0)	0.147	9,258 (45.1)	455 (47.9)	0.271
Present	10,708 (52.3)	656 (51.3)		10,687 (52.1)	489 (51.5)	
Unknown	555 (2.7)	8 (0.6)		578 (2.8)	5 (0.5)	
Venous invasion, <i>n</i> (%)						
Absent	7,488 (36.6)	494 (38.7)	0.339	7,520 (36.6)	342 (36.0)	0.371
Present	12,415 (60.6)	774 (60.6)		12,402 (60.4)	602 (63.4)	
Unknown	575 (2.8)	10 (0.8)		601 (2.9)	5 (0.5)	
SEMs, <i>n</i> (%)						
Absent	19,240 (94.0)	1,163 (91.0)	<0.001	–	–	
Present	859 (4.2)	88 (6.9)		–	–	
Unknown	379 (1.9)	27 (2.1)		–	–	
SCRCs, <i>n</i> (%)						
Absent	–	–		19,240 (93.7)	859 (90.5)	<0.001
Present	–	–		1,163 (5.7)	88 (9.3)	
Unknown	–	–		120 (0.6)	2 (0.2)	

CRCs, colorectal cancers; EMs, extracolorectal malignancies; SCRCs, synchronous CRCs; SEMs, synchronous EMs.

had multiple types of malignancies; therefore, there were 3,752 EMs in total. Stomach cancer was the most frequent in males, followed by prostate and lung cancers. Breast cancer was the most common EM in females, followed by uterus/ovary, stomach, and lung cancers.

Locations of Multiple CRCs

The combinations of the sites of multiple CRCs are presented in Figure 4. CRCs were distributed evenly throughout the right side of the colon to the rectum. However, relatively few patients had cancer only in the rectal area.

Discussion

MPMs are defined as 2 or more malignancies that independently develop in a patient. The criteria were initially established by Warren and Gate [18] and are still widely used: (1) each tumor must present a definite picture of a malignancy, (2) each tumor must be distinct, and (3) the probability of one being a metastasis of the other must be excluded. Since the metachronous MPMs in our database had a fairly wide range of onset and the information about these lesions was insufficient, we focused on

Table 2. Logistic regression analyses for the risk of SEMs

	Univariate <i>p</i> value	Multivariate		
		<i>p</i> value	OR	95% CI
Age (<70 vs. ≥70 years)	<0.001	<0.001	1.58	1.39–1.81
Sex (female vs. male)	<0.001	<0.001	1.61	1.40–1.86
Primary tumor location (colon vs. rectum)	0.010	0.060	0.88	0.76–1.01
SCRCs (absent vs. present)	<0.001	<0.001	1.54	1.23–1.94

SEMS, synchronous extracolorectal malignancies; SCRCs, synchronous colorectal cancers.

Fig. 2. Kaplan-Meier curves of OS (**a, b**) and RFS (**c, d**) according to the presence of EMs and multiple CRCs. OS, overall survival; RFS, relapse-free survival; CRCs, colorectal cancers; EMs, extracolorectal malignancies; SEMs, synchronous EMs; SCRCs, synchronous CRCs.

Table 3. Cox proportional hazard models of OS

	Univariate <i>p</i> value	Multivariate		
		<i>p</i> value	HR	95% CI
Age (<70 vs. ≥70 years)	<0.001	<0.001	2.02	1.88–2.16
Sex (female vs. male)	<0.001	<0.001	1.36	1.27–1.46
Primary tumor location (colon vs. rectum)	<0.001	<0.001	1.21	1.12–1.29
SCRCs (absent vs. present)	0.024	0.590	1.04	0.91–1.19
SEMs (absent vs. present)	<0.001	<0.001	2.21	1.96–2.48
Histological type (well/mod vs. others)	<0.001	<0.001	1.57	1.41–1.76
T factor (T1–T2 vs. T3–T4)	<0.001	<0.001	1.89	1.73–2.07
pN factor (absent vs. present)	<0.001	<0.001	2.03	1.86–2.21
Lymphatic invasion (absent vs. present)	<0.001	<0.001	1.32	1.22–1.43
Venous invasion (absent vs. present)	<0.001	<0.001	1.27	1.17–1.38
Adjuvant chemotherapy (absent vs. present)	<0.001	<0.001	0.61	0.56–0.66

OS, overall survival; SEMs, synchronous extracolorectal malignancies; SCRCs, synchronous colorectal cancers.

Table 4. Cox proportional hazard models of RFS

	Univariate <i>p</i> value	Multivariate		
		<i>p</i> value	HR	95% CI
Age (<70 vs. ≥70 years)	<0.001	<0.001	1.52	1.43–1.61
Sex (female vs. male)	<0.001	<0.001	1.29	1.22–1.37
Primary tumor location (colon vs. rectum)	<0.001	<0.001	1.39	1.31–1.48
SCRCs (absent vs. present)	0.045	0.683	1.02	0.91–1.15
SEMs (absent vs. present)	<0.001	<0.001	1.69	1.52–1.89
Histological type (well/mod vs. others)	<0.001	<0.001	1.31	1.19–1.45
T factor (T1–T2 vs. T3–T4)	<0.001	<0.001	2.16	2.00–2.34
pN factor (absent vs. present)	<0.001	<0.001	1.92	1.79–2.07
Lymphatic invasion (absent vs. present)	<0.001	<0.001	1.29	1.21–1.38
Venous invasion (absent vs. present)	<0.001	<0.001	1.33	1.24–1.43
Adjuvant chemotherapy (absent vs. present)	<0.001	<0.001	0.77	0.72–0.83

RFS, relapse-free survival; SEMs, synchronous extracolorectal malignancies; SCRCs, synchronous colorectal cancers.

synchronous MPMs, for which more reliable information was available, in the prognostic analysis. We examined the distribution of MPMs combined with metachronous and synchronous MPMs to provide suggestions for pre-operative screening and postoperative surveillance.

Multivariate analyses revealed that older age (OR 1.58), male sex (OR 1.61), and the presence of SCRCs (OR 1.54) were associated with SEMs. Notably, the presence of SCRCs was thought to be an important independent factor for SEMs, comparable to age and sex. We can provide some reasonable explanations for these results. One possible explanation is genetic background. While we excluded the patients with a hereditary colorectal disease,

there can be potential effects of genetic abnormalities. Microsatellite instability (MSI) is broadly known to be a risk factor not only for CRC but also for various types of malignancies, including cancers of the stomach, small intestine, and ovaries and transitional cell carcinoma of the upper urological tract [19]. Another possible reason is that both SCRCs and SEMs have common risk factors, such as smoking and drinking habits, environmental exposure, and comorbidities such as obesity and diabetes. Because these are risks for not only CRC but also various other malignancies [20], patients with SCRCs and SEMs sharing such risk factors is possible. In any case, in this large, multi-institutional study, patients with SCRCs had

Table 5. Incidence of EMs by sites

Type of EMs	Sex		Total (%)
	male (%), <i>n</i> = 12,857	female (%), <i>n</i> = 9,030	
Stomach	683 (5.3)	223 (2.5)	906 (4.1)
Lung	351 (2.7)	164 (1.8)	515 (2.4)
Breast	17 (0.1)	350 (3.9)	367 (1.7)
Prostate	350 (2.7)	–	350 (1.6)
Uterus/ovary	–	258 (2.9)	258 (1.2)
Hepatobiliary/pancreas	227 (1.8)	99 (1.1)	326 (1.5)
Esophagus	160 (1.2)	18 (0.2)	178 (0.8)
Head and neck	121 (0.9)	54 (0.6)	175 (0.8)
Kidney	112 (0.9)	47 (0.5)	159 (0.7)
Urinary tract	125 (1.0)	31 (0.3)	156 (0.7)
Hematopoietic/lymphoid	81 (0.6)	44 (0.5)	125 (0.6)
Skin	30 (0.2)	10 (0.1)	40 (0.2)
Brain/nerve	15 (0.1)	5 (0.1)	20 (0.1)
Bone/soft tissue	10 (0.1)	9 (0.1)	19 (0.1)
Unknown	15 (0.1)	5 (0.1)	20 (0.1)
Others	91 (0.7)	47 (0.5)	138 (0.6)
Total	2,388 (18.6)	1,364 (15.1)	3,752 (17.1)

EMs, extracolorectal malignancies.

Fig. 3. Accumulative incidences of cancer-related death. Kaplan-Meier curves of accumulative incidences of death due to CRC (**a**) and EM (**b**). CRC, colorectal cancer; EM, extracolorectal malignancy.

a 1.54 times greater risk of SEMs compared to those without SCRCs. Thus, patients with SCRCs should be surveyed for SEMs with special care. Specifically, as described later, stomach cancer and lung cancer were particularly common and associated with worse prognoses; thus, gas-

troscopy (GS) and chest CT (not only for screening for lung metastases from CRC but also for screening for primary lung cancer) should be considered for these patients.

Fig. 4. Distribution of the multiple CRCs. CRCs, colorectal cancers; RC, right-side colon; LC, left-side colon.

The influence of MPMs on CRC prognoses was not fully investigated until now. In particular, there have been few reports on the prognoses of patients with EMs. In the present study, we investigated the prognostic impact in both SCRCs and SEMs. The multivariate analysis showed that the presence of SEMs was strongly associated with a poor prognosis. Notably, the presence of SEMs (HR 2.21) was the strongest poor prognostic factor, exceeding age (HR 2.02), primary T factor (HR 1.89), and N factor (HR 2.03). We also performed a multivariate analysis using stomach, lung, prostate, and breast cancers, which were the most common types of EM, as independent variables (online suppl. Table). The results suggested that stomach and lung cancers, which generally have worse prognoses than CRC, are associated with a poor prognosis, while breast and prostate cancers, which have better prognoses, may not be associated with a poor prognosis for CRC. Since CRC has a relatively good prognosis, and long-term survival can be achieved with appropriate treatment, it is important not only to consider the disease stage of primary CRC but also preoperative screening and postoperative surveillance of EMs, which have a worse prognosis than CRC, and to control them. In most previous reports that described the prognoses of patients with CRC, the SEMs factor was not recognized and just regarded as another cause of death in the evaluation of OS and RFS [14]. However, the finding that SEMs have a greater prognostic impact than other factors is extremely important; thus, clinicians should keep in mind that pa-

tients with CRC may die of cancers other than CRC when deciding treatment options and surveying. Furthermore, when conducting research to evaluate CRC prognoses, we must design studies that take into account the presence of SEMs- and EMs-related death. By contrast, SCRCs did not affect prognoses in the present study, which is consistent with many previous reports [21, 22]. Several other studies reported that the presence of SCRCs was a poor prognostic factor. Nosho et al. [10] and Oya et al. [11] showed that the patients with SCRCs had poorer prognoses than those without SCRCs in the univariate analysis; conversely, there was no significant difference in the multivariate analysis adjusted for disease stage and curability. Moreover, none of these previous reports considered the presence of SEMs in the multivariate analyses. Patients with SCRCs are more likely to develop distant or lymph node metastasis concomitantly than those without SCRCs, which could be associated with the poorer prognoses. However, as shown by our results and many previous reports [11, 12, 22], the prognoses do not appear to differ when comparing patients who receive curative resection and adjusting for disease stage.

Several hereditary diseases are known to lead to CRC. For example, Lynch syndrome is known to have mutations in the mismatch repair gene, which leads to a risk of colorectal, endometrial, stomach, ovarian, biliary tract, ureteral, and small intestinal cancers [23]. As shown in Table 5, stomach cancer was the most common type in the present study, followed by lung, breast, prostate, and uterine cancers. This population's characteristics differ from Lynch syndrome in that there was a large proportion of breast and prostate cancer. According to a report from the Japanese Ministry of Health, Labour, and Welfare, except for CRC, stomach cancer has the highest incidence rate among malignant diseases in Japan, with a rate of 136.1 per 100,000 population, followed by lung cancer (115.4 per 100,000) and prostate cancer (96.0 per 100,000). Breast cancer (93.7 per 100,000) is the most common in women, followed by stomach cancer (58.2 per 100,000) and lung cancer (48.9 per 100,000) [5]. Our results are similar to these findings, but there was a notably high proportion of stomach cancer in our population. In men, in particular, there were nearly twice as many cases of stomach cancer than lung cancer and prostate cancer. Kato et al. [7] reported a large proportion of stomach cancer as MPMs in patients with CRC. They noted that the incidence of stomach cancer with CRC was significantly higher compared to the healthy population collected

from mass screenings (0.53 vs. 0.03%, $p < 0.001$, OR 18.8) [7]. We obtained a result supporting that of Kato et al. [7] in a larger, multi-institute cohort. Although there are some limitations as shown below, MPMs with CRC were characterized by a higher proportion of stomach cancers, which differs from the general population and Lynch syndrome. Therefore, the stomach should be carefully surveyed, such as via GS in preoperative screening, in patients with CRC.

The reported distribution of multiple CRCs greatly varies [11, 21, 24]. In the present study, CRCs were evenly distributed throughout the large intestine. In addition, there was a relatively small population with multiple CRCs only in the rectum. Therefore, it is important to examine the entire colon and rectum for preoperative screening and postoperative surveillance.

There are several limitations in this study. First, it was retrospective. The other limitation was based on the selection biases. For example, many patients with CRC undergo chest CT before surgery. GS is also often performed in Japan. Conversely, serum PSA testing is rarely performed. These screening tests generally increase the apparent incidence of cancer through early detection. The resulting selection bias may affect the frequency and distribution of MPMs. Besides, because exhaustive surveillance for all types of cancers was not routinely performed during the postoperative follow-up period, information about EMs during this period might be insufficient. Another limitation was that disease stage of the second CRC is not fully described in our data. We must consider that there might be contained pathological in situ cancers as secondary CRCs in multiple patients with CRC. Furthermore, the lack of information, such as genetic background (i.e., p53, MSI, and RAS), family history, social history, comorbidities, and *H. pylori* infection, is also a major limitation. Information about the onset and disease stage of metachronous MPMs was missing from our data. The proportions of MEM and SEM among EM-related deaths were also unknown. Genetic information containing MSI was inadequate because the study population included patients from a relatively older era when hereditary CRC was not well recognized. It should be noted that SCRC might be more prone to being MSI high due to mutations in the MMR gene, even in sporadic CRCs. MSI-high CRC is generally considered to have a better prognosis than MSI-stable CRC, except in the case of recurrent or metastatic CRC [25], which may consequently mask the effects of secondary CRC. In addition, the number of excluded hereditary CRCs was

only 30 in 22,379 patients. The incidence of hereditary CRC has been reported to be up to 5–7% among all CRCs [26]; our results were much lower than this. The diagnoses of hereditary diseases generally require detailed family history and prior medical history in addition to genetic information; however, this information might not be specified in the medical record, where it might be listed as underdiagnosis. Further studies focusing on the above issues are required in the future.

In conclusion, the presence of SEMs was a strong poor prognostic factor for patients with stage I–III CRC. Patients with SCRCs were more likely to have SEMs. Because stomach and lung cancers were common as SEMs, it is recommended that they are surveyed when treating patients with CRC, particularly in those with SCRCs.

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Statement of Ethics

The Ethics Committee of the University of Tokyo (No. 2018028NI-[1]) and local ethics committees in each participant institute approved the study protocol. The study was conducted in accordance with the Declaration of Helsinki. Informed consent was replaced by the obligation of information to the participants and the right of participants to opt out due to the study's retrospective nature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Kentaro Ochiai designed the study and wrote the initial draft of the manuscript. Kazushige Kawai contributed to analysis and interpretation of the data and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation and have critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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