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Second primary cancers and recurrence in patients after resection of colorectal cancer: An integrated analysis of trials by Japan Clinical Oncology Group: JCOG1702A

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Abstract

Background: Improvements in early detection and treatment have resulted in an increasing number of long-term survivors of colorectal cancer (CRC). For the survivors, second primary cancer and recurrence are important issues; however, evidence for an appropriate surveillance strategy remains limited. This study aimed to investigate the frequency and timing of second primary cancer in patients after surgery for exploring an appropriate surveillance strategy by using an integrated analysis of three large-scale randomized controlled trials in Japan.

Methods: The eligibility criteria of three trials included histologically confirmed CRC and having received surgery. The timing, site and frequency of second primary cancers and recurrence were investigated. Risk factors associated with second primary cancers were also examined. The standardized incidence ratio (SIR) of second primary cancers compared with the national database of the Japan Cancer Registry was estimated.

Results: A total of 2824 patients were included in this study. The cumulative incidence of second primary cancer increased over time. The SIR of any second primary cancer was 1.07 (95% CI: 0.94–1.21). The SIR for second primary cancers of colon was 1.09 (95% CI: 0.79–1.47). The cumulative incidence of recurrence almost reached plateau at 3 years.

Conclusions: A common surveillance strategy for the general population can be applied even for curatively resected CRC patients, as the risk of second primary cancers was almost the same as that of the general population.

Key words: second primary cancers, colorectal cancer, appropriate surveillance after surgery, an integrated analysis

Introduction

Improvements in early detection techniques and treatment have resulted in an increasing number of long-term survivors of cancer. For survivors, second primary cancers and recurrence of primary cancer are important issues. The National Cancer Institute's Surveillance, Epidemiology and End Results Programme reported that ~16% (1/6) of cancer patients develop second primary cancers (1). Recent studies have reported that the overall risk of developing second primary cancer among survivors of colorectal cancer (CRC) was higher than the risk of developing primary cancer among the general population (2–7). Therefore, an adequate surveillance strategy is important to detect second primary cancers in the colon and other organs.

In the current surveillance strategies of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2016 for the Treatment of Colorectal Cancer (8), medical examination, tumour marker and computed tomography (CT) every 3–6 months, and colonoscopy annually for 3 years are recommended. By contrast, in the guidelines of other countries (9, 10), although the suggested medical examination and tumour marker schedule are almost identical to that of the JSCCR Guidelines, the recommended schedule of CT and colonoscopy are every 6–12 months only for high-risk or stage III cancer. Colonoscopy was mainly performed for the purpose of detecting second primary CRC, precancerous lesions (adenoma) and local anastomotic recurrence, with other examinations being performed for detecting other second primary cancers and recurrence, with the exception of anastomotic recurrence. The JSCCR Guidelines are based predominantly on two prospective studies performed in the 1990s (8, 11) and have not changed since 2009, despite the revision of the guidelines in 2016. However, the standard adjuvant chemotherapy has since changed, which may alter the features of second primary cancers and recurrence. Therefore, the current surveillance strategy recommended in the JSCCR Guidelines may not be appropriate in terms of early detection and cost-effectiveness for patients receiving current standard adjuvant therapy.

In the Colorectal Cancer Study Group of the Japan Clinical Oncology Group (JCOG), large-scale randomized controlled trials have been conducted for patients with CRC to confirm the efficacy of adjuvant chemotherapies or surgical techniques. Among these clinical trials, the enrolled patients received adjuvant 5-fluorouracil (5-FU)-based chemotherapy according to each trial protocol; the patients also received follow-up surveillance with predetermined modalities, and the follow-up schedules were almost identical to those recommended by the JSCCR Guidelines.

Based on the above, the present study planned to investigate the frequency and timing of second primary cancers, in addition to recurrence, in patients after surgery using three trials for exploring an appropriate surveillance strategy (primary analysis), and to identify risk factors associated with second primary cancers (exploratory analysis).

Methods

Study selection

An integrated analysis was planned using data from clinical trials conducted by JCOG and completed over a 5-year follow-up of second primary cancers and recurrence. Three large-scale randomized trials (JCOG0205, JCOG0212 and JCOG0404) conducted by the Colorectal Cancer Study Group of JCOG in the 2000s were selected for analysis (Fig. 1).

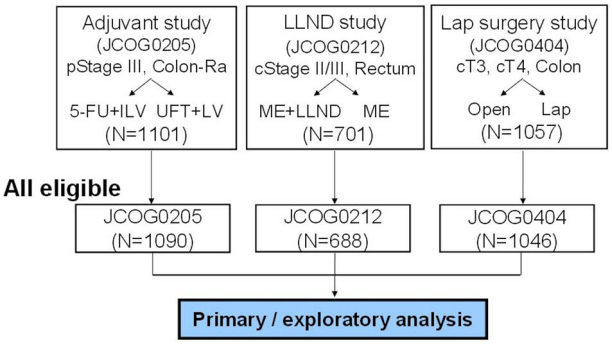

Figure 1. Study design, 5-FU, 5-fluorouracil; ILV, levofolinate; LV, leucovorin; UFT, uracil/tegafur; c, clinical; ME, mesorectal excision; LLND, lateral lymph node dissection; Open, open surgery; Lap, laparoscopic.

JCOG0205 (12) was a randomized controlled trial to confirm the non-inferiority of oral adjuvant chemotherapy uracil/tegafur (UFT)/leucovorin (LV) to intravenous 5-FU/levofolinate (l-LV) with respect to disease-free survival in patients with stage III CRC who have undergone Japanese D2/D3 lymph node dissection (UMIN Clinical Trials Registry [http://www.umin.ac.jp/ctr/index.htm]: C000000193). JCOG0212 (13) was a randomized controlled trial to confirm the non-inferiority of mesorectal excision (ME) alone to ME with lateral lymph node dissection in terms of efficacy for clinical stage II/III lower rectal cancer (UMIN Clinical Trials Registry: C000000034). Patients with pathological (p) Stage III received 5-FU/l-LV in JCOG0212. JCOG0404 (14) was a randomized controlled trial to confirm the non-inferiority of laparoscopic surgery to open surgery with D3 dissection for stage II/III colon cancer (UMIN Clinical Trials Registry: C000000105). Patients with pStage III received 5-FU/l-LV in JCOG0404.

All patients in the three trials were diagnosed as having histologically confirmed CRC and underwent surgery. Patients with pStage III received 5-FU-based adjuvant chemotherapy. Tumour location was divided into colon and rectum.

Follow-up of the three trials

All three trials had started prior to publication of the JSCCR Guideline first edition. Consequently, the schedules of medical examination, tumour marker and CT in all of the three trials were the same as that recommended in the JSCCR Guidelines. However, the colonoscopy schedule in all three trials differed from that recommended in the JSCCR Guidelines. The JSCCR Guidelines recommend colonoscopy be performed every year for 3 years post-surgery. However, in all three trials, if a patient had not received a full assessment of the whole colon with colonoscopy prior to surgery, for example, due to constriction of the colon, they were required to undergo colonoscopy within 6 months post-surgery only. Only in JCOG0205 did all patients receive colonoscopy at 1 year post-surgery.

Definition of second primary cancer and recurrence

Second primary cancer. In the three clinical trials, second primary cancer was defined as any type of cancer, with the exception of recurrence, and the event date was defined as either of the following.

(1) When any modality of image (chest X-ray, ultrasonography, CT or magnetic resonance imaging) reveals second primary cancer, the date of examination is regarded as the second primary cancer date. If more than two modalities reveal a second primary cancer, the earliest date of examination is regarded as the date of occurrence of second primary cancer.

(2) When a second primary cancer is confirmed by cytology or biopsy, the earliest examination date is regarded as the date of occurrence of second primary cancer.

(3) When a second primary cancer is clinically diagnosed without confirmation by imaging, the date of judgement is considered the date of occurrence of second primary cancer. The objective findings indicating second primary cancer are to be recorded on the patient's medical record and case report form (CRF).

We classified sites of second primary cancers into eight categories (liver, colon, rectum, lung, stomach, prostate, breast and others), which included the most common sites of primary cancer and recurrence after resection of CRC.

Recurrence. In three clinical trials, recurrence was defined as any types of recurrence including local sites; however, an increase in tumour marker values only was not regarded as recurrence. Carcinoma *in situ* and intra-mucosal carcinoma were not defined as recurrence because they could be cured by local treatments. The event date was defined as either of the following.

(1) When any modality of image reveals recurrence, the date of examination is regarded as the date of recurrence. If more than two modalities reveal recurrence, the earliest date of examination is considered the date of recurrence.

(2) When a recurrence was clinically diagnosed without confirmation by imaging, the date of judgement is considered as the date of recurrence. The objective findings indicating recurrence should be recorded on the medical record and CRF.

(3) When recurrence is not confirmed by imaging or clinical judgement but confirmed by cytology or biopsy, the earliest date of examination is considered the date of recurrence.

The sites of recurrence were classified into seven categories: liver, lung, peritoneum or local site (excluding anastomotic part), local site (anastomotic part), lymph node, bone and others.

Statistical analysis

In each trial, the time from enrolment to second primary cancer was analysed, accounting for death as a competing risk. The cumulative incidence of second primary cancers was estimated by the cumulative incidence function. The Fine and Grey model was used to estimate hazard ratio (HR) and confidence interval (CI). The time from enrolment to recurrence was analysed in the same manner, accounting for death as a competing risk. In addition, the time from enrolment to recurrence or second primary cancer (earlier one), accounting for death as a competing risk and the time from enrolment to death were analysed in the same manner.

The standardized incidence ratio (SIR) of second primary cancers compared with general population was estimated, being adjusted with sex and age by 5 years. Data of general population from 2003 to 2012, according to the trial period, were extracted from national database of Japan Cancer Registry (15). SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA), was used for all analyses.

The protocol of the present study (JCOG1702A) was approved by the JCOG Protocol Review Committee and Institutional Review Board of National Cancer Center, Tokyo.

Results

Thirty-three patients were excluded because they were enrolled in each study but did not meet the eligibility criteria of each study (Fig. 1). A total of 2824 patients were included in the present study. The median follow-up time of all patients was 6.0 years (interquartile range: 5.0–7.2 years). The median age was 62 years old (range: 23–75 years old), the male/female ratio was 58.0%/42.0%, and the proportions of stage 0, I, II, III and IV were 0.2%, 8.7%, 25.4%, 64.8% and 0.9%, respectively. In terms of location, tumours were present in the colon (70.6%) and rectum (29.4%). A total of 62.6% of patients received 5-FU-based adjuvant chemotherapy (Table 1).

Among the 2824 patients, the numbers of patients with recurrence, second primary cancer and who succumbed to death were 610, 240 and 377, respectively (Table 2).

The number of second primary cancers increased constantly over time. Among 240 events of second primary cancers, the common sites of second primary cancers were the lung (37 events), stomach and colon (Table 3). The SIR of any second primary cancers was 1.07 (95% CI: 0.94–1.21). The incidence of second primary cancer, with the exception of breast cancer, did not increase in the population with a history of CRC.

In the multivariable analysis, age (>64 years old) and sex (male) were risk factors of second primary cancer (age HR: 1.60 [95% CI: 1.24–2.06], sex HR: 1.36 [95% CI: 1.04–1.78]) (Table 4).

In the exploratory subgroup analyses, the SIR of any second primary cancer for older (>64 years old) and male patients were 0.74 (95% CI: 0.61–0.88) and 0.96 (95% CI: 0.82–1.12), respectively (Table 5).

The cumulative incidence of recurrence reached 18.7% and almost reached a plateau at 3 years, and only a small number of recurrences were observed after 5 years (Fig. 2). Among the 610 events of recurrence, the common sites of recurrence were the liver (220 events), lung and lymph nodes (Table 3).

Discussion and conclusion

The frequency and the timing of second primary cancers and recurrence in patients after resection of CRC were investigated using the data of 2824 patients who are rigorously followed up in randomized controlled trials. Essentially, the findings may justify the surveillance strategy specified in the current Japanese guidelines.

The present study revealed that the incidence of second primary cancers, with the exception of breast cancer, did not increase in the population with a history of CRC. Previous studies have reported that a history of CRC was one of the risk factors for second primary cancer of the colon (3–8, 11, 16–18), and the SIRs reported for second primary cancer of the colon were 1.73 (95%CI: 1.69–1.78) (7) and 1.6 (95%CI: 1.2–2.2) (11). Based on these reports, the JSCCR (8) has stated that metachronous CRC occurs more frequently in patients with a history of CRC resection than in the general population, and as such, regular colonoscopy is recommended (recommendation/evidence level 1B). However, the present study revealed that the SIR for second primary cancer of the colon was only 1.09, which is in contrast to earlier reports (3–7, 11). This suggests that the overall risk of developing second primary cancer of the colon after resection of CRC was almost the same as the

Table 1. Characteristics of patients

		JCOG 0205 n = 1090	JCOG 0212 n = 688	JCOG 0404 n = 1046	Total n = 2824	
Age	Median (range)	61 (23–75)	61 (26–75)	64 (28–75)	62 (23–75)	
Sex	Female	500	225	460	1185	(42%)
	Male	590	463	586	1639	(58%)
Tumour location	Colon	947	0	1046	1993	(71%)
	Rectum	143[a]	688[b]	0	831	(29%)
pStage (UICC-TNM sixth edition)	0	0	0	6	6	(<1%)
	I	0	129	116	245	(9%)
	II	0	252	466	718	(25%)
	III	1090	306	433	1829	(65%)
	IV	0	1	24	25	(<1%)
	Unknown	0	0	1	1	(<1%)
Adjuvant Cx (5-FU based)	No	14	409	633	1056	(37%)
	Yes	1076	279	412	1767	(63%)
	Unknown	0	0	1	1	(<1%)

Data are n (%). ME, mesorectal excision; LLND, lateral lymph node dissection.
Colon: from Cecum to RS (recto sigmoid).
[a]Ra, rectum above the peritoneal junction.
[b]Ra and lower rectum.
[c]Lower rectal cancer was defined as tumours of which the lower margin was below the peritoneal reflection.

Table 2. The number and cumulative incidence of events

Events	Number	Cumulative incidence (95% CI)			
		1-year	3-year	5-year	7-year
second primary cancers	240	1.4% (1.0%–1.8%)	3.8% (3.2%–4.6%)	6.3% (5.5%–7.3%)	8.6% (7.5%–9.7%)
recurrence	610	7.7% (6.8%–8.8%)	18.7% (17.3%–20.2%)	20.8% (19.3%–22.3%)	21.9% (20.4%–23.5%)
Death	377	0.6% (0.3%–0.9%)	4.4% (3.7%–5.2%)	9.8% (8.7%–10.9%)	14.5% (13.1%–16.0%)

Table 3. The number of recurrence by site; the number of second primary cancers by site and the SIRs compared with the first cancer of the national database of the Japan Cancer Registry (JCR)

Site	Cases of recurrence	Cases of second primary cancer	Cases of cancer expected by JCR	SIR (95% CI)	P value
All	610	240	224.2	1.07 (0.94–1.21)	0.31
Liver	220	8	14.7	0.54 (0.23–1.07)	0.087
Lung	219	37	30.0	1.23 (0.87–1.70)	0.24
Lymph node	120	–	–	–	–
Peritoneum + local site (excluding anastomotic part)	101	–	–	–	–
Local site (anastomotic part)	34	–	–	–	–
Bone	16	–	–	–	–
Others	30[a]	77	66.1	1.17 (0.92–1.46)	0.20
Colon + Rectum	–	43 (colon:32, rectum:11)	39.4	1.09 (0.79–1.47)	0.61
Stomach	–	35	38.1	0.92 (0.64–1.28)	0.69
Prostate	–	29	22.0	1.32 (0.88–1.90)	0.17
Breast	–	24	11.4	2.11 (1.35–3.14)	0.0014

[a]Brain, adrenal, uterus, ovary, thyroid and skin (incision area).

risk of primary colon cancer in the general population. One of the reasons for the discrepancy is that colonoscopy was performed for the whole colon and precancerous lesions (adenoma) were resected by polypectomy prior to surgery, or within 6 months after surgery in patients who could not undergo whole colon examination prior to surgery. Therefore, patients who did not receive colonoscopy were excluded from the present study due to the possibility of unknown suspicious lesions or multiple CRC at enrolment. Based on the results of the present study, it is recommended that the frequency of colonoscopy after surgery, at least for patients receiving whole

Table 4. Risk factors of second primary cancers

		Events/*N*	5-year cumulative incidence (95% CI)	Univariable analysis		Multivariable analysis (simultaneous)	
			Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	*P*-value	
Age	≦64	116/1676	4.8% (3.8%–5.9%)	1		1	
	>64	124/1148	8.6% (7.1%–1.0%)	1.63 (1.27–2.10)	<0.001	1.60 (1.24–2.06)	<0.001
Sex	Female	81/1185	5.5% (4.3%–6.9%)	1		1	
	Male	159/1639	6.9% (5.7%–8.2%)	1.27 (1.02–1.60)	0.014	1.36 (1.04–1.78)	0.025
Tumour location	Colon	157/1993	6.3% (5.3%–7.5%)	1		1	
	Rectum	83/831	6.3% (4.8%–8.1%)	1.09 (0.82–1.43)	0.56	1.03 (0.78–1.37)	0.83
pStage	0 or I	29/251	7.6% (4.7%–11.3%)	1		1	
	II	74/718	7.4% (5.7%–9.5%)	0.93 (0.61–1.42)	0.74	0.92 (0.60–1.42)	0.72
	III	137/1829	5.8% (4.8%–6.9%)	0.69 (0.47–1.03)	0.069	0.73 (0.49–1.10)	0.13
	IV	0/25	0%	NE	NE	NE	NE
Adjuvant Cx (5-FU based)	No	107/1056	7.1% (5.6%–8.7%)	1			
	Yes	133/1767	5.9% (4.8%–7.0%)	0.77 (0.60–1.00)	0.047		
	Unknown	0/1	0%	NE	NE		
Adjuvant Cx among pStage III	No	4/72	2.8% (0.5%–8.8%)	1			
	Yes	133/1756	5.9% (4.9%–7.1%)	1.41 (0.53–3.78)	0.49		
	Unknown	0/1	0%	NE	NE		

Table 5. Subgroup analyses; the number of second primary cancers by the SIRs compared with the first cancer of the national database of the Japan Cancer Registry (JCR) in age and sex

		N	Cases of second primary cancer	Cases of cancer expected by JCR	SIR (95% CI)	*P* value
Age	≦64	1676	116	56.02	2.07 (1.71–2.48)	<0.0001
	>64	1148	124	168.20	0.74 (0.61–0.88)	0.0004
Sex	Female	1185	81	58.93	1.37 (1.09–1.71)	0.0073
	Male	1639	159	165.29	0.96 (0.82–1.12)	0.66

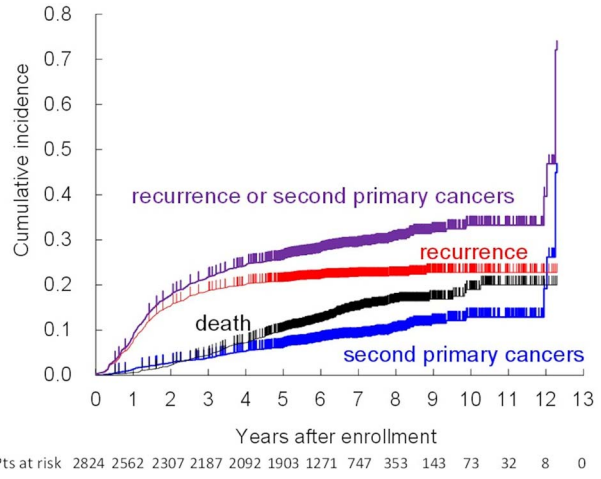

Figure 2. Cumulative incidences of second primary cancers, recurrence and death.

colonoscopy prior to surgery, should be same as that for the general population.

By contrast, the SIR for second primary cancer of the breast was 2.11, which was similar to a previous report (5). Both clinical and experimental studies have reported that female hormones, including oestrogen, suppressed CRC development (19–21). Therefore, the association between resection of CRC and the occurrence of second primary cancer of the breast requires further investigation in the future. For those in the population with BRCA1 or BRCA2 mutations at high-risk of breast cancer, the NCCN guideline (22) recommends the intensive screenings. However, there is limited data that the risk of breast cancer for CRC survivors is as high as that for the population with BRCA1 or BRCA2 mutations. Other studies have reported that the overall risk of developing second primary cancer of the breast after resection of CRC was almost the same as the risk of primary breast cancer of the general population (3, 4). Therefore, at this point, the surveillance strategy for second primary cancer of the breast should be same as that for primary breast cancer in the general population.

The results demonstrated that the cumulative incidence of recurrence almost reached a plateau at 3 years, and only a few recurrences were observed after 5 years. Watanabe T et al. (8) revealed a recurrences rate of 17.3% among patients with pStage I-III CRC. They also reported that ~80% of recurrences were observed within 3 years after surgery and recurrence after 5 years was rare. In the present study, the site and frequency of recurrence were almost identical to those reported in previous studies, with change to adjuvant chemotherapy or surgical technique for CRC. The use of adjuvant chemotherapy and surgical technique used for CRC has been developing; however, the pattern of recurrence after surgery has not changed.

In daily practice, many patients do not follow guidelines-recommended surveillance and may be omitted. Ellis CT et al. (23) reported that adherence to guidelines-recommended surveillance was poor for patients with rectal cancer in the United State. In Japan, less intensive follow-up is sometimes performed and desired in daily

Table 6. Current surveillance strategy for patients with stage I-III CRC

Modality	Follow-up schedule				
	Japan 2016[a]	ASCO 2013[b]	ESMO 2013[c]	NCCN 2016[d]	
				Stage I/II	Stage III
Examination, interview	Every 3–6 mo. for 3 yrs Every 6 mo. for 4–5 yrs	Every 3–6 mo. for 5 yrs	Every 3–6 mo. for 3 yrs Every 6–12 mo. for 4–5 yrs	Every 3–6 mo. for 2 yrs Every 6 mo. for 3–5 yrs	
Tumour marker (CEA)	Every 3–6 mo. for 3 yrs Every 6 mo. for 4–5 yrs	Every 3 mo. for 2 yrs for stage II/III	Every 3–6 mo. for 3 yrs Every 6–12 mo. for 4–5 yrs	Every 3–6 mo. for 2 yrs Every 6 mo. for 3–5 yrs	
Computed tomography (chest and abdomen)	Every 6 mo. for 3 yrs Annually for 4–5 yrs	Annually, or every 6–12 mo. for 3 yrs only for high-risk cancer	Every 6–12 mo. only for stage II/III	Every 6–12 mo. for 5 yrs only for high-risk cancer	Every 6–12 mo. for 5 yrs
Ultrasonography (abdomen)	-	-	Every 3–6 mo.	-	
Colonoscopy	Annually for 3 yrs	At 1 yr, and every 5 yr after that	At 1 yr; every 3–5 yr thereafter	At 1 yr and 3 yr, then every 5 yr after that; annually if advanced adenoma is detected	
Digital rectal examination (in case of rectal cancer)	Every 6 mo. for 3 yrs	Every 6 mo. for 5 yrs	Every 3–6 mo. for 3 yrs Every 6 12 mo. for 4–5 yrs	Every 3–6 mo. for 2 yrs Every 6 mo. for 3–5 yrs	

mo., months; yr(s), year(s).

[a]Japan, Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2016 for treatment of colorectal cancer.

[b]ASCO, American Society of Clinical Oncology Guidelines 2013.

[c]ESMO, European Society for Medical Oncology Guidelines 2013.

[d]NCCN, National Comprehensive Cancer Network Guidelines 2016.

practice due to the cost-effectiveness and side-effects, particularly in colonoscopy. In fact, the frequency of colonoscopy in the present study is low. Since the results of this integrated analysis show that the SIR of any second primary cancer is no different from ordinary people, we do not consider it necessary to follow the guidelines-recommended surveillance at least more intensively to detect second primary cancers.

The recommendation about the schedules of CT and colonoscopy in the JSCCR Guidelines are more intensive than that in the guidelines in Europe or the USA (Table 6). One of the reasons for the different recommendation between Japan and other countries is that cost-effectiveness is emphasized in Europe and the USA (24). Recently, in Italy, Spain and the USA, a clinical trial comparing intensive with less intensive surveillance revealed that intensive surveillance imaging enabled earlier diagnosis of recurrence than a protocol involving less-frequent imaging (but with carcinoembryonic antigen (CEA) testing and physical examination at similar intervals, every 4 months for 2 years, every 6 months for 3–4 years and at 5 years); however, the earlier diagnosis had no significant effect on the overall survival (HR: 1.14, 95% CI: 0.87–1.48) (25). In the intensive arm of the clinical trial, colonoscopy and chest X-ray were performed annually for 5 years, and ultrasonography was performed every 4 months for 1.5 years and annually for 2–5 years. Although chest and abdomen CT were not performed, the schedule in the intensive arm of this trial was more intensive than that of Japan. By contrast, in the less intensive arm of the clinical trial, the surveillance modalities comprised only CEA testing, physical examination, colonoscopy (at 1 year and 4 years), and liver ultrasonography (at 4 months and 16 months). This was less intensive than that of Japan and other countries, and more cost-effective. As the results of this clinical trial suggest that a less intensive strategy may not deteriorate overall survival, a similar clinical trial comparing the JSCCR surveillance strategy and a less intensive strategy is necessary in Japan.

In the multivariable analysis, age (>64 years old) and sex (male) were risk factors of second primary cancer. The risk factors were the same as those described in previous reports (2, 17, 18). In previous studies, it was concluded that patients with these risk factors should receive intensive exploration of second primary cancers after resection of CRC. From the subgroup analyses of the SIR in the present study for second primary cancer in age and sex, the SIR in the patients >64 years was 0.74, and that in male patients was almost 1, this indicates that older patients have a high-risk of second primary cancer but that the risk itself is marginally less than the risk of developing primary cancer in general population. However, as these results were of subgroup analyses only, curatively resected CRC patients with those risk factors (>64 years old and male) may require intensive surveillance to detect second primary cancer.

In the univariable and multivariable analysis, pStage III showed lower risk for developing of second primary cancer than pStage 0-I (HR: 0.69 [95% CI: 0.47–1.03] in the univariable analysis), although the *P* value was larger than 5%. Since almost all pStage III patients (96.0%) received 5-FU based adjuvant chemotherapy, the benefit of adjuvant chemotherapy may have reduced the risk of developing second primary cancer. The presence of adjuvant chemotherapy is significantly reduced the risk of developing secondary cancer (HR: 0.77 [95% CI, 0.60–1.00] in the univariable analysis). However, a univariable analysis of the presence or absence of adjuvant chemotherapy in pStage III patients, the group with adjuvant chemotherapy was high risk (HR: 1.41 [95% CI, 0.53–3.78]). There are few pStage III patients without adjuvant chemotherapy (4.0%), and those patients' background is considered specific. Thus, it is difficult to judge which is the risk factor, pStage or adjuvant chemotherapy.

The present study has several limitations. None of the following information was collected in the three trials (i) whether CRC is hereditary or sporadic, (ii) no data of smoking history or family history, (iii) opportunities for the identification of second primary cancer or recurrence and (iv) the clinical course of second primary cancer including its stage and following treatment. These data are important in order to discuss what modalities can be omitted and/or should be mandatory in the strategy of surveillance. In addition, no detailed information was collected regarding the distinction between second primary cancer and recurrence. This was predominantly dependent on a doctors' decision, and biopsy was not mandatory. In the JCOG studies, primary investigators and JCOG Data Center/Operations Office reviewed the data of second primary cancer and recurrence, therefore, the criterion for determination was unified.

In conclusion, a common surveillance strategy for the general population can be applied even for patients with curatively resected

CRC, as the risk of second primary cancer was almost same as that of the general population. However, patients with curatively resected CRC with the risk factors of being a male and aged >64 years old may require intensive surveillance to detect second primary cancer.

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