RESEARCH ARTICLE

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Synchronous Advanced Colorectal Neoplasia: Clinicopathologic Features and Prognostic Significance

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Abstract

Objective: This study aimed to compare the clinico-pathologic features, recurrence rate and disease-free survival between colorectal cancers (CRCs) with synchronous advanced colorectal neoplasia (SCN) and solitary CRCs to determine the prognostic significance of SCN. **Methods:** A retrospective review of prospectively collected data of patients with CRCs was conducted in Phramongkutklao Hospital from January 2009 to December 2014. Patients were categorized in 3 groups: 1) solitary CRCs, 2) CRCs with advanced colorectal adenomas (ACAs) but having no another cancer and 3) synchronous colorectal cancers (S-CRCs) with or without ACAs. Patients undergoing curative resection and complete standard adjuvant treatment were recruited to evaluate the prognostic significance of SCN. Clinicopathologic features, recurrence rate and disease-free survival were analyzed to compare among different groups. **Result:** Among 328 recruited patients, 282 were classified as solitary CRCs (86%), 23 as CRCs with ACAs (7%) and 23 as S-CRCs (7%). Patients with CRCs with SCN (groups 2 and 3) were significantly older than patients with solitary CRCs ($p < 0.01$), and SCN was found more commonly among males (15.2%) than females (12.3%) ($p=0.045$). In all, 288 patients achieved a curative resection and accomplished complete standard postoperative adjuvant treatment. Of these, the accumulative number of patients experiencing tumor recurrence was 11.8, 21.2, 24.6, 26.4 and 26.7% at the 1-, 3-, 5-, 7- and 10-year surveillance period, respectively. The disease-free survival of the groups with SCN was marginally higher than that of solitary CRCs groups ($p=0.72$) (solitary CRCs, 120.7±4.4 months; CRCs/ACAs, 127.4±13.9 months and S-CRCs: 126.2±13.6 months). **Conclusion:** CRCs with SCN were found at a more advanced age than those with solitary CRCs. SCN was found more often among males than females. After achieving curative resection and complete adjuvant treatment, the recurrence rate and disease-free survival of CRCs with SCN did not significantly differ from those of solitary CRCs.

Keywords: Advanced colorectal neoplasia- disease-free survival- recurrence rate- synchronous advanced adenoma

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Introduction

A vast majority of colorectal cancers (CRCs) arise from progression of adenomas to CRCs through a multistep process from precursor lesions (Winawer, 1999; Bond, 2000) associated with mutations in various genes (Levi et al., 2013). This adenoma-carcinoma sequence often takes several years before the tumor manifestation (Aarons et al., 2014). Advanced colorectal adenoma (ACAs) is a neoplastic lesion with a high risk histomorphology. It has been recognized as a precursor lesion of CRCs, especially when the lesion exhibits severe dysplasia. Colonoscopy is the most effective tool that can be used to detect and treat all suspicious lesions. The findings from the initial colonoscopy, such as the number of adenomas, have been used for predetermining when subsequent colonoscopies should be performed (van Enckevort et al., 2014). Several risk factors including large serrated polyps (≥10 mm) and serrated sessile lesions (SSLs) were associated with an increased risk of synchronous advanced colorectal neoplasia (SCN) (Tao et al., 2020; Shiu et al., 2021). SSLs are considered to be an etiology of developing interval CRCs via the so-called serrated pathway (Kalady, 2013; Meester and Ladabaum, 2020). Studies have reported that adenomatous polyps with high risk histopathologic features, three or more adenomas, and sessile serrated lesions are associated with an increased risk of metachronous lesions (Melson et al., 2016; Tao et al., 2020; Shiu et al., 2021). Therefore, current practice guidelines recommend that patients with any of these high risk features should have a follow-up colonoscopy in three years (Melson et al., 2016). Regarding the size of polyp, in a pooled analysis of data from 12 international cohorts of patients undergoing colonoscopy revealed that diminutive polyps with advanced histologic features do not increase risk for metachronous advanced neoplasia (Vleugels et

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al., 2019). The US Multi-Society Task Force (USMSTF) categorizes patients with sessile serrated polyps without cytologic dysplasia of <10 mm in size as low risk for metachronous advanced neoplasia (Melson et al., 2016). The rate of advanced neoplasia upon surveillance among patients with initial low risk sessile serrated polyps is comparable to that of patients with initial high risk tubular adenoma but higher than among patients with initial isolated low risk tubular adenomas. The study suggested that surveillance interval for patients with sessile serrated polyps, even in small lesions without cytoplasitc dysplasia, should be considered (Melson et al., 2016).

For CRCs with synchronous adenomas, a related study revealed that synchronous neoplastic lesions developed most frequently in the distal colon and less frequently in the proximal colon, the rectum being the least frequent site (Li et al., 2019). Approximately 45% of synchronous advanced lesions were subcentimeter polyps; nevertheless, 9.3% of diminutive and small adenomas were found to be advanced neoplasia (Li et al., 2019). CRCs with SCN were found to have an increased incidence of metachronous advanced neoplasia following surgical resection (Yabuuchi et al., 2018), and presence of synchronous polyps was shown to be an independent predictor of metachronous lesions after CRC removal (Pozza et al., 2016).

CRCs with SCN require detailed clearing of the remainder of the large bowel, and clearance of SCN must be ascertained in all cases to avoid residual synchronous advanced lesions. For postoperative follow-up examination, a more cautious approach should be taken. Despite having a normal colonoscopy, a positive fecal immunochemical test was reported as a significant risk factor for metachronous advanced colorectal neoplasia (Omata et al., 2021). Synchronous advanced colorectal neoplasia (SCN) is described as two or more colorectal tumors found in a single patient simultaneously. SCN can present as a synchronous malignant tumor or synchronous ACAs. ACAs has been defined as an adenoma greater than 1 cm in diameter or with at least 25% villous components or severe dysplasia features.

Although the occurrence of SCN increases risk of metachronous advanced neoplasia, the prognostic significance of SCN remains inconclusive. Therefore, this study aimed to compare the clinico-pathologic features, recurrence rate and disease-free survival of patients with CRCs with and without SCN to determine the prognostic significance of SCN.

Materials and Methods

This study was reviewed and approved by the Institutional Review Board of The Royal Thai Army, Medical Department before initiating. A retrospective review of prospectively collected data in department-based electronic medical records of consecutively resected colorectal adenocarcinoma was conducted in Phramongkutklao Hospital from January 1, 2009 through December 31, 2014. All patients underwent a complete pre-operative or peri-operative colonic examination within 3 to 6 months after surgery to detect and remove all advanced synchronous lesions. Patients with polyposis syndrome were excluded from this study. The clinicopathologic features of individual patients were reviewed for primary tumor location, stage and histopathologic features including tumor differentiation, presence of the mucinous component, and lymphatic or vascular invasion. All concomitant neoplastic lesions were reviewed to document locations, number and histopathologic features. Pathologic diagnosis and staging were based on the AJCC classification of malignant tumors, 8th edition (Weiser, 2018). The most advanced pathologic lesion was defined as the index lesion in cases of synchronous cancer. Complete resections were ascertained using postoperative imaging and colonoscopy. Curative resections were indicated when the primary tumor, metastatic diseases and all synchronous advanced lesions were completely removed. When SCN was located within the operative field, both the primary tumor and the SCN were removed at the same time. When SCN was located beyond the operative field, the SCN was removed by either endoscopic resection or surgical resection as appropriate. All patients with CRC were regularly followed up using routine physical examination, serum markers, colonoscopy surveillance and imaging studies (CT, MRI or PET scan). Disease-free survival was calculated from the date that the primary tumor, metastatic diseases and all synchronous advanced lesions were completely resected to the date of clinical re-appearance, CEA rising, or imaging detection of recurrence/metastatic diseases depending on the date of the event that occurred first. A flow diagram for this study is shown in Figure 1.

Patients were categorized in three groups as shown in Figure 1. Each group was defined according to the presence and the type of synchronous neoplasia. Group 1, solitary CRCs, was defined as CRC without SCN. Group 2, CRCs/ACAs, was defined as CRCs with ACAs, but without another cancer. Group 3, S-CRCs, was defined as synchronous CRCs with or without ACAs. The disease-free survival and accumulative number of patients experiencing tumor recurrence were calculated and analyzed for comparison among groups.

Statistical Analysis: Disease-free survival was calculated using the Kaplan-Meier method to determine prognostic significance of SCN. Patients lost to follow up or dying from other causes unrelated to colorectal cancer were considered excluding. Categorical variables were analyzed using the Pearson's Chi-square test or Fisher's exact test where appropriate to determine association with each type of SCN. Any p-value of less than 0.05 was considered as statistically significant.

Results

The results of this study were reported according to the STROBE Statement checklist. Altogether, 351 patients received a diagnosed of CRCs. Of these, 23 were excluded due to incomplete colonoscopy within six months after surgery, death within six months or incomplete data. A total of 328 patients with CRCs were analyzed with mean age was 64.6±11.6 years. Totally, 198 (60.4%) males and 130 (39.4%) females were enrolled.

Table 1. Patients' Demographics, Tumor Stages According to the 8th Edition of the AJCC Cancer Staging, and Histopathologic Features

	Groups			Total	p-value
	Solitary-CRCs (N = 282)	CRCs/ACA (N = 23)	S-CRCs (N = 23)	(N = 328)	
Gender					
N (%)					
Male	168 (59.6)	30 (47.8)	19 (82.6)	198 (60.4)	0.045*
Female	114 (40.4)	16 (52.2)	4 (17.4)	130 (39.4)	
Age	63.7 (11.5)	66.7 (11.6)	72.6 (10)	64.6 (11.6)	0.01#
Mean (SD)					
Depth of invasion					
N (%)					
Tis-T2	37 (13.1)	3 (13)	2 (8.7)	42 (12.8)	0.82
T3-T4	245 (86.9)	20 (87)	21 (91.3)	286 (87.2)	
Nodal involvement					
N (%)					
No	151 (53.5)	13 (56.5)	9 (39.1)	173 (52.7)	0.384
Yes	131 (46.5)	10 (43.5)	14 (60.9)	155 (47.3)	
Histologic grading N (%)					
Low	244 (86.5)	17 (73.9)	21 (91.3)	282 (86)	0.184
High	38 (13.5)	6 (26.1)	2 (8.7)	33 (14)	
Lymphovascular					
Invasion					
N (%)					
No	210 (74.5)	12 (52.2)	15 (65.5)	237 (72.3)	0.053
Yes	72 (22.5)	11 (47.8)	8 (34.8)	91 (27.7)	
Mucinous component					
No	245 (86.9)	18 (86.9)	21 (91.3)	284 (86.6)	0.35
Yes	37 (13.1)	5 (21.7)	2 (8.7)	44 (13.4)	

*, chi-square test ; #, Independent t-test

Of these, 7% (23/328) presented synchronous ACAs and 7% (23/328) exhibited S-CRCs. Furthermore, 1.8% (6/328) presented both ACAs and S-CRCs. SCN was found more frequently among males (15.2%) than females (12.3%) (p=0.045) and was found at a more advanced age than solitary CRCs (p<0.01). Demographics, tumor staging and histopathologic features of these patients are summarized in Table 1. The site, number and anatomical correlation of the primary and synchronous advanced neoplasia are demonstrated in Table 2 and Figure 2. In all, 288 patients achieved a curative resection and completed standard postoperative adjuvant treatment. The numbers of patients categorized as group 1 (solitary CRCs), group 2 (CRCs/ACA) and group 3(S-CRCs) were 250, 20 and 18, respectively.

This study revealed that CRCs with SCN tended to present at a higher rate of lymphovascular invasion (p= 0.053) than those without SCN (group 1), as shown in Table 1. The total accumulative number of patients experiencing tumor recurrence was 34 (11.8%), 61 (21.2%), 71 (24.6%), 76 (26.4%) and 77 (26.7%) of 288 at the 1-, 3-, 5-, 7- and 10-year surveillance period

Table 2. The Site, Number, and Anatomical Correlation of the Primary Tumor and Synchronous Advanced Neoplasia.

	Type of synchronous lesions	
	Synchronous ACA (N=23)	Synchronous CRCs (N=23)
Number of lesions (min-max)	1-8	1-3
Anatomical correlation:		
(Primary-Synchronous)		
Same anatomical segment	4(17.4%)	3(13%)
Contiguous anatomical segment	7(30.4%)	7(30.4%)
Across anatomical segment	12(52.2%)	13(56.6%)

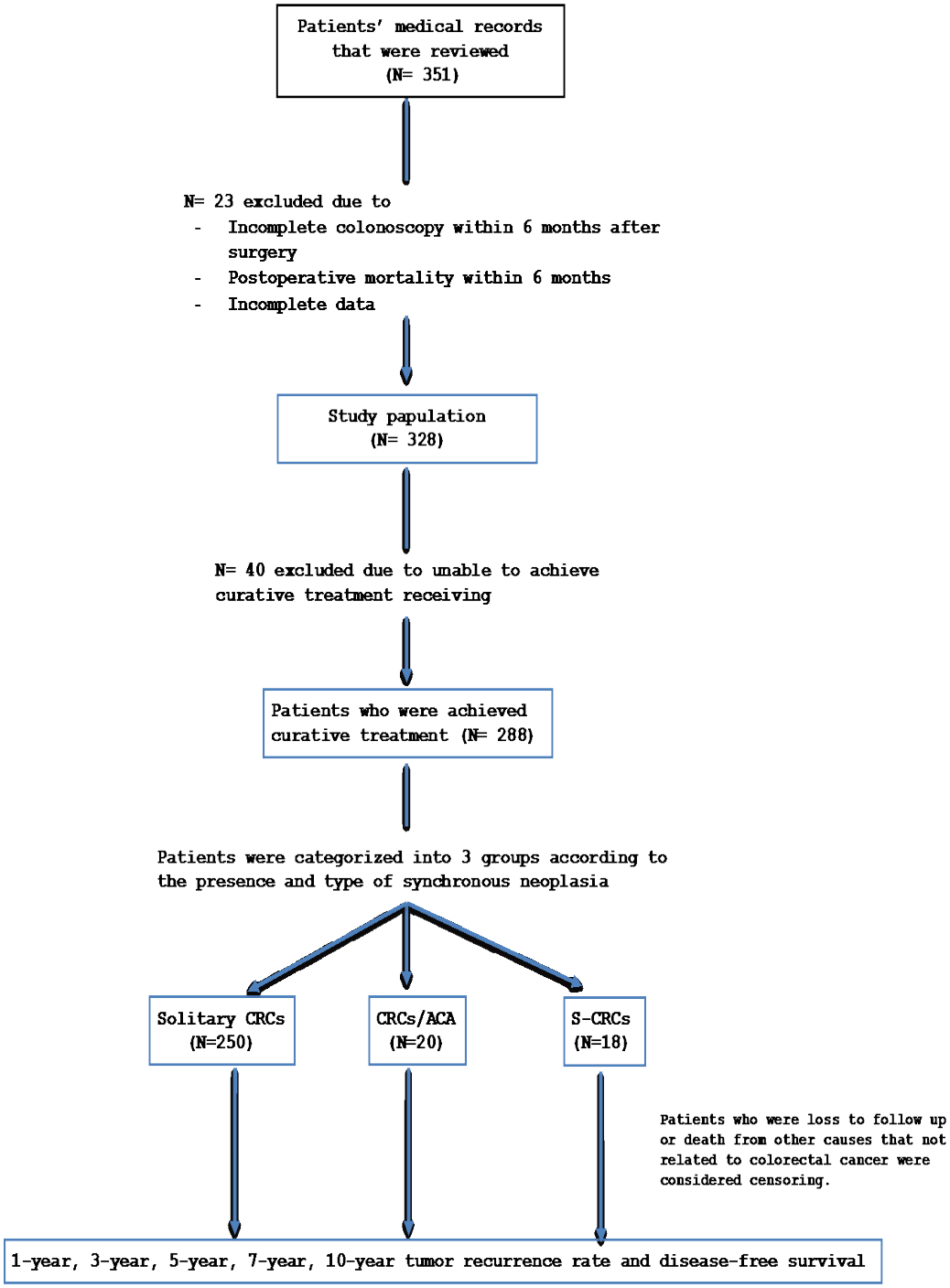

Figure 1. Flow Diagram for the Study

respectively. The 10-year accumulative number of patients experiencing tumor recurrence was 69 (27.6%) of 250 group 1 patients; 4 (20%) of 20 group 2 patients; and 4 (22.2%) of 18 group 3 patients, as shown in Table 3.

The presence of SCN did not significantly influence the recurrence rate and disease-free survival. In addition, the disease-free survival of the groups with SCN (groups 2 and 3) was marginally better than that in the solitary CRCs

Table 3. Cumulative Incidence of Recurrence

Group N (%)	1 year (%)	3 years (%)	5 years (%)	7 years (%)	10 years (%)	p-value
In evaluated cohort (N=288)	34 (11.8)	61 (21.2)	71 (24.6)	76 (26.4)	77 (26.7)	0.72
Solitary CRCs (N=250)	34 (11.8)	61 (21.2)	71 (24.6)	76 (26.4)	77 (26.7)	
CRCs/ACA (N=20)	2 (10)	3 (15)	4 (20)	4 (20)	4 (20)	
S-CRCs (N=18)	2 (11.1)	2 (11.1)	4 (22.2)	4 (22.2)	4 (22.2)	

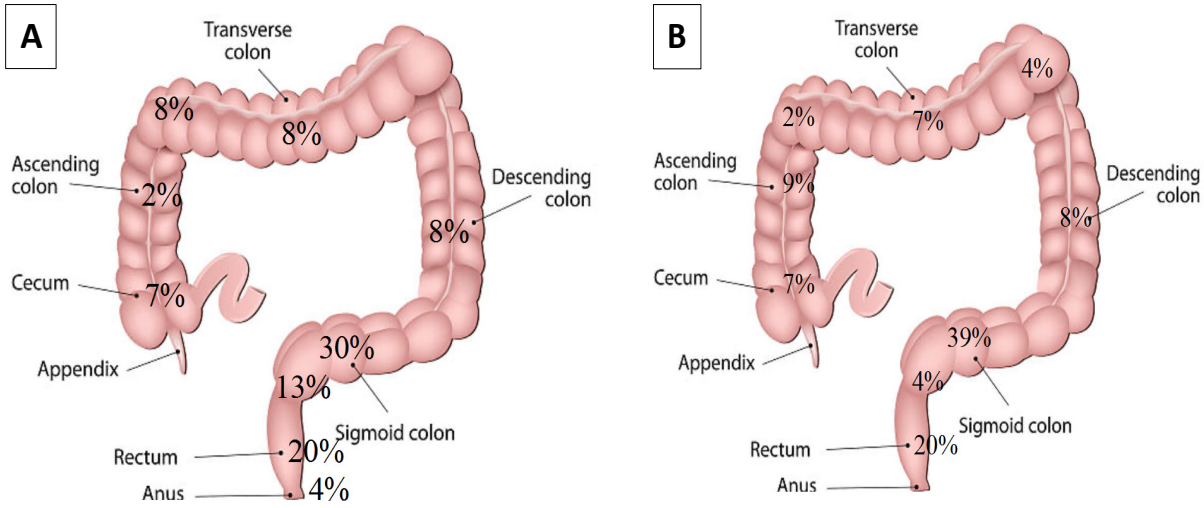

Figure 2. Distribution of Primary Cancer (A) and Synchronous Advanced Neoplasia (B) by Anatomical Locations in the Large Bowel.

Table 4. Disease-Free Survival (Months) Categorized by Groups.

Group	Disease-free survival (month)		p-value
N (%)	Mean (SD)	95%(CI)	
In evaluated cohort (N=288)	122.0 (4.0)	114.10-130	0.72
Solitary CRCs (N=250)	120.7 (4.4)	112.1-129.3	
CRCs/ACA (N=20)	127.4 (13.9)	101.1-154.7	
S-CRCs (N=18)	126.2 (13.6)	99.5-152.9	

group but without statistical significance (solitary CRCs, 120.7±4.4 months; CRCs/ACA, 127.4±13.9 months; and S-CRCs, 126.2±13.6 months) as shown in Table 4 and Figure 3.

Discussion

Synchronous advanced neoplasia (SCN) is defined as any advanced adenoma or any carcinoma detected at the same time. Advanced adenoma is an adenoma with a diameter of ≥10 mm, high-grade dysplasia, or ≥25% villous features (Imperiale et al., 2002). Related studies revealed that the prevalence of synchronous carcinomas ranged from 2 to 5% (Evers et al., 1988; Vasilevsky and Gordon, 1988; Adloff et al., 1989; Pinol et al., 2004). ACAs were found to have a prevalence of 5.2 to 9.6%

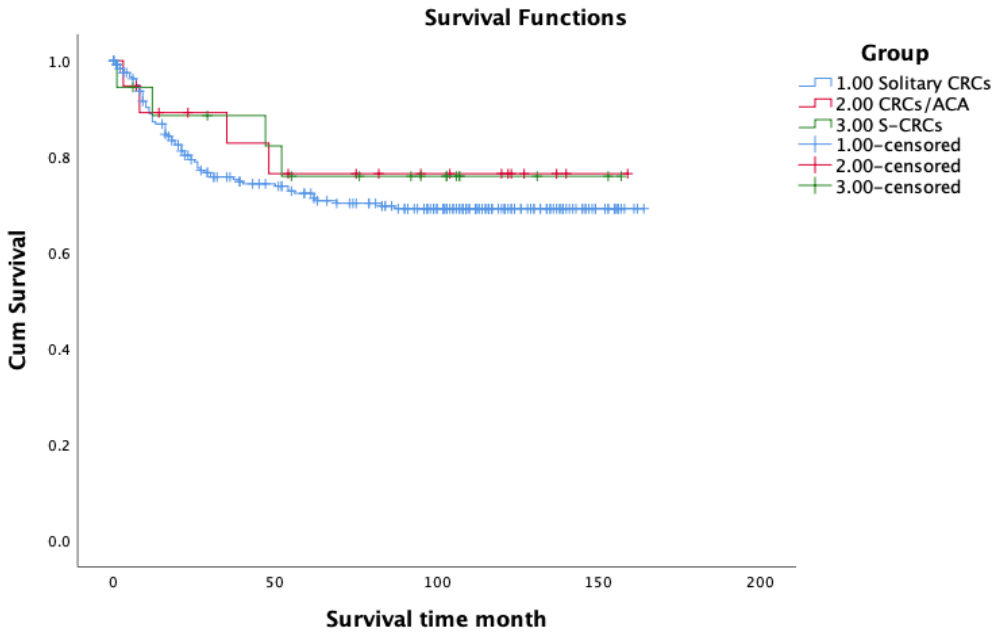

Figure 3. A Kaplan-Meier Survival Analysis of Disease-Free Interval Categorized by Occurrences and Types of SCN

in asymptomatic average-risk populations (Lieberman et al., 2000; Soon et al., 2008). The present study found that the prevalence of ACAs in CRCs was 7%, but the actual prevalence of SCN could be higher because a few patients were excluded from this study due to incomplete data. Clearance of SCN must be ascertained in all cases due to a higher risk for malignant transformation of the residual ACA, because the presence of SCN may result in a worse prognosis due to the higher susceptibility of colonic mucosa to neoplastic transformation (Mulder et al., 2011). Based on a related study (Moon et al., 2010), CRCs with synchronous ACAs rendered a higher chance of metachronous advanced neoplasia than CRCs with no ACAs. Many studies have been conducted to determine the effect of synchronous colorectal carcinomas on survival of patients with CRCs. Nosho et al., 2009 reported that synchronous colorectal carcinomas were associated with poor prognosis compared with solitary colorectal cancer. In contrast, a few related studies (Lam et al., 2006; Lam et al., 2011; Hu et al., 2013) failed to detect significant associations between the occurrence of synchronous CRCs and the shortening of overall survival. The variety of results may be attributed to molecular subtypes and genetic mutations; those may have confounded the effect of S-CRC methylation concerning outcome. Malesci et al., 2014 reported that CRCs with synchronous ACAs had a poorer prognosis among patients with microsatellite stability (MSS), but not among patients with microsatellite instability (MSI). Furthermore, the BRAF mutation was unrelated to the occurrence and the aggressiveness of MSS SCN. Therefore, SCN may only represent a phenotypic characteristic resulting from variation in the genetic pattern rather than an independent prognostic indicator. Our study found that CRCs with SCN were found at a more advanced age than solitary CRCs, and SCN was found more commonly among males. In cases that achieved a curative resection (a complete removal of the primary lesion, metastatic lesions and all synchronous advanced lesions), the present study revealed that the recurrence rate and the disease-free survival of CRCs with SCN did not significantly differ from solitary CRCs. In addition, this study also found that the disease-free survival of CRCs with SCN was marginally higher than that of solitary CRCs, but without statistical significance, consistent with some related studies (Lam et al., 2006; Lam et al., 2011; Hu et al., 2013). Nevertheless, many other factors apart from the occurrence of SCN could have affected the prognosis of patients with CRC, such as molecular heterogeneity, completeness of adjuvant therapy and environmental factors, as demonstrated in some related studies (Lam et al., 2014; Malesci et al., 2014). Lacking information on molecular genetic analysis to address the existence and types of germline mutations was one limitation of our study.

For CRC patients diagnosed with SCN, clearance of SCN and the residual advanced lesions of the remainder of large bowel must be ascertained. A more cautious approach should be taken for postoperative follow-up examination. Since the occurrence of SCN increased risk of metachronous advanced neoplasia (Melson et al., 2016), a more intensive surveillance interval should be suggested for CRC patients with SCN after achieving curative resection.

In conclusion, among patients with CRCs and SCN achieving a complete removal, the presence of SCN did not affect the recurrence rate and had marginally better disease-free survival than solitary CRCs.

Author Contribution Statement

Dr. Sahaphol reviewed literature for this manuscript, collected data, discussed of study findings, statistical analyzed and provided description of the introduction, results and discussion. Dr. Thirayost reviewed literature, reviewed tissue specimens, collected data, provided a description of the results and participated in preparing the manuscript. Dr. Chinakrit reviewed literature, participated in collecting data, provided a description of the results and participated in preparing the manuscript. Dr. Piyapan provided description of the background, participated in collecting data and participated in preparing the manuscript. All authors read and approved the final manuscript.

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Ethics statement

This study was reviewed and approved by the Institutional Review Board of The Royal Thai Army, Medical Department prior to initiation. IRB waived the requirement of written informed consent owing to the use of deidentified medical record and anonymous record to protect confidentiality.

Statement of Conflict of Interest

Authors declares no conflict of interest.

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