RESEARCH ARTICLE

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Prognostic Significance of Synchronous Colorectal Adenocarcinoma: A Matched-Pair Analysis

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Abstract

Objective: To determine the prognostic significance of the synchronous colorectal cancer (S-CRC) on survival and recurrence rate. **Methods:** Authors conducted an analysis of 90 colorectal adenocarcinoma patients who received a curative (R0) resection with a full course of standard adjuvant treatment. A total of 45 patients diagnosed with S-CRC at the time of initial presentation were individually matched to a group of 45 solitary CRC patients in pair at a ratio of 1:1. The case-matched criteria included age (± 5 years), gender, tumor location, and tumor stage. For S-CRC, the most advanced pathologic lesion was defined as the index lesion, and the matching cancer stage was categorized according to the index lesion. The N-stage was determined based on all lymph nodes. **Result:** There were a higher number of retrieved nodes in patients with S-CRC than those with solitary CRC. The median (min, max) of the total number of retrieved nodes for S-CRC was 18 (3, 53) nodes, compared to 14 (4, 45) nodes for solitary CRC ($p < 0.01$). All patients were without distant metastasis (stage I to III). The total accumulative number of patients experiencing tumor recurrence was 9 (20%) amongst the solitary CRC patients and 18 (40%) amongst the S-CRC patients at the 15-year surveillance period ($p<0.05$). The disease-free survival (DFS) (mean + SD) was 147.6 + 9.3 months in the solitary CRC group, compared to 110.5 + 11.7 months in the S-CRC group ($p<0.05$). Amongst S-CRC patients, those having primary and synchronous tumors located across anatomical segments had poorer DFS (70.5 months) and higher 15-year tumor recurrence rate (17.8%) than those with all tumors in the same or contiguous anatomical segments. In addition, the S-CRC patients with all tumors located in contiguous segment had a longer DFS (123.7 months) than the other types of anatomical correlation. **Conclusion:** Patients with S-CRC had worse prognosis than those with solitary CRC. For S-CRC, the anatomical correlation between the primary and the synchronous tumors may influence DFS and recurrence rate.

Keywords: Prognostic significance- Colorectal cancer- Synchronous colorectal cancer- Disease-free survival

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Introduction

Colorectal cancer (CRC) is a common cause of cancer-related death worldwide and the third most common cancer in the West [1]. The prevalence and clinical significance of synchronous neoplastic lesions widely differ by race and geographic location [2]. The prevalence of synchronous adenomatous polyps ranges from 15% to 50% [2], whereas the prevalence of advanced colorectal adenoma is between 5.2 and 9.6% [3, 4]. In cases with CRC, a complete clearance of all synchronous advanced lesions in the remainder of large bowel must be ascertained [4]. A former study in CRC with synchronous advanced colorectal neoplasia (SCN) revealed that the presence of SCN did not affect the recurrence rate and disease-free survival when a complete removal of all advanced lesions was achieved.

Synchronous colorectal carcinoma (S-CRC) is described as 2 or more primary colorectal carcinomas detected in a single patient at the initial presentation. The prevalence of synchronous cancer ranges from 2% to 8% [5-9]. S-CRC is associated with an older age group than solitary CRC with male preponderance [6, 10-12, 7, 13]. The presence of multiple colorectal carcinomas may be an independent predictive factor for survival rates [12]. Conditions related to multiple fields of dysplastic precancerous lesions such as inflammatory bowel diseases, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer increase the risk of developing multiple carcinomas [12]. A former study found that patients with S-CRC had family history of tumors more often than those with solitary CRC. S-CRC also exhibits different molecular and clinicopathologic features compared with solitary CRC [14]. The occurrence of multiple primary

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CRC may be associated with prognosis, and more intensive post-surgical surveillance strategies need to be implemented. Presently, the oncological outcomes and prognostic significance of S-CRC is still inconclusive due to its relatively low incidence and insufficient available data. To determine whether S-CRC is an independent predictive factor for survival rates and whether S-CRC bears specific recurrence and survival profiles, authors conducted this study using a match-paired analysis. Every S-CRC patient was individually matched with the control group of solitary CRC patients. The data was stratified based on age, sex, tumor location, and tumor stage. This match-pair study was designed to balance some predefined variables that might be related to prognosis. Based on this match-pair study, both S-CRC and solitary CRC groups demonstrated comparable clinicopathologic features except the presence of synchronous CRCs. This would elicit a strong conclusion on prognostic significance of S-CRC.

Materials and Methods

Patients

An analysis of prospective collected data of patients diagnosed with colorectal adenocarcinoma was conducted in Phramongkutklao Hospital from January 1, 2007, through December 31, 2017. A total of 45 patients were diagnosed with S-CRC at the time of initial presentation and received a successful curative resection (R0 resection). A group of 45 solitary CRC patients were individually matched to synchronous CRC patients in pair at a ratio of 1:1. The case-matched criteria included age (± 5 years), gender, tumor location, and tumor stage.

Eligibility

To detect synchronous carcinomas, all eligible patients underwent an R0 resection with complete preoperative or peri-operative colonic examinations within 3 to 6 months after surgery. Patients with polyposis syndrome were excluded from this study. Curative resections were ascertained by postoperative imaging and colonoscopy. Surgery was performed by colorectal surgeons. All the operations were performed according to oncological principles. The resection of colon cancer was made by an en bloc resection with clear margins including the lymph-node-bearing mesentery. The resection of rectal cancer was followed by total mesorectal resection with clear lateral margins. When indicated, standard regimens of adjuvant treatment were given. Patients who failed to complete the adjuvant treatment were excluded.

Tumor assessment

The clinicopathologic features of individual patients were reviewed for primary tumor location, stage, and histopathologic features including tumor differentiation, mucinous component, lymphatic invasion, and vascular invasion. All concomitant neoplastic lesions were reviewed to document location, number, and histopathologic features. Pathological diagnosis and staging were based on the AJCC classification of malignant tumors, 8th edition [15]. The most advanced pathologic lesion was defined as the index lesion in cases of synchronous cancer.

Assessment of survival

All colorectal carcinoma patients were given regular follow-ups using routine physical examination, serum markers, colonoscopy surveillance, and imaging studies (CT, MRI, or PET scan). Disease-free survival (DFS) was calculated from the date that the primary lesion, metastatic diseases, and all synchronous cancers were completely resected to the date of clinical appearance, CEA rising, or imaging detection of recurrence/metastatic diseases depending on the date of the event that happened first.

Matched-pair analysis

Patients with S-CRC were individually matched to solitary CRC in pair at a ratio of 1:1. The case-matched criteria included age (± 5 years), gender, tumor location, and tumor stage. The pathologic stage was determined according to the 8th edition of the American Joint Committee on Cancer staging manual [15]. In S-CRC patients, the most advanced pathologic lesion was defined as the index lesion and the matching cancer stage was categorized according to the index lesion. The N stage classification was determined based on examination of all lymph nodes.

Results

The results of this study were reported according to the STROBE Statement checklist [16]. A total of 90 patients those were recruited into the present study, consisting of 24 (26.7%) females and 66 (73.3%) males. The mean (SD) age of the patients at the time of diagnosis was 67.9 (11.2) years for all patients, 67.7 (11.5) years for solitary CRC, and 68.1 (11.0) years for S-CRC. Forty-five S-CRC patients were individually paired with 45 solitary CRC patients with stratification based on age, sex, tumor location, and tumor stage. Demographics, tumor staging, and histopathologic features were summarized in Table 1. The primary tumors were located within the right hemicolon between the cecum and the transverse colon in 22 patients (11 solitary CRC and 11 S-CRC patients), within the left hemicolon between the descending colon and the sigmoid colon in 48 patients (24 solitary CRC and 24 S-CRC patients), and within the rectum in 20 patients (10 solitary CRC and 10 S-CRC patients). There were higher numbers of retrieved nodes in patients with S-CRC than those with solitary CRC. The median (min, max) of the total number of retrieved nodes was 18(3,53) in S-CRC cases and 14 (4,45) for solitary CRC cases ($p < 0.01$). The present study was conducted using match-pair study design, therefore no statistically significant difference between the two groups for common clinicopathologic features. The operative procedures for S-CRC were demonstrated in Table 2. Amongst all patients without metastasis (stage I to III), a R0 resection with a course of standard adjuvant treatment was achieved in all patients. The location, number, and anatomical correlation of the primary and synchronous tumors are demonstrated in Table 2.

The present study found that the S-CRC had a

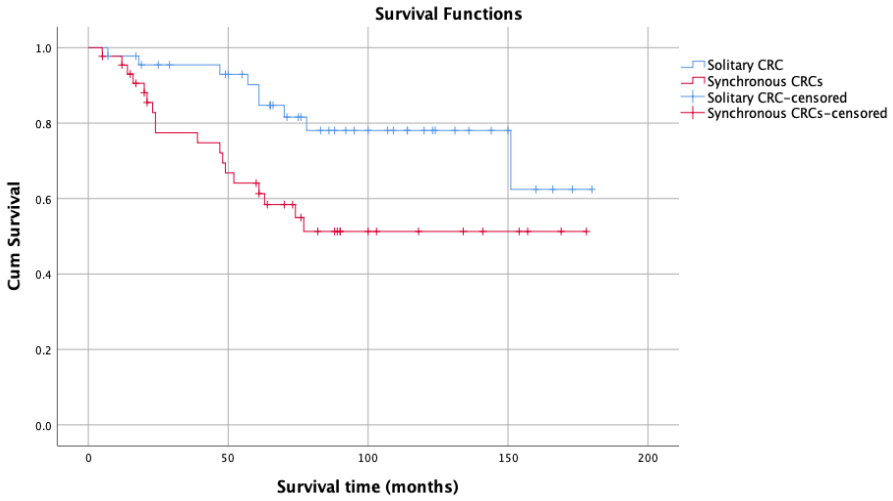

Figure 1. A Kaplan-Meier Survival Analysis of Disease-Free Survival in Patients with Solitary CRC and Patients with Synchronous CRC.

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

	Groups		Total N (%)	p-value
	Solitary-CRC N (%)	S-CRCs N (%)		
Gender N (%)				
Male	33 (73.3)	33 (73.3)	66 (73.3)	1
Female	12 (26.7)	12 (26.7)	24 (26.7)	
Age	67.7 (11.5)	68.1 (11.0)	67.9 (11.2)	0.85
Mean (SD)				
Preoperative CEA(ng/ml)	6.05 (1.07,132.3)	5.91 (0.69,117.6)	5.98 (0.69,132.3)	0.93
Median (Min,Max))				
≤ 5	20 (44.4)	21 (46.70)	41 (45.6)	1
> 5	25 (55.6)	24 (53.3)	49 (54.4)	
Location of index cancer				
Right colon	11 (24.4)	11 (24.4)	22 (24.4)	0.967
Left colon	24 (53.3)	24 (53.3)	48 (53.3)	
Rectum	10 (22.2)	10 (22.2)	20 (22.2)	
Depth of invasion N (%)				
T1-T2	4 (8.9)	3 (6.7)	7 (7.8)	1
T3-T4	41 (91.1)	42 (93.3)	83 (92.2)	
Total number of retrieved lymph node				
Median(Min,Max)	14 (4,45)	18 (3,53)	14.5 (3,53)	0.001*
Nodal involvement N (%)				
No	17 (37.8)	17 (37.8)	34 (37.8)	1
Yes	28 (52.2)	28 (52.2)	56(52.2)	
Tumor staging				
Stage 1-2	17 (37.8)	17 (37.8)	34 (38.9)	1
Stage 3	28 (52.2)	28 (52.2)	56 (61.1)	
Differentiation N (%)				
Well	5 (11.1)	7 (15.6)	11 (13.3)	0.949
Mederately	38 (84.4)	36 (80)	75 (82.3)	
Poorly	2 (4.4)	2 (4.4)	4 (4.4)	
Lymphovascular invasion	2 (4.4)	2 (4.4)	4 (4.4)	
No	26 (57.8)	26 (57.8)	52 (57.8)	1
Yes	19 (42.2)	19 (42.2)	38 (42.2)	

* Statistically significant (Mann-Whitney U test)

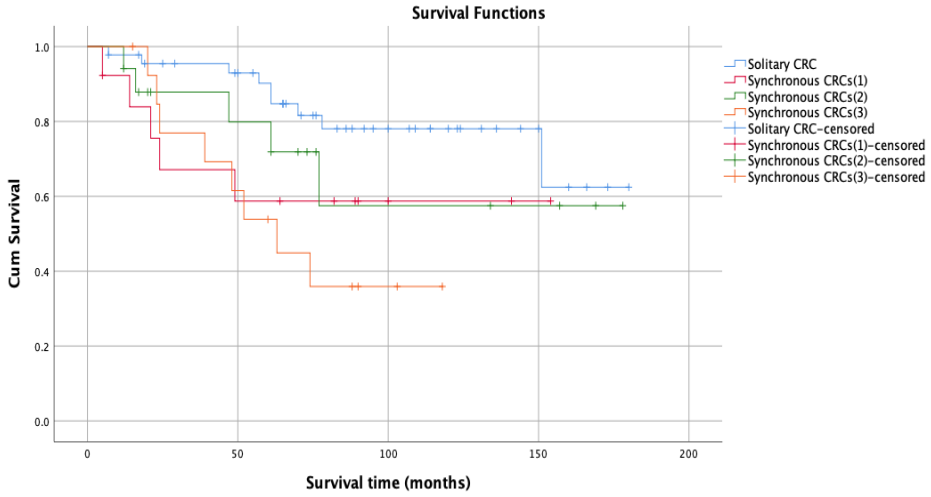

Figure 2. A Kaplan-Meier Survival Analysis of Disease-Free Survival in Patients with Solitary CRC and Patients with Synchronous CRC as Categorized by Anatomical Correlation of Primary and Synchronous Cancers.

Table 2. Anatomical Correlation of Primary and Synchronous Cancers and Operative Procedures Performed.

Synchronous CRCs (N=45)			Operative procedure	
Primary cancer	Synchronous cancer	Number		
Right colon	Right colon	4	Right hemicolectomy	4
(N=11)	Left colon	7	Right hemicolectomy with endoscopic removal	1
			Subtotal colectomy	5
			Total colectomy	1
Left colon	Left colon	10	Anterior recestion	8
			Extended left hemicolectomy	1
			Low anterior resection	1
(N=20)	Right colon	6	Subtotal colectomy	3
			Total colectomy	2
			Left colectomy with cecectomy	1
	Rectum	4	Low anterior resection	4
Sigmoid	Left colon	3	Anterior recestion	3
(N=4)	Rectum	1	Low anterior resection	1
Rectum	Right colon	2	Low anterior resection with endoscopic removal	1
(N=10)			Total proctocolectomy	1
	Left colon	6	Low anterior resection	5
			Total proctocolectomy	1
	Sigmoid	2	Low anterior resection	1
			Hartmann's procedure	1

Table 3. Cumulative Incidence of Recurrence in Patients with Solitary CRC and in Patients with Synchronous CRCs as Categorized by Anatomical Correlation of Primary and Synchronous Cancers.

Group	Number	1 year	3 years	5 years	7 years	10 years	15 years	p-value
N(%)	(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	
Solitary cancer	45(100)	1(2.2)	2(4.4)	4(8.9)	8(17.8)	8(17.8)	9(20)	0.034*
Synchronous cancer	45(100)	2(4.4)	9(20%)	14(31.1)	18(40)	18(40)	18(40)	
Anatomical correlation (Primary- Synchronous CRCs)								
Same anatomical segment	13(28.8)	1(2.2)	4(8.9)	5(11.1)	5(11.1)	5(11.1)	5(11.1)	
Contiguous anatomical segment	18(40)	1(2.2)	2(4.4)	3(6.7)	5(11.1)	5(11.1)	5(11.1)	
Across anatomical segment	14(31.2)	0(0)	3(6.7)	6(13.3)	8(17.8)	8(17.8)	8(17.8)	

*, Statistically significant (Log rank test)

Table 4. Disease-Free Survival (Months) Categorized by the Presence of Synchronous Cancers and Anatomical Correlation between Primary and Synchronous Cancers.

Group	Disease-free survival (month)		p-value
Number	Mean (SD)	95%(CI)	
All CRCs (N=90)			
Solitary CRC (No synchronous cancer) (N=45)	147.6 (9.3)	129.2-165.9	0.034*
Synchronous CRCs	110.5 (11.7)	87.5-133.5	
Categorized by anatomical correlation (primary-synchronous CRCs) (N=45)			
Same anatomical segment (N=13)	99.9 (18.7)	63.1-163.7	
Contiguous anatomical segment (N=18)	123.7 (19.6)	85.4-162.1	
Across anatomical segment(N=14)	70.5 (10.9)	49.1-91.9	

*, Statistically significant (Log rank test)

significantly higher recurrence rate (Table 3) and poorer disease-free survival (DFS) than solitary CRC (Table 4 and Figure 1). The total accumulative number of patients experiencing tumor recurrence was 8 (17.8%) for solitary CRC vs 18 (40%) for S-CRC patients at the 10-year surveillance period and 9 (20%) for solitary CRC vs 18(40%) for S-CRC patients at the 15-year surveillance period (p=0.034). The DFS (mean + SD) was 147.6 + 9.3 months in solitary CRC patients and 110.5 + 11.7 months in S-CRC patients (p=0.034).

To determine the prognostic impact of the anatomical correlation between the primary and the synchronous tumors, the S-CRC patients were categorized into 3 groups: group 1, both primary and synchronous tumors located in the same anatomical segment (N=13); group 2, primary and synchronous tumors located in the contiguous anatomical segment of the large intestine (N=18); and group 3, primary and synchronous tumors located across anatomical segments of the large intestine (N=14). Group 3 patients were shown to have a poorer DFS (70.5 months) and a higher 15-year tumor recurrence rate (17.8%) than the other two groups. In addition, group 2 patients were seen to have a better DFS than group 1 patients (123.7 months in group 2 vs 99.9 months in group 1), but with a comparable tumor recurrence rate of 11.1% in both groups (Figure 2).

Discussion

In the present study and in former studies, most of the patients with S-CRC had two, but up to six carcinomas in single patient have previously been reported [12]. Compared to solitary CRC, S-CRC more commonly involves the right-side colon [5, 12] and is found to have higher association with sessile serrated polyps/hyperplastic polyposis and microsatellite instability [17, 12, 18]. Patients with S-CRC also have a higher incidence of mucinous carcinoma, family history of malignant diseases, and neoplastic polyps [5]. It is plausible that hereditary oncologic factors may be associated with the occurrence of synchronous carcinomas, and the molecular biology may account for various predisposing factors for synchronous CRCs such as chromosomal instability, microsatellite instability, and gene methylation.

Presently, the prognostic significance of S-CRC remains controversial. Robust scientific evidence is needed to reach a conclusion. Nosho et al. [19] proposed that S-CRC had poor clinical outcomes due to the higher incidence of complications and spreading from multiple colorectal carcinomas. Patients with S-CRC may have a worse prognosis compared to those with solitary CRC. Van Leersum et al. [7] reported that S-CRC was associated with a higher risk of severe postoperative complications and reinterventions [7]. Some previous studies demonstrated that the presence of S-CRC reduced overall survival [19, 20, 8]. Arakawa et al. [8] reported that 92 (7.1%) out of 1,295 consecutive CRC had S-CRC. The study found significantly higher incidence of mucinous adenocarcinoma and poorer relapse-free survival in patients with S-CRC than those with solitary CRC. He et al. [13] also demonstrated that the prognosis of patients with S-CRC was poorer than those with solitary CRC. However, many previous studies reported that S-CRC had a comparable or even slightly better prognosis than solitary CRC [10, 11, 21, 12, 9]. Oya et al. [6] conducted a comparative study including 834 solitary CRC and 42 S-CRC. The study found that solitary CRC and S-CRC had similar clinical characteristics and pathological features. The study revealed the prognosis of patients with synchronous CRC was not different from solitary CRC when having the same pathological stage and achieving a curative resection. The study concluded that S-CRC did not influence the prognosis. To determine the prognostic significance of S-CRC, authors conducted this present study by using a matched-pair analysis. This matched-pair design was beneficial to achieve a comparable group on predefined associated variables. The present study found there was a higher number of retrieved nodes in patients with S-CRC than those with solitary CRC. This could be explained by the fact that the S-CRC patients underwent a more extensive surgical procedures than those with solitary CRC. Therefore, a larger mesenteric specimen

removal rendered a higher number of retrieved lymph nodes that were located alongside the resected mesenteric vasculature. The present study demonstrated that patients with S-CRC had a worse prognosis compared to patients with solitary CRC, confirming previous studies [19, 20, 22]. The present study also examined the prognostic significance of the anatomical correlation between primary and synchronous tumors. Noteworthy, this study found that the group of patients whose primary and synchronous tumors located across anatomical segments (S-CRC group 3) had poorer DFS and higher accumulative number of patients with tumor recurrence at 15-year (17.8%) than the other two groups. It is possible that patients whose primary and synchronous tumors were located across anatomical segments harbored a higher chance of nodal metastases along multiple main mesenteric vasculatures and spreading routes. On the contrary, tumor spread might be confined to a specific main mesenteric vasculature and spreading route when the primary and the synchronous tumors were in the same anatomical segment. Given that cancer is a genetic disease and mainly arises due to the disorder of cellular biology, research on S-CRC at the molecular level could be beneficial to determine the impact of hereditary oncologic factors on clinicopathologic features and prognosis. A previous study demonstrated that vast majority of S-CRC are microsatellite stable cancers that present with multiple advanced lesions and have a worse prognosis than corresponding solitary CRC [22]. Some hereditary oncologic factors might be associated with the occurrence of S-CRC in various locations and their anatomical correlation. Further studies with a larger number of patients on specific types of relevant molecular biology of S-CRC might provide a guidance for personalized cancer treatment to achieve better treatment outcomes in S-CRC patients.

Author Contribution Statement

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

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Ethical Declaration

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.

Conflict of Interest

Authors declares no conflict of interest.

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