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Breast and Bowel Cancer

RESEARCH ARTICLE

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Double versus Single Primary Malignant Neoplasm of Breast and Colorectal Cancer: A Case-Control Study

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Abstract

Purpose: Breast cancer (BC) and colorectal cancer (CRC) are common in female. This study compared survival time between women affected with both cancers with ones with single BC or single CRC. **Method:** Medical records of subjects with both BC & CRC (June 1, 2010, to June 30, 2021) were reviewed. Age-matched subjects who had BC or CRC alone were used as control. Survival analysis using Kaplan-Meier method was performed. **Result:** There were 63 double cancers [40 BC first (D_{BC}): 23 CRC first (D_{CRC}), mean age±SD 60.5±9.9 and 60.9±12.2 years] and 76 subjects in single cancer group [53 S_{BC}: 23 S_{CRC}, mean age 57.4±11.3 and 61.1±12.5 years]. The 5-year survival rate of the double cancer group was 74.6% and the single cancer group was 63.2%. D-group had slightly longer survival time than S-group (116.5±4.0 vs. 101.3±5.5, p=0.055). In D-group, the occurrence of addition of other primary cancers were more common (p=0.015). The second cancer occurred 61.7±45.3 months later in D_{BC} group, and 39.1±26.6 months later in D_{CRC} group (p=0.016). S_{CRC} had shorter survival time vs. D_{CRC} group (p=0.031). S_{BC} and D_{BC} had no different in mean survival time. **Conclusion:** BC and CRC could occur as a part of multiple primary cancers. Detection of more than one cancer did not lead to decrease survival if the second cancer was early detected and treated. The occurrence of the second cancer might be beyond 5 years after the diagnosis of the first cancer. Thus, longer surveillance may be warranted. Awareness and provision of early screening should be offered to individuals diagnosed with either primary cancer. Detection of more than one cancer did not lead to shorter survival.

Keywords: Breast cancer- Colorectal cancer- Multiple cancer- Survival

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Introduction

Multiple primary malignant neoplasms (MPMNs) are defined as occurrence of multiple cancers in different organs or pathological origin [1, 2]. Reported incidence was 2.8% from surgical and necropsy cases and was found in 2.2% of female patients [3]. In female with breast cancer was found to have second primary colon cancer more than 50% of the expected number in normal population [4]. In 4.5% of persons with primary colorectal cancer were found to have associated extracolonic primary malignant tumor including breast cancer [5]. Breast cancer and colon cancer were the most and second most common cancer in Thai female, respectively [6]. Five percent of patients with colon cancer had other primary cancer and 3-11% of patients with breast cancer would have other primary cancer [7, 8]. These cancers from different sites may be related by *intrinsic susceptibility* of the individuals, e.g. impaired immunity; extrinsic predisposition to common environmental factors, e.g. lifestyle and occupation; genetic factors, e.g. *BRCA1* mutation [2, 9] and Lynch syndrome [10]; or therapeutic effects of the first tumor, e.g. radiotherapy of the first primary cancer resulted in increased risk of second primary cancer [2]. Another simple explanation could be that the improved treatment strategies had prolonged the patients' life until the development of the new cancer [7]. The second cancer could occur as synchronous (within 6 months after the diagnosis of the first cancer) or metachronous lesions (later than 6 months after the diagnosis of first cancer [10]. Criteria to differentiate multiple primary tumors from metastatic diseases were (1) each tumor has different histology (2) each tumor arise in various locations (3) no evidence of recurrence, metastasis, or local spreading of the first tumor [3, 11]. With improvement of cancer treatment and longer survival, increasing numbers of survivors of colorectal and breasts cancers were seen. Later, some of them suffered from the other second primary cancer. Breast cancer and colorectal cancer were two of the leading cancers in female population in our

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region [6]. However, these two cancers have not been in routine screening program and subjects with either one of these cancers would not be routinely screened for the other. This study was aimed to compare survival difference between patients with single breast cancer or large bowel cancers, and patients with double breast and bowel cancers.

Materials and Methods

Retrospective case-control study was performed by reviewing of the hospital records of patients treated at the King Chulalongkorn Memorial Hospital, a tertiary institute in Bangkok, Thailand, between June 1, 2010, to June 30, 2021. Subjects who developed both breast and large bowel cancers, in either sequence, during this period were studied. Age-matched patients with single breast cancer or single colorectal cancer diagnosed during this period, were used as control with the ratio of about 1:1.3 for double cancer (breast cancer first): single breast cancer, and 1:1 for double cancer (colorectal cancer first):single colorectal cancer. Patient with incomplete medical records were excluded. Flow of enrollment is shown in Figure 1. Data including age of diagnosis, staging groups (early, locally advanced, or metastatic disease), histopathology and treatment of the breast and/or large bowel cancer in patients with double/single cancer(s); time to diagnosis of second primary cancer, symptoms of second cancer, family history of cancer, and other additional cancer were retrieved. Stages of tumors were divided in to 3 groups; early-tumor is small and confined to local area of origin (T1,T2 N0 M0), locally advanced- tumor is of moderate site and depth but still confined to the organ of origin, directly invade to adjacent organ or regional lymph nodes without distant metastasis (T3,T4 N-positive M0) and metastatic- tumor has spread to distant organ (Tany Nany M1) [12, 13].

This study had been approved by Institutional Board of Faculty of Medicine, Chulalongkorn University no. 1027/64, the institutional review board of Faculty of Medicine, Chulalongkorn University and the director of King Chulalongkorn Memorial hospital waived the informed consent from the subjects [IRB no.1027/64]. All methods were performed in accordance with the relevant guidelines and regulations.

Statistical analysis

Demographic data were presented as mean and standard deviation. Comparison between double-cancer group and single-cancer group were performed by Fisher Exact test for categorical data. Independent t-test was used to compare continuous variable. Survival analysis using Kaplan-Meier curves and Log-rank test were conducted to compare difference between group. A p-value of <0.05 was considered statistical significance for all analysis. All statistical analysis was conducted using the SPSS version 22.0 (Armonk, NY: IBM Corp.).

Results

During the study period (June 1, 2010 to June 30, 2021), there were 63 subjects with double breast and colorectal cancer; 40(63.5%) of these presented with breast cancer first (mean age at diagnosis±SD 60.5±9.9 years) and 23 (36.5%) presented with colorectal cancer first (mean age 60.9±12.2 years), respectively. In the control group, there were 53 subjects with single breast cancer (mean age 57.4±11.3) and 23 subjects with single colorectal cancer (mean age 61.1±12.5 years). All subjects were female. Mean follow up time was 6.8±3.6 years (range 1-24 years). Table 1 shows demographic data in detail.

Most subjects were symptomatic by the time of diagnosis of the first cancer. In double cancer group with initial breast cancer, ratio of early: locally advanced: metastatic cancer was 28: 11: 1, respectively. This was significantly different from the group with single breast cancer which was 21: 24: 8. In double cancer group with initial colorectal cancer, the ratio was 4: 15: 4 and in the single colorectal cancer group, the ratio was 5: 14: 4, respectively. These showed no significant difference.

Double cancer group had significantly higher number of patients with multiple primary neoplasm than the single cancer group (p=0.005). Eight patients in double cancer with initial breast cancer (D_{BC}) and 4 patients in single breast cancer (S_{BC}) were additionally diagnosed with other cancers. Five patients in double cancer with initial colorectal cancer (D_{BC}) but none of single colorectal cancer (S_{CRC}) group were found to have additional cancers. Additional other cancers in the doubled cancer groups with initial breast cancer included carcinoma of ampulla of Vater (1), pancreatic carcinoma(1), neuroendocrine tumor of lung(1), hepatocellular carcinoma(2), papillary thyroid cancer(1), ovarian cancer(1), endometrial cancer(1). One patient who developed hepatocellular carcinoma also had pulmonary adenocarcinoma subsequently. In the group with initial colorectal cancer, other cancers were endometrial cancer (3), ureteric cancer(1) and lung cancer(1). All patients who had additional cancer, developed the third (and forth) cancer after the diagnosis of breast and large bowel cancer, except a patient with ureteric cancer who had been diagnosed and treated prior to the study period.

There was no significant difference in the number of subjects with family history of cancer between groups. Less than 50% of patients with family history of cancer received genetic counselling and testing. Four patients in double cancer groups were positive for genetic mutation, namely Li Fraumeni syndrome, *BRCA1* mutation and CDH1 mutation. One patient in the single colorectal cancer group was a member of a family with MSH2 mutation.

In double cancer group, ages at diagnosis of the second cancer are shown in Table 2. Priority was metachronous cancer. Time to second cancer of 61.7±45.3 months in breast cancer first group and 39.1±26.6 months in colorectal cancer first group which was significantly shorter (p=0.016).

Breast cancer

In double cancer group, up to 70% of breast cancer presented in the early stage compared to only 40% in single breast cancer group (p=0.049). Seventy-eight

Table 1. Characteristic of Patients with Double and Single Breast and/or Colorectal Cancer

	Double cancer (D)###		Single cancer (S) ###		
	Breast first (D_{BC}) (n=40)	CRC first (D_{CRC}) (n=23)	Breast (S_{BC}) (n=53)	CRC (S_{CRC}) (n=23)	*p*-values
Age of diagnosis (mean±SD, years)	60.5 ± 9.9,	60.9 ± 12.2	57.4 ± 11.3	61.1 ± 12.5	0.276###
Range (years)	39-79	42-89	29-82	39-90	
p-values	0.882		0.201		
Symptomatic at diagnosis	39 (96%)	23 (100%)	39 (74%)	23 (100%)	
Stage of cancer					
Early	28 (70%)	4 (17%)	21 (40%)	5 (22%)	0.001###
Locally advanced	11 (27.5%)	15 (66%)	24 (45%)	14 (61%)	
Metastatic	1(2.5%)	4 (17%)	8 (15%)	4 (17%)	
More than 2 cancers	8 (20%)	5 (22%)	4 (7.5%)	0 (0%)	0.008###
Family history of cancer	8 (20%)	6 (26%)	11(21%)	2 (9%)	
	14 (22%)		12 (16%)		0.821###
Gene tested (positive)	4 (3^{+})	2(1^{++})	0	1 (1^)	
Location (Right:Left)		8:15		5:18	
Cecum-ascending/ Hepatic flexure/ Transverse colon		4/2/2		4/1/0	
Sigmoid/Rectosigmoid/Rectum		11/0/4		5/4/0	
Subtype of breast cancer		(2^{nd}) breast cancer			
Luminal A/ Luminal B	22/ 6	12/4	23/ 11		
Triple negative	3	2	7		
HER-2	3	4	11		
Recurrence at primary site	2 (5%)	0 (0%)	3 (6%)	3 (13%)	@1-3 years
Mean follow-up time (year±SD)	7.5±4.7		5.9±2.6		

BC, breast cancer; CRC, colorectal cancer; +1 Li Fraumeni syndrome, 2 *BRCA1* mutation, ++1 CDH1 mutation, ^1 MSH2 mutation; ###S, (Single cancer group) vs. D (Double cancer group)

percent of patients with second primary breast cancer were symptomatic. Most had palpable mass and a few with breast pain which led to further work up. Eight of 40 subjects in D_{BC} and 4 of 53 subjects in S_{BC} had more than 2 cancers (p=0.117). Eight and 11 subjects from the respective groups had family of cancer (p=0.512). Three of 4 subjects who had been tested for genetic mutation were found to have Li Fraumeni syndrome (n=1) and *BRCA-1* mutation (n=2). Breast cancer subtypes were prominently luminal A in D_{BC} compared to a higher number of HER-2 subtype in S_{BC} group (p=0.237).

Colorectal cancer

There was no difference in the distribution of stage of cancer between double and single cancer groups. Five of 23 subjects in D_{CRC} group and none of 23 subjects in S_{CRC}

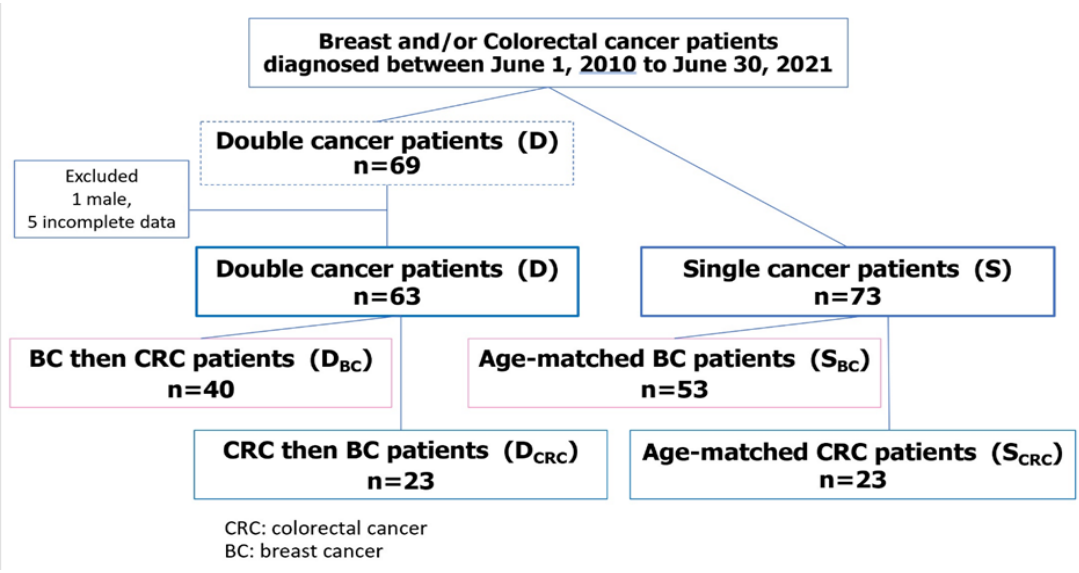

Figure 1. Flow of Enrollment

Table 2. Details of the Second Cancer in the Double Cancer Group

	Breast first (D_{BC}) (n=40)	CRC first (D_{CRC}) (n=23)	p-values
Age of diagnosis of 2nd cancer (mean±SD, years)	65.7±10.4	64.5±11.6	
synchronous: metachronous	4:36	3:20	
Time to 2nd cancer (months)	61.7±45.3	39.1±26.6	0.016
Symptomatic	36 (90%)	18 (78 %)	
Stage of 2nd cancer	Colorectal cancer	Breast cancer	
Early	13 (32.5%)	15 (65%)	0.005
Locally advanced	11 (27.5%)	7 (30%)	
Metastatic	16 (40%)	1 (5%)	

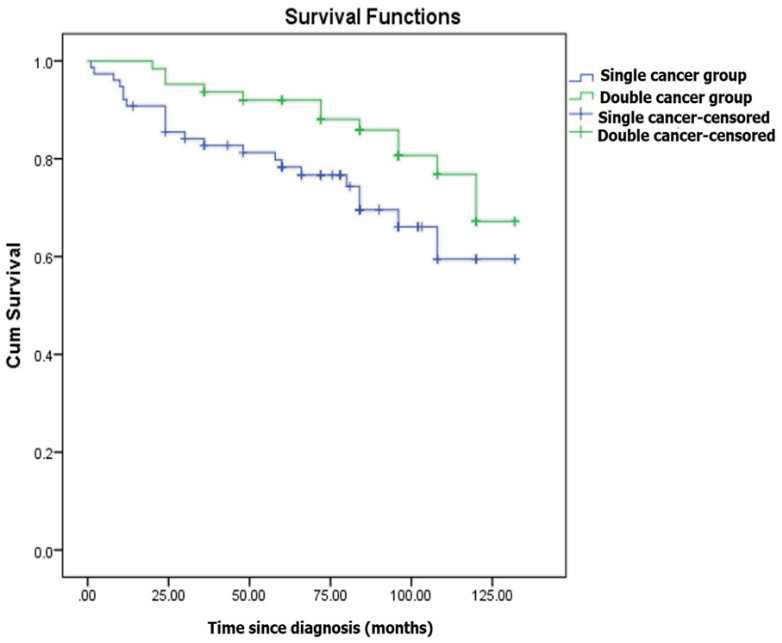

Figure 2. Survival of Subjects with double vs. Single Cancer

Table 3. Means Survival Time of Subjects with Double and Single Breast and/or Colorectal Cancer

	Double cancer group (D)		Single cancer group (S)		p-value
	Breast first (D_{BC})	CRC first (D_{CRC})	Breast (S_{BC})	CRC (S_{CRC})	
Mean (months)	113	124	104.9	86.9	
95%CI	102.7-123.3	113.2-134.8	92.8-117.0	67.3-106.5	
	116.5±4.0		101.3±5.5		0.055###
					0.511*
					0.374Δ
					0.031□
Stage of primary cancer					
Early	117.7±4.7		120.5±6.4		0.729###
Locally advanced	119.2±6.1		110.2±6.9		0.363###
Metastatic disease	83.2±20.3		43.6±10.6		0.047###
					<0.001*
					0.232Δ
					0.007□
Censored (%)¶	12 (19)		12 (23)	8 (35)	

###S, (Single cancer group) vs. D (Double cancer group); *S_{BC} (Single cancer group: breast cancer) vs. S_{CRC} (Single cancer group: colorectal cancer); ΔS_{BC} (Single cancer group: breast cancer) vs. D_{BC} (Double cancer group: breast cancer first); □S_{CRC} (Single cancer group: colorectal cancer) vs. DCRC (Double cancer group: colorectal cancer first); ¶, Censored, death or loss to follow-up

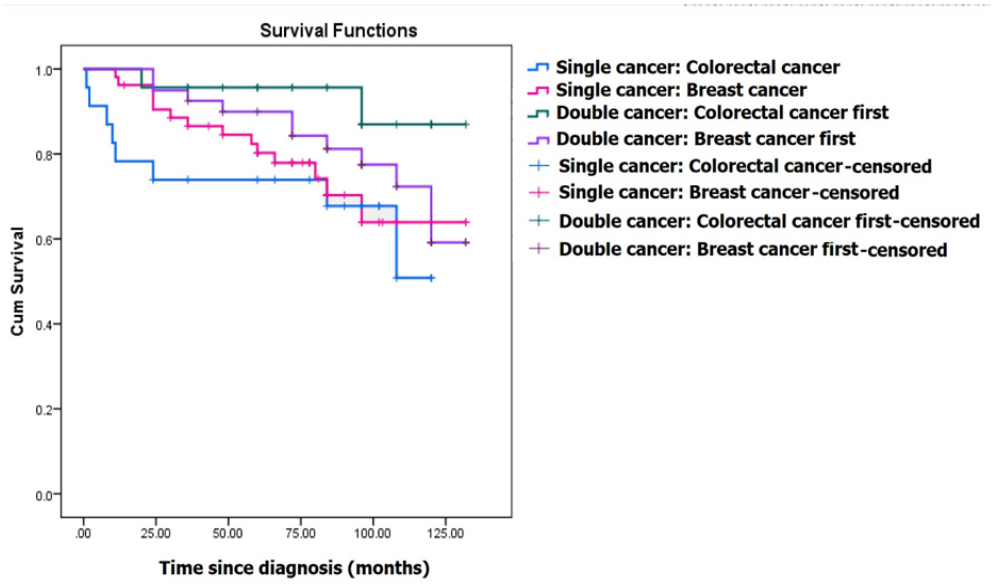

Figure 3. Survival of Subjects with Double Cancers: breast cancer first, colorectal cancer first, single breast cancer and single colorectal cancer

group had more than 2 cancers (p=0.049). There was no difference between groups regarding family history of cancer. However, in the double cancer group has slightly higher number of subjects with family history (6 vs. 2, p=0.243). Only two subjects in double cancer group get genetic testing which was found to be positive for CDH1 mutation. In the single cancer group, MSH1 mutation was found in the only subject who had been tested. In both groups, CRC were more likely located in left-sided colon. Patients were symptomatic in 90% of second primary colorectal cancer (bowel habit change, colonic obstruction, mucous bloody stool, or palpable mass). S_{CRC} had 13% recurrent rate, but none in the D_{CRC} group.

Survival analysis

Survival time was calculated from the time of diagnosis to the time of last follow-up or death (point of censoring). The 5-year survival rate of the double cancer group was 74.6% and the single cancer group was 63.2%. In double-cancer group; mean survival time ±SE was 116.5±4.0 months which was slightly longer than 101.3 ±5.5 months in the single cancer group (p=0.055) (Figure 2). Mean survival of each group is shown in Table 3. There was no difference in survival between 2 double-cancer groups (D_{BC} vs. D_{CRC}). There was no difference in breast cancer survival between D_{BC} and S_{BC} groups. Colorectal cancer survival was significantly shorter in the single cancer group. When compare by stage, there was no significant difference in survival between double or single cancer groups (p=0.114). Figure 2 showed survival function of single-cancer vs. double-cancer groups. Figure 3 and Figure 4 demonstrated survival

a

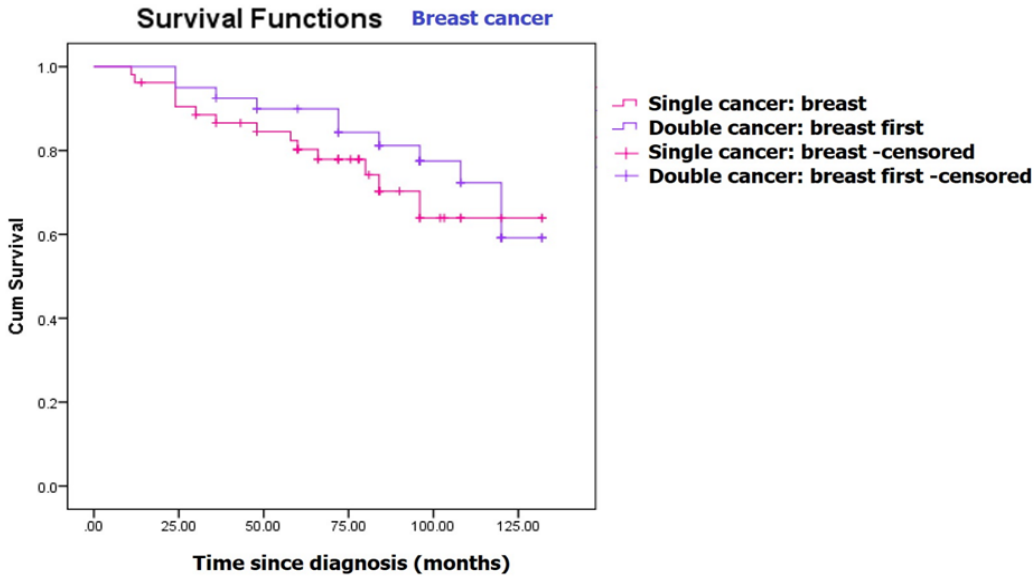

Figure 4a. Survival Function of Breast Cancer: single breast cancer vs. double-cancer group with breast cancer first

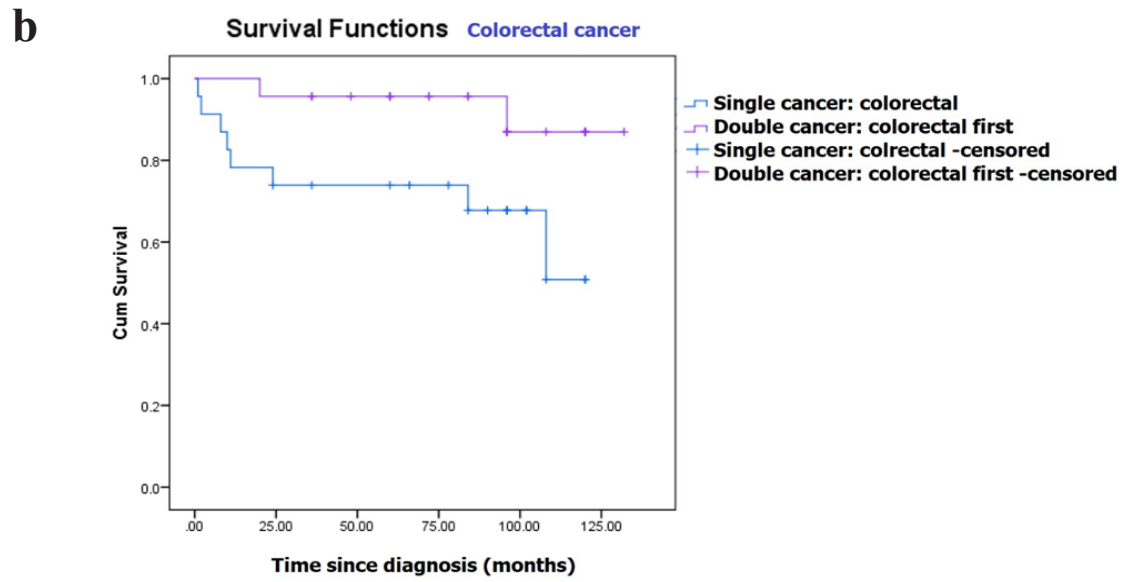

Figure 4b. Survival Function of Colorectal Cancer: single colorectal cancer vs. double-cancer group with colorectal cancer first

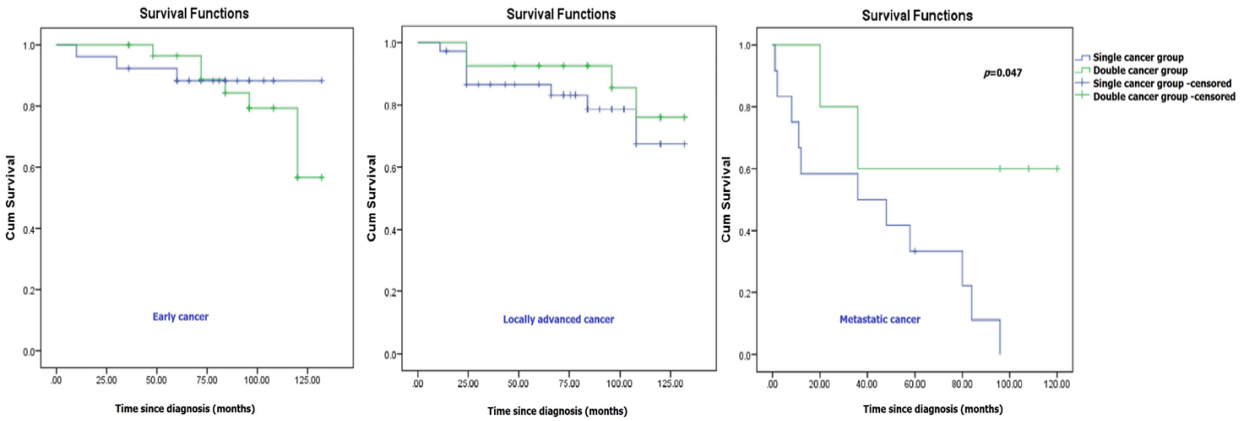

Figure 5. Comparison of Survival by Stages

function of subgroups (Figure 4a; single-cancer group: S_{BC} vs. S_{CRC} and Figure 4b; double-cancer groups: D_{BC} vs. D_{CRC}). When consider the stage of disease at presentation, there were trends that subjects with double cancer had lower survival times when compared to single cancer group (Figure 5). This was statistically significant when the presentation was at metastatic stage.

Discussion

Multiple primary malignant neoplasm was seen in 5% of autopsy cases [13]. Breast cancer was found in 23% and colorectal cancer was found in 25.6% of female with multiple cancers [13]. Etiology of developing multiple cancers in the same individual could be explained by 1) familial cancer syndrome or genetic susceptibility 2) exposure to common pathogen such as alcohol and tobacco 3) effect of previous cancer treatment [14]. Other possibility is that the longer survival after the first cancer treatment leads to another probability of developing the second primary cancer [15]. Age of onset of the first cancer in the double cancer group was not significantly different from the single cancer groups. All colorectal cancer patients and most of the patients with breast cancer were symptomatic at presentation. These may infer to the lack of mandatory screening program. The reason could be the reimbursement process. Cost of cancer investigational procedures could be reimbursed only when the patient is symptomatic. Thus, no active voluntary screening is not popular. For breast cancer first in double cancer group, most subjects presented in early stage which resulted in good prognosis. Thus, the longer survival of the first cancer might lead to natural possibility to develop the other cancer. Time to diagnosis of the second colorectal cancer was around 5 years after the diagnosis of breast cancer. The first colorectal cancer, in the double cancer group, were mostly found at locally advanced stage. Time to second cancer in this group is only about 3.5 years. Explanation could be the underlying likelihood of these individuals to develop multiple cancer and an increasing

prevalence of colorectal cancer in population worldwide [16]. Five to 10 percent of breast and colorectal cancer are hereditary [17, 18]. Majority of hereditary breast cancer were caused by *BRCA1* and *BRCA2* genes mutation [18]. Examples for minor non-BRCA mutations were *PALB2, TP53, PTEN, CDH1, ATM, CHEK2* [17]. Hereditary colorectal cancer could result from chromosomal instability or microsatellite instability, which is phenotype of mutation of mismatch repair genes, including *MLH1, MSH2, MSH3, MSH6*, and *PMS2* [18]. Genetic testing was not widely accepted by patients in our institute. This may be due to high cost and concern of anxiety and stress after knowing of genetic result. *BRCA1* mutation was found to be associated with increased risk of colorectal cancer [9, 19]. Thus, *BRCA1* mutation carrier should be offered colonoscopy at 3- to 5-year intervals between the ages of 40 and 50 years [19]. Li-Fraumeni syndrome, an autosomal dominant mutation of TP53 gene increases risk of multiple cancer at early age, including breast and colorectal cancers [20]. In this syndrome, colorectal cancer could occur in small polyps and were mostly located in left-sided colon [20]. Recommendation is colonoscopy every 2-5 years starting at 25 years old or 5 years before the earliest known colorectal cancer in the family [21]. *CDH1* mutation was found to associate with development of breast cancer and colorectal cancer [22]. *MSH2* is one of the DNA mismatch repair genes that their mutation is associated with Lynch syndrome [23]. Cumulative risk of colorectal cancer in person with MSH2 mutation was 33-52% and breast cancer risk 1.5-2.8% [24]. Genetic testing may predict the likelihood of cancer occurrence and guide appropriate screening program. Without genetic testing, family history of breast cancer or colorectal cancer was associated with increased likelihood of having up-to-date screening of these cancers [25]. Yamamoto (2006) reported that after treatment of colorectal cancer, 14.7% of female developed the second cancer which breast was the third common site (following uterus and stomach) [26]. Halamkova (2021) found that 33% of subjects with colorectal cancer had been previously diagnosed with breast cancer [27]. In this study, there was lack of screening test for the second primary cancer. Thus, the second primary cancers were mostly symptomatic at presentation. Higher proportion of early stage of breast cancer compared to colorectal cancer could be explained by the superficial organ location and breast cancer awareness in female. Breast mass could be self-detected and other symptoms such as nipple discharge and breast pain could elicit patients' concern and seeking of medical advice. From survival analysis, survival of double cancer group that presented with breast cancer first and single breast cancer groups had no different in mean survival time. The second breast cancer after colorectal cancer did not seem to effect survival. Colorectal symptoms were more ambiguous, thus lead to delay in diagnosis. A group of single colorectal cancer had the lowest mean survival time compared to other groups. This could not be clearly explained by either the stage at diagnosis, but the recurrent rate was highest in this group. The better survival in the double cancer group, even statistically non-significant, is consistent with previous description by Lynch (1981) that increased survival is a natural history of hereditary cancer [28]. Also, there was higher recurrence of S_{CRC} than D_{CRC}. By stage, single cancer group that presented in metastatic stage also had significant shorter mean survival time than the double cancer group (Figure 5). Survival in double cancer group could be affected by the treatment of the initial and second cancers. In the premenopausal women with hormonal positive breast cancer usually receive adjuvant tamoxifen, a selective estrogen receptor modulator. Some literatures suggested modestly increased risk of large bowel cancer in female receiving tamoxifen as adjuvant therapy for breast cancer [29, 30]. However, some laboratory data showed promising effect of tamoxifen in prohibiting colon cancer cells [31, 32]. In this study, the effect of treatment of primary cancer on the second cancer could not be concluded due to limited accuracy of retrospective review of antiestrogen usage. For S_{BC} and D_{BC} , there was no different in mean survival time. For colorectal cancer, S_{CRC} had significantly shorter survival rates than the D_{CRC} . Whether this was due to the effect of treatment of the second cancer (breast) or a natural history of the hereditary breast and nonpolyposis colon cancer [28, 33] is not known.

From this study, there were overall trends of longer survival in double cancer group, in term of 5-year-survival rate and mean survival time. However, there were limitations in the retrospective nature of data collection. Firstly, the lack of information about the subjects who were censored by loss of hospital contact. Secondly, the treatment details of systemic therapy and radiotherapy could not be clearly retrieved. Thus, protecting factors of double cancer could not be considered. Further detailed study with prospective data collection would give more explanation to this finding. Moreover, further improvement in survival could be added to both single cancer and double cancer groups if timely and appropriate screening for breast and colorectal cancer were applied. The occurrence of the first cancer should lead to increased awareness of the possibility of second cancer by both patient and physician.

In conclusion, breast cancer and colorectal cancer could be a part of multiple primary malignant neoplasms. The presence of both cancers showed slightly longer survival than presence of either one of them. Diagnosis of the first cancer should lead to awareness of the second cancer and appropriate and timely screening should be offered. Active surveillance, early detection and treatment could lead to prolonged survival even in the presence of double cancers. Without genetic testing, family history of cancer and/or personal history of the first primary cancer should elicit cancer screening for individual at appropriate intervals. The occurrence of the second cancer might be beyond 5 years after the diagnosis of the first cancer. Thus, longer surveillance may be warranted.

Author Contribution Statement

KT: Design of the study, literature search, data acquisition, data analysis and interpretation, manuscript preparation; PJ, SS, SM, MV,PV, VV: Data acquisition and data analysis; SS: IRB coordination; SM, MV: Data

approval and interpretation

Acknowledgements

Scientific and Ethical approval

This study has been approved by the director of King Chulalongkorn Memorial hospital and the Institutional Review Board of Faculty of Medicine, Chulalongkorn University, which the waived of the informed consent from the subjects had been applied [IRB no.1027/64]. All methods were performed in accordance with the relevant guidelines and regulations. This study has been approved by WHO trial registration (Thailand section): TCTR20230826011.

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Conflicts of interest

All authors had no conflicts of interest. This study had no funding.

Data availability statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

This study has been approved by WHO trial registration (Thailand section): TCTR20230826011.

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