Metachronous carcinomas in colorectum and its clinicopathological significance

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ABSTRACT

PURPOSE: The study was designed to examine the significance of colorectal metachronous carcinoma in a large cohort of patients.

METHODS: Over a mean follow-up period of 10 years, the clinicopathological features, microsatellite instability (MSI) and clinical follow-up of 56 patients with metachronous colorectal carcinoma were analysed.

RESULTS: The prevalence of metachronous colorectal carcinoma was 2.1%. The metachronous colorectal carcinomas appeared between 7 to 246 months (mean=66 months) after surgical resection of the index colorectal carcinomas. Thirty-six per cent (n=20) of the metachronous carcinoma occurred more than 5 years after the operation of the index carcinoma. Of the 56 patients, 20% (n=11) of the metachronous colorectal carcinomas were mucinous adenocarcinoma. Cancers detected in the secondary operations (metachronous colorectal carcinomas), when compared with the primary index cancers, were smaller, showed higher proportions of mucinous adenocarcinoma and more often located in the proximal colon. Patients with metachronous colorectal cancers had higher prevalence of mucinous adenocarcinoma, loss of staining for microsatellite instability markers and better survival rates than other patients with colorectal cancers.

CONCLUSIONS: Patients with metachronous colorectal carcinomas have characteristic features and attention to these features is important for better management of this group of cancer.

Keywords: metachronous; multiple; colorectal; cancer; carcinoma.

INTRODUCTION

A metachronous colorectal carcinoma is the presence of more than one primary colorectal carcinoma detected consecutively in a single person after a set time interval. The second cancer must be unequivocally new, not a recurrence, not a metastasis and diagnosed on histology. Although metachronous colorectal carcinoma is recognized as an important entity, its prognosis, clinical and pathological features are still controversial. The difficulties of assessing the characteristics of metachronous colorectal carcinoma may be partly related to its relatively low prevalence and lack of studies with long-term follow up. It is worth noting that many of the previous studies in this area were based on reports of a small number of cases [1-10]. On the other hand, though large population-based studies presented good demographic data and correlation statistics, these studies lacked presentation of detailed features of the disease entity.

The objectives of this study were to investigate, in depth, the various clinicopathological features of patients with metachronous colorectal carcinoma in a large cohort of patients with long term follow-up data. The difference between the primary cancer and the metachronous cancer were analysed. In addition, the findings were also compared with those from patients with other colorectal cancers. It is anticipated that the picture drawn from this study can bridge the gap of information between the larger population-based studies and smaller clinical series.

METHOD

Patients with metachronous carcinoma in the large intestine were collected from the main teaching hospitals in Queensland, Australia. The characteristics of these metachronous colorectal carcinomas were compared with those of other consecutive colorectal carcinomas presenting in the same study period. The study data was collected with ethical approvals (HREC/11/QRBW/93, MSC/05/06/HREC) from Queensland Health and Griffith University. The results were entered in a computerized database and its accuracy ensured through the employment of research assistants for data entry and rechecking a random selection of patients on the database against the original data sources by the corresponding author (AL).

The main sources of the demographical, clinical, surgical and postoperative data were patients' medical records including specialist and/or general practitioner referral letters, pre-operative assessment records, admission notes, operative and anaesthetic records, inpatient progress notes, discharge summaries and direct consultation with patients at the time of presentation or at a follow up visit. The pathological information was obtained from the pathology reports and checked by the authors. In addition to regular follow ups, further information about the survival of patients was obtained by accessing the state's main registry of death (Queensland Registry of Births, Deaths and Marriages) database. All colorectal carcinomas in the study were re-classified according to the recent AJCC TNM staging system [11].

The patients were followed up at 3 months and 6 months after their operation. Subsequently, they would be seen every 6 months for at least 5 years after the operation. If there was no suspicion of cancer metastases or other complications, a CT scan would be performed at 1 year after operation. If there was any suspicion of residual or recurrent cancer, a CT scan would be performed at 3 months after the

operation. Routine colonoscopy would be done at 1 year and 3 years following resection.

Microsatellite instability (MSI) tests using immunohistochemistry were performed in the colorectal cancers (including metachronous or non-metachronous lesions) reported in the most recent years according to the revised Bethesda guidelines [12]. MSI involves the inactivation of genes in the DNA Mismatch Repair (MMR) family either by aberrant methylation or by somatic mutation [13].

About 15% of colorectal cancers are characterized by genomic microsatellite instability (MSI), and of these, only 1 in 5 (2%–4% overall) are due to hereditary non-polyposis colorectal cancer (HNPCC). Immunohistochemistry and BRAF mutation detection are the recommended algorithm for workup [14]. Patients with HNPCC almost exclusively develop MSI colorectal cancers due to the presence of germline mutations in the MMR genes, which include *MLH1*, *MSH2*, *MSH6*, and *PMS2*. In contrast, sporadic MSI colorectal cancers typically have a loss of MMR activity as the result of silencing of *MLH1* by aberrant methylation. Thus, in the study, MSI markers used for immunohistochemistry were MLH1, PMS2, MSH2 and MSH6. A positive test is one in which there is detectable nuclear staining of neoplastic cells and any such case was labelled as MSI negative. A negative test is one where there is complete absence of detectable nuclear staining. If there is no detectable MSH6 and MSH2, the case is labelled as MSI positive. If there is a loss of expression of MLH1 and PMS2, the situation may be related to hypermethylation of MLH1 gene promoter or HNPCC. *BRAF* V600E mutation tested will then be performed. If the *BRAF* V600E mutation was detected, the case was labelled as sporadic MSI positive (high) colorectal cancer. On the other hand, if *BRAF* V600E mutation was negative, the case was suggestive of hereditary MSI positive cancer.

Metachronous colorectal adenocarcinoma was defined as an occurrence of another primary colorectal adenocarcinoma more than 6 months after the detection of the primary index colorectal adenocarcinoma. Cancers found at the site of anastomosis were classified as cancer recurrence and excluded from the study. Only colorectal adenocarcinoma (including conventional adenocarcinoma or mucinous adenocarcinoma) was included in the study. Adenoma and other types of malignancies were excluded.

The index carcinoma detected in the first resection was labelled as “primary carcinoma” whereas the carcinoma noted in the subsequent resection was labelled as “metachronous carcinoma”. The pathological features of both the primary and metachronous colorectal carcinomas were studied. The histological grade (differentiation), histological subtype (mucinous adenocarcinoma), size (largest dimension), location and T-staging of primary and metachronous cancers in every patient was analysed and entered into the database for analysis.

Management was by a pre-agreed standardized multidisciplinary protocol. The use of post-operative adjuvant therapy was based on the pathological stage of the cancer. The follow-up period was defined as the interval between the date of surgery for colorectal carcinoma and the date of death or closing date of the study. The time interval of occurrence between the primary carcinoma and the metachronous colorectal carcinoma was defined as the time between the surgical removal of the primary colorectal carcinoma and metachronous carcinoma. The actuarial survival rate of the patients was calculated from the date of surgical resection of the colorectal carcinomas to the date of death or last follow-up. Only cancer-related death was counted as the end point in the statistical analysis.

Statistical analysis

Fisher's exact test or likelihood ratio was used for categorical variables. Student t-test with Yates correction was used for continuous variables. The significance of various parameters on survival was analysed by the Kaplan-Meier method with log-rank test. Significance level was taken at $p < 0.05$. All statistical tests were performed with the program, Statistical Package for Social Sciences (SPSS version 20, Chicago, IL, USA).

RESULT

Clinicopathological features of metachronous carcinomas

Fifty-six patients (33 men; 23 women) with metachronous colorectal carcinoma were noted. In the same period, 2623 patients underwent surgery for colorectal carcinomas. Thus, the overall prevalence of the metachronous colorectal carcinoma was 2.1%. The median age of the 56 patients was 68 years (range, 37 to 79). In these patients, 5.4% (n=3) had synchronous colorectal carcinomas. Two patients had synchronous cancers detected at the first operation and one patient had synchronous cancers noted on the second operation. Co-existing inflammatory bowel disease or familial adenomatous polyposis was not detected in these patients.

The metachronous colorectal carcinomas were resected between 7 months to 246 months after the surgery of the primary colorectal carcinomas (mean = 66months; median = 46 months). Sixty-four per cent (n= 36) of the metachronous colorectal carcinoma occurred less than 5 years after the operation of the primary colorectal carcinoma. Other than these, 18% (n= 10) of the metachronous colorectal carcinomas were detected between 5 to 10 years after operation of the primary carcinoma and 18% (n= 10) of the metachronous colorectal carcinomas were detected more than 10 years after resection of the primary colorectal carcinoma.

A shorter time interval between the primary and metachronous carcinoma occurred in patients with more advanced age ($p=0.005$). In patients with age 70 or above, the mean interval between the primary and metachronous cancer was 42 months. In other patients, the mean time interval was 84 months. This equates to an odds-ratio of 1.116 (95%CI= 0.535-2.327) for a patient over 70 to develop metachronous cancer within 4 years of initial diagnosis. There was no gender difference in the time of occurrence of the metachronous cancer.

Of the 56 patients, 20% (n=11) had at least one of their cancers being mucinous adenocarcinoma. One of these cases had signet-ring tumour cells. Three patients presented with both the primary and metachronous colorectal carcinomas as mucinous adenocarcinomas. At the first operation, 15% of patients had mucinous adenocarcinomas whereas at the second operation, 20% of patients had mucinous adenocarcinomas. The difference in prevalence of mucinous adenocarcinoma between patients with metachronous colorectal cancers and other patients with colorectal cancer was significant ($p=0.03$).

Comparison between the primary index and metachronous cancers [Table 1]

The size of the primary colorectal carcinomas were significantly larger than the metachronous cancers (mean maximum extent = 52 mm versus 37 mm, $p=0.002$). Also, 15% (8 of the 56) of the patients had the metachronous carcinoma presented at higher T stage than the primary carcinoma. The other 85% of patients had metachronous cancers of identical or lower T stages than the primary cancers. In addition, the TNM staging of the metachronous cancers were different from those of the primary cancer ($p=0.045$). Metachronous cancers had a higher prevalence of stage I cancer than the primary cancer (30% versus 16%).

In relation to cancer location, the primary carcinoma was more often noted in the distal colon and rectum (descending colon, sigmoid colon and rectum) than in the proximal colon (caecum, ascending colon and transverse colon). The primary carcinoma was in the proximal colon in 34% (n=19) and in distal colorectum in 66% (n=37). On the other hand, metachronous carcinoma was more often identified in the proximal colon. The metachronous carcinoma was present in the proximal colon in 61% (n=34) and in distal colorectum in 39% (n=22). This difference was significant

($p=0.008$). Finally, the primary and metachronous colorectal carcinomas did not differ significantly in the frequency of different histological grades and prevalence of mucinous carcinoma ($p>0.05$).

Survival analysis

The follow-up period of the 56 patients ranged from 4 to 301 months (mean = 117 months; median = 91 months). Thirty per cent ($n=17$) of the patients died of causes related to colorectal carcinoma in the study period. The mean survival of the whole group was 213 months. The survival rates of these patients were compared with patients with synchronous cancer and solitary cancer resected in the same period. The survival rate of patients with metachronous cancer was better than those with synchronous cancer or those with solitary cancer ($p=0.001$) (Figure 1). There was no statistically significant difference in survival rates between patients with solitary cancer and those with synchronous cancer. Other than this, these categories of cancers did not differ in patients' age, gender, size or site of cancer, presence of obstructive symptoms, pre-operative serum carcinoembryonic antigen (CEA) level, histological subtype or pathological stage ($p > 0.05$).

Microsatellite instability

Microsatellite instability (MSI) as detected by immunochemistry was performed in 240 patients. In non-metachronous solitary colorectal cancer, 23% (53/230) of the cases were labelled as MSI positive by showing negativity to 2 of the 4 markers. For metachronous cancers, 60% (6/10) showed loss of 2 of the 4 markers. This difference was significant ($p=0.016$). Of the 6 positive cases, 5 showed *BRAF* V600E mutation and were labelled as hypermethylation of MLH1 gene promoter type.

Three of the 6 positive cases were mucinous carcinoma, including the case with signet ring cancer cells. All the 4 MSI negative cases were conventional adenocarcinomas. Nevertheless, of the 65 metachronous cancers, none showed definite clinical and histological evidence of HNPCC such as presence of associated endometrial carcinoma.

DISCUSSION

In our previous study, we noted that ulcerative colitis, familial adenomatous polyposis and hyperplastic polyposis accounted for 2%, 4% and 2% of synchronous colorectal carcinoma [15]. In this study, ulcerative colitis and familial adenomatous polyposis were not found to be associated with metachronous colorectal carcinoma. It is likely that patients with these predisposing lesions will have a large portion of the large intestine removed at the diagnosis of the primary carcinoma and there will be little or no chance to develop metachronous carcinoma. Three patients (5.4%) were found to have both metachronous and synchronous colorectal carcinomas. Thus, synchronous and metachronous may have different characteristics and warrant separate analysis.

The prevalence of metachronous colorectal carcinoma has been varied. The variation in prevalence is likely to be directly proportional to the length of time of follow-up, characteristics of the patient population and sample size. Shorter follow-up periods yielded lower prevalence rates. The longer a patient survives after removal of the index carcinoma, the more likely they are to develop a metachronous carcinoma. In the recent literature based on reasonable sample sizes, the prevalence of metachronous colorectal carcinoma ranged from approximately 0.2 to 3.2% [Table 2]. In the current series, we have analysed the features of the largest number of patients with metachronous colorectal carcinoma so far assembled and had a mean follow-up of slightly less than 10 years. The prevalence of the current series, 2.1%, falls in the range reported by the other series [1-10].

In some studies, metachronous and synchronous colorectal carcinomas were studied together as multiple primary lesions [1-4]. However, metachronous and synchronous colorectal cancer seem to be different in many important aspects. In this

series, the survival rate of patients with metachronous cancer was noted to be much better than patients with synchronous cancers. Also, in the majority of the clinical series published to date, the prevalence of metachronous colorectal carcinoma is much lower than that of synchronous colorectal carcinoma. In the study period, 100 synchronous cancers were noted (excluding cases with both synchronous and metachronous cancers). Thus, the ratio of the synchronous colorectal cancer to metachronous colorectal cancer is 1.9 to 1 (100 to 53). This figure falls within the range of ratio of 1.8 - 4 to 1 previously reported in the literature.

Mucinous adenocarcinomas account for 5 to 15% of colorectal adenocarcinomas [16] although Leopoldo and colleagues have reported a prevalence of 38.5% [17]. In our previous study on the clinical and pathological features of 36 mucinous adenocarcinomas, mucinous adenocarcinomas accounted for 14% of colorectal adenocarcinomas [16]. In this study, we also noted that 14% of the primary index cancers were mucinous adenocarcinoma. Thus, it is not possible to predict the chance of occurrence of metachronous colorectal carcinoma on the basis of the presence of mucinous adenocarcinoma histology. Nevertheless, in the metachronous colorectal carcinomas themselves, 20% were mucinous adenocarcinomas. Mucinous adenocarcinoma therefore appears to be more common in the secondary lesions of patients with metachronous cancer. This may be related to the fact that they are most often noted in the proximal colon. It is also worth noting that MSI positivity was often detected in metachronous cancers and mucinous adenocarcinomas.

Signet-ring carcinoma is a rare histologic type of colon cancer and signet-ring tumour cells can occur as part of mucinous carcinoma [18]. The cancer can occur in the setting of synchronous colorectal cancer. Also, a higher proportion of MSI-high tumours have been detected in signet-ring carcinoma when compared to conventional

adenocarcinoma. In the current study, one metachronous cancer showed the presence of signet ring cancer cells. Also, all the 3 cases with mucinous adenocarcinoma (including the one with signet ring cells) tested for MSI showed positive results. They were sporadic MSI tumours as many of these metachronous cancers carry the *BRAF* V600E mutation that is associated with the serrated neoplasia pathway [13].

Studies have reported many metachronous carcinomas occur within 5 years or less of detection of the primary carcinoma [1, 3, 6, 8, 10]. In the current series, it was noted that 64% of the metachronous carcinomas occurred less than 5 years after operation for the primary cancer. Also, the median interval between the diagnosis of the cancers was 46 months. These findings concur with the recommendation of a colonoscopic surveillance period of 5 years. However, it is worth noting that 36% of the metachronous cancers occurred more than 5 years after the first operation.

A shorter time interval was noted in patients with more advanced age. The reason for this is complex. This may be partly attributed to the reduced tumour inhibitory mechanisms in advanced age. However, this may be related to the fact that as patients age, they tend to die from other causes and thus be unable to develop a carcinoma later on. The broad 95% confidence interval of the odds ratio analysis would seem to support this idea, though despite the large size of the current series, we may have insufficient numbers to properly resolve the effect of age on the development of metachronous cancer.

In the current study and other series, the metachronous colorectal carcinomas were smaller and had lower T stages than the index primary carcinomas. It is likely that this difference is due to their being detected earlier as many of these metachronous carcinomas were noted in the intensive 5-year post-operative follow-up period.

Our results also indicated that the primary index cancers often appeared in the distal portion (left side) of the large intestine. These observations are in line with previous studies showing that clinical features and molecular pathways are different in proximal and distal colorectal cancers [18-21]. The site prediction of the index cancers were also noted in a few studies on metachronous colorectal cancers in Asian populations [2, 5, 6, 8]. However, the majority of these studies showed that index cancers were more often noted in the proximal (right) colon. The complex issues of clinical, genetic and environmental factors on site predilection need to be investigated in future studies.

The time taken for metachronous colorectal carcinoma to develop after resection for the primary cancer varies greatly [1-10]. In the literature, metachronous cancer has been reported up to 41 years after the resection of the primary cancer [22]. In the current series, the longest interval between the carcinomas was 20.5 years. Also, 18% of the cases have a time interval between the cancers larger than 10 years. Overall, this means that metachronous colorectal carcinomas can be a lifelong risk for patients with colorectal carcinoma.

Patients with metachronous cancer in our study have a better prognosis than other patients with solitary cancer. Thus, we do not recommend a different follow-up regimen for this group of patients. At the moment, there are no reliable markers to predict metachronous cancer, making such differential treatment impossible. On the other hand, metachronous cancers had a higher prevalence of MSI detected by immunohistochemistry. These findings should be confirmed with more cases being tested. It is also worth noting that colorectal cancers exhibiting MSI are associated with a better prognosis and difference in treatment response compared to colon cancers without MSI as well as those with a familial tendency of cancer [23]. A more

liberal approach for testing MSI in colorectal cancer may predict patients with higher risk of metachronous cancer. Longer and closer follow-up may also be indicated for high risk groups as metachronous cancer can be a lifelong risk.

To conclude, the current series is the largest series examining the features of patients with metachronous cancer with a long follow-up period yet published.

Patients with metachronous colorectal carcinomas have characteristic features and attention to these features is important for better management of this group of cancers.

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Figure Legend

Figure1. The survival curve of patients with different colorectal cancers: M – metachronous cancer; S- synchronous cancer; C – solitary cancer (control group). Patients with metachronous cancer have the best survival rates.

Table 1.**Comparison between the primary and the metachronous colorectal carcinoma**

	Primary (n=56)	Metachronous (n=56)	p-value
<hr/>			
Grade			
Well	3 (5%)	4 (7%)	0.46
Moderate	42 (75%)	36 (64%)	
Poor	11 (20%)	16 (29%)	
Histological subtype			
Adenocarcinoma	49 (88%)	45(80%)	0.44
Mucinous adenocarcinoma	7 (12%)	11 (20%)	
Location			
Caecum	3 (5%)	11 (20%)	0.05
Ascending colon	7 (12%)	10 (18%)	
Hepatic flexure	1 (2%)	2 (4%)	
Transverse colon	7 (13%)	11 (20%)	
Splenic flexure	2 (4%)	4 (7%)	
Descending colon	8 (14%)	3 (5%)	
Sigmoid colon	14 (25%)	7 (12%)	
Rectum	14 (25%)	8 (14%)	
Proximal	19 (34%)	34 (61%)	
Distal	37 (66%)	22 (39%)	
Mean maximum dimension (in mm)	52	37	0.002
T staging			
1	3 (5%)	9 (16%)	0.11
2	7 (13%)	12 (21%)	
4	40 (71%)	30 (54%)	
4	6 (11%)	5 (9%)	
LN status			
Positive	15	14	1
Negative	41	42	
TNM staging			
I	9 (16%)	17 (30%)	0.045
II	31 (55%)	24 (43%)	
III	10 (18%)	14 (25%)	
IV	6 (11%)	1 (2%)	

Table 2 Large series of colorectal metachronous cancer reported in the literature from the last 25 years (1997-2011)

Author/year of publication/country	prevalence	Remarks
Bekdash/1997/UK	22/1009 (2%)	better survival than patients with synchronous cancer; S:M= 1:8: 1
Chen/2000/Taiwan	13/1780 (0.7%)	on early colorectal cancer, primary cancer often in the right-side; S:M=4:1
Wang/2004/China	22/1348 (1.6%)	55% diagnosed within 3 years; 41% after 8 years; S:M =0.7:1
Lan/2005/Taiwan	43/3846 (0.2%)	mean interval between cancers =71 months, Primary index carcinoma often in the left side
Velayos/2005/USA	33/2884 (1.1%)	microsatellite instability high cancers were detected at younger age; S:M = 2.3: 1
Park/2006/Korea	39/5447 (0.7%)	age younger than sporadic cancer, more common in right colon, diagnosed more at early stage, mean interval between cancers =39 months with 1/3 occurred after 5years
Ballesté/2007/Spain	7/355 (1.9%)	no association with microsatellite instability or family history
Yoon/2008/Korea	7/1669 (0.4%)	mean age = 60, mean interval between cancers was 37 months (28-49), Primary cancer in right colon in 71%; metachronous colorectal carcinoma often stage II; S: M= 2.7:1
Tziris/2008/Greece	9/280 (3.2%)	interval: 18months-14 year
Hollington/2011/Australia	14/569 (2.5%)	nearly half within 3 years follow-up (median 65 months); median age =74; all except one early detected metachronous cancer were stage 2 or lower
Lam/2012/Australia	56/2623 (2.1%)	primary index cancer more often in the left side, S:M = 1.9:1; mean interval between cancers = 66 months with 36% occurred after 5 years; metachronous carcinomas are smaller; high prevalence of mucinous carcinoma and microsatellite instability high cancers; better survival rates than other colorectal cancers

S:M = ratio of synchronous to metachronous cancer; only series with more than 5 cases were included.