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**Synchronous colorectal cancer: Clinical, pathological and molecular implications**

Lam AKY *et al.* Synchronous colorectal cancer

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**Abstract**

Synchronous colorectal carcinomas refer to more than one primary colorectal carcinoma detected in a single patient at the time of the initial presentation. A review of the literature shows that the prevalence of the disease is approximately 3.5% of all colorectal carcinomas. This disease was more often seen in males with the male to female ratio of 1.8-1. Synchronous colorectal carcinoma was reported to be more common in men. The mean age at presentation of the patients with synchronous colorectal cancer was in the early half of the seventh decade of life. Patients with inflammatory bowel diseases (both ulcerative colitis and Crohn’s disease), hereditary non-polyposis colorectal cancer, familial adenomatous polyposis and serrated polyps/hyperplastic polyposis are known to have a higher chance of synchronous colorectal carcinomas. These predisposing factors accounted for slightly more than 10% of synchronous colorectal carcinomas. Synchronous colorectal carcinomas were more commonly noted in the right colon when compared to solitary colorectal cancers. On pathological examination, some synchronous colorectal carcinomas were mucinous adenocarcinomas. They are usually associated with adenomas and metachronous colorectal carcinomas. Most of the patients with synchronous colorectal cancers had 2 carcinomas in an individual but up to 6 synchronous carcinomas in an individual have been reported. Patients with synchronous colorectal carcinomas have a higher proportion of microsatellite instability cancers than patients with a solitary colorectal carcinoma. Also, limited data revealed that in many synchronous colorectal carcinomas, the carcinomas in the same patient had different patterns of microsatellite instability status, *p53* mutation and *K-ras* mutation between the carcinomas in a given individual. Overall, the prognosis of patients with synchronous colorectal carcinomas is not significantly different from those with a solitary colorectal carcinoma though a marginal better prognosis has been reported in patients with synchronous colorectal carcinoma in some series. A different management approach and long term clinical follow-ups are recommended for some patients with synchronous colorectal cancers.

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**Key words:** Synchronous carcinoma; Colorectal; Prevalence; Microsatellite instability; Review

**Core tip:** Synchronous colorectal carcinoma accounts for approximately 3.5% of colorectal carcinoma. This type of carcinoma has different clinical, pathological and molecular features from solitary colorectal carcinoma. There is lack of comprehensive review of this entity in the recent years.

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**INTRODUCTION**

Synchronous colorectal carcinoma denotes to more than one primary colorectal carcinoma detected in a single patient. On the other hand, metachronous colorectal carcinoma is the presence of more than one primary colorectal carcinomas detected consecutively in a single person after a set time interval. In the literature, many studies have mixed these 2 entities together in their analysis.

**DATA COLLECTION**

The literature between 1981 and 2013 recorded in PubMed was searched for the research papers on synchronous colorectal carcinoma. Keywords include “synchronous”, “colorectal”, “colon”, “rectum”, “cancer”, “carcinoma” etc. were used. Only original full text publications were reviewed. The eligibility criteria included articles in English, adequate sample numbers and description of the cases. Case reports were excluded from the analysis. The demographic details of the series were entered into a computer database. If the same cases were reported more than once, only one entry was entered. The data were analysed by Statistical Package for Social Sciences version 22.0 (IMB SPSS Inc., New York, United States) for analysis. Overall, 51 studies were selected with data sufficient for review[1-54]. The characteristics of the selected series were shown in Table 1. This is to ensure comprehensive understanding of the characteristics of the disease entity in the setting of recent decades.

**PREVALENCE**

In the literature, the prevalence of synchronous colorectal carcinoma ranged from approximately 1.1%-8.1%[1-54]. In some series, the number of cases analyzed was small and the figures quoted are unlikely to be representative. On the other hand, in large population studies, many clinical and pathological characteristics of the synchronous colorectal carcinomas were not analyzed. Differences in the range of prevalence of synchronous colorectal carcinoma were obtained from studies from Europe, Asia and America (Europe 1.1%-8.1%; Asia 1.1%-8.1% and America -1.2%-7.0%). In the literature, there are 3 large studies with more than 10000 colorectal cancers analyzed. The prevalence of synchronous colorectal carcinoma in these 3 series was 3.1%, 3.7% and 3.9% respectively[2,38,47]. Also, pooling the data from 39 series in which the prevalence of synchronous colorectal cancers could be found, the overall prevalence of synchronous colorectal carcinoma is 3.5% (3667 of 105686) of colorectal cancers[1-13, 15,16, 18,19, 24, 26-29, 30-35, 37-40, 43, 46-48, 52-54].

**GENDER PREFERENCE**

Patients with synchronous colorectal cancer are more often seen in men. In the majority of the series analyzed, the male to female ratio of patients with synchronous colorectal cancer was more than one. By pooling the data from the 38 series with the gender of the patients mentioned, the male to female ratio was 1.8-1.0 (2260 men versus 1241 women)[1-2, 3-14, 16-19, 23, 24, 26-33, 38-40, 43, 46-48, 52-54]. It has also been shown that when compared to solitary colorectal carcinoma, synchronous colorectal carcinoma had a higher male to female ratio[46]. There is no obvious reason for the higher male predominance for this entity. Investigations may help to detect if any genetic and environmental factors can contribute to gender difference in prevalence.

**AGE AT PRESENTATION**

There is no common consensus on whether patients with synchronous colorectal carcinoma are occurring in a different age range when compared to solitary colorectal carcinoma. In the literature, the mean age at presentation of synchronous colorectal carcinoma ranged from 47 to 79[27,31]. By pooling the data from 32 series in the analysis, the mean age at presentation of patients with synchronous colorectal carcinoma was 63[4,6-14,16,18,19,23,24,26-34,37, 40,43,46, 48, 52-54]. In many of the series, the mean age at presentation for synchronous colorectal cancer was higher than solitary colorectal cancer. However, in large series such as that presented by Latourniere and colleagues, the age at diagnosis for solitary colorectal and synchronous colorectal carcinoma was similar[38].

**PREDISPOSING CONDITIONS**

Patients with inflammatory bowel diseases, hereditary non-polyposis colorectal cancer and familial adenomatous polyposis are known to have higher chance of synchronous colorectal cancers[5,45,46,51]. The reason behind this is obvious and related to a multiple field of dysplasia (adenomas) that can occur in these patients. Also, synchronous colorectal carcinoma was noted to be associated with more adenomas than solitary colorectal cancer[4,7,9,10,14,18]. In recent years, precursor multiple serrated sessile serrated adenomas/hyperplastic polyposis were more commonly noted in synchronous colorectal cancer[46,49].

 Synchronous colorectal carcinomas were often reported in patients with ulcerative colitis. Liu *et al*[51] reported a series of 108 inflammatory bowel associated colorectal cancer (95 with ulcerative colitis and 13 with Crohn’s disease), 20% (*n* = 22) had synchronous colorectal carcinomas. All synchronous carcinomas were noted in the patients with ulcerative colitis. In another large series presented with 240 inflammatory bowel diseases (176 with ulcerative colitis and 64 with Crohn’s disease) associated colorectal carcinoma, synchronous colorectal carcinoma occurred in both types of inflammatory bowel diseases. Similarly, patients with ulcerative colitis had a significant higher chance of developing synchronous colorectal cancer than patients with Crohn’s disease[45].

 A study performed by Greenstein and colleagues reported that synchronous carcinoma accounted for 2.5% of de novo colorectal carcinoma, 18% of ulcerative colitis-related carcinoma and 21% of familial adenomatosis polyposis-related carcinoma[5]. However, the relative prevalence of these predisposing factors in synchronous colorectal carcinoma was rarely documented. One of the reasons is that in many studies on synchronous colorectal carcinomas, patients with these predisposing lesions were excluded. Nevertheless, in a series obtained from a general population of colorectal carcinoma, patients with known predisposing conditions may account to slightly more than 10% of synchronous colorectal cancer[46]. Thus, other unknown factors may be the cause of the synchronous colorectal carcinoma.

**LOCATION OF SYNCHRONOUS CANCERS**

Common sites of synchronous colorectal cancer are the sigmoid colon or rectum. The relative frequencies of the carcinomas in a different portion of the large intestine were different for synchronous and solitary colorectal carcinomas[46]. When compared to solitary colorectal carcinoma, synchronous carcinoma appeared to be more often involving the proximal portion of the colon, in particular the ascending colon. These findings were in concurrence with the right side predominance effect of some genetic predisposing factors. Some authors reported that many synchronous colorectal carcinomas occurred in the same segment of the large intestine or very close to each other[2,12,38]. On the other hand, there are a large proportion of cancers noted in different segments of the large intestine. The finding stresses the importance of thorough pre-operative examination of synchronous colorectal cancers.

**PATHOLOGY**

Mucinous adenocarcinoma is a type of colorectal adenocarcinoma and accounts for approximately 14% of colorectal carcinomas[55]. The carcinoma was reported to be slightly more common in patients with synchronous colorectal adenocarcinoma[9]. It is worth noting that mucinous adenocarcinoma is a pathological feature of colorectal carcinoma in the setting of HNPCC which in terms can predispose to synchronous or metachronous colorectal carcinoma. In a large series of 102 patients with synchronous colorectal carcinoma and 56 patients with metachronous colorectal carcinoma, mucinous adenocarcinoma was not more common in synchronous colorectal carcinoma when compared to solitary colorectal carcinoma[56]. On the other hand, this type of carcinoma is more common in the metachronous (subsequent) carcinoma[56]. In some patients, the cancers in the same patient can be mucinous adenocarcinoma[45]. The other cancer(s) detected in the patients with synchronous colorectal carcinomas were usually smaller, lower pathological grade and T staging than the index cancer[45]. Also, metachronous carcinoma can also occur in some patients with synchronous colorectal carcinoma[45].

 The majority of patients with colorectal synchronous carcinoma reported in the literature had only two carcinomas in the large intestine. In some cases, more than 2 colorectal cancers were found in each patient. The percentages of patients with synchronous colorectal carcinomas having 3 or more cancers range from 1.8% to 16.7%[13,38]. Up to 6 synchronous carcinomas have been reported in the large intestine of a single patient[10,46].

**MOLECULAR BIOLOGY**

The majority of research in molecular biology on synchronous colorectal carcinomas focused on the analysis of microsatellite instability (MSI) in these carcinomas[41,43,52]. Microsatellites are simple repetitive DNA sequences scattered throughout the genome. Due to their repetitive nature they are susceptible to errors during DNA replication which are usually corrected by mismatch repair genes. Failure of the mismatch repair system results in accumulation of alterations in microsatellite lengths, a process described as microsatellite instability. MSI positive colorectal carcinomas can occur in familial settings known as hereditary nonpolyposis colorectal cancer (HNPCC)[57-59]. Patients with HNPCC inherit a germline mutation in one of the mismatch repair genes. However, many of the MSI positive colorectal carcinomas are sporadic resulting from methylation of mismatch repair genes, rather than by germline mutation as in HNPCC. Sporadic MSI cancers show methylation of MLH1 promoters, a condition which is strongly correlated to the V600E mutation of human gene *braf (v-Raf murine sarcoma viral oncogene homolog B1*).

 Studies showed that patients with synchronous colorectal carcinoma have a high proportion of MSI positive cancers than patients with solitary colorectal carcinoma. Also, methylation of multiple genes or *braf* mutation status in these cancers suggests that many of these cancers were sporadic rather than familial[27,36,42,43]. It is likely that the higher portion of MSI cancers in synchronous colorectal cancer is sporadic and may be due to the local carcinogenic environment in the large intestine.

Patients with individual cancers discordant for MSI status had the worst clinical outcome, whereas those with individual cancers concordant for MSI-deficient status had the best clinical outcome[50]. The result was in concur with the fact patients with that MSI positive colorectal carcinoma had a better prognosis than those with MSI negative colorectal carcinoma[60].

 Other than MSI, *K-ras* and *p53* mutations are commonly studies in colorectal carcinomas[57-61]. *K-ras* mutations are predictive markers of resistance to monoclonal antibody therapies for metastatic colorectal carcinoma which targets the epidermal growth factor receptor. *p53* mutations are common in human cancers and often found in more aggressive cancers. In many studies, there is a portion of synchronous colorectal carcinoma with discordant MSI status, *p53* mutation and *K-ras* mutation between the synchronous colorectal carcinomas in a given individual[14,17,23,40,41]. These findings suggest that mechanism of formation of synchronous colorectal carcinomas is complex and is unlikely to be linked to known genetic mutations commonly found in colorectal carcinomas.

Lastly, genetic polymorphism of *glutathione S-transferases* (null GSRM1 phenotype) was found in a study to be associated with synchronous colorectal carcinoma[54]. The Glutathione S-transferases (GSTs) form a group of multi-gene isoenzymes involved in the cellular detoxification of both xenobiotic and endobiotic compounds[62]. They are related to cancer risk characterization and chemotherapy resistance. This result needs to be confirmed in future studies.

**PROGNOSTIC IMPACT**

The prognosis of patients with synchronous carcinoma has been documented to be better, the same or worse than those with solitary colorectal carcinoma[2,19,20]. The variation is likely due to the differences in the sample size, length of clinical follow-up etc. and needs to be interpreted with caution. The first prospective study on the effect of synchronous colorectal carcinoma on survival as compared to solitary colorectal cancer was presented by Nosho and colleagues in United States in 2009[43]. The study showed that synchronous colorectal carcinomas were significantly associated with poor prognosis. The reasons proposed are more related to the predicted clinical effects of the higher chance of complications and metastases in multiple colorectal carcinomas. However, in the majority of the studies and many of the recent studies involving a larger number of cases, the survival of synchronous colorectal carcinoma was reported to be no different from solitary colorectal carcinoma. In the studies by Hu and coauthors in 2012[52] and also from our group in 2011 and 2012[46,56], marginal survival benefits of patients with synchronous colorectal carcinomas were noted. Hu and co-authors proposed that the reason for the better survival rates in this type of carcinoma may be related to the genetic difference in a portion of cancers[52]. Nevertheless, it is likely that the prognosis of patients with colorectal carcinoma depends on many factors and the occurrence of synchronous colorectal carcinoma is not strong enough as an independent predictive factor for survival rates.

**MANAGEMENT**

An extensive operation would be needed for patients with synchronous colorectal cancers in the settings of known predisposing factors like familial adenomatous polyposis, ulcerative colitis or HNPCC. For the other cases, appropriate surgical resection with colonoscopic examination of follow-up should be recommended. If one of the synchronous cancers is of early-stage colorectal cancers, colonoscopic resection (endoscopic mucosal resection or endoscopic submucosal resection) may be used. Otherwise, dual colon resection may be needed if the synchronous cancers are a large distance apart and of advanced stages. Depending on the resources available, life-long clinical follow-up of some patients with synchronous colorectal carcinoma may be recommended.

A complete colonoscopy may not be possible in all patients to detect synchronous colorectal carcinoma before an operation due to the presence of synchronous carcinoma proximal to a stenosing colorectal carcinoma[46]. Even with a complete colonoscopy, synchronous carcinoma may also be missed as a result of a small size or being very close to the main cancer. CT colonography have been used to detect synchronous cancers proximal to stenosing colorectal cancers[63]. Nevertheless, it has limited capability in differentiating advanced adenoma from colorectal carcinoma.

**CONCLUSION**

Synchronous colorectal cancer is different from solitary colorectal cancer in many aspects. The features are summarized in Table 1. It is likely that both environmental and genetic factors account for the presence of synchronous colorectal carcinoma. These factors may lead to a higher chance of further cancers in this group of patients. However, there is yet no strong predictive parameter for the presence of synchronous cancer or metachronous cancer to occur. The molecular biology of the tumours is complex. A long term clinical follow-ups are recommended for patients with synchronous colorectal cancers.

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**Table 1 Characteristics of synchronous colorectal cancer as compared to solitary colorectal cancer**

|  |
| --- |
| Higher male to female ratio |
| More likely to associated precursor lesions like adenomas and in the settings of inflammatory bowel diseases, hereditary non-polyposis colorectal cancer and familial adenomatous polyposis |
| More noted in the proximal portion of the colon  |
| Higher incidence of mucinous adenocarcinoma |
| Higher likelihood of having microsatellite instability  |