World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i22.6815

World J Gastroenterol 2014 June 14; 20(22): 6815-6820
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Synchronous colorectal cancer: Clinical, pathological and molecular implications

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Received: October 3, 2013 Revised: December 6, 2013
Accepted: March 19, 2014
Published online: June 14, 2014

Abstract

Synchronous colorectal carcinoma refers to more than one primary colorectal carcinoma detected in a single patient at initial presentation. A literature review has shown that the prevalence of the disease is approximately 3.5% of all colorectal carcinomas. This disease has a male to female ratio of 1.8:1. The mean age at presentation of patients with synchronous colorectal cancer is in the early half of the seventh decade. Patients with inflammatory bowel diseases (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 risk of synchronous colorectal carcinoma. These predisposing factors account for slightly more than 10% of synchronous colorectal carcinomas. Synchronous colorectal carcinoma is more common in the right colon when compared to solitary colorectal cancer. On pathological examination, some synchronous colorectal carcinomas are mucinous adenocarcinomas. They are usually associated with adenomas and metachronous colorectal carcinomas. Most of the patients with synchronous colorectal cancer have two carcinomas but up to six have been reported in one patient. Patients with synchronous colorectal carcinoma have a higher proportion of microsatellite instability cancer than patients with a solitary colorectal carcinoma. Also, limited data have revealed that in many synchronous colorectal carcinomas, carcinomas in the same patient have different patterns of microsatellite instability status, *p53* mutation and *K-ras* mutation. Overall, the prognosis of patients with synchronous colorectal carcinoma is not significantly different from that in patients with solitary colorectal carcinoma, although a marginally better prognosis has been reported in patients with synchronous colorectal carcinoma in some series. A different management approach and long-term clinical follow-up are recommended for some patients with synchronous colorectal cancer.

Key words: Synchronous carcinoma; Colorectal carcinoma; 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 has been a lack of comprehensive reviews of this entity in recent years.

Lam AKY, Chan SSY, Leung M. Synchronous colorectal cancer: Clinical, pathological and molecular implications. *World J Gastroenterol* 2014; 20(22): 6815-6820 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i22/6815.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i22.6815

INTRODUCTION

Synchronous colorectal carcinoma denotes more than one primary colorectal carcinoma detected in a single patient. Metachronous colorectal carcinoma is the presence

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

Higher male to female ratio
More likely to be associated with precursor lesions such as adenoma, and in the settings of inflammatory bowel diseases, hereditary nonpolyposis 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

of more than one primary colorectal carcinoma detected consecutively in a single person after a set time interval. In the literature, many studies have mixed these two entities together in their analysis.

DATA COLLECTION

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

PREVALENCE

The prevalence of synchronous colorectal carcinoma ranged from 1.1% to 8.1%[1-54]. In some series, the number of cases analyzed was small and the figures quoted are unlikely to be representative. In contrast, in large population studies, many clinical and pathological characteristics of synchronous colorectal carcinoma were not analyzed. Differences in the range of prevalence of synchronous colorectal carcinoma were obtained from studies in Europe, Asia and America (Europe 1.1%-8.1%, Asia 1.1%-8.1%, and America 1.2%-7.0%). There were three large studies with > 10000 colorectal cancers analyzed. The prevalence of synchronous colorectal carcinoma in these three 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 cancer could be found, the overall prevalence of synchronous colorectal carcinoma was 3.5% (3667 of 105686) of colorectal cancers[1-13,15,16,18,19,24,26-35,37-40,43,46-48,52-54].

GENDER PREFERENCE

Synchronous colorectal cancer is more often seen in men. In the majority of the series analyzed, the male to female ratio of patients with synchronous colorectal cancer was > 1. By pooling the data from the 38 series with the sex of the patients mentioned, the male to female ratio was 1.8 : 1.0 (2260 men *vs* 1241 women)[1-14,16-19,23,24,26-33,38-40,43,46-48,52-54]. 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 the sex difference in prevalence.

AGE AT PRESENTATION

There is no common consensus on whether synchronous colorectal carcinoma occurs 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 years[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 a 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 risk of synchronous colorectal cancer[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 is associated with more adenomas than solitary colorectal cancer[4,7,9,10,14,18]. In recent years, precursor multiple serrated sessile serrated adenoma/hyperplastic polyposis were more commonly noted in synchronous colorectal cancer[46,49].

Synchronous colorectal carcinoma is often reported in patients with ulcerative colitis. Liu *et al*[51] reported a series of 108 patients with cancer associated with inflammatory bowel disease (95 with ulcerative colitis and 13 with Crohn's disease), and 22 (20%) had synchronous colorectal carcinoma. All synchronous carcinoma was noted in the patients with ulcerative colitis. In another large series of 240 patients with colorectal carcinoma associated with inflammatory bowel diseases (176 with ulcerative colitis and 64 with Crohn's disease), synchronous colorectal carcinoma occurred in both types of inflammatory bowel diseases. Similarly, patients with ulcerative colitis had a significantly higher risk 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 carcinoma, 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 for 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 CANCER

Common sites of synchronous colorectal cancer are the sigmoid colon or rectum. The relative frequencies of carcinoma in a different portion of the large intestine differ for synchronous and solitary colorectal carcinoma[46]. When compared to solitary colorectal carcinoma, synchronous carcinoma appears to more often involve the proximal portion of the colon; in particular the ascending colon. These findings were in concurrence with the right-side predominance of some genetic predisposing factors. Some authors have reported that many synchronous colorectal carcinomas occurred in the same segment of the large intestine or close to each other[2,12,38]. In contrast, there a large proportion of cancers are noted in different segments of the large intestine. This stresses the importance of thorough preoperative examination of synchronous colorectal cancer.

PATHOLOGY

Mucinous adenocarcinoma is a type of colorectal adenocarcinoma and accounts for approximately 14% of colorectal carcinomas[55]. Mucinous adenocarcinoma is 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 hereditary nonpolyposis colorectal cancer (HNPCC), which can predispose to synchronous or metachronous colorectal carcinoma. In a large series of 102 patients with synchronous colorectal carcinoma and 56 with metachronous colorectal carcinoma, mucinous adenocarcinoma was not more common in synchronous colorectal carcinoma when compared to solitary colorectal carcinoma[56]. In contrast, this type of carcinoma is more common in the metachronous (subsequent) carcinoma[56]. In some cases, cancers in the same patient can be mucinous adenocarcinoma[45]. The other cancers detected in the patients with synchronous colorectal carcinomas are usually smaller, with 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 two colorectal cancers were found in each patient. The percentages of patients with synchronous colorectal carcinomas with three or more cancers ranged from 1.8% to 16.7%[13,38]. Up to six 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 carcinoma has focused on analysis of microsatellite instability (MSI)[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 MSI. MSI-positive colorectal carcinoma can occur in familial settings known as 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*).

Some studies have shown that patients with synchronous colorectal carcinoma have a higher 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 are 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 have the worst clinical outcome, whereas those with individual cancers concordant for MSI-deficient status have the best outcome[50]. This result concurs with the fact patients with MSI-positive colorectal carcinoma have better prognosis than those with MSI-negative carcinoma[60].

Other than MSI, *K-ras* and *p53* mutations are commonly studied in colorectal carcinoma[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 cancer and are often found in more aggressive cancer. 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 the mechanism of formation of synchronous colorectal carcinoma is complex and is unlikely to be linked to known genetic

mutations commonly found in colorectal carcinoma.

Lastly, genetic polymorphism of *glutathione S-transferases* (null GSRM1 phenotype) is associated with synchronous colorectal carcinoma[54]. The glutathione S-transferases 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 and length of clinical follow-up 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 the United States in 2009[43]. The study showed that synchronous colorectal carcinoma was 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 patients with synchronous colorectal carcinoma was reported to be no different from that of solitary colorectal carcinoma. In the studies by Hu and co-authors in 2012[52] and also from our group in 2011 and 2012[46,56], marginal survival benefits of patients with synchronous colorectal carcinoma were noted. Hu and co-authors have 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

Extensive surgery is needed for patients with synchronous colorectal cancer with known predisposing factors such as familial adenomatous polyposis, ulcerative colitis or HNPCC. For other cases, appropriate surgical resection with colonoscopic examination of follow-up is recommended. If one of the synchronous cancers is early-stage colorectal cancer, 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 at an advanced stage. Depending on the resources available, life-long clinical follow-up of some patients with synchronous colorectal carcinoma may be recommended.

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 complete colonoscopy, synchronous carcinoma may also be missed as a result of its small size or being close to the main cancer. Computed tomography colonography has 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 risk of further cancer in this group of patients. However, there is yet no strong predictive parameter for the presence of synchronous cancer or metachronous cancer. The molecular biology of the tumors is complex. Long-term clinical follow-up is recommended for patients with synchronous colorectal cancers.

ACKNOWLEDGMENTS

The authors would like to thank Ms Sharon Philips for her help in editing the manuscript.

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P- Reviewers: Ghosn M, Morini S, Park SH, Quigley EMM
S- Editor: Qi Y **L- Editor**: Kerr C **E- Editor**: Ma S

Published by **Baishideng Publishing Group Inc**
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ISSN 1007-9327