Synchronous Colorectal Cancers: A Review of Clinical Features, Diagnosis, Treatment, and Prognosis

Jun Yang Jia-Yuan Peng Wei Chen

Department of Surgery, The Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai, China

Key Words

Synchronous colorectal cancer · Colorectal cancer · Adenomas, concurrent

Abstract

Background/Aims: With the development of early diagnostic technologies, more synchronous colorectal cancers (SCRCs) can be clinically detected. Although SCRCs are recognized as a significant clinical entity, their clinical features, diagnosis, treatment, and prognosis have yet to be definitively established. In order to obtain a comprehensive understanding of this disease and to establish an efficient profile by which to recognize individuals at high risk of developing SCRCs, we carried out a review of the relevant literature.

Methods: The PubMed database was searched for publications of 'synchronous colorectal carcinoma/cancer/adenocarcinoma' and 'multiple colorectal carcinomas'. All publications up to January 2011 were considered, and then only articles in English were retrieved for inclusion in this review.

Results: The incidence of SCRCs was found to be higher in older and male patients. The prognosis in patients with SCRCs was equivalent to that in patients with solitary CRC. The failure to diagnose synchronous lesions before and during the operation was associated with repeated surgery.

Conclusion: SCRCs possess distinctive features compared to solitary CRC. While all colorectal patients should be carefully assessed to rule out the presence of concurrent colon

adenomas, since missed lesions can result in additional surgery and poor prognosis, particular attention should be given to the high-risk group of older male patients.

Copyright © 2011 S. Karger AG, Basel

Introduction and Methods

Colorectal cancer (CRC) is one of the most common gastrointestinal cancers in the world today. Historically, CRC has been relatively rare in Asians, but the recent socioeconomic development and adaptation to a western lifestyle in the Asia-Pacific region have been accompanied by a significant increase in the incidence of CRC. In addition, synchronous colorectal cancers (SCRCs) [1] have also risen globally, challenging the current treatment strategies and adversely affecting the overall prognosis of CRC.

The Warren and Gates criteria were established to clinically diagnose SCRCs [2] on the basis of pathological findings in CRC biopsies. These criteria are in widespread use and include the following key elements: (1) each tumor must present a definite picture of malignancy; (2) each tumor must be distinct; (3) the probability of one being a metastasis of the other must be excluded, and (4) the synchronous lesions must be diagnosed simultaneously or within 6 months of the initial diagnosis [3]. In SCRC, the most advanced cancer (as determined by tu-

Table 1. List of major studies on SCRCs

First author, Ref. No.	Year of publication	Type	Cases with SCRC, n	Cases with CRC, n
Oya [4]	2003	nonrandomized, retrospective	42	834
Papadopoulos [7]	2004	nonrandomized, retrospective	26	1,160
Wang [9]	2004	nonrandomized, retrospective	15	1,311
Latournerie [10]	2008	nonrandomized, retrospective	596	14,966
Kaibara [11]	1984	nonrandomized, retrospective	763	23,866
Chen [12]	2000	nonrandomized, retrospective	52	1,728
Passman [15]	1996	nonrandomized, retrospective	160	4,718
Fukatsu [17]	2007	nonrandomized, retrospective	249	2,812
Nosho [29]	2009	prospective, cohort	47	2,021
Dykes [31]	2003	retrospective	77	2,807

Fig. 1. Flow chart of article selection.

mor TNM staging) is usually designated as the index cancer; the less advanced cancers (with lower TNM stage) are then considered as concurrent lesions of the index cancer. In SCRC cases presenting with two or more lesions at an identical pathological stage, the largest lesion is designated as the index cancer [4].

Despite the growing incidence of SCRC, very little is known about its risk factors and prognosis. A comprehensive overview of the SCRC profile, including patient features, lesion characteristics, treatments, and outcomes, will not only help clinicians to more readily identify high-risk patients and design more effective treatment strategies but will help guide researchers' efforts to elucidate the underlying molecular mechanisms of SCRC pathogenesis. To this end, we reviewed all journal articles in PubMed under the key words 'synchronous colorectal carcinoma/cancer/adenocarcinoma' and 'multiple colo-

rectal carcinomas' published up to January 2011. A total of 71 articles were identified. This list was restricted to English-language articles only, resulting in 11 articles being excluded. After retrieval and review of the remaining articles, 15 more were excluded because upon closer inspection the content was not relevant to this review. The selection strategy is shown in figure 1. Finally, 45 articles were included in this review, 10 of which are summarized in table 1.

SCRC Epidemiology

Prevalence

The prevalence of SCRCs has been reported as ranging from 2.3 to 12.4% [5, 6]. The estimates of prevalence are relatively broad due to the fact that there is no consistent definition of synchronous events which could guide studies in the literature. Some studies defined 'synchronous' as a second carcinoma diagnosed less than 6 months after the diagnosis of the index tumor [3, 7–10], while others defined it as a carcinoma arising 1 year or more after the initial diagnosis [4, 11–13]. In addition, the SCRC populations have varied significantly in size and clinical and demographic characteristics between studies, and the study periods have also been very different.

In earlier studies, the concepts of 'synchronous' and 'metachronous' had not yet been fully distinguished, and as a result the two were often mixed together in the analysis, causing an overestimation of the synchronous incidence. Over time, advances in imaging technologies and diagnostic procedures have led to increased and earlier detection of lesions; for example, colonoscopy is more effective than barium enema in detecting SCRCs [10], and

Table 2. Gender distribution of patients with SCRCs and CRC in the major studies

First author, Ref. No.	SCRCs		CRC		p
	male	female	male	female	
Oya [4]	33 (78.6%)	9 (21.4%)	492 (60%)	342 (40%)	0.018
Papadopoulos [7]	15 (57.7%)	11 (42.3%)	645 (55.6%)	515 (44.4%)	0.09
Takeuchi [8]	8 (89.9%)	1 (11.1%)			
Wang [9]	11 (73%)	4 (27%)			
Latournerie [10]	387 (64.9%)	209 (35.1%)	8,216 (54.9%)	6,750 (45.1%)	<0.001
Kaibara [11]	524 (68.7%)	239 (31.3%)			
Chen [12]	34 (65%)	18 (35%)	923 (53%)	805 (47%)	0.088
Fukatsu [17]	175 (70.3%)	74 (29.7%)	1,624 (58%)	1,624 (58%)	<0.01
Tziris [18]	7 (58.3%)	5 (41.7%)	157 (58.6%)	111 (41.4%)	

its widespread application has coincided with increased diagnosis. Nonetheless, the most current estimates of incidences are still considered to be inaccurate since not all tumors are discovered clinically and the amount of related population studies is still relatively low.

Age

Previous studies have not reached consensus on the relationship between age and the incidence of SCRCs. Several authors indicated that patients with SCRCs were older than those with CRC [6, 14, 15], while others found that SCRC was present more often in the younger patients [3, 16]. Three more recent studies, however, concluded that there was no significant difference in age of individuals with CRC and those with SCRC [4, 12, 17]. It is possible that in the earlier studies the reliance on basic statistical approaches limited their ability to determine the association of age with SCRC. When Fukatsu et al. [17] stratified the 249 SCRC patients in their study by tumor location, they found that patients with synchronous lesions in the right or in both sides of the colon were significantly older than those with lesions in the left colon (right/both vs. left: $71.9 \pm 9.1/69.4 \pm 9.5$ vs. 64.4 ± 11.0 years, $p < 0.0167$). Likewise, when Latournerie et al. [10] investigated the complex associations of risk factors with SCRC by using advanced statistical approaches, including multivariate logistic regression, they found that patients aged 75 years and over were more likely than younger patients to have SCRCs (odds ratio: 1.31).

Gender

As shown in table 2, several studies have found that men are at higher risk of SCRCs [4, 7–12, 17, 18]. As the largest scale study in recent years, Latournerie et al. [10]

determined that the male/female ratio of SCRCs was 1.85, whereas in CRC it was 1.22 ($p < 0.001$). Oya et al. [4] also reported a similar male predominance in SCRC cases, but observed an even higher ratio in their study population ($p = 0.018$). Fukatsu et al. [17] further determined that the lesions of male patients principally occurred in the left colon or bilaterally; however, lesions that occurred exclusively in the right colon were not associated with a male or female bias. Their analysis indicated that the male gender was a significant risk factor only for those with both tumors located in the left colon [17]. Until now, there has been no obvious explanation for this phenomenon.

Pathological Characteristics

Number and Location of the Lesions

Most SCRCs consist of 2 lesions, but some patients have 3 or even 4. In an exceptional case, Kaibara et al. [11] reported a patient with 7 simultaneous colon cancers. When making comparisons between locations of SCRCs and single carcinomas, most studies have found that SCRCs are more frequently located in the right colon [12, 15, 19]. However, Oya et al. [4] and Finan et al. [20] reported a predominance in the left colon. Location of the index and concurrent lesion is important since it can affect the treatment strategy; for example, if the lesions are located far away from each other, then a more extensive resection may be required. Passman et al. [15] found that the majority of patients (63.8%; 102/160) had lesions located in different segments of the colon. The study by Kaibara et al. [11], however, found opposite results, with 62.5% (405/648) of patients having lesions in the same segment and only 2.3% (15/648) of the lesions were lo-

cated in completely separate segments. Latournerie et al. [10] also found that more of the patients had lesions in the same segment of the colon, but the percentage was not as distinctive from those with different segment location (54 vs. 46%, respectively).

Characteristics of Synchronous Lesions

Comparison between SCRCs and CRC

Oya et al. [4] studied 876 surgically resected primary colorectal carcinomas and their study was the only one to specifically compare SCRCs with CRC. They found that synchronous carcinomas were significantly smaller in size ($p < 0.001$), more frequently located in the left colon ($p = 0.001$), penetrated the wall less ($p < 0.001$), and were more common in advanced lesions ($p = 0.003$) than CRC.

Comparison between Index Lesions and Concurrent Lesions in SCRCs

The index lesion is clinically defined as the pathologically most advanced lesion. Four of the studies specifically reported on the characteristics that distinguished the index lesion from the concurrent lesions [4, 12, 20]. Not surprisingly, the index lesions were usually larger in size, more frequently moderately differentiated, more deeply penetrated, and more often ulcerated in morphology than the concurrent lesions. Moreover, one study reported that lymphatic invasion was also more frequent in index lesions than in concurrent lesions [4].

Comparison between Index Lesions of SCRCs and CRC

Oya et al. [4] made comparisons between the index lesions of SCRCs and CRC to determine if there were differences in key features of the tumor pathology that would serve as diagnostic or prognostic markers. While the authors found no differences in size, differentiation, location, pathological stage, morphology, or lymphatic invasion, they did discover that distant metastasis and venous invasion were more common in index lesions of synchronous cases.

The Incidence of Concurrent Adenomas

Most studies have reported that the incidence of concurrent adenomas was significantly higher in patients with SCRCs than in those with solitary cancer [3, 12, 13, 21]. Latournerie et al. [10] reported that 34.1% of patients with SCRCs had adenomas compared with 19.1% of the single cancers. They also showed that patients with SCRCs, in which both tumors were in the right colon, were likely to have concurrent adenomas in the right side.

Similarly, if both tumors were in the left colon, the adenomas tended to occur in the left colon. Evers et al. [3] also found that in SCRCs, 52% had adenoma remnants; this result was similar to the findings of Latournerie et al. [10] in a pathological examination, which revealed adenomatous remnants in 24.3% of SCRCs but only 12.7% of single cancers. These data collectively support the hypothesis of an adenoma-carcinoma sequence in SCRC. Thus, patients with a history of adenoma or early carcinoma polyps should be carefully screened for SCRC upon discovery of new colon lesions, as suggested by Cunliffe et al. [6].

Potential Risk Factors

A few studies have investigated potential risk factors for the development of SCRCs. Kimura et al. [16], in particular, explored the relation between the family history of cancer and the incidence of synchronous lesions, but found no significant correlation between the two. Borda et al. [22] explored the potential contribution of body mass index (BMI) and determined that BMI < 21 might act a protective factor against synchronous lesions. However, this correlation was lost in more detailed statistical analyses when the sexes were stratified, and it was assumed that the overall lower BMI in the females of their study population may have influenced the original finding. Tobacco and alcohol consumption have been evaluated in several CRC studies, and are considered a risk factor for CRC. When Borda et al. [22] investigated both habits in relation to SCRC, they found that these habits were statistically associated with the male sex but not with synchronous lesions. Maekawa et al. [23], however, reported that if the accumulated amount of alcohol (alcohol weekly average multiplied by years of drinking) exceeded 9,800, the risk of SCRCs was approximately 6.8-fold higher than in nondrinkers; this association was not affected by the type of alcohol beverages consumed. The biological mechanisms of alcohol-related carcinogenesis are largely undefined, but alcohol intake may render the entire colorectal mucosa unstable, making it generally more susceptible to malignant changes [23].

Genetic Analysis

The molecular explanation for SCRCs is uncertain. The genetic events underlying CRC, however, have been thoroughly studied and CRC can be divided into three distinct phenotypes. Chromosomal instability denotes tumors with frequent karyotypic abnormalities and chromosomal gains and losses. Microsatellite instability (MSI) denotes tumors with altered lengths of short nucle-

otide repeat sequences. Finally, the CpG island methylation phenotype (CIMP) denotes tumors in which transcriptional inactivation has occurred by the epigenetic mechanism of cytosine methylation in promoters of tumor suppressor genes. Each of these genetic features has been demonstrated to play a significant role in pathological and biological characteristics of CRC [24].

One of the most important tumor suppressor genes is p53. This gene is considered to be the most prevalent genetic alteration in human neoplasms. Eguchi et al. [25] found that in SCRCs, the p53 mutations in left-sided and rectal carcinomas were different from those in right-sided carcinomas ($p = 0.04$), supporting the idea that SCRCs may be of multicentric origin [26]. In addition, Yalcinkaya et al. [27] showed that p53 expression in SCRCs was strongly associated with aggressiveness and poor prognosis; specifically, adenocarcinomas with poor differentiation and deeper invasion had higher expression of p53.

Gonzalo et al. [28] found that the gene promoter methylation status was associated with SCRCs, particularly in MGMT1, MGMT2 and RASSF1A genes. Nosho et al. [29] also showed that SCRCs more frequently contained mutations in the cell cycle signaling gene BRAF ($p = 0.0041$), were largely of the CIMP ($\geq 6/8$ methylated promoters using the 8-marker CIMP panel, $p = 0.013$), and had high methylation levels on the long interspersed nuclear element-1 retrotransposon sequences ($p = 0.0072$) and on CpG islands ($p < 0.0001$).

Pedroni et al. [30] reported 32% MSI in SCRCs, similar to the 32% incidence of MSI reported in the research by Dykes et al. [31]. Nosho et al. [29] also found that the MSI-high phenotype, defined as the presence of instability in $\geq 30\%$ of the markers, was more common in SCRCs ($p = 0.037$). These data suggest that the MSI phenotype is more common in SCRC lesions than in those that arise as solitary lesions. However, Brueckl et al. [32] reported that only 10% of patients with SCRCs were characterized as MSI. The MSI phenotype, then, may actually describe a yet unrecognized subtype of SCRC pathology or patients.

Diagnosis

Preoperative or intraoperative diagnosis of SCRCs is very important. Failure to diagnose leads to errors in treatment and poor prognosis. It is important to palpate the entire colon carefully before the end of the operation for CRC so that a misdiagnosis of SCRCs can be avoided. Unfortunately, however, such intraoperative palpation is relatively insensitive and associated with a greater than

50% failure rate in detecting lesions of SCRCs [33], especially when the tumor is at an earlier histological stage [34]. For this reason, full clinical and radiological investigation is essential prior to the operation. In the early 1970s, examination of patients with large bowel symptoms was mainly based on barium enema and rigid sigmoidoscopy. Over the past few years, though, there have been important changes in diagnostic procedures for CRC. Extensive use of preoperative colonoscopy is recommended in order to thoroughly evaluate the colorectal cancer status and promote detection of SCRCs. Kaibara et al. [11] reported a 60.1% frequency of preoperative diagnosis of SCRCs by double-contrast barium examination or colonoscopy, whereas Takeuchi et al. [8] reported that using both methods resulted in an overall preoperative accuracy of 77.8%. However, neither of these diagnosis rates was optimal and an unacceptable amount of SCRCs goes undiagnosed.

The barium enema may fail to make a diagnosis because visualization of the tumor may be obscured by bleeding or inadequate bowel preparation and retained feces. The presence of an annular carcinoma may also interfere with preparative cleansing and passage of barium through the lesion, effectively masking proximal lesions. With colonoscopy, the quality of the view is better in most cases, but good preparation of the large bowel is still essential. However, scirrhous cancers may prevent the passage of the endoscope through the lumen and hinder detection of additional lesions.

There is still some controversy about which examination is better to fully detect SCRCs. Nowadays, virtual colonoscopy has become a viable alternative method for the evaluation of the whole colon. CT colonography is above all of value in those patients with stenosis or colon elongation that leads to incomplete colonoscopy. It is not only useful in the evaluation of the proximal bowel, but can also provide surgeons with accurate information about staging and tumor localization [35, 36]. Other technical advances, such as magnetic resonance colonography [37] and the combination of CT colonography with PET [38], have been reported as useful tools for the preoperative evaluation of SCRCs. Intraoperative endoscopy is another available method to perform a complete examination of the colon and rectum in cases where a preoperative colonoscopy is not feasible, such as in emergency situations. While this approach provides sufficient results, it is time-consuming and makes closure of the abdomen difficult since the bowel becomes distended with air [39].

Treatment Option and Prognosis

Surgical resection is the primary treatment option for SCRCs. Passman et al. [15] recommended that patients with lesions in adjacent segments receive a more extensive resection, including removal of proximal intestinal regions and local lymph nodes in some cases. There is still some controversy on how to best treat synchronous lesions in separate segments. Some authors have suggested that total or subtotal colectomy should be performed [9, 14, 40, 41], because if synchronous lesions are overlooked at the time of surgery, the patient may soon have to undergo repeated surgery and the lesions are likely to have advanced in their pathological stage and to be associated with a poorer prognosis [4]. Some authors have suggested the utility of extensive procedures such as proctocolectomy with J-pouch ileoanal anastomosis, total abdominal colectomy with ileorectal anastomosis, and proctosigmoidectomy with coloanal anastomosis [33].

A more conservative policy consisting of multiple segmental resections which aim to retain the normal colon has been suggested by some [19]. The reasons for such an approach are that a subtotal colectomy may increase stool frequency, and synchronous colon anastomoses do not appear to be associated with an increased risk of complications [42]. Based on the available evidence, it appears that when the patient's general condition is suitable for undergoing an operation or when the patient is at an increased risk of anastomotic complications, such as in cases of malnourishment, immunosuppression or sepsis, then subtotal colectomy seems a justifiable choice [34, 40, 42]. In some case reports, the authors treated T1 rectal cancer with SCRCs by transanal endoscopic microsurgery before performing a radical operation for the second lesion [43]. In another report, a single-incision laparoscopic total abdominal colectomy with an ileorectal anastomosis and intraoperative CO₂ colonoscopy was successfully performed for a patient with SCRCs of the cecum and the sigmoid colon [44].

The expected 5-year survival rates of patients affected by SCRCs are still controversial. While one study found a higher survival in patients with SCRCs [45], others have demonstrated that patients with single colon primary tumors are more likely to survive [4, 41]. In the first prospective study carried out to eliminate sources of considerable bias that were inevitably present in retrospective case-control studies, Nosho et al. [29] showed that SCRC cases were significantly associated with poor prognosis. Poor prognosis of SCRCs is thought to be due mainly to the relatively frequent distant metastasis that occur in synchronous cases [4]. However, even more studies have shown that there is no difference in survival between SCRCs and CRC when the pathological stages of tumors were identical and the resections were curative [7, 10, 12, 15, 16, 19, 21].

Conclusion

With the development of early diagnostic technologies, more SCRCs have been diagnosed. Compared with the solitary CRC, SCRCs possess distinctive features. These should be fully investigated in preoperative clinical workups to avoid the possibility of accessory lesions being overlooked and not resected. Older male patients with concurrent adenomas in the colon are at a particularly high risk of SCRCs and close attention should be paid to them. The extent of surgical resection relies on the location and the number of lesions. The resected region should include enough intestinal length and regional lymph nodes to capture any local spread, thereby guarding against recurrence or subsequent malignant change. Of course, the mechanisms regarding the formation of multicentricity need to be fully elucidated in order to gain insight into SCRC genesis and development, which will ultimately benefit molecular therapies and improve patient survival.

References

- 1 Fenger C: I. Surgery of the ureter. *Ann Surg* 1894;20:257–296.
- 2 Warren S, Gates O: Carcinoma of ceruminous gland. *Am J Pathol* 1941;17:821–826.
- 3 Evers BM, Mullins RJ, Matthews TH, Broghamer WL, Polk HC Jr: Multiple adenocarcinomas of the colon and rectum. An analysis of incidences and current trends. *Dis Colon Rectum* 1988;31:518–522.
- 4 Oya M, Takahashi S, Okuyama T, Yamaguchi M, Ueda Y: Synchronous colorectal carcinoma: clinico-pathological features and prognosis. *Jpn J Clin Oncol* 2003;33:38–43.
- 5 Welch JP: Multiple colorectal tumors. An appraisal of natural history and therapeutic options. *Am J Surg* 1981;142:274–280.
- 6 Cunliffe WJ, Hasleton PS, Tweedle DE, Schofield PF: Incidence of synchronous and metachronous colorectal carcinoma. *Br J Surg* 1984;71:941–943.
- 7 Papadopoulos V, Michalopoulos A, Basdanis G, Papapolychroniadis K, Paramythiotis D, Fotiadis P, Berovalis P, Harlaftis N: Synchronous and metachronous colorectal carcinoma. *Tech Coloproctol* 2004;8(suppl 1):s97–s100.

- 8 Takeuchi H, Toda T, Nagasaki S, Kawano T, Minamisono Y, Maehara Y, Sugimachi K: Synchronous multiple colorectal adenocarcinomas. *J Surg Oncol* 1997;64:304–307.
- 9 Wang HZ, Huang XF, Wang Y, Ji JF, Gu J: Clinical features, diagnosis, treatment and prognosis of multiple primary colorectal carcinoma. *World J Gastroenterol* 2004;10:2136–2139.
- 10 Latournerie M, Jooste V, Cottet V, Lepage C, Faivre J, Bouvier AM: Epidemiology and prognosis of synchronous colorectal cancers. *Br J Surg* 2008;95:1528–1533.
- 11 Kaibara N, Koga S, Jinnai D: Synchronous and metachronous malignancies of the colon and rectum in Japan with special reference to a coexisting early cancer. *Cancer* 1984;54:1870–1874.
- 12 Chen HS, Sheen-Chen SM: Synchronous and ‘early’ metachronous colorectal adenocarcinoma: analysis of prognosis and current trends. *Dis Colon Rectum* 2000;43:1093–1099.
- 13 Ueno M, Muto T, Oya M, Ota H, Azekura K, Yamaguchi T: Multiple primary cancer: an experience at the Cancer Institute Hospital with special reference to colorectal cancer. *Int J Clin Oncol* 2003;8:162–167.
- 14 Slater G, Aufses AH Jr, Szporn A: Synchronous carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1990;171:283–287.
- 15 Passman MA, Pommier RF, Vetto JT: Synchronous colon primaries have the same prognosis as solitary colon cancers. *Dis Colon Rectum* 1996;39:329–334.
- 16 Kimura T, Iwagaki H, Fuchimoto S, Hizuta A, Orita K: Synchronous colorectal carcinomas. *Hepatogastroenterology* 1994;41:409–412.
- 17 Fukatsu H, Kato J, Nasu JI, Kawamoto H, Okada H, Yamamoto H, Sakaguchi K, Shiratori Y: Clinical characteristics of synchronous colorectal cancer are different according to tumour location. *Dig Liver Dis* 2007;39:40–46.
- 18 Tziris N, Dokmetzioglou J, Giannoulis K, Kesisoglou I, Sapalidis K, Kotidis E, Gambros O: Synchronous and metachronous adenocarcinomas of the large intestine. *Hipokratia* 2008;12:150–152.
- 19 Adloff M, Arnaud JP, Bergamaschi R, Schloegel M: Synchronous carcinoma of the colon and rectum: prognostic and therapeutic implications. *Am J Surg* 1989;157:299–302.
- 20 Finan PJ, Ritchie JK, Hawley PR: Synchronous and ‘early’ metachronous carcinomas of the colon and rectum. *Br J Surg* 1987;74:945–947.
- 21 Nikoloudis N, Saliangas K, Economou A, Andreadis E, Siminou S, Manna I, Georgakis K, Chrissidis T: Synchronous colorectal cancer. *Tech Coloproctol* 2004;8(suppl 1):s177–s179.
- 22 Borda A, Martinez-Penuela JM, Munoz-Navas M, Prieto C, Betes M, Borda F: Synchronous neoplastic lesions in colorectal cancer. An analysis of possible risk factors favouring presentation. *Rev Esp Enferm Dig* 2008;100:139–145.
- 23 Maekawa SJ, Aoyama N, Shirasaka D, Kuroda K, Tamura T, Kuroda Y, Kasuga M: Excessive alcohol intake enhances the development of synchronous cancerous lesion in colorectal cancer patients. *Int J Colorectal Dis* 2004;19:171–175.
- 24 Ogino S, Goel A: Molecular classification and correlates in colorectal cancer. *J Mol Diagn* 2008;10:13–27.
- 25 Eguchi K, Yao T, Konomoto T, Hayashi K, Fujishima M, Tsuneyoshi M: Discordance of p53 mutations of synchronous colorectal carcinomas. *Mod Pathol* 2000;13:131–139.
- 26 Konecny RJ, King TC, Schechter S, McLean SF, Lodowsky C, Wanebo HJ: Synchronous colon carcinomas: molecular-genetic evidence for multicentricity. *Ann Surg Oncol* 1996;3:136–143.
- 27 Yalcinkaya U, Ozturk E, Ozgur T, Yerci O, Yilmazlar T: P53 expression in synchronous colorectal cancer. *Saudi Med J* 2008;29:826–831.
- 28 Gonzalo V, Lozano JJ, Munoz J, Balaguer F, Pellise M, Rodriguez de Miguel C, Andreu M, Jover R, Llor X, Giraldez MD, et al: Aberrant gene promoter methylation associated with sporadic multiple colorectal cancer. *PLoS One* 2010;5:e8777.
- 29 Noshio K, Kure S, Irahara N, Shima K, Baba Y, Spiegelman D, Meyerhardt JA, Giovannucci EL, Fuchs CS, Ogino S: A prospective cohort study shows unique epigenetic, genetic, and prognostic features of synchronous colorectal cancers. *Gastroenterology* 2009;137:1609–1620.e1–3.
- 30 Pedroni M, Tamassia MG, Percesepe A, Roncucci L, Benatti P, Lanza G Jr, Gafa R, Di Gregorio C, Fante R, Losi L, et al: Microsatellite instability in multiple colorectal tumors. *Int J Cancer* 1999;81:1–5.
- 31 Dykes SL, Qui H, Rothenberger DA, Garcia-Aguilar J: Evidence of a preferred molecular pathway in patients with synchronous colorectal cancer. *Cancer* 2003;98:48–54.
- 32 Brueckl WM, Limmert T, Brabletz T, Guenther K, Jung A, Hermann K, Wiest GH, Kirchner T, Hohenberger W, Hahn EG, et al: Mismatch repair deficiency in sporadic synchronous colorectal cancer. *Anticancer Res* 2000;20:4727–4732.
- 33 Arenas RB, Fichera A, Mhoon D, Michellasi F: Incidence and therapeutic implications of synchronous colonic pathology in colorectal adenocarcinoma. *Surgery* 1997;122:706–709, discussion 709–710.
- 34 Hancock RJ: Synchronous carcinoma of the colon and rectum. *Am Surg* 1975;41:560–563.
- 35 Kim MS, Park YJ: Detection and treatment of synchronous lesions in colorectal cancer: the clinical implication of perioperative colonoscopy. *World J Gastroenterol* 2007;13:4108–4111.
- 36 McArthur DR, Mehrzad H, Patel R, Dadds J, Pallan A, Karandikar SS, Roy-Choudhury S: CT colonography for synchronous colorectal lesions in patients with colorectal cancer: initial experience. *Eur Radiol* 2010;20:621–629.
- 37 Achiam MP, Holst Andersen LP, Klein M, Chabanova E, Thomsen HS, Rosenberg J: Preoperative evaluation of synchronous colorectal cancer using MR colonography. *Acad Radiol* 2009;16:790–797.
- 38 Kinner S, Antoch G, Bockisch A, Veit-Haibach P: Whole-body PET/CT-colonography: a possible new concept for colorectal cancer staging. *Abdom Imaging* 2007;32:606–612.
- 39 Kaibara N, Kimura O, Nishidoi H, Miyano Y, Koga S: Intraoperative colonoscopy for the diagnosis of multiple cancers of the large intestine. *Jpn J Surg* 1982;12:117–121.
- 40 Eason AM, Cotterchio M, Crosby JA, Sutherland H, Dale D, Aronson M, Holowaty E, Gallinger S: A population-based study of the extent of surgical resection of potentially curable colon cancer. *Ann Surg Oncol* 2002;9:380–387.
- 41 Enker WE, Dragagevic S: Multiple carcinomas of the large bowel: a natural experiment in etiology and pathogenesis. *Ann Surg* 1978;187:8–11.
- 42 Holubar SD, Wolff BG, Poola VP, Soop M: Multiple synchronous colonic anastomoses: are they safe? *Colorectal Dis* 2010;12:135–140.
- 43 Ikeda Y, Koyanagi N, Mori M, Akahoshi K, Ueyama T, Sugimachi K: Transanal endoscopic microsurgery for T1 rectal cancer in patients with synchronous colorectal cancer. *Surg Endosc* 1999;13:710–712.
- 44 Bardakcioglu O, Ahmed S: Single incision laparoscopic total abdominal colectomy with ileorectal anastomosis for synchronous colon cancer. *Tech Coloproctol* 2010;14:257–261.
- 45 Copeland EM, Jones RS, Miller LD: Multiple colon neoplasms. Prognostic and therapeutic implications. *Arch Surg* 1969;98:141–143.