Clinicopathologic characteristics and survival rate in patients with synchronous or metachronous double primary colorectal and gastric cancer

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Purpose: Double primary colorectal cancer (CRC) and gastric cancer (GC) represent the most common multiple primary malignant tumors (MPMT) in Korea. The recognition and screening of hidden malignancies other than the primary cancer are critical. This study aimed to investigate the clinicopathologic characteristics and survival rates in patients with synchronous or metachronous double primary CRC and GC.

Methods: Between January 1994 and May 2018, 11,050 patients were diagnosed with CRC (n = 5,454) or GC (n = 5,596) at Gil Medical Center. MPMT and metastatic malignant tumors were excluded from this study. A total of 103 patients with double primary CRC and GC were divided into two groups: the synchronous group (n = 40) and the metachronous group (n = 63). The incidence, clinicopathologic characteristics, and survival rate of the two groups were analyzed.

Results: The incidence of synchronous and metachronous double primary CRC and GC was 0.93%. Double primary CRC and GC commonly occurred in male patients aged over 60 years with low comorbidities and minimal previous cancer history. There were significant differences between the synchronous and metachronous groups in terms of age, morbidity, and overall survival. Metachronous group patients were 6 years younger on average (P = 0.009), had low comorbidities (P = 0.008), and showed a higher 5-year overall survival rate (94.8% and 61.3%, P < 0.001) in contrast to synchronous group.

Conclusion: When primary cancer (CRC or GC) is detected, it is important to be aware of the possibility of the second primary cancer (GC or CRC) development at that time or during follow-up to achieve early detection and better prognosis.

Keywords: Multiple primary neoplasms, Second primary neoplasm, Colorectal neoplasm, Stomach neoplasm

INTRODUCTION

Although advanced diagnostic modalities and techniques have enabled the early detection of cancer, and the development of mini-

mally invasive cancer treatments has enhanced the survival rate of cancer patients, the long-term survival of cancer patients increases the possibility of developing other primary malignancies. Therefore, in order to detect and treat other primary cancer as early as possible, it is important to identify the characteristics of double primary cancer patients.

The entity of “multiple primary malignant tumors (MPMT)” was first defined by Billroth in 1889 as the occurrence of more than two different malignant tumors in the same or different systems simultaneously or consecutively [1]. If the second malignant tumor is detected simultaneously or within 6 months, it is defined as synchronous; if the second cancer is found after 6 months of the first diagnosis, it is defined as metachronous [2,3].

MPMT are sporadic and rare in most cases, but they develop more often in the organs of the same system than in those of other systems [4]. In Korea and Japan, colorectal cancer (CRC) and gastric cancer (GC) occur synchronously or metachronously in patients more frequently than by chance. Some studies have reported
an increased risk of GC among CRC patients [5-8], whereas other studies have shown that the risk of CRC was increased in GC patients [9-12]. Even though many studies have suggested possible associations between CRC and GC in terms of genetic and/or environmental factors, the mechanisms of development of double primary CRC and GC remain unclear. Therefore, it is important to investigate the various clinical, pathological, and treatment characteristics of patients with primary malignant tumors with or without a second primary cancer to better predict the risk of developing additional malignant tumors.

In this study, we compared the differences in the incidence, clinicopathologic characteristics, and survival rate between the synchronous and metachronous groups of patients with double primary CRC and GC to highlight the importance of surveillance for secondary primary cancer upon the initial detection of primary cancer.

**METHODS**

**Patients**

A total of 11,050 patients were diagnosed with CRC or GC at Gil Medical Center between January 1994 and May 2018 (Fig. 1), with 5,454 patients diagnosed with CRC and 5,596 patients diagnosed with GC. Diagnoses of CRC and GC were pathologically confirmed in all patients. Hereditary cancers and MPMT other than CRC and GC were excluded in this study. Data of 166 patients who were diagnosed with only CRC and GC at the same time were reviewed, retrospectively. Among them, 63 patients with metastatic tumor from another site were also excluded. Finally, 103 patients with double primary CRC and GC were selected; 40 patients were diagnosed with synchronous double primary CRC and GC, whereas 63 patients were diagnosed with metachronous double primary CRC and GC. All procedures were conducted in accordance with the ethical standards of the respective committees on human experimentation (institutional and national) and with the 1964 Declaration of Helsinki and later versions. The study was approved by the Institutional Review Board of Gachon University (GDIRB2018-357). The informed consent was waived.

**Methods**

The clinicopathologic characteristics of 103 patients who were synchronously or metachronously diagnosed with double primary CRC and GC were reviewed, retrospectively. Age, body mass index (BMI), comorbidities, previous cancer history, family cancer history, and levels of carcinoembryonic antigen (CEA), carbohydrate antigen (CA 19-9), and microsatellite instability (MSI) were recorded based on the date of diagnosis of the first primary cancer. Pathologic stage was classified according to the American Joint Committee on Cancer (8th edition). All patients who underwent surgery were followed up every 3 months for the first 3 years, every 6 months until 5 years, and annually thereafter. A physical examination and laboratory measurements of serum CEA and CA 19-9 were performed at each follow-up. Abdominoperineal computed tomography (CT) and chest CT were performed annually. To define double primary CRC and GC, Warren and Gates criteria [13] for multiple primary cancers were used: (1) each tumor had to histopathologically present a definite picture of malignancy; (2) each tumor had to be clearly differentiated and locally isolated; and (3) the probability that one of the tumors was metastatic from the other had to be excluded. Moertel [3] definition was used to define chronicity. In synchronous double primary CRC and GC, both cancers occur at the same time or within first 6 months of diagnosis of the first primary cancer; in metachronous cancer, the second primary cancer occurs more than 6 months after the first primary cancer. The time interval between the two primary cancers was defined as the date from the first cancer surgery to the date of the secondary cancer surgery. The overall survival rate was defined as the time from the first primary cancer surgery to the last follow-up or death from any cause.

**Statistics**

For statistical analysis, the chi-square test, Fisher exact probability test, or linear-by-linear association analysis were used to compare clinicopathologic characteristics between the two groups, as appropriate. Independent sample t-test was used for continuous variables. Median value and range were recorded. The overall survival curve was calculated using Kaplan-Meier curve analysis, and the survival rate was compared using log-rank tests. All statistical analyses were performed using IBM SPSS Statistics for Windows version 23.0 (SPSS Inc., Chicago, IL, USA). P-values < 0.05 (two-sided) were considered statistically significant.
RESULTS

Clinicopathologic characteristics of synchronous or metachronous colorectal and gastric cancer

As shown in Fig. 1, the incidence of double primary CRC and GC commonly occurred in male patients aged over 60 years with a BMI of 23 kg/m². However, the patients in the synchronous group tended to be an average of 6 years older than the metachronous group patients (P = 0.009). In both groups, patients had a low rate of comorbidities such as hypertension, diabetes mellitus, and tuberculosis, and so on. The metachronous group had significantly low comorbidities in contrast to the synchronous group (P = 0.008). Although patients without a previous cancer history or family cancer history were common in both groups, most patients in the synchronous group had no previous cancer history (95%, P = 0.028). When the first primary cancer was detected, no significant differences in the CEA, CA19-9, and MSI levels were found between the two groups. In both CRC and GC, early-stage cancer was predominant: CRC (stage I or II) and GC (EGC). Even though CRC stage and GC type were not classified in seven and nine metachronous patients respectively, early-stage cancer was significantly more common in the metachronous group than in the synchronous group (P = 0.005 for CRC, P = 0.003 for GC). Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) was performed more frequently in the metachronous group in contrast to the synchronous group (23.8% vs. 17.5% in CRC, 33.3% vs. 17.5% in GC), though there was no significant difference between the two groups.

Time intervals between each primary cancer and the cancer occurrence sequence

Table 2 and Fig. 2 describe the time intervals between each primary cancer. The average time interval between synchronous double primary CRC and GC was less than 1 month, whereas it was 63 months in the metachronous group. In the synchronous group (both synchronous and metachronous) was 0.93%. Clinicopathologic characteristics of the synchronous or metachronous double primary CRC and GC are listed in Table 1. In both groups, double primary CRC and GC commonly occurred in male patients aged over 60 years with a BMI of 23 kg/m². However, the patients in the synchronous group tended to be an average of 6 years older than the metachronous group patients (P = 0.009). In both groups, patients had a low rate of comorbidities such as hypertension, diabetes mellitus, and tuberculosis, and so on. The metachronous group had significantly low comorbidities in contrast to the synchronous group (P = 0.008). Although patients without a previous cancer history or family cancer history were common in both groups, most patients in the synchronous group had no previous cancer history (95%, P = 0.028). When the first primary cancer was detected, no significant differences in the CEA, CA19-9, and MSI levels were found between the two groups. In both CRC and GC, early-stage cancer was predominant: CRC (stage I or II) and GC (EGC). Even though CRC stage and GC type were not classified in seven and nine metachronous patients respectively, early-stage cancer was significantly more common in the metachronous group than in the synchronous group (P = 0.005 for CRC, P = 0.003 for GC). Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) was performed more frequently in the metachronous group in contrast to the synchronous group (23.8% vs. 17.5% in CRC, 33.3% vs. 17.5% in GC), though there was no significant difference between the two groups.

Table 2. Time interval and cancer occurrence sequence between each primary cancer

| Time interval between primary cancers (mo) | Synchronous CRC and GC (n = 40) | Metachronous CRC and GC (n = 63) |
|------------------------------------------|---------------------------------|---------------------------------|
| Cancer occurrence sequence               | C-G 40 (100)                    | C-G 0                            |
|                                          | C-G 0                            | G-C 32 (50.8)                    |
|                                          | G-C 0                            | G-C 31 (49.2)                    |

Values are presented as mean ± standard deviation or number (%). CRC, colorectal cancer; GC, gastric cancer; C-G, synchronous colorectal and gastric cancer; C-G, colorectal cancer followed by gastric cancer metachronously; G-C, gastric cancer followed by colorectal cancer metachronously.

Table 1. Clinicopathologic characteristics between synchronous and metachronous double primary colorectal and gastric cancer patients

| Characteristic                | Synchronous CRC and GC (n = 40) | Metachronous CRC and GC (n = 63) | P-value |
|------------------------------|---------------------------------|---------------------------------|---------|
| Age (yr)                     | 66.5 ± 10.7                     | 60.9 ± 10.1                     | 0.009   |
| Sex                          |                                 |                                 |         |
| Male                         | 36 (90.0)                       | 52 (82.5)                       |         |
| Female                       | 4 (10.0)                        | 11 (17.5)                       |         |
| BMI (kg/m²)                  | 23.2 ± 3.5                      | 22.9 ± 3.1                      | 0.694   |
| Comorbidity                  |                                 |                                 |         |
| ≤ 1                          | 28 (70.0)                       | 57 (80.5)                       | 0.008   |
| ≥ 2                          | 12 (30.0)                       | 6 (9.5)                         |         |
| Previous cancer history      |                                 |                                 | 0.028   |
| None                         | 38 (95.0)                       | 50 (79.4)                       |         |
| Yes                          | 2 (5.0)                         | 13 (20.6)                       |         |
| Family cancer history        |                                 |                                 | 0.177   |
| None                         | 27 (67.5)                       | 50 (79.4)                       |         |
| Yes                          | 13 (32.5)                       | 13 (20.6)                       |         |
| CEA                          | 4.1 ± 4.8                       | 3.1 ± 7.3                       | 0.515   |
| CA 19-9                      | 15.6 ± 10.5                     | 25.3 ± 76.8                     | 0.462   |
| MSI                          |                                 |                                 | 0.248   |
| No data                      | 17 (42.5)                       | 39 (61.9)                       |         |
| MSS                          | 21 (52.5)                       | 20 (31.7)                       |         |
| MSI-L                        | 1 (2.5)                         | 2 (3.2)                         |         |
| MSI-H                        | 1 (2.5)                         | 2 (3.2)                         |         |
| CRC stage                    |                                 |                                 |         |
| Not classified                | 0                               | 7 (11.1)                        | 0.005   |
| I or II                      | 24 (60.0)                       | 44 (69.8)                       |         |
| III or IV                    | 16 (40.0)                       | 12 (19.0)                       |         |
| GC type                      |                                 |                                 | 0.003   |
| Not classified                | 0                               | 9 (14.3)                        |         |
| EGC                          | 26 (65.0)                       | 44 (69.8)                       |         |
| AGC                          | 14 (38.8)                       | 10 (15.9)                       |         |
| CRC surgery                  |                                 |                                 | 0.446   |
| EMR or ESD                   | 7 (17.5)                        | 15 (23.8)                       |         |
| Surgery                      | 33 (82.5)                       | 48 (76.2)                       |         |
| GC surgery                   |                                 |                                 | 0.078   |
| EMR or ESD                   | 7 (17.5)                        | 21 (33.3)                       |         |
| Surgery                      | 33 (82.5)                       | 46 (66.7)                       |         |

Values are presented as mean ± standard deviation or number (%). CRC, colorectal cancer; GC, gastric cancer; BMI, body mass index; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; MSI, microsatellite instability; MSS, microsatellite stable; MSI-L, microsatellite instability low; MSI-H, microsatellite instability high; EGC, early gastric cancer; AGC, advanced gastric cancer; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

aComorbidity: hypertension, diabetes mellitus, tuberculosis, and so on. bPrevious cancer history other than colorectal or gastric cancer.
double primary CRC and GC were detected at the same time in more than 30 patients. In the metachronous group, the second primary cancer was detected within 75 months after the first primary cancer was detected in more than 40 patients. The cancer occurrence sequence was analyzed in the metachronous group, and CRC was diagnosed first in 32 patients, whereas GC was diagnosed first in 31 patients.

Survival rate
There was a significant difference in the survival rate between the two groups (Fig. 3). The 5-year overall survival rate was 61.3% and 94.8% in the synchronous and metachronous groups, respectively (P < 0.001).

DISCUSSION
Along with advancements in minimally invasive treatment and surgical techniques, long-term cancer survival rates have increased. However, it may increase the probability of the incidence of a second primary cancer at the same time. If the possibility of other primary carcinomas is overlooked upon detection of the first primary cancer, the opportunity for early cancer detection and minimally invasive treatment may be missed. Therefore, physicians should be more careful of hidden, concomitant malignancy. This study was planned from the perspective that when one primary cancer is detected, it should alert to the possibility of another primary cancer being present at the same time or occurring subsequently.

Since Billroth defined the concept of the “MPMT” and Warren and Gates established its criteria, many studies have focused on this subject [1,13], most of which investigated the incidence of multiple primary cancers and its distribution [14,15]. Multiple primary cancers typically occur by chance at any organ and any time, though some types of cancer have been found to coexist more frequently, including breast cancer and thyroid cancer, common bile duct cancer and pancreatic cancer, CRC and GC, and so on [16-20]. According to Lim et al. [21], the incidence of synchronous GC in patients with sporadic CRC in Korea is about 2%, and GC screening before CRC surgery was shown to assist early detection [22]. Among GC patients, 2% to 5% were found to have second primary CRC on simultaneous colonoscopy [23,24], and our
Previous studies have demonstrated that older age, male sex, familial history of solid tumors, and colorectal lesions are important risk factors for GC screening in CRC patients [14]. In our study, synchronous CRC and GC group had older age, higher comorbidities, and advanced cancer stage than metachronous CRC and GC group. Notably, synchronous patients were an average of 6 years older than the metachronous patients. In this study, each patient’s age was recorded at the time of detection of the first primary cancer, and the first primary cancer was detected at a younger age in the metachronous group, with the second primary cancer being detected during the follow-up period. Similarly, the frequency of comorbidities appears to be significantly lower in the metachronous group than in the synchronous group, as the first primary cancer occurred at a younger age in the metachronous group.

According to previous studies, both CRC and GC, together or associated with other digestive tract tumors, are frequently detected at an early stage [10]. In our study, double primary CRC and GC was more frequently detected at an early stage in both groups. However, the synchronous group had more advanced CRC or advanced gastric cancer (AGC) in contrast to the metachronous group. This is likely due to the fact that if advanced cancer was diagnosed at the time of the primary cancer detection, preoperative screening for metastasis was usually performed and the second primary cancer was incidentally detected. Overall, surgery was performed more frequently than EMR/ESD in both groups. However, EMR/ESD tended to be performed more frequently in the metachronous group in contrast to the synchronous group, which indicates that minimally invasive treatment occurred more frequently in the metachronous group, as second primary cancer is more easily detected at an early stage due to continuous follow-up surveillance. If double primary cancer detection at an early stage were more common, minimally invasive treatment could be applied to both groups more freely.

According to our data, even though the metachronous group had an approximately 5-year time interval between the detection of the second primary cancer and the first primary cancer, there was no exact cancer occurrence sequence. In previous studies, patients with multiple metachronous primary cancers showed better survival rates in contrast to the synchronous group [25]. Similar to previous studies, the 5-year survival rate was higher in the metachronous group than in the synchronous group in our study. One reason may be that because the survival rate was analyzed from the date of the first primary cancer surgery, a longer time interval between each primary cancer may have prolonged the overall survival rate in the metachronous group. Another reason may be that metachronous group patients were relatively younger and had less comorbidity when the first cancer was detected. Lastly, as a routine follow-up examination is common after the first primary cancer surgery, second primary cancer may be detected at an early stage during the regular follow-up period. All of these factors may contribute to superior survival rates.

There are a few limitations in this study. First, because it was a single-institute retrospective study, the small number of enrolled patients may preclude generalization of our results and some information may be insufficient. We did not present the results of any additional analyses based on subgroups, such as tumor location or type of surgery, owing to the small number of cancers. Second, the data for CRC-only patients or GC-only patients were not included in this study. We sought to present the clinicopathologic findings and oncologic outcomes of the treatment of synchronous or metachronous CRC and GC in actual clinical practice. In the future, prospective multi-center studies on this subject may be needed to overcome the limitations of our retrospective study.

In conclusion, we examined the clinicopathologic characteristics of both synchronous and metachronous double primary CRC and GC. Even though the incidence of the double primary CRC and GC is as low as about 1%, if the second primary cancer is detected at an early stage, better prognosis may be expected for those patients. Therefore, when a patient is diagnosed with CRC or GC, it is important for physicians to be vigilant about the possibility of other hidden cancers at that time or during follow-up. Heightened awareness of the characteristics of double primary CRC and GC patients may enable minimally invasive interventions and improve survival rates.

CONFICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Watson TA. Incidence of multiple cancer. Cancer 1953;6:365-71.
2. Ha TK, An JY, Youn HG, Noh JH, Sohn TS, Kim S. Surgical outcome of synchronous second primary cancer in patients with gastric cancer. Yonsei Med J 2007;48:981-7.
3. Moertel CG. Multiple primary malignant neoplasms: historical perspectives. Cancer 1977;40(4 Suppl):1786-92.
4. Watanabe S, Kodama T, Shimosato Y, Arimoto H, Sugimura T, Suemasu K, et al. Multiple primary cancers in 5,456 autopsy cases in the National Cancer Center of Japan. J Natl Cancer Inst 1984;72:
5. Bae JS, Lee JH, Ryu KW, Kim YW, Bae JM. Characteristics of synchronous cancers in gastric cancer patients. Cancer Res Treat 2006;38:25-9.

6. Kaibara N, Maeta M, Ikeguchi M. Patients with multiple primary gastric cancers tend to develop second primaries in organs other than the stomach. Surg Today 1993;23:186-8.

7. Ikeguchi M, Ohfuji S, Oka A, Tsujitani S, Maeda M, Kaibara N. Synchronous and metachronous primary malignancies in organs other than the stomach in patients with early gastric cancer. Hepatogastroenterology 1995;42:672-6.

8. Lee JH, Bae JS, Ryu KW, Lee JS, Park SR, Kim CG, et al. Gastric cancer patients at high-risk of having synchronous cancer. World J Gastroenterol 2006;12:2588-92.

9. Ikeda Y, Saku M, Kawanaka H, Nonaka M, Yoshida K. Features of second primary cancer in patients with gastric cancer. Oncology 2003;65:113-7.

10. Dinis-Ribeiro M, Lomba-Viana H, Silva R, Moreira-Dias L, Lomba-Viana R. Associated primary tumors in patients with gastric cancer. J Clin Gastroenterol 2002;34:533-5.

11. Cho I, An JY, Kwon IG, Choi YY, Cheong JH, Hyung WJ, et al. Risk factors for double primary malignancies and their clinical implications in patients with sporadic gastric cancer. Eur J Surg Oncol 2014;40:338-44.

12. Eom BW, Lee HJ, Yoo MW, Cho JJ, Kim WH, Yang HK, et al. Synchronous and metachronous cancers in patients with gastric cancer. J Surg Oncol 2008;98:106-10.

13. Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and a statistical study. Am J Cancer 1932;16:1358-414.

14. Yoon SN, Oh ST, Lim SB, Kim TW, Kim JH, Yu CS, et al. Clinicopathologic characteristics of colorectal cancer patients with synchronous and metachronous gastric cancer. World J Surg 2010;34:2168-76.

15. Lee WS, Lee JN, Choi S, Jung M, Baek JH, Lee WK. Multiple primary malignancies involving colorectal cancer: clinical characteristics and prognosis with reference to surveillance. Langenbecks Arch Surg 2010;395:359-64.

16. Zhang L, Wu Y, Liu F, Fu L, Tong Z. Characteristics and survival of patients with metachronous or synchronous double primary malignancies: breast and thyroid cancer. Oncotarget 2016;7:52450-9.

17. Yano K, Yamashita T, Chishiki M, Osaki T, Sugio K, Yasumoto K. Two cases of synchronous superficial double cancers in the esophagus and stomach. J UOEH 2002;24:225-32.

18. Onoue S, Katoh T, Chigira H, Matsuoka K, Suzuki M, Shibata Y, et al. Synchronous multiple primary cancers of the stomach and duodenum in aged patients: report of two cases. Surg Today 2000;30:735-8.

19. Sato K, Maekawa T, Yabuki K, Tamasaki Y, Maekawa H, Kudo K, et al. A case of triple synchronous cancers occurring in the gallbladder, common bile duct, and pancreas. J Gastroenterol 2003;38:97-100.

20. Kim HJ, Choi MC, Jang JH, Jung SG, Park H, Joo WD, et al. Clinicopathologic characteristics of double primary endometrial and colorectal cancers in a single institution. J Obstet Gynaecol Res 2018;44:944-50.

21. Lim SB, Jeong SY, Choi HS, Sohn DK, Hong CW, Jung KH, et al. Synchronous gastric cancer in primary sporadic colorectal cancer patients in Korea. Int J Colorectal Dis 2008;23:61-5.

22. Kim HJ, Kim N, Choi YJ, Yoon H, Shin CM, Park YS, et al. Clinicopathologic features of gastric cancer with synchronous and metachronous colorectal cancer in Korea: are microsatellite instability and p53 overexpression useful markers for predicting colorectal cancer in gastric cancer patients? Gastric Cancer 2016;19:798-807.

23. Park DI, Park SH, Yoo TW, Kim HS, Yang SK, Byeon JS, et al. The prevalence of colorectal neoplasia in patients with gastric cancer: a Korean Association for the Study of Intestinal Disease (KASID) Study. J Clin Gastroenterol 2010;44:102-5.

24. Suzuki A, Koide N, Takeuchi D, Okumura M, Ishizone S, Suga T, et al. Prevalence of synchronous colorectal neoplasms in surgically treated gastric cancer patients and significance of screening colonoscopy. Dig Endosc 2014;26:396-402.

25. Kim JH, Rha SY, Kim C, Kim GM, Yoon SH, Kim KH, et al. Clinicopathologic features of metachronous or synchronous gastric cancer patients with three or more primary sites. Cancer Res Treat 2010;42:217-24.