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Retrospective Cohort Study

Clinical analysis of multiple primary gastrointestinal malignant tumors: A 10-year case review of a single-center

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Abstract

BACKGROUND

Multiple primary malignant tumors (MPMTs) was first described by Billroth as early as 1889, with the first report published by Warren and Gates in 1932. Since then, numerous cases have been reported. A literature review of 1104269 patients with cancer revealed that the incidence of MPMTs ranged from 0.73 to 11.7%. In recent years, however, there has been a significant upward trend in the incidence of this phenomenon, which may be associated with many different factors, including the advancement of modern diagnostic procedures facilitating the examination and diagnosis of more MPMTs, increased exposure to chemotherapy and radiotherapy that exacerbate the risk of new malignant tumors in patients with cancer, and prolonged survival of patients with cancer allowing sufficient time for the development of new primary cancers.

AIM

To analyze the incidence, clinical features, treatment factors, prevalence, and prognosis of patients with MPMTs in the gastrointestinal tract treated in a single center. Additionally, we analyzed the different tumor combinations, time interval between the occurrence of tumors, and staging.

METHODS

This retrospective cohort study analyzed 8059 patients with pathologically confirmed gastrointestinal malignant tumors treated at the Gansu Province Hospital in Lanzhou, Gansu, China between June 2011 and June 2020. Of these, 85 patients had MPMTs. The clinical features, treatment factors, prevalence, and prognosis of this latter cohort were analyzed.

RESULTS

The incidence of MPMTs in patients with gastrointestinal malignant tumors was 1.05% (85/8059), including 83 double primary malignant tumors and two triple primary malignant tumors of which 57 (67.06%) were synchronous MPMTs (SMPMTs) and 28 (32.94%) were metachronous MPMTs (MMPMTs). The most frequent associations were found between the rectum colon cancers within the SMPMT category and the gastric-colon cancers within the MMPMT category. For the MMPMTs, the median interval was 53 months. The overall 1-, 3- and 5-year survival rates from diagnosis of the first primary cancer were 91.36%, 65.41%, and 45.97%, respectively; those from diagnosis of the second primary cancer were 67.90%, 29.90%, and 17.37%, respectively.

CONCLUSION

MPMTs in the gastrointestinal tract have a high incidence and poor prognosis. Thus, it is necessary to perform both gastroscopy and colonoscopy in patients with gastrointestinal tumors. Multidisciplinary comprehensive diagnosis and treatment may improve the diagnosis rate and treatment efficiency of MPMTs.

Key Words: Multiple primary malignant tumors; Clinical characteristics; Gastrointestinal tract; Prognosis; Epidemiology

Core Tip: Despite improvement in understanding of multiple primary malignant tumors (MPMTs), their pathogenesis remains unclear. Herein, we analyzed the incidence of MPMTs in the gastrointestinal tract, the different tumor combinations, time intervals between the occurrence of tumors, staging, clinical course, and prognostic features. Our aim was to determine whether the gastrointestinal tract is particularly susceptible to second or third primary cancers, and to promote early diagnosis. Our results suggested that MPMTs in the gastrointestinal tract have a high incidence and poor prognosis, and both gastroscopy and colonoscopy are necessary in patients with gastrointestinal tumors. Multidisciplinary comprehensive diagnosis and treatment may improve MPMT diagnosis and treatment.

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INTRODUCTION

Multiple primary malignant tumors (MPMTs) are defined as the coexistence of two or more independent primary malignancies of different histologies in a single patient, either simultaneously or consecutively. MPMT was first described by Billroth as early as 1889, with the first report published by Warren and Gates in 1932[1]. Since then, numerous cases have been reported. A literature review of 1104269 patients with cancer revealed that the incidence of MPMTs ranged from 0.73% to 11.7%[2]. In recent years, however, there has been a significant upward trend in the incidence of this phenomenon, which may be associated with many different factors, including the advancement of modern diagnostic procedures facilitating the examination and diagnosis of more MPMTs[3], increased exposure to chemotherapy and radiotherapy that exacerbate the risk of new malignant tumors in patients with cancer[4,5], and prolonged survival of patients with cancer allowing sufficient time for the development of new primary cancers[6]. By analyzing the clinicopathologic data of 15321 patients with malignancies, Zhai *et al*[7] found that the most common MPMTs were digestive system malignancies, and the most frequent associations of MPMTs sites in the same system were digestive-digestive system malignancies. The major site of MPMTs within the digestive system was the large intestine (colon, rectum), followed by the stomach[8].

This study aimed to analyze the incidence, tumor combinations, time interval between the occurrence of tumors, staging, clinical course, and prognostic features of MPMTs in the gastrointestinal tract. The overarching aim of this investigation was to thereby determine whether the gastrointestinal tract is particularly susceptible to second or third primary cancers, and to aid in the early diagnosis of these lesions by clarifying any such tendency.

MATERIALS AND METHODS

For this retrospective cohort study, data from a total of 8059 patients with pathologically-proven gastrointestinal malignant tumors treated at our hospital (The Gansu Province Hospital, Lanzhou, Gansu, China) between June 2011 and June 2020 were analyzed. Of these, 85 patients were diagnosed with MPMTs.

We adopted the criteria proposed by Warren and Gates in 1932 for the diagnosis of MPMTs: (1) Each tumor must be a pathologically proven as malignant; (2) Each tumor must be histologically distinct; and (3) the possibility of the tumor resulting from the metastasis of another must be excluded[1]. MPMTs can be sub-classified into either synchronous

MPMTs (SMPMTs) and metachronous MPMTs (MMPMTs), according to their time interval, defined as the time between the date of diagnosis of the first primary cancer and the date of diagnosis of the second primary cancer. Patients are considered to have SMPMTs if the interval time is within 6 months; if the interval time is > 6 months, they are considered to have MMPMTs[9]. All patient details have been de-identified. The reporting of this study conforms to the strengthening the reporting of observational studies in epidemiology statement guidelines[10].

Statistical analysis

Data were analyzed for patient characteristics, tumor pathology, and treatments received. Kaplan–Meier survival analysis was performed to estimate overall survival using Graphpad Prism version 8.0.2 (GraphPad Software, San Diego, California). Descriptive data are presented as numbers and percentages, and differences between groups were evaluated using chi-square tests. A *P*-value of < 0.05 was considered statistically significant.

RESULTS

Clinical features

Among 8059 patients with pathologically-proven gastrointestinal malignant tumors, 85 had MPMTs, representing an incidence of 1.05%. Among these 85 patients, 83 cases were double primary malignant tumors and two were triple primary malignant tumors. Of these, 57 were males and 28 were females, with a male-to-female ratio of 2.04:1. The median ages at diagnosis for the first and second primary cancers were 58 years (range, 26–89 years) and 61 years (range, 35–89 years), respectively. Of these patients, 59 (69.41%) and 67 (78.82%) were aged > 50 years at diagnosis of the first and second primary cancers, respectively.

Among the 85 patients with MPMTs, 28 (32.94%) had SMPMTs, and 57 (67.06%) had MMPMTs. Of the 28 SMPMTs, 27 had double primary malignant tumors and one had a triple primary malignant tumor. Of the 57 MMPMTs, 56 cases were double primary malignant tumors and one case was triple primary malignant tumor. The median interval between diagnoses of the first primary and second primary cancers was 24 months (range, 0–318 months). Among the MMPMTs, the median interval was 53 months (range, 6–318 months; Table 1).

Prevalence

The major site for MPMTs in the gastrointestinal tract was the colon (38.37%), followed by the rectum (33.14%) and stomach (26.16%; Table 2). Common tumor associations in double primary malignancies mainly included rectum-colon cancers (n = 20), gastric-colon cancers (n = 18), and colon-rectum cancers (n = 17). In the SMPMT group, the most common associations were found between the rectum-colon cancers (n = 10) and colon-rectum cancers (n = 6), followed by colon-gastric cancers (n = 3; Figure 1A). In the MMPMT group, the most common associations were found between the gastric-colon cancers (n = 15) and gastric-rectum cancers (n = 13), followed by colon-rectum cancers (n = 11; Figure 1B). Overall, we found that nearly all tumors were adenocarcinomas, with the exception of one neuroendocrine carcinoma and one gastrointestinal stromal tumor (GIST) (Table 1).

Clinical staging

According to the American Joint Committee on Cancer 8th edition, malignancy clinical staging was possible in 62.35% (53/85), 85.88% (73/85), and 100% (2/2) of the first, second, and third primary cancers, respectively. The most common stages of the first, second, and third primary cancers were III, II, and II, respectively (Table 1).

Treatment factors

To ascertain the treatment modalities applied in these patients, complete clinical information regarding the cancer therapy received was collected for further study. Among the first primary cancers, 17.65% (15/85) underwent only surgery, 76.47% (65/85) underwent surgery and chemotherapy, 3.53% (3/85) underwent only chemotherapy and/or radiotherapy, and 2.35% (2/85) received the best supportive care. The total resection rate was 94.12% (80/85). Among the second primary cancer, 14.12% (12/85) underwent only surgery, 48.23% (41/85) underwent surgery and chemotherapy, 21.18% (18/85) underwent only chemotherapy and/or radiotherapy, and 16.47% (14/85) received the best supportive care. The total resection rate was 62.35% (53/85). Compared with the first primary cancer, the resection rate of the second primary cancer was lower (P < 0.05). In MMPMTs, 14.04% (8/57) of cases underwent only surgery and 85.96% (49/57) underwent chemotherapy or radiotherapy before the diagnosis of the second primary cancer (Table 1).

Prognosis

Until April 30, 2021, 81 (95.29%) patients with MPMTs were effectively monitored, while four were lost to follow-up, resulting in a missing rate of 4.71%. Among the patients who attended follow-up, 62 died, while 19 remained alive. The overall 1-, 3-, and 5-year survival rates from diagnosis of the first primary cancer of the 81 patients were 91.36%, 65.41%, and 45.97%, respectively (Figure 2A), while those from diagnosis of the second primary cancer were 67.90%, 29.90%, and 17.37%, respectively (Figure 2B). The MMPMT group showed a longer survival time than the SMPMT group ($P < 10^{-3}$) after diagnosis of the first primary cancer (Figure 2C). Following diagnosis of the second primary cancer, no difference was observed in the survival rate among the two groups; however, within the first year, the MMPMT group had a longer survival time than the SMPMT group, although this situation was reversed after another year (Figure 2D).

Table 1 Clinicopathological features of multiple primary malignant tumors, % (*n*/*N*)

Variable	First primary tumor	Second primary tumor	Third primary tumor
No. of patients, *n*	85	85	2
Median age, yr (range)	58 (26-89)	61 (35-89)	
Sex, *n*			
Male	57	57	0
Female	28	28	2
P value		> 0.1	
Age, *n*			
≤ 50 yr	26	18	0
> 50 yr	59	67	2
P value		> 0.1	
Tumor distribution			
Stomach	41.46 (34/85)	12.94 (11/85)	0
Small bowel	1.18 (1/85)	3.53 (3/85)	0
Colon	32.94 (28/85)	43.53 (37/85)	50 (1/2)
Rectum	25.88 (22/85)	40.00 (34/85)	50 (1/2)
P value		< 0.05	
Pathological type			
Adenocarcinoma	100 (85/85)	97.65 (83/85)	100 (2/2)
Neuroendocrine carcinoma	0	1.18 (1/85)	0
GIST	0	1.18 (1/85)	0
P value		> 0.1	
Clinical stage			
Tis	11.32 (6/53)	8.22 (6/73)	
I	13.20 (7/53)	12.33 (9/73)	50 (1/2)
II	30.19 (16/53)	28.76 (21/73)	50 (1/2)
III	37.74 (20/53)	27.40 (20/73)	
IV	7.55 (4/53)	23.29 (17/73)	
P value		> 0.1	
Treatment			
Surgery	17.65 (15/85)	14.12 (12/85)	50 (1/2)
Surgery + chemotherapy	76.47 (65/85)	48.23 (41/85)	50 (1/2)
Chemotherapy ± radiotherapy	3.53 (3/85)	21.18 (18/85)	
Best supportive care	2.35 (2/85)	16.47 (14/85)	
P value		< 0.001	

All statistical comparisons were between the first primary tumor and the second primary tumor by independent χ^2-test. Due to the small number of samples of the third primary tumor, statistical comparisons were not performed. MPMTs: Multiple primary malignant tumors; GIST: Gastrointestinal stromal tumors.

DISCUSSION

With the advancement of anti-cancer therapies and modern diagnostic procedures, along with the expansion of the aging population, an increasing number of MPMTs have been diagnosed. However, the incidence of MPMTs varies from region to region. A literature review of 1104269 patients with cancer reported that the incidence of MPMTs was 0.73%–11.7%[2].

Table 2 Cases and ratios of multiple primary malignant tumors in the gastrointestinal tract

Sites	Number of MPMTs	Total number	Incidence (%)	Incidence (%) in gastrointestinal MPMTs
Stomach	45	3618	1.24	26.16
Small bowel	4	126	3.17	2.33
Colon	66	1450	4.55	38.37
Left colon	41			23.84
Right colon	25			14.53
Rectum	57	2865	1.99	33.14

MPMTs: Multiple primary malignant tumors.

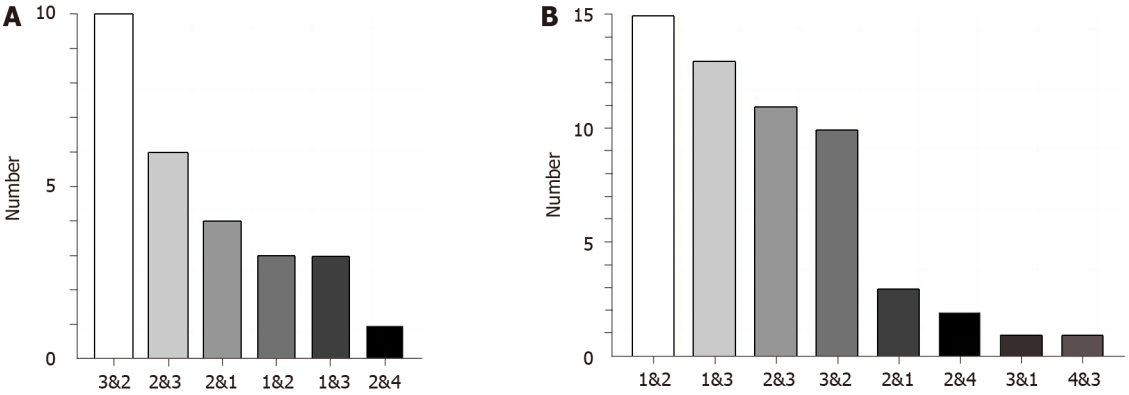

Figure 1 Tumor associations in patients with synchronous multiple primary malignant tumors and metachronous multiple primary malignant tumors. A: Number of patients with different tumor associations in the synchronous multiple primary malignant tumors; B: Number of patients with different tumor associations in the metachronous multiple primary malignant tumors. 1: Gastric cancer, 2: Colon cancer, 3: Rectum cancer, 4: Small bowel cancer.

Further, the incidence was estimated at 8% by the National Cancer Institute's Surveillance, Epidemiology, and End Results data[11]. A review of from 2919023 malignant cancers in 69 European cancer registries revealed 183683 cases of MPMTs, representing an overall incidence of 6.3%, ranging geographically from 0.4% (Italy) to 12.9% (Iceland)[12]. In China, different studies have reported incidence rates of MPMTs varying between 0.4% and 3.66%[13]. Zhai *et al*[7] found that the ratio of MPMTs sites in the same system was 27.54%, 93.48% of which were in the digestive system. The most common tumor pairs were digestive-digestive tumors (25.75%). The major site for MPMTs of the digestive system was the large intestine (colon, 23.17%; rectum, 25.82%), followed by the stomach (23.17%)[8]. Analysis of 8059 gastrointestinal cancer cases revealed an incidence of 1.05% for MPMTs in the gastrointestinal tract. In order to improve the diagnosis rate of MPMTs, we performed colonoscopy for patients with gastric cancer and gastroscopy for patients with colorectal cancer. The most common tumor pairs were rectum-colon cancers, followed by gastric-colon cancers and colon-rectum cancers. In the MMPMT group, 28 of 56 patients (50%) with double primary malignant tumors had gastric cancer as the first primary lesion. Of these, 15 (53.57%) had a second primary cancer in the colon and 13 (46.43%) had one in the rectum. However, among 16 patients who had colon cancer as the first primary lesion, 11 (68.75%) had second primary lesions in the rectum and only three (18.75%) had them in the stomach. Among 11 patients with rectum cancer as the first primary lesion, 10 (90.91%) had second primary lesions in the colon and only one (9.09%) had them in the stomach. In summary, the first primary gastric cancer was more likely to develop into second primary colorectal cancer, while the first primary colorectal cancer was more likely to develop into the second primary colorectal cancer, and rarely developed into the first second gastric cancer. In this study, men were more likely to suffer from MPMTs than women, with a sex ratio of 2.04:1. This result was higher than the male-to-female incidence ratio (1.18:1[12]) of MPMTs in total cancer, but similar to the male-to-female incidence ratio of gastrointestinal cancer found in past studies, which revealed male:female ratios of 2.4:1[14] in gastric cancer and 1.28:1[15] in colorectal cancer. In our study, 78.82% of the patients were over 50 years old when the second primary cancer was diagnosed, which is generally consistent with earlier studies[16]. Furthermore, the second primary cancer most frequently occurs 5 to 10 years after the first primary cancer[17]. Our results showed that the median interval was 53 months (range, 6–318 months) in the MMPMTs. These results indicate that clinicians should be more concerned about patients who have survived for more than 5 years from diagnosis of the first primary cancer, as well as those who are > 50 years of age. In addition, we also found that the proportion of patients with stage IV tumors in the second primary cancer was higher than that in the first primary cancer. This may be related to the fact that many patients fail to follow up promptly after the first primary cancer is diagnosed. Clinicians should therefore encourage cancer patients to adhere to timely follow-up appointments.

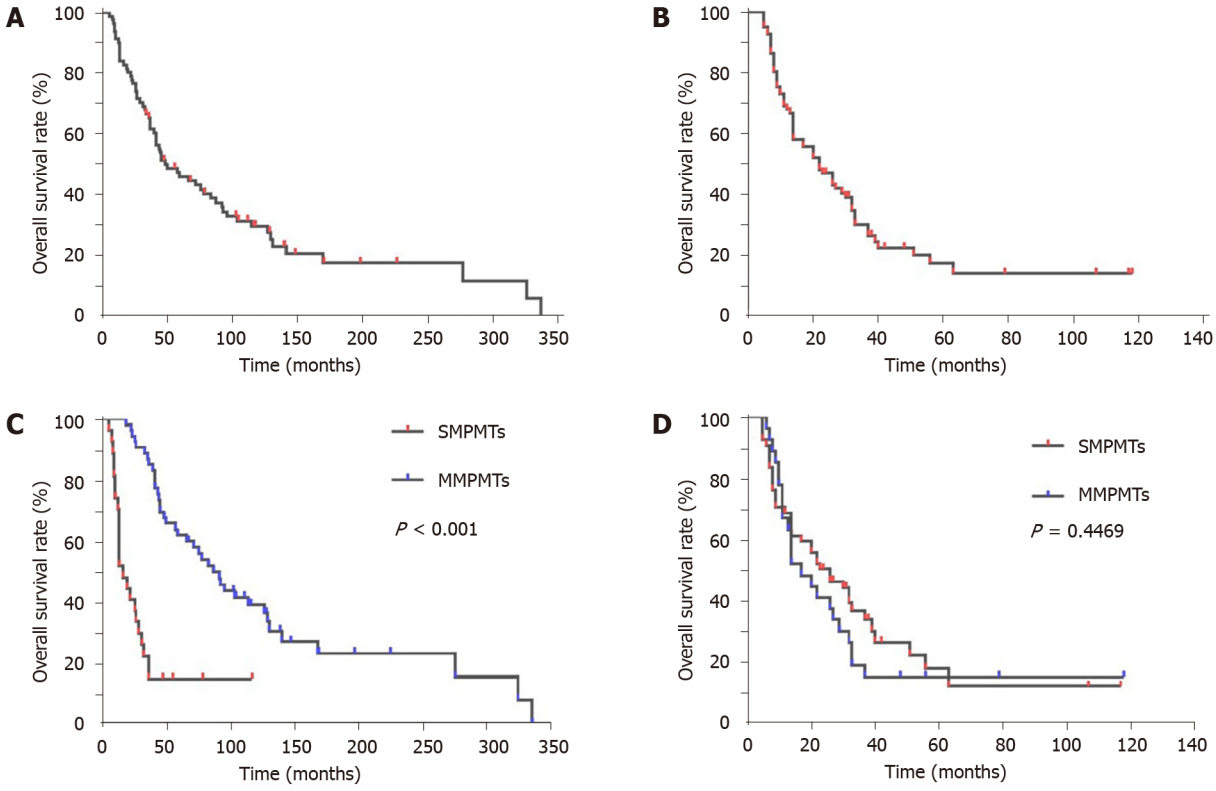

Figure 2 Survival times of patients with multiple primary malignant tumors. A: Survival times of 85 patients with multiple primary malignant tumors (MPMTs) after diagnosis of the first primary cancer; B: Survival times of 85 patients with MPMTs after diagnosis of the second primary cancer; C: Survival times for the synchronous MPMT (SMPMT) and metachronous MPMT (MMPMT) groups after diagnosis of the first primary cancer; D: Survival times for the SMPMT and MMPMT groups after diagnosis of the second primary cancer. SMPMTs: Synchronous multiple primary malignant tumors; MMPMTs: Metachronous multiple primary malignant tumors.

Due to a large number of studies reported in recent years, MPMTs are now better understood. However, their pathogenesis remains unclear. Many papers have reported that intense exposure to carcinogens (such as tobacco, alcohol, and environmental toxins), unhealthy lifestyle, hormonal and nutritional factors[6], genetic susceptibilities[17], and antineoplastic therapies (radio/chemotherapy and hormonal treatment)[18] could be significant factors contributing to the development of MPMTs. Indeed, many studies have confirmed that both chemotherapy and radiotherapy exert carcinogenic effects. Radiotherapy elevates the risk of various tumors including gastrointestinal tumors[19], while chemotherapy agents such as arsenic trioxide, alkylating agents, topoisomerase II inhibitors, and anthracyclines can cause acute myeloid leukemia[4]. Alkylating agents can also induced the occurrence of sarcomas, as well as bone and lung cancers[20,21]. The use of cyclophosphamide and tamoxifen have also been associated with bladder[22] and endometrial cancer[23], respectively. Of the MMPMT patients enrolled in this study, 85.96% (49/57) had undergone chemotherapy before the second primary cancer was diagnosed. This suggests that chemotherapy may play an important role in the initiation of MPMTs.

Close relationships between many genes, such as *BRCA1/BRCA2, TP53, ATM, POLD1, PABL2, SMAD4, MMR,* and *EGFR*, and the occurrence of MPMTs have been previously established[17]. Some of these genes are involved in genetic syndromes including Lynch, Li-Fraumeni, Cowden, Hereditary breast-ovarian cancer, PTEN hamartoma tumor, and Peutz-Jeghers. These genetic syndromes are also associated with MPMTs[24]. In addition to gene mutation and genetic syndromes, the microsatellite stability (MSI) phenotype can also cause MPMTs[25]. Therefore, clinical workers should pay more attention to the important role of genetic instability in the occurrence and development of MPMTs. Testing for MSI in the first primary cancer may help to identify patients at high risk of developing MPMTs. Furthermore, some tumors have a high risk for developing MPMTs; for example, 6%–8% of patients with soft tissue sarcoma (STS) and 10%–20% of patients with GIST developed MPMTs[17]. Thus, patients with GIST and STS should be monitored closely due to their increased susceptibility. However, in this study, we found that all of the tumors were adenocarcinomas, with the exception of one neuroendocrine carcinoma and one GIST. Therefore, the relationship between STS, GIST, and gastrointestinal MPMTs needs further study.

The therapeutic principle for MPMTs depends on the location and stage of each tumor, pathological tumor types, and physical condition of the patient. Treatment options for patients with MPMTs should be determined by multi-disciplinary teams of experts from oncology surgery, oncology medicine, radiotherapy, pathology, endoscopy, and other departments. The economic capability and willingness of patients may also influence both treatment plans and outcomes. Our study found that surgery combined with chemotherapy was the dominant treatment strategy for both the first and second primary cancers. This result was also consistent with the treatment strategies for gastrointestinal malignant tumors. The resection rate of the second primary cancer was lower than that of the first primary cancer. A possible reason

for this is the high proportion of stage IV second primary cancers caused by failed timely reviews following diagnosis of the first primary cancer. In addition, some patients were unwilling to undergo surgical treatment.

In this study, the MMPMT group showed a longer survival time from diagnosis of the first primary cancer than the SMPMT group. However, the survival rate from diagnosis of the second primary cancer among the two groups showed no difference. This suggests that the second primary cancer may be the main factor affecting the survival time of patients with MMPMTs. Concurrently, we found that the short-term survival rate of patients with SMPMT was lower than that of patients with MMPMT, while the long-term survival rate was higher from the diagnosis of the second primary cancer. The reason for this may be that patients with SMPMTs have a higher short-term mortality due to higher tumor load, while patients with MMPMTs are more likely to develop resistance to chemotherapy caused by previous chemotherapy for the first primary cancer, and thus have poorer long-term survival rates. It is also worth mentioning that one patient in our study who was 84 years of age, with four primary tumors, had survived for more than 50 years. If MPMTs can be detected early, the prognosis is better than that for a single recurrence or metastasis of the primary tumor.

Our study has some limitations. Firstly, we collected and analyzed only 85 MPMTs in patients with gastrointestinal malignant tumors from a single hospital. Additionally, the sample size selected for this study was not scientifically calculated. Furthermore, we did not analyze the etiology of MPMTs in gastrointestinal malignant tumors, as this was a retrospective study with non-standardized data and records, and genetic testing was rarely performed on this cohort.

CONCLUSION

Because of the high incidence and poor prognosis of MPMTs in the gastrointestinal tract, colonoscopy should be performed among for patients with gastric cancer, while gastroscopy should be performed for patients with colorectal cancer. Despite this investigation, the etiology of MPMTs in gastrointestinal malignant tumors remains unknown and further studies with large sample sizes are needed. Increasing the awareness of MPMTs among clinicians and patients with cancer contributes to early diagnoses and treatment, as well as better prognoses. Surgery combined with chemotherapy remains the primary treatment method for MPMTs in the gastrointestinal tract. Multidisciplinary comprehensive diagnosis and treatment may improve the diagnosis rate and treatment efficiency of MPMTs.

ARTICLE HIGHLIGHTS

Research background

A literature review of 1104269 patients with cancer revealed that the incidence of multiple primary malignant tumors (MPMTs) ranged from 0.73% to 11.7%. In recent years, however, there has been a significant upward trend in the incidence of this phenomenon.

Research motivation

The overarching motivation of this investigation was to thereby determine whether the gastrointestinal tract is particularly susceptible to second or third primary cancers, and to aid in the early diagnosis of these lesions by clarifying any such tendency.

Research objectives

The aim of this study was to analyze the incidence, clinical features, treatment factors, prevalence, and prognosis of patients with MPMTs in the gastrointestinal tract treated in a single center.

Research methods

The study analyzed 8059 patients with pathologically confirmed gastrointestinal malignant tumors between June 2011 and June 2020. Of these, 85 patients had MPMTs. The clinical features, treatment factors, prevalence, and prognosis of this latter cohort were analyzed.

Research results

The incidence of MPMTs in patients with gastrointestinal malignant tumors was 1.05%, including 83 double primary malignant tumors and two triple primary malignant tumors of which 67.06% were synchronous MPMTs (SMPMTs) and 32.94% were metachronous MPMTs (MMPMTs). The most frequent associations were found between the rectum colon cancers within the SMPMT category and the gastric-colon cancers within the MMPMT category.

Research conclusions

MPMTs in the gastrointestinal tract have a high incidence and poor prognosis.

Research perspectives

It is necessary to perform both gastroscopy and colonoscopy in patients with gastrointestinal tumors. Multidisciplinary comprehensive diagnosis and treatment may improve the diagnosis rate and treatment efficiency of MPMTs.

FOOTNOTES

Author contributions: Zhu CL and Peng LZ made significant contributions to the conceptualization and the design of this study; Zhu CL and Peng LZ collected all the data; Zhu CL and Peng LZ were the main contributors to this manuscript; Zhu CL and Peng LZ made significant revisions to this manuscript; All authors contributed to the article and approved the submitted version.

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author at plz198996@163.com.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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