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Original Article

Clinical retrospective analysis of 20 cases with digestive tract multiple primary malignant neoplasms

Hailu Wu, Qin Lu, Nan Li, Ting Xie, Yan Liang, Lu Chen, Ruihua Shi

Department of Gastroenterology, Zhongda Hospital Affiliated to Southeast University, 87 Dingjiaqiao Road, Nanjing 210000, China

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Abstract: Digestive tract multiple primary malignant neoplasms (MPMN) are relatively rare, but their diagnostic rate has increased because of endoscopic development. The aim of this study was to determine the clinical features, treatment factors, and prognosis of patients with digestive tract MPMNs. In order to improve its diagnosis and therapy. Clinical data of 20 patients with digestive tract MPMNs who were admitted to the department of gastroenterology, Zhongda Hospital affiliated to Southeast University from January 2012 to January 2017 were collected and analyzed retrospectively. We found that among 20 patients with MPMNs, 4 (20%) patients had synchronous tumors and 16 (80%) patients had metachronous tumors. And the average age in the SMPMN and MMPMN group was 63 and 54.9 years old respectively. The most common locations of MPMNs were esophagus, cardia, stomach, rectum and colon. The median survival time of SMPMN was 30 months, longer than that MMPMN (16 months); The first and second primary tumors all treated with endoscopic submucosal dissection (ESD) has a longer survival time than those treated with else. The results of the present study demonstrate that patients with high risk factors for gastrointestinal malignancy neoplasms should be performed with gastrointestinal endoscopy. Early diagnosis and treatment thereby do improve the prognosis of patients with digestive tract MPMNs.

Keywords: Gastrointestinal tumor, multiple primary, gastrointestinal endoscope, diagnosis, treatment

Introduction

Multiple primary malignant neoplasms (MPMNs) are defined as two or more malignanc ies in an individual without any relationship occurs in the body at the same time or one after another. Second primary tumors were most common, whereas third, fourth, and higher primary tumors were relatively rare [1]. According to the primary tumor discovery time interval, MPMNs can be divided into two main types: synchronous MPMNs (SMPMN) and metachronous MPMNs (MMPMN). SMPMN are defined as the tumors occur simultaneously or within 6 months of one another, whereas MMPMN are indicated if the interval time is more than 6 months. MMPMN was more frequent than SMPMN, with a ratio of 2.7:1 [2].

The most frequent sites for primary tumor location in all cases of MPMNs were the breast, esophagus and gastric followed by cardia and colon. Whereas the leading localization of the second metachronous tumor were cardia and stomach, followed by colon, breast and lung. There are a variety of combinations of MPMNs, especially the digestive tract ~ digestive tract and digestive tract ~ breast are most common [3].

Chinese epidemiological studies have shown that digestive system tumors incidence accounted for more than one half of all the malignant tumors in China. During these, the gastric, colorectal and esophageal tumors are most common. The occurrence of digestive tract MPMNs has increased in recent years due to the development of modern new endoscopic technology, like the magnifying endoscopy, electronic dyed endoscopy, laser confocal endoscopy continue to emerge. The extended survival time is also brought by the increased capability on cancer diagnosis and treatment. Further studies are needed to help understand this disease.

Table 1. Age distribution of 20 patients with digestive tract MPMN (eg)

Age (years)	MMPMN	SMPMN
≥40-49	2	0
≥50-59	8	2
≥60-69	4	1
≥70	2	1
Total	16	4

MPMN: multiple primary malignant neoplasms; SMPMN: synchronous MPMNs; MMPMN: metachronous MPMNs.

In this study, we analyzed the clinical characteristics, therapy and prognosis of patients with digestive tract MPMNs in our hospital from January 2008 to February 2015. We also examined the risk factors associated with poor prognosis for patients with digestive tract MPMNs.

Material and methods

Diagnostic criteria

The diagnostic principles of MPMNs are based on the following standards provided by Warren [4], combined with the Moertel's [2] about how to define synchronous MPMNs (SMPMN) and metachronous MPMNs (MMPMN), and also the Liu Fusheng's added standard [5]: 1) Each tumor is malignant, 2) Each tumor has its own pathological features, 3) Tumors occur in different parts or organs, and are not continuous with each other, and 4) Each tumor has its own metastatic pathway and the diagnosis of metastatic or recurrent tumors can be excluded. 5) Synchronous tumors refer to cases in which the second primary cancer is diagnosed within 6 months of the primary cancer; metachronous tumors refer to cases in which the second primary cancer is diagnosed more than 6 months after the diagnosis of the first primary cancer.

Data collection

A total of 2530 patients in our hospital (Zhongda Hospital Affiliated to Southeast University, 87 Dingjiaqiao Road, Nanjing 210000, China.) with a diagnosis of various types of digestive tract tumors between January 2012 and January 2017 were reviewed, but only 20 cases among them were MPMTs according to the above criteria.

Follow-up

A total of 20 patients were followed up with the deadline of February 1, 2017 by either telephone or in-patient. Then they were followed up between 4 to 60 months, with a median follow-up time of 29 months. No cases were lost, and the follow-up rate was 100%. 19 cases remain alive to date. For patients with SMPMN, the survival time was calculated according to the confirmed date of the first tumor, whereas for MMPMN, survival time was calculated from the confirmed date of the last diagnosis of the tumor.

Statistical analysis

All data were statistically analyzed using the SPSS19.0 software; the median was used for count data; the log-rank test was used to compare the survival time between different groups, and $P < 0.05$ was considered to be statistically significant. Statistical significance of observed differences between groups was determined by the Student t-test and one-way analysis of variance (ANOVA). Values of $P < 0.05$ were considered to be significant.

Results

Clinical features of MPMNs patients

In total, 2,530 patients were diagnosed with digestive tract tumors in our hospital between January 2012 and January 2017. Of these, 20 (0.79%) patients were diagnosed with MPMNs. Among the 20 patients, 4 patients (20%) had 2 synchronous tumors, and 16 (80%) patients had 2 metachronous tumors.

These 20 patients had an age of 48-81 years old, with an average age of 59.2 years old and median age of 59 years old. In the synchronous cancer group, the average age was 63 years old; the median age was 60 years old. In the metachronous cancer group, the average age was 54.9 years old, the median age was 56.5 years old (**Table 1**).

Tumor distribution

There were 40 primary malignant tumor lesions in 20 cases of MPMN patients with a total of 40 primary tumors, and the specific distribution of tumors shown in **Table 2**.

Tumor interval time

The interval time (the time between the date of diagnosis of the first primary cancer and the second primary cancer) was evaluated only for

Table 2. Distribution of tumor (eg)

Classification	Cardia	Esophagus	Rectum	Stomach	Colon
First tumor	4	3	5	5	3
Second tumor	4	7	1	4	4

The colon consists of the left half, the right half, the transverse and thesigmoid colon; MPMN: Multiple primary malignant neoplasms.

metachronous tumors. In 16 cases with MMPMN, the median interval time between the first and second tumor was 13.5 months (range, 6-25 months) (**Table 4**).

Tumor treatment

Of these 20 patients with digestive tract MPMNs, 10 cases of both the first and secondary primary tumor underwent the endoscopic submucosal dissection (ESD). Nine cases of the first and secondary primary tumors underwent ESD and surgical resection respectively, of which 3 cases were supplemented by chemotherapy according to clinical staging and pathological results. 1 case of primary and secondary primary tumors was both underwent surgical treatment, without the radiotherapy or chemotherapy (**Tables 3**, **4**).

Survival and prognostic factors

The median survival time of the SMPMN patients was 30 months, longer than that of the MMPMN patients (the median survival time was 16 months) (P=0.00); With regard to treatment, the median survival time of patients differed significantly between the first and second primary tumor both underwent ESD group and the comprehensive therapy group (including surgery-based therapy combined with chemotherapy or ESD). The median survival time in these group was 22 and 14.5 months respectively, and the difference was statistically significant (P=0.02); However, there were no detectable differences regarding age, gender, or the interval time based on the Student t-test analyses (**Table 5**).

Discussion

In the 21st century, cancer has become a serious hazard to human health. It is reported that there were about 4292,000 newly diagnosed cancer cases in 2015 in China, death cases were about 2.814 million, corresponding to almost 12,000 new cancer diagnoses on average each day, and 0.75 million people died of cancer. Lung cancer is the highest morbidity and mortality of the tumor, followed by gastric cancer, esophageal cancer, colorectal cancer and liver cancer [6]. So the prevention and treatment of gastrointestinal cancer cannot be ignored. As the development of modern new endoscopic technology, the diagnostic rate in the digestive tract tumors, especially in the early digestive tract tumors is constantly improving.

MPMNs are special phenomenon in tumorigenesis. In recent years, MPMNs has been widely studied in the world. Since the phenomenon of MPMNs first described by Warren and Gates in 1932, numerous cases have been reported by several authors. Studies have reported that the incidence of MPMNs was 0.52% to 3.66% in China compared with 0.73% to 11.7% in other countries [5, 7]. The diverse incidence in this result may due to different geographical regions, environmental factors, diagnostic methods and follow-up information. The predilection site of MPMNs in different races and areas is also very different. In Japan, the incidence of gastric cancer with colorectal cancer was reported to be high. However, in the Guangdong region of China, nasopharyngeal cancer is the most common MPMNs. A rare domestic and foreign literature of digestive tract MPMNs was reported. In this report, we collected 20 cases of digestive tract MPMNs during the past five years in our hospital, and then a retrospectively studied has been done.

In these 20 cases of digestive tract MPMNs, 4 cases are simultaneous MPMNs, and the other 16 cases are metachronous MPMNs. Digestive tract MPMNs were most frequently found in the esophagus, stomach, followed by the cardia, colon and rectum. The incidence ratio between the SMPMN to MMPMN group was 1:4. This result emphasized the importance of giving high-risk patients with gastrointestinal cancer both the endoscopy and colonoscopy examination at the same time. And also that once the patient primary gastrointestinal has clearly diagnosed, in the future, regular endoscopy and colonoscopy examinations should be performed.

MPMNs can occur at any age. Several studies reported that patients with MPMNs tend to be older than those with a single primary cancer, and in most reports, more than 75% of patients

Table 3. Clinicopathological data of patients with digestive tract SMPMN

Case	Gender	Age (years)	First primary tumor		Second primary tumor		Survival time	Interval time (months)
			Clinical stage	Treatment method	Clinical stage	Treatment method		
1	Female	59	Cardiac Tis	ESD	Esophageal T1a	ESD	31 months still survive	Simultaneously
2	Male	61	Cardiac T1b	ESD	Esophageal T1b	ESD	27 months still survive	Simultaneously
3	Male	81	Esophageal Tis	ESD	Stomach Tis	ESD	35 months still survive	Simultaneously
4	Male	51	Rectal T1b	ESD	Esophageal Tis	ESD	29 months still survive	Simultaneously

SMPMN: synchronous MPMNs; ESD: endoscopic submucosal dissection.

Table 4. Clinicopathological data of patients with digestive tract MMPMN

Case	Gender	Age (years)	First primary tumor		Second primary tumor		Survival time	Interval time (months)
			Clinical stage	Treatment method	Clinical stage	Treatment method		
1	Male	59	Rectal T3NIaM0	Surgery+Chemotherapy	Cardiac Tis	ESD	15 months still survive	11 months
2	Female	48	Stomach T2	ESD	Colon T1N0M0	ESD	19 months still survive	14 months
3	Female	68	Esophageal Tis	ESD	Rectal T1N0M0	ESD	25 months still survive	10 months
4	Male	50	Stomach Tis	ESD	Esophageal Tis	ESD	19 months still survive	11 months
5	Female	68	Cardiac Tis	ESD	Colon T1N0M0	Surgery	23 months still survive	13 months
6	Male	73	Rectal T1N0M0	Surgery	Stomach Tis	ESD	10 months still survive	25 months
7	Male	53	Stomach T2	ESD	Esophageal Tis	ESD	10 months still survive	22 months
8	Female	60	Cardiac T1b	ESD	Colon T3N0M0	Surgery	9 months still survive	18 months
9	Female	59	Rectal T3N0M0	Surgery	Cardiac T1b	ESD	17 months still survive	17 months
10	Male	50	Esophageal Tis	ESD	Stomach T2	ESD	9 months still survive	11 months
11	Male	54	Colon T3N0M0	Surgery	Esophageal Tis	ESD	21 months still survive	8 months
12	Female	63	Colon T3N0M0	Surgery	Cardiac Tis	ESD	9 months still survive	21 months
13	Male	49	Cardiac Tis	ESD	Colon T2N2aM0	Surgery+Chemotherapy	9 months	20 months
14	Male	73	Colon T3N0M0	Surgery	Stomach T2	Surgery	15 months still survive	14 months
15	Male	51	Stomach Tis	ESD	Esophageal Tis	ESD	19 months still survive	6 months
16	Female	54	Colon T3N2BM0	Surgery+Chemotherapy	Cardiac Tis	ESD	14 months still survive	13 months

MMPMN: metachronous MPMNs; ESD: endoscopic submucosal dissection.

Table 5. Univariate analysis of prognosis of patients with gastrointestinal MPMN

	Case	Median survival time (months)	*P*
Classification			0.00
SMPMN	4	30	
MMPMN	16	16	
MMPMN Interval time			0.32
≤1 year	10	19	
>1 year	10	12	
Treatment method			0.02
Both ESD	10	22	
Not both ESD	10	14.5	
Age			0.41
≤60 years old	13	17	
>60 years old	7	23	
Gender			0.96
Male	12	17	
Female	8	18	

SMPMN: synchronous MPMNs; MMPMN: metachronous MPMNs; ESD: endoscopic submucosal dissection.

with MPMNs were more than 50 years of age [8-10]. Our results were consistent with these reports; there were 90% of patients being over 50 years old. It is noteworthy that in our study the median age of digestive tract SMPMN is 60 years old, and the MMPMN group is 56.5 years old, that may implicated that the younger people are more likely to suffer from digestive tract MMPMN.

Consistent with other reports [11, 12], our results also showed that men were more frequent than women among both the digestive tract synchronous and metachronous groups in our study. The main reasons lead to this phenomenon maybe tobacco and alcohol consumed by men. These results indicate that doctors should carefully to do the screening work among the men to prevent the digestive tract tumors.

In Japan, digestive tract MPMNs predilection site were the stomach, colon and rectum [13].

In our study, the most frequent sites of localization of digestive tract MPMNs were the stomach and esophagus. Such differences may result from the following factors: 1. Gastric and esophageal cancers have several similar genetic changes. And these 2 types of cancer potentially share similar molecular mechanisms for pathogenesis [14]. 2. The stomach and the esophagus are both part of the digestive system and closely linked, exposed to the same pathogenic factors.

Moreover, in our study, we found that the survival time of SMPMN patients was much longer than MMPMN. This difference is mainly related to the stage of the tumor and the relevant treatment. For 4 cases of SMPMN, the first and second primary tumors were both early digestive tract tumors, using the treatment of endoscopic submucosal dissection (Endoscopic submucosal dissection, ESD). And of 16 cases of MMPMN were advanced tumors of the digestive tract, so the treatment includes ESD, surgery, and surgery combined with chemotherapy. Endoscopic submucosal dissection (ESD) is an innovative endoscopic technique that allows for en bloc resection of superficial gastrointestinal tumors regardless of their size. It can achieve a larger lesion of the whole block, and provide accurate pathological diagnosis staging. With the development of various endoscopic tools, devices, increased experience, and growing expertise in ESD. ESD has become the first treatment of early cancer and precancerous lesions of the digestive tract. The 5-year overall survival and disease survival rates were 36.2%-97.1% and 100% for ESD treatment of early gastric cancer [15, 16]. With ESD treatment of early esophageal cancer, 5-year survival rate was 100% when lesions confined to the epithelium or mucosal lamina propria layer, while the depth of the lesion exceed the lamina propria layer the 5-year survival rate was 85% [17]. And the resection rate and curative resection rate of colorectal were 82.8% and 75.5% respectively [18]. In the univariate analysis, we found that the first and second primary tumors all treated with endoscopic submucosal dissection (ESD) has a longer survival time than those treated with else, like surgery or surgery combined with chemotherapy. These results suggest that do early diagnosis and treatment by gastrointestinal endoscopy in patients with high risk of digestive tract tumors can significantly improve the patient prognosis.

The cause of digestive tract MPMNs is not yet elucidated, but may be related to the following four main factors. First, intrinsic factors can lead to MPMN, which include susceptibility, immune status, endocrine and embryonic development. Immune surveillance and immune defenses will not function in cancer patients, and cancer-causing factors will have increased sensitivity to those prone to MPMNs [19]. The second cause is related to environmental factors and personal lifestyle, including long-term exposure to radiation and industrial pollution of the environment. In addition, someone who has the alcohol and tobacco hobby, or who eats the pickled, moldy and acidic food for a long time. Third, infection and chronic inflammatory response may be associated with digestive tract tumors. Such as inflammation caused by infection, its fundamental role is to remove pathogens. However, in some inflammatory reactions, some of the factors with tumorigenic effects establish their own long-term, low-level, chronic persistent uncontrollable inflammatory response by destroying the body's normal immune regulation of the balance. And thus eventually lead to the occurrence and progress of tumors. Such as the relations between the HP and gastric cancer, Barrett esophagus and esophageal cancer, colonic villous adenoma and colon cancer can all be referred to. The final cause of MPMNs may be related to the genetic factors. Recently, several studies have shown that many genes are associated with the development of MPMNs, such as BRCA1/BRCA2 is thought to be associated with gastric cancer, colorectal cancer, and pancreatic cancer; ATM is high in gastric and esophageal cancers [20].

In summary, sufficient clinical attention should be paid to digestive tract MPMNs to avoid misdiagnosis and missed diagnosis. In addition, early detection, early diagnosis, and early treatment by digestive endoscopy are all essential for efficient treatment of digestive tract MPMNs. However, our study has some limitations. Comprehensive analysis of digestive tract MPMTs requires a retrospective study of a large sample size, well defined population for ≥10 years.

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Disclosure of conflict of interest

None.

Address correspondence to: Ruihua Shi, Department of Gastroenterology, Zhongda Hospital Affiliated to Southeast University, 87 Dingjiaqiao Road, Nanjing 210000, China. Tel: +86 25 83262833; Fax: +86 25 83262830; E-mail: ruihuashi@126.com

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