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Retrospective Cohort Study

Clinical features and survival of patients with multiple primary malignancies

Wang XK *et al*. Clinical features and survival of MPM patients

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Abstract

BACKGROUND

Multiple primary malignancies (MPM) are characterized by two or more primary malignancies in the same patient, excluding relapse or metastasis of prior cancer. We aimed to elucidate the clinical features and survival of MPM patients.

AIM

To elucidate the clinical features and survival of MPM patients.

METHODS

A retrospective study of MPM patients was conducted in our hospital between June 2016 and June 2019. Overall survival (OS) was calculated using the Kaplan-Meier method. The log-rank test was used to compare the survival of different groups.

RESULTS

A total of 243 MPM patients were enrolled, including 222 patients with two malignancies and 21 patients with three malignancies. Of the 222 patients with two malignancies, 51 (23.0%) hadsynchronous MPM, and 171 (77.7%) hadmetachronous

MPM.The most common first cancers were breast cancer (33, 14.9%) and colorectal cancer (31, 14.0%). The most common second cancers were non-small cell lung cancer (NSCLC) (66, 29.7%) and gastric cancer (24, 10.8%). The median OS from diagnosis of the second cancer was 35.4 mo. There was no survival difference between synchronous and metachronous MPM patients (36.4 *vs* 35.3 mo, P = 0.809). Patients aged > 65 years at diagnosis of the second cancer hada shorter survival than patients ≤ 65 years (28.4 *vs* 36.4 mo, P = 0.038). Patients with distant metastasis had worse survival than patients without metastasis (20.4 *vs* 86.9 mo, P = 0.000). Following multivariate analyses, age > 65 years and distant metastasis were independent adverse prognostic factors for OS. Twelve patients with concomitant NSCLC and breast cancerhad a median OS of 79.8 mo. Ten patients with NSCLC and gastric cancer, and with colorectal and gastric cancer, had median OS of 16.7 mo and not reached, respectively. In 21 patients with three malignancies, the median OS from diagnosis of thethird cancer was 14.4 mo.

CONCLUSION

During follow-up of a first cancer, the occurrence of a second or more cancers should receive greater attention, especially for common concomitant MPM, to ensureearly detection and treatmentof the subsequent cancer.

Key Words: Multiple primary malignancies; Overall survival; Prognostic factor

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Core Tip: In the paper we investigated the clinical features and survival of 243 patients with multiple primary malignancies (MPM), including 222 patients with two malignancies and 21 patients with three malignancies. There was no survival difference between synchronous and metachronous MPM patients. After multivariate analyses, age > 65 years and distant metastasis were independent adverse prognostic factors for overall survival (OS). Twelve patients were with concomitant non-small cell lung cancer and breast cancer, with the median OS of 79.8 mo. In 21 patients with three malignancies, the median OS from the diagnosis of third cancer was 14.4 mo. Therefore, in clinical procedure and follow-up of initial cancer, the occurrence of second or more cancer should be paid great attention to, especially for some common concomitant MPM, so as to have early detection and therapy of the subsequent cancer.

INTRODUCTION

Multiple primary malignancies (MPM) arecharacterized by two or more different primary malignancies in thesame patient, excluding relapse or metastases of prior cancer[1]. An increased incidence of MPM has beenobserved with the rapid development of medical techniquesand prolonged life expectancy[2,3]. The causes of MPM may be associated with genetic alterations, the environment and iatrogenic factors[4].

Colorectal cancer, breast cancer and head and neck cancerhave been reported as the most common first primary malignancies, and lung cancer, breast cancer and colorectal cancer as the most common subsequent primary malignancies[5,6].The most common MPM pairs were head and neck-lung cancer, and breast-gynecologic cancer[7]. According to the interval between initial cancer and subsequent cancer, MPM can be divided into synchronous MPM (within 6 mo) and metachronous MPM (more than 6 mo)[8]. Metachronous MPM account for most of the patients with MPM, with a 5-year OS, ranging from 61% to 68%[7,9]. In some reports, patients with metachronous MPM had better survival than patientswithsynchronous MPM[7,9], while thissurvival advantage was not observed in the study by Xu and Gu[10].

In the present study, we retrospectively analyzed the clinical features and survival of patients with MPM in our hospital over the past three years, in order to provide helpful information for the diagnosis, treatment, prognosis and follow-up of these patients.

MATERIALS AND METHODS

Patients

A retrospective study of MPM patients was conducted in our hospital between June 2016 and June 2019. The diagnosis of each malignancy in MPM patients was identified by histopathology. Hematological malignancies were excluded in our study, and only solid malignant tumors were included. A total of 27055 patients with solid malignant tumors were consecutively identified. Of these patients, 260 had MPM. After further review, 17 patients were excluded from our study, including 11 patients with no pathological diagnosis of one tumor, and 6 patients who were lost to follow-up. Therefore, a total of 243 MPM patients with complete clinical and follow-up data were enrolled in the study, including 222 patients with two malignancies and 21 patients with three malignancies. In patients with two primary malignancies, synchronous MPM was defined as two malignancies diagnosed within 6 mo, and metachronous MPM as two malignancies diagnosed within more than 6 mo between the first and second cancer. The study was approved by the institutional review board of our hospital (2020KY018-KS001).

Statistical analysis

Continuous and categorical variables were summarized as the median with range, and the count with percentage, respectively. For patients with two malignancies, overall survival (OS) was defined as the time from diagnosis of the second malignancy to death due to any cause, or to the last follow-up. For patients with three malignancies, OS was defined as the time from diagnosis of the third malignancy to death due to any cause, or to the last follow up. The end of follow-up was December 2019. OS was calculated using the Kaplan-Meier method. The log-rank test was used to compare the survival of different groups. Multivariate Cox regression models were used to find the prognostic factors for OS. All the data were analyzed using IBM SPSS statistics software (version 22). P value < 0.05 was considered statistically significant.

RESULTS

A total of 26795 patients with one solid malignant tumor were found. The five most common cancers were non-small cell lung cancer (NSCLC) (18.3%), colorectal cancer (12.5%), breast cancer (10.6%), gastric cancer (9.4%) and liver cancer (7.3%). Patients with MPM accounted for 0.96% (260/27055) of all patients with solid malignant tumor.

The characteristics of patients with two malignancies

A total of 243 patients with MPM were included in our study. Of these patients, 222 with two malignancies were identified, and the demographics and clinical characteristics of these patients are shown in Table 1. Fifty-one patients (23.0%) hadsynchronous MPM, and 171 patients (77.7%) hadmetachronous MPM. In the synchronous, metachronous and total MPM groups, 32 patients (62.7%), 87 patients (50.9%) and 119 patients (53.6%) were male, respectively; the median age at diagnosis of the first cancer was 62 years, 55 years and 56 years respectively; the median interval between the first and second cancer diagnoses was 0.2 mo, 73.2 mo and 43.6 mo, respectively; distant metastasis was found in 16 (31.4%) patients, 83 (48.5%) patients and 99 (44.6%) patients, respectively.

In 222 patients with two malignancies, the most common first cancers were breast cancer (33, 14.9%), colorectal cancer (31, 14.0%), and gastric cancer (17, 7.7%). The most common second cancers were NSCLC (66, 29.7%), gastric cancer (24, 10.8%) and esophageal cancer, liver cancer (16, 7.2%), respectively. In 51 synchronous MPM patients, the most common first cancer was esophageal cancer (9, 17.6%), colorectal cancer (8, 15.7%) and bladder cancer, thyroid cancer, hypopharyngeal cancer (4, 7.8%, respectively). The most common second cancers were NSCLC (12, 23.5%), gastric cancer (9, 17.6%) and esophageal cancer, renal cancer (6, 11.8%, respectively). In 171 metachronous MPM patients, the most common first cancers were breast cancer (31, 18.1%), colorectal cancer (23, 13.7%) and gastric cancer (14, 8.2%). The most common second cancers were NSCLC (54, 31.6%), gastric cancer (15, 8.8%) and liver cancer (13, 7.6%).

The most common MPM in patients with two malignancies and their survival

In the 222 patients with two malignancies, the most common MPM and their median OS are shown in Table 2. Twelve patients were found to have NSCLC and breast cancer, and the median OS of these patients was 79.8 mo (Figure 1A). Ten patients were found to have NSCLC and gastric cancer, and the median OS was 16.7 mo (Figure 1B). Colorectal cancer and gastric cancer were identified in ten patients, with the median OS not reached (Figure 1C). Esophageal cancer and gastric cancer were identified in nine patients, with a median OS of 36.2 mo (Figure 1D).

The prognostic factors of OS in patients with two malignancies

The univariate and multivariate analyses of prognostic factors for OS inpatients with two malignancies are presented in Table 3. The median OS in all 222 patients was 35.4 mo (Figure 2A). The median OS in synchronous MPM and metachronous MPM patients were 36.4 mo and 35.3 mo, respectively, which was not significantly different (Figure 2B). The median OS between male and female patients was also not significantly different. However, patients aged > 65 years at the second cancer diagnosis hada shorter survival than patients ≤ 65 years (28.4 mo *vs* 36.4 mo, $P = 0.038$, Figure 2C). Patients with distant metastasis had worse survival than patients without metastasis (20.4 mo *vs* 86.9 mo, $P = 0.000$, Figure 2D). Furthermore, multivariate analyses showed that age and metastases remained statistically different, indicating that age > 65 years and distant metastasis were independent adverse prognostic factors for OS.

The characteristics and survival of patients with three malignancies

A total of 21 patients with three malignancies were identified in our study. Their clinical features are shown in Table 4 and Table 5. Eleven patients (52.4%) were male, and 12 patients (57.1%) had distant metastases. The median age at the first, second and third cancer was 47 years, 54 years and 57 years, respectively. The most common cancers in all patients were colon cancer (9, 14.3%), rectal cancer (7, 11.1%) and breast cancer (5, 7.9%). The median OS from diagnosis of the third cancer was 14.4 mo (Figure 3).

DISCUSSION

In this study, we retrospectively analyzed the clinical features and survival of 243 MPM patients, including 222 patients with two malignancies and 21 patients with three malignancies. The most common MPM were NSCLC and breast cancer (12 cases), NSCLC and gastric cancer (10 cases), and colorectal cancer and gastric cancer (10 cases), with the median OS of 79.8 mo, 16.7 mo and not reached, respectively. The median OS of patients with two malignancies and three malignancies were 35.4 mo and 14.4 mo, respectively. Age > 65 years and distant metastases were independent adverse prognostic factors for OS in patients with two malignancies.

In a retrospective study of 278 MPM patients, 120 (43%) patients presented with synchronous MPM, and 158 patients (57%) with metachronous MPM[9]. In our study, we had fewer patients with synchronous MPM (51, 23%) and more patients with three malignancies. The median interval between two cancers in patients with metachronous MPM in the above study was 30.98 mo, less than the median interval in our study of 73.2 mo. In the above study, the most common first cancers were breast, head and neck, and colorectal cancer; the most common second cancers were breast, colorectal and uterine body cancer. In our study, breast and colorectal cancer were also the most common. In addition, other common cancers inour study were NSCLC and digestive system malignancies, such as stomach, esophagus and liver, which were different from those in the above report.

The survival differences of synchronous and metachronous MPM have been reported inconsistently in different studies. Some reported that survival in patients with metachronous MPM was better than in synchronous MPM[7,9]. However, no survival differences between synchronous and metachronous MPM were noted in our study, andin another study[10]. Of note, the starting point of calculated survival time in metachronous MPM was not consistent in previous studies, some were calculated from the date of the first cancer diagnosis, some from the date of the last cancer diagnosis. Besides, Different cancer constituents may account for the inconsistent results.

In a report of 350 MPM patients with lung cancer, the most common associated malignancies were esophageal cancer, breast cancer, gastric cancer and colorectal cancer[11]. In another report of 268 metachronous MPM patients with lung cancer, colorectal cancer, breast cancer and gastric cancer were the most common associated primary cancers[12]. Unfortunately, the survival of patients with lung MPM was not reported. Similarly, in our study, the most common concomitant malignancies in MPM patients with NSCLC were breast cancer, gastric cancer and bladder cancer, with a median OS of 79.8 mo, 16.7 mo and 31.2 mo, respectively.

In a report of 55 MPM patients with colorectal cancer, stomach cancer was the most commonly associated lesion[13]. In another study of 117 MPM patients with colorectal cancer, the most commonly associated cancer was gastric cancer, followed by lung and breast cancer[14]. In our study, gastric cancer was also the most frequently observed associated cancer in patients with colorectal cancer. A total of ten patients with colorectal and gastric cancer were found in our 222 MPM patients with two malignancies. The median OS of patients with colorectal and gastric cancer was not reached.

In a respective study of 170 MPM patients[10], 17 cases with esophageal and gastric cancer were found. The median survival of 42 gastrointestinal MPM, including the above 17 cases, was 40 mo, which was close to our 36.2 mo in nine patients with esophageal and gastric cancer. Chen *et al*[15] analyzed 192 patients with esophageal and gastric cancer from a database in the United States, and found that the median OS of these patients was approximately 59 mo, but with longer follow-up time, none of these patients survived.

Following univariate and multivariate analyses, older age and distant metastasis were independent poor prognostic factors for OS. In the study by Etiz *et al*[7], elderly and young patients showedno differences in survival. However, Wang *et al* reported that the OS of patients < 60 years was significantly better than that of patients ≥ 60 years, which was also showed in the multivariate analysis[11].It is generally believed that cancer patients with distant metastasis have a poor prognosis[16,17]. Distant metastasis was also an adverse prognostic factor in our MPM patients.

In our 243 MPM patients, 21 patients with three primary malignancies were identified, whereas only two patients with three primary malignancies in 170 MPM patients were found in the study by Xu and Gu[10]. Compared with our study, the study by Xu and Gu[10] was conducted at least six years ago, and insufficient diagnosis and therapy may have resulted in the fewer patients being diagnosed with three malignancies. In another report of 30 patients with three primary malignancies[18], the median OS from the initial cancer diagnoses was 11.2 years. Our 21 patients with three malignancies had a median OS of 14.4 mo from the third cancer diagnoses. Due to the 10-years interval between the first and third cancer in our study, it is justified to consider that these two patients groups had a similar survival.

There are two limitations in our respective study. Firstly, the prognostic characteristics and treatment response of different cancers vary widely. Therefore, cancer types and treatment methods are important prognostic factors. However, these two factors were not included in our survival analysis. Secondly, MPM patients, especially those with three primary malignancies, may have potential genetic and environmental pathogenic factors, which are important in cancer prevention and treatment. However, these underlying pathogenic factors were not investigated in our study and deserve further detailed study.

CONCLUSION

During the diagnosis, treatment and follow-up of the initial cancer, more attention should be paid to the occurrence of a second, or even a third cancer in patients with MPM, to ensure early detection and treatment of the subsequent cancer. In particular, for common MPM pairs, such as NSCLC and breast/gastric cancer, colorectal and gastric cancer, the risk of concomitant MPM should be closely monitored.

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