RESEARCH ARTICLE

Clinical Features of Multiple Primary Malignancies: a Retrospective Analysis of 72 Chinese Patients

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Abstract

There is a scarcity of reports addressing patients with multiple primary malignancies (MPM), especially for Chinese cses. The aim of this study was to present a detailed analysis of Chinese patients presenting with at least two primary malignancies. Particularly, the clinical characteristics and survival between synchronous and metachronous MPM were compared. Out of 6,545 cases, 72 patients (1.1%) including 39 males (54.2%) and 33 females (45.8%) were diagnosed as MPM, giving a male: female sex ratio of 1.2:1. Of these, there were 16 (22.2%) cases of synchronous MPM (7 males, 9 females), 55(76.4%) metachronous (31 males, 24 females), and 1 "mixed form". For first tumor diagnosis time, synchronous MPM patients generally presented later than the metachronous cases. The top three sites for malignancies with metachronous MPM were colorectum, head and neck, and lung, while for synchronous they were lung, colorectum and breast. Among MPM patients, the median survival time was 15.7 years and the 5-year survival was 56%, and there was statistical difference in MPM categories ($P < 0.05$). The median survival time was 17.3 years and 3.8 years for metachronous and synchronous MPM patients, respectively. In comparison with synchronous MPM patients, those metachronous had a longer survival. This studies increase understanding of the clinical features of Chinese MPM patients and suggest that those presenting with metachronous cancers have a higher incidence and a better prognosis.

Keywords: Multiple primary malignancies - clinical features - epidemiology

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Introduction

Multiple primary malignancies (MPM) is an infrequently occurring syndrome that is defined as two or more malignancies without subordinate relationship detected in the same or other organs of an individual patient. It is also called multiplicity cancer. Depending on the diagnosis time of each malignancy, MPM could be classified into two categories. Synchronous MPM refers to the malignancies occurring at the same time or within an interval of six months, while metachronous MPM refers to malignancies following in sequence and more than six months apart (Moertel, 1977). Of all the MPM patients, most are duplex primary malignancies. There are many possible reasons for the development of secondary neoplasms, involving genetic susceptibility, tumor immunity and iatrogenic factors, including radiotherapy and chemotherapy. Improved understanding of the causes of MPM should help in protecting the patient from developing further tumors. In this paper, we intend to present our experience with a small fraction of Chinese patients presenting with at least two primary malignant tumors. Particularly, the clinical characteristics and survival between synchronous and metachronous MPM were compared.

Materials and Methods

Ethics Statement

For the use of these clinical materials for research purposes, prior written informed consent from all the patients and approval from the Ethics Committees of the Shanghai Jiao Tong University Affiliated First People's Hospital were obtained.

Patients and clinical analysis

Records of tumor patients were retrospective reviewed, collected from department of oncology in Shanghai Jiao Tong University Affiliated First People's Hospital within a period September 2009 to February 2013. The diagnosis of MPM must meet the criteria as follows. Each of the tumors must present a definite picture of malignancy, each tumor must be histologically distinct and the probability of one being a metastasis of the other must be excluded (Warren et al., 1932). But if multiple tumors arise from different anatomical subsites demonstrating similar histological subclassification, or tumors possess varying histologies arising from the same anatomical site, both of them could be labeled as multiplicity cancer (Sakashita et al., 1996). MPM was classified as being synchronous if diagnosed within 6 months of each other; otherwise they were

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Table 1. Comparison of the Number of Multiple Malignancies by Anatomical Site in the MPM Patients

Anatomical site	Metachronous MPM(n tumors)			Synchronous	"Mixed form"
	The first malignancy	The second malignancy	The third and fourth malignancy	MPM(n tumors)	(n tumors)
Head and neck	10	7		4	
Esophagus		4		1	
Stomach	7	5	1	4	1
Colorectum	9	11	2	6	
Small intestine	1	4		1	
Liver	2	1			
Cholecyst				1	
Pancreas		2	1		
Breast	8	8		5	
Lung	6	10		6	1
Prostate	1				
Female reproductive system	6	1		2	
Bladder and ureter	1	2		1	
Kidney	1		1		
Skin					3
Hematologic System	3				
Omentum majus				1	

MPM refers to multiple primary malignancies

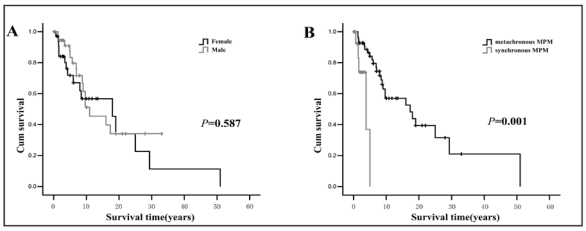

Figure 1. Comparison of Overall Survival in Gender (A) and MPM Categories (B) for Patients with Multiple Primary Malignancies. There was no statistically significant difference between the sexes ($P > 0.05$), but the difference in MPM categories had statistical significance ($P < 0.05$)

classified as metachronous (Moertel, 1977). Patients with malignancies were diagnosed through detailed medical history, complete physical examination, appropriate radiographic or/and endoscopic examinations, and were confirmed by pathologic finding. Records of these patients were electronically retrieved and retrospectively analyzed, and an exhaustive chart review was performed in an attempt to extract data relating to epidemiological features, clinical characteristics, syndrome outcome and survival. The patients were followed up by outpatient department visits, letters or telephones.

Statistical analysis

For statistical processing, SPSS computer package was employed. The significance of the data was determined using the Student t-test (two-tailed), Mann-Whitney test (two-tailed). In addition, the Life Tables and Kaplan–Meier test were used for survival analyses. P values less than 0.05 were considered to be statistically significant.

Results

Epidemiology

Out of 6545 cancer cases retrieved from our department of oncology over the study period, 72 patients (1.1%) were diagnosed as MPM. Of these, 67 patients had two primary malignancies, which accounted for 93.0%. 3 patients harbored three (4.2%), 1 patient harbored four (1.4%), and 1 patient harbored five primary malignant tumors (1.4%). Thirty-nine of the 72 patients were male (54.2%) and 33 female (45.8%). This gave a male: female sex ratio of 1.2:1. The mean ± SE age of the patient at the initial diagnosis was 53.6±1.6 years, and no statistical significance was found between the sexes: the mean ± SE age was 53.1±2.5 years for men, and 54.1±1.9 years for women ($P > 0.05$).

Synchronous and metachronous occurrence of malignancies

Among the MPM patients, there were 16 (22.2 %) cases for synchronous (7 males, 9 females), and 55 (76.4 %) for metachronous (31 males, 24 females). In contrast to metachronous MPM patients, those synchronous were less common. Another patient who had five primary malignancies was a "mixed form" (Bittorf et al., 2001) (i.e. both synchronous and metachronous lesions existed in the same patient). With regard to age at first tumor diagnosis, it was noted that synchronous MPM patients generally occurred later than those metachronous, irrespective of the "mixed form". The mean ± SE age for synchronous lesions was 58.5±2.5 years (men 62±1.9; women 55.8±4.1 years). While for those metachronous patients, the figures were 52.1±2.0 years (men 50.9±3.1; women 53.5±2.2years). But the difference had not statistical significance ($P > 0.05$). In fact, the age of "mixed form" patient for first diagnosis was 58 years.

Tumors localization

Numbers and anatomical locations of malignancies in synchronous MPM, metachronous MPM and "mixed form" patients according to tumor site are detailed in Table 1. In metachronous MPM, the top three sites for the first tumors were the head and neck, colorectum and breast, whereas for second tumors the colorectum was the most frequent, followed by the lung and breast. When classified

according to gender, the top three sites for first tumor in males were the stomach, lung and head and neck. The leading tumor site for second tumor in males was also the colorectum. In females, either the first or second tumor, the leading tumor site was the breast. While for synchronous MPM, the common sites were lung, colorectum and breast.

Inter-tumor intervals

In metachronous MPM patients, the median interval between the first and second tumors was 5.5 years, range from 0.8 to 47.3 years. For men, the median interval was 4.5 years, as in women 5.8 years. But this gender differences had no statistical significance ($P > 0.05$). In synchronous MPM patients, 11 cases occurred synchronously, 2 cases within one month, 1 case within two months, and 2 cases within six months.

Survival analysis

By February 2013, 29 of the 72 patients had already survived (17 males, 12 females). Here, survival times of patients were calculated from the time of establishment of the diagnosis of the first malignancy to death or deadline of follow-up (February 2013). Of all MPM cases, the median survival time was 15.7 years and the 5-year survival was 56%. Seven patients survived at least 20 years including one patient for 51 years, 11 patients had already survived for between 10 and 20 years, 20 patients for between 5 and 10 years, 29 patients for between 1 and 5 years, and 5 patients for less than 1 year. The median survival time was 11.0 year and 18.0 years for males and females, respectively, but there was no statistically significant difference between the sexes ($P > 0.05$) (Figure 1A). When classified according to MPM category, the median survival time was 17.3 years and 3.8 years for metachronous MPM patients and those synchronous, respectively, and the difference had statistical significance ($P < 0.05$, Figure 1B). In comparison with synchronous MPM patients, those metachronous had a longer survival.

Discussion

MPM was first described by Billroth in the form of case report (Billroth et al., 1889). Ever since, there have been numerous reports addressing the occurrence of secondary primary malignancies. MPM is still quite rare, but the occurrence is on the rise and differs by region and time. Age, diagnostic technique improvements, and longer life spans are all contributing factors. A literature review of 1,104,269 cancer patients concluded that the prevalence of MPM varies from 0.73% to 11.7% (Demandante et al., 2003). The wide variation in reporting was concluded to be related to the experience and varying capabilities of hospitals and their doctors. Besides that, a male predominance for MPM was generally reported. The male: female ratio ranged from 0.9: 1 to 3.5: 1 (Gursel et al., 2011). In our studies, the overall incidence of MPM was 1.1%, and the male: female ratio was 1.2:1. Compared to synchronous MPM patients, those metachronous had a higher incidence (76.4 % vs. 22.2%).

MPM can occur at any age. Our studies showed the mean age of the patients at the initial diagnosis was 53.6 years. One thing to note in our investigations is that synchronous MPM (58.5±2.5 years) generally occurred later than metachronous MPM (52.1±2.0 years), but the difference had no statistical significance.

For the inter-tumor intervals, Feyerabend T (Feyerabend et al., 1991) and Bittorf B (Bittorf et al., 2001) reported that a first interval were 5.7 and 4.0 years, respectively. Our observation showed that, among metachronous MPM patients, the median interval between the first and second tumors was 5.5 years. Moreover, an analysis of duplex primary malignancies revealed a longer interval in women (Santos et al., 1994). In our research, the median interval for men was 4.5 years, as in women 5.8 years. It seemed that the interval in women was longer, but this gender differences had no statistical significance. Of synchronous MPM patients, most cases have occurred at the same time.

Most malignancies with MPM involve those of the respiratory, gastrointestinal, and genitourinary systems (Demandante et al., 2003). In our studies, whether synchronous or metachronous MPM patients, gastrointestinal malignancies were common. The combinations of colorectal malignancies with the other digestive system neoplasms including stomach and small intestinal tumors (10 males; 3 females) were frequently observed. Living habits may be an important contributing factor, such as unhealthy diet, tobacco smoking and alcohol consumption (Keshishian et al., 1998; Gursel et al., 2011), lack of exercise and so on. Not surprisingly, breast cancer was the most frequent first and second tumor among females in the present study, and consistent with the literature reported (Munker et al., 1999). Interestingly, a high association breast/breast cancer occurring together was observed. Thus, we audaciously presume that a woman who had breast cancer in one breast has an increased risk of getting cancer in her other breast. Similar risk also exists in lung.

The median survival time of our patients was 15.7 years and the 5-year survival was 56%. A more interesting result was that the median survival time of metachronous MPM patients was longer than those synchronous (17.3 vs. 5.8 years), and this difference had statistical significance ($P < 0.05$). In comparison with metachronous MPM patients, those synchronous seemed to have a worse prognosis. How to explain these phenomena? To begin with, immunity abnormality (Mckeown 1991; Santos et al., 1994) is thought to exist in MPM patients. We speculate that the immunity of an organism is first impaired, but then is triggered and becomes strengthened by cytokines and growth factors secreted by tumor and other cells, and finally exhausted. This triggered and strengthened immunity is likely to contribute to the longer survival time of metachronous MPM patients. For those synchronous, the immunity of an organism, which is damaged seriously at first by tumors burden during a short period, cannot be triggered and strengthened, leading to the shorter survival time. Unfortunately, we no longer have access to the blood specimens for our cases because too much time has passed. However, we detected immunology indexes for some newly collected MPM patients and the results supported our hypotheses (unpublished data). It still needs further study and verification. Besides, individual

genetic susceptibility and other factors, such as hormonal stimulation, iatrogenic factors, and environmental degradation are etiologically related with this syndrome (Slaughter et al., 1953; Bedi et al., 1996; Carey 1996; Demandante et al., 2003). The whole-genome sequencing is currently being performed to detect the blood DNA samples from our quadruple primary malignancies patient and his family members. We hope this technology could help us to identify some genetic susceptibility candidate loci for MPM syndrome. Last but not least, statistical accuracy must be considered owing to small number of cases of multiple primaries, and future research need to base upon more large survey sample.

Many hypotheses have been proposed to explain the carcinogenesis and pathogenesis of MPM (Lauchlan 1968; Iioka et al., 2000; Travis et al., 2005), but the detailed etiology and mechanism still need further clarification. Our studies increase understanding of the malignancies in Chinese patients by investigating the clinical features of MPM, and can also remind the people to attach importance to this syndrome.

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