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Original Article

Survival and clinical characteristics of patients with multiple primary cancers: a hospital-based study

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Abstract: Aim: Multiple primary cancers (MPCs) are a group of rare tumors of increasing incidence in recent years. Many issues in terms of epidemiologic features, pathogenesis, and treatment of MPCs are not well understood. Moreover, little data are available in China. Therefore, we aimed to analyze the association between clinical characteristics and prognoses of Chinese patients with MPCs to assess their impact on patient survival. Methods: We examined the incidence, clinical characteristics, and survival in 316 MPC patients. Cox proportional hazards analysis was used to identify independent prognostic factors. Results: Of all patients, 286 developed two primaries and 30 developed three or more primaries. The primaries were synchronous in 87 and metachronous in 229 patients; 136 patients survived, 169 died, and 11 were lost to follow-up. The median overall survival 1 (interval between the first cancer diagnosis and death, or the end of follow-up, OS1) was 66 months; the median overall survival 2 (interval between the second cancer diagnosis and death, or the end of follow-up, OS2) was 22 months. The median OS1 was longer in patients with metachronous primaries (84 months) than in those with synchronous primaries (25 months). The 5-year survival rates were 70.7% and 21.8%, respectively. For metachronous primaries, the median OS1 was 132 months in patients with > 5-year interval and 52 months in patients with < 5-year interval between the first and second primaries. Differences between the groups were significant ($P < 0.05$). Sex, interval between the first and second primaries, and initial cancer stage were significantly associated with OS ($P < 0.05$). Conclusions: Sex, interval between the first and second primaries, and initial cancer stage are independent prognostic factors in MPC patients. Additional tumors in cancer patients may be metastatic or novel lesions. Therefore, the possibility of metachronous or synchronous malignancy should be considered. Postoperatively, a prolonged follow-up is necessary.

Keywords: Multiple primary cancers, cancer survivors, prognosis

Introduction

Multiple primary cancers (MPCs) are two or more independent primary cancers that occur at different locations in an individual and are not an extension, recurrence, or metastasis. If the interval between the first and second cancer diagnoses is less than 6 months, then the patients are considered to have synchronous multiple primary cancers (SMPCs). If the interval is more than 6 months, then they are considered to have metachronous multiple primary cancers (MMPCs) [1]. Advances in diagnostic technologies and treatments have prolonged survival of patients with malignant tumors. Therefore, the incidence of MPCs is increasing. Since the documentation of 1259 MPCs by Warren and Gates in 1932 [1], an increasing amount of research has been conducted on MPCs. Currently, the incidence of MPCs ranges from 0.7-11.7% in different populations and is still increasing [2]. According to the American Cancer Institute, the incidence of second primary cancers increased from 9% between 1975 and 1979 to 19% between 2005 and 2009 [3]. However, in China, the reported incidence of MPCs was 0.4-2.4% [4]. Additionally, the number of cases in those articles was small and could not represent all populations. Compared with other countries, our understanding of MPCs is inadequate, which may lead to misdiagnosis.

The etiology of MPCs is multifactorial. Host and environmental factors clearly play a role, but it is difficult to define those contributions. Superimposed on this general population risk for second and subsequent primary cancers are treatment-associated malignancies, where chemotherapy and radiotherapy for the primary

Table 1. Clinical presentation of 316 patients with multiple primary cancers

	Index primary *n* (%)	Second primary *n* (%)
Age at diagnosis		
< 65	204 (4.6)	143 (45.3)
≥ 65	112 (35.4)	173 (54.7)
Sex		
Male	102 (32.3)	102 (32.3)
Female	214 (67.7)	214 (67.7)
Primary site	371	266
Head and neck	9 (2.4)	9 (3.4)
Lung	46 (12.4)	52 (19.5)
Breast	24 (6.5)	11 (4.1)
Esophagus	39 (10.5)	19 (7.1)
Stomach	99 (26.7)	47 (17.7)
Colorectal	125 (33.7)	75 (28.2)
Renal	3 (0.8)	2 (0.8)
Liver and biliary	4 (1.1)	11 (4.1)
Pancreas	1 (0.3)	8 (3)
Cervix	2 (0.5)	1 (0.4)
Endometrium	4 (1.1)	3 (1.1)
Prostate	3 (0.8)	8 (3)
Ovary	2 (0.5)	2 (0.8)
Bladder	2 (0.5)	2 (0.8)
Ureter	1 (0.3)	2 (0.8)
Hematologic system	7 (1.9)	14 (5.3)
Treatment		
Surgery	136 (43)	89 (28.2)
Surgery + CT	126 (39.9)	75 (23.7)
Surgery + CRT	18 (5.7)	10 (3.2)
Surgery + RT	11 (3.5)	10 (3.2)
CT	23 (7.3)	48 (15.2)
RT	1 (0.3)	4 (1.3)
CRT	0 (0)	8 (2.5)
Palliative/no treatment	1 (0.3)	17 (5.4)
Present status		
Alive	136 (43)	136 (43)
Dead	169 (53.5)	169 (53.5)
Lost to follow-up	11 (3.5)	11 (3.5)

RT = radiotherapy; CRT = chemoradiation; CT = chemotherapy.

cancer can increase risk for a subsequent cancer [3]. This risk may be modified by host and environmental factors that affect risk of primary cancer, such as lifestyle, workplace, and home exposures to carcinogens, viruses, age, gender, genetics, infection, immune function, hormone levels, and interactions of all of these factors. But it is difficult to evaluate disease separate from known genetic associations with those cancers or separate from exposure to specific therapeutic modalities used to treat those malignancies.

Multiple primary cancers represent a population that is prone to generate cancer. It is beneficial to study the causes, diagnosis, and treatment of cancer. Although many studies have examined the epidemiology and clinical characteristics of MPCs, most are case reports and few have addressed patient survival with different results. Ethnic differences of incidences in MPCs have been reported [2, 3], but the data vary greatly. Moreover, little data is available in China. In this study, we retrospectively analyzed the clinical features, treatments, and survival of 316 patients with MPCs treated at the Third Affiliated Hospital of Soochow University in China to improve our understanding of MPCs and to assess the impact of multiple neoplasms on patient survival.

Patients and methods

Patient selection

Clinical data from 316 patients with MPCs treated between January 2010 and October 2016 at the Third Affiliated Hospital of Soochow University was collected for this study. All diagnoses were confirmed by pathologic analysis. In this study, MPCs were defined according to the third edition of the *International Rules for Multiple Primary Cancers (International Classification of Diseases for Oncology)* [5]. The rules for the diagnosis of MPCs were as follows: 1) Recognition of the existence of two or more primary cancers does not depend on time. 2) A primary cancer is one that originates at a primary site or tissue, and is not an extension, recurrence, or metastasis. 3) Only one tumor is recognized as arising in an

Table 2. Clinical presentation of metachronous and synchronous multiple primary cancers

	SMPCs *n* (%)	MMPCs *n* (%)	*P* value
Patients	87 (27.5)	229 (72.5)	
Age at diagnosis			
< 65	33 (37.9)	119 (52)	0.026
≥ 65	54 (62.1)	110 (48)	
Sex			
Male	69 (79.3)	80 (34.9)	< 0.001
Female	18 (20.7)	149 (65.1)	
Cancer stage			
Stage I	17 (19.5)	46 (20.1)	0.450
Stage II	15 (17.2)	44 (19.2)	
Stage III	36 (41.4)	74 (32.3)	
Stage IV	19 (21.9)	65 (28.4)	
Primary site			
Head and neck	3 (2.2)	6 (2.6)	0.019
Lung	15 (11.2)	31 (13.5)	
Breast	0 (0)	24 (10.5)	
Esophagus	17 (12.7)	22 (9.6)	
Stomach	38 (28.4)	61 (26.6)	
Colorectal	53 (39.6)	72 (31.4)	
Renal	1 (0.7)	2 (0.9)	
Liver and biliary tract	3 (2.2)	1 (0.4)	
Pancreas	1 (0.7)	0 (0)	
Cervix	0 (0)	2 (0.9)	
Prostate	0 (0)	3 (1.3)	
Ovary	1 (0.7)	1 (0.4)	
Bladder	0 (0)	2 (0.9)	
Hematologic system	2 (1.5)	5 (2.2)	
Present status			
Alive	45 (51.7)	91 (39.7)	0.096
Dead	38 (43.7)	131 (57.2)	
Lost to follow-up	4 (4.6)	7 (3.1)	
5-year survival rate	21.8%	70.7%	

organ or pair of organs or a tissue. Multifocal tumors are discrete masses that are apparently not in continuity with other primary cancers at the same primary site or tissue, e.g. the bladder is counted as a single cancer. 4) Rule 3 does not apply in two circumstances: systemic (or multicentric) cancers potentially involving many different organs (e.g., Kaposi's sarcoma and tumors of the hematopoietic system) are only counted once and neoplasms of different morphologies are regarded as multiple cancers even when diagnosed simultaneously at the same site.

Follow-up

The last follow-up examination was on October 30, 2017. Overall survival 1 (OS1) was defined as the interval between the first cancer diagnosis and death, or the end of follow-up. Overall survival 2 (OS2) was defined as the interval between the second cancer diagnosis and death, or the end of follow-up. Clinical staging of SMPCs was conducted according to the tumor of the highest stage.

Statistical analysis

Differences between groups were evaluated using the χ^2 test. Clinical features of the groups were compared using the χ^2 test. Survival curves were plotted using the Kaplan-Meier method, and group differences in survival curves were investigated using the log-rank test. A Cox proportional hazards model was used to identify variables independently associated with OS. All statistical tests were two-sided and a P value < 0.05 was considered statistically significant. SPSS version 16.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

Clinical characteristics

Of 39600 consecutive cancer patients treated between January 2010 and October 2016, 39284 (99.2%) had a single primary neoplasm and 316 (0.8%) had multiple neoplasms. Patients with multiple primaries comprised 286 (90.5%) patients with two primaries, 27 (8.5%) with three, two (0.6%) with four, and one with eight (0.4%) [6]. Of 316 patients with MPCs, 102 were men and 214 were women. Their ages at initial cancer diagnosis ranged from 26-87 years, and the median age was 60 years. Their ages at diagnosis of the second neoplasm ranged from 28-88 years, and the median age was 65 years. The initial cancers, mainly colorectal (33.7%), stomach (26.7%), and lung (12.4%) cancers, numbered 371. The second primary tumors, mainly colorectal (28.2%), lung

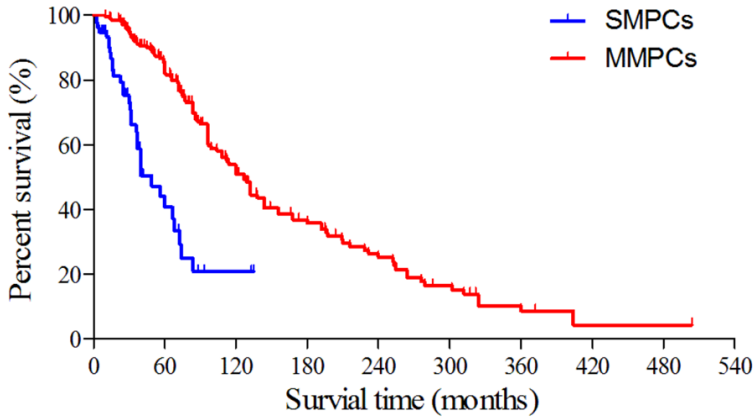

Figure 1. Overall survival 1 of patients with synchronous and metachronous multiple primary cancers.

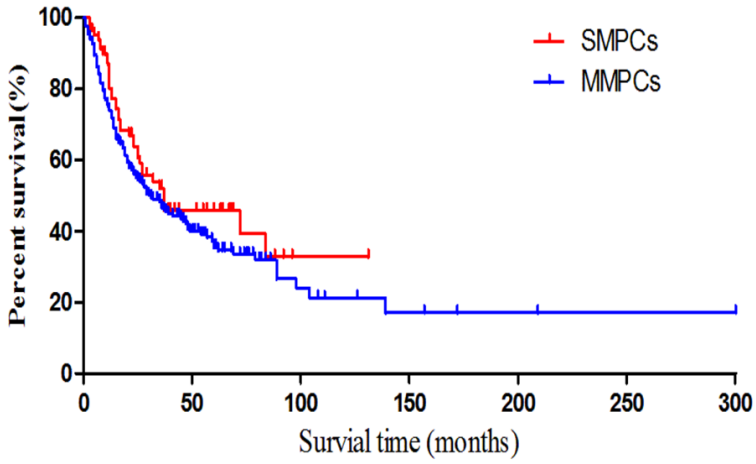

Figure 2. Overall survival 2 of patients with synchronous and metachronous multiple primary cancers.

(19.5%), and stomach (17.7%) cancers, numbered 266. Of the initial tumors, 92.1% were resected, 39.9% underwent surgery combined with chemotherapy, 5.7% underwent surgery combined with chemotherapy and radiotherapy, 3.5% underwent surgery combined with radiotherapy, 7.3% received chemotherapy alone, and 0.3% did not undergo any treatment. Regarding the second primary tumors, 75.6% were resected, 23.7% underwent surgery combined with chemotherapy, 3.2% underwent surgery combined with chemotherapy and radiotherapy, 3.2% underwent surgery combined with radiotherapy, 15.2% received chemotherapy alone, 2.5% received radiotherapy alone, and 17 patients did not undergo any treatment. The mean interval between the index and second primaries was 69.6 months, with a median of 43.5 months. Among the 316 patients, 87 (27.5%) had SMPCs and 229 (72.5%) had MMPCs. Of the 87 patients with SMPCs, 69 (79.3%) were men and 18 (20.7%) were women; 32 (36.7%) had Stage I-II cancers and 55 (63.3%) had Stage III-IV cancers. The primary tumors were mainly colorectal (39.6%), stomach (28.4%), and esophageal (12.7%) tumors. Of the 229 patients with MMPCs, 80 (34.9%) were men and 149 (65.1%) were women; 90 (39.3%) had Stage I-II cancers and 139 (60.7%) had Stage III-IV cancers. The primary sites were mainly colorectal (31.4%), stomach (26.6%), and lung (13.5%). The clinical characteristics of the 316 patients with MPCs are shown in **Tables 1** and **2**.

Patient survival

By the last follow-up, 136 (40.3%) of the 316 patients with MPCs were still alive, 169 (53.5%) had died, and 11 (3.5%) were lost to follow-up. The OS1 was 3-504 months, and the median OS1 was 66 months. The OS2 was 1-300 months, and the median OS2 was 22 months. The median OS1 was longer in patients with MMPCs (84 months) than in patients with SMPCs (25 months; χ^2 = 25.5, P < 0.001; **Figure 1**). Their 5-year survival rates were 70.7% and 21.8%, respectively. The median OS2 in patients with MMPCs was 23 months, and that in patients with SMPCs was 21 months. There was no statistical difference between the groups (χ^2 = 2.6, P = 0.107; **Figure 2**). Regarding MMPCs, the median OS1 was 132 months in 109 (47.6%) patients with an interval of more than 5 years, and 52 months in 120 (52.4%) patients with an interval of less than 5 years, between the first and second primaries. There was a significant difference between the groups (χ^2 = 76.6, P < 0.001;

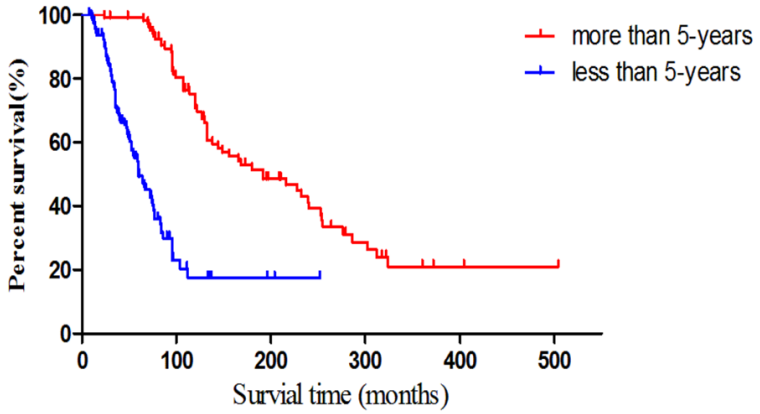

Figure 3. Overall survival 1 of patients with metachronous multiple primary cancers with intervals of more and less than 5 years between the first and second primaries.

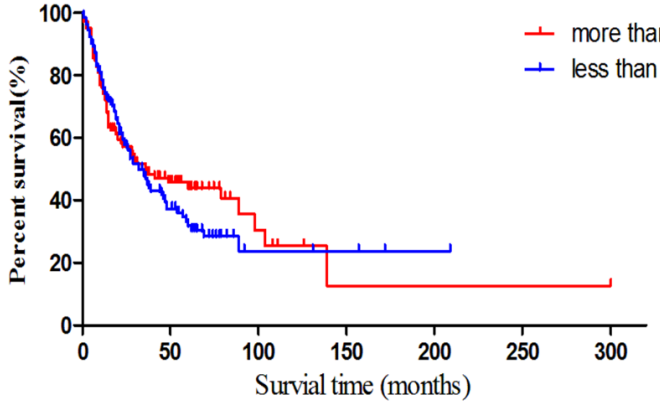

Figure 4. Overall survival 2 of patients with metachronous multiple primary cancers with intervals of more and less than 5 years between the first and second primaries.

Figure 3). Their median OS2 was 22 and 20 months, respectively, and there was no statistical difference between the groups (χ^2 = 1.4, P = 0.236; **Figure 4**). Cox regression analysis showed that sex, the interval between the first and second primaries, and the stage of the initial cancer were significantly associated with OS (P < 0.05; **Table 3**).

Discussion

Compared with the general population, cancer survivors have a 14% increased risk of developing a second primary cancer [7]. There is a large difference (1-37%) in the incidence of MPCs among cancer survivors in the literatures, which may be related to the analyses used, the timing of data collection, the variations in diagnosis and treatment at different hospitals, and the race. In this study, the incidence of MPCs was 0.8% for patients initially diagnosed between 2010 and 2016 at our hospital, which is lower than that reported in Western literature [3], but is consistent with Chinese reports [4]. This may reflect the poor understanding of MPCs in China, leading to misdiagnosis.

The detection of multiple primaries in cancer survivors may be related to an increased awareness of MPCs, may occur secondary to previous therapies, or may be due to shared risk factors, including environmental, lifestyle, and genetic factors [8]. Patients who initially present with thyroid, urinary bladder, prostate, cervical, and uterine cancers are more liable to develop a second cancer, than those with hepatic, biliary tract, and pancreatic cancers and acute leukemia, who rarely develop a second malignancy [9]. This may be explained by the poor prognosis of these patients, who do not survive long enough to develop second primaries. In this study, the most common initial primaries among cancer survivors with MPCs were colorectal, stomach, and lung cancers. This may be related to the incidences of these cancers in our region.

Patients with multiple primaries usually present with initial tumors of a lower stage than the second primaries [9]. In this study, the initial cancers in 218 (70%) patients were Stage I-II, whereas the second cancers in only 103 (32.6%) patients were Stage I-II. However, the third primary cancers in 13 (48.1%) patients were Stage I-II. This implies that patients with primary cancers of an earlier stage are more likely to develop a second primary cancer, and a greater number of primary cancers indicated a longer survival. In contrast, late stage of the

Table 3. Cox multivariate regression analysis of prognostic factors for 316 multiple primary cancers

	β	SE	Wald value	RR	95% CI	*P* value
Sex						
Female				1		
Male	0.745	0.215	12.008	2.106	1.382-3.21	0.001
Age at diagnosis						
< 65				1		
≥ 65	0.014	0.009	2.31	1.014	0.996-1.033	0.129
Interval between the first and second primaries						
< 5 years				1		
≥ 5 years	0.02	0.002	98.801	0.98	0.976-0.984	< 0.001
Stage of the initial cancer						
Stage I-II				1		
Stage III-IV	0.42	0.204	4.221	1.521	1.02-2.27	0.040
Surgery						
No				1		
Yes	0.008	0.329	0.001	0.992	0.521-1.89	0.981

initial cancer was associated with shorter survival. This suggests that patients with more than three primaries may have a better prognosis.

Many studies have investigated the role of anti-tumor therapies for MPCs [10, 11]. Chemotherapy leads to the occurrence of second primary cancers typically in a few months to 9 years, whereas radiation or hormone therapies cause cancers to go through a longer incubation period, typically 5-10 years [12]. In this study, the proportion of patients who underwent surgery was 43% for the initial cancer, but 28.2% for the second primary cancer. Only one patient (0.3%) did not undergo treatment for the initial cancer, whereas 17 patients (5.4%) received no treatment for the second primary cancer. This was associated with the earlier stage of the initial cancer and later stage of the second primary cancer, and suggests that we should focus on the long-term follow-up of cancer survivors to detect second primaries earlier. However, the occurrence of second primary cancers cannot be solely attributed to anti-tumor therapies, but is the result of multiple factors, including genetic predisposition, lifestyle, and environmental factors.

Genetic susceptibility is an important risk factor for MPCs. Mutations in the *breast cancer (BRCA) 1* and *BRCA2* genes are associated with a high risk of secondary breast cancer. Retinoblastoma, which is associated with germline mutations in the *RB1* gene at Chromosome 13q14, is the most common hereditary syndrome associated with MPCs after childhood cancer. Survivors of retinoblastoma have a significantly increased risk of sarcomas, leukemia, melanomas, and epithelial tumors such as breast and lung cancers. Li-Fraumeni syndrome, which is associated with germline mutations in the *TP53* gene at Chromosome 17q13, is characterized by an increased risk of breast cancer, sarcomas, leukemia, brain tumors, adrenocortical carcinomas, and gonadal germ-cell tumors [13]. Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, is an autosomal dominantly inherited cancer-susceptibility disorder caused by germline mutations in DNA mismatch-repair genes including *MLH1, MSH2, PMS1* and *MSH6* [14]. In this study, a patient with eight primary cancers was confirmed by genetic testing to have Lynch syndrome. The patient's younger brother was also recently diagnosed with Lynch syndrome.

Overall, patients with multiple primaries have a better survival rate than those with single primaries [15]. With early diagnosis, the prognosis of MPCs is significantly better than that of recurrence or metastasis of a single primary cancer. Reportedly, the 10-year survival rate of MPCs is about 69.3% [16]. The prognosis of MMPCs is considered better than that of SMPCs. The longer the interval between the

occurrence of two tumors in patients with MMPCs, the better the prognosis. In this study, the 5-year survival rate of the MMPCs group was 70.7%, whereas that of the SMPCs group was 21.8%. The OS1 of the MMPCs group was significantly higher than that of the SMPCs group, and the difference was statistically significant ($\chi^2 = 25.5$, $P < 0.001$). However, there was no statistical difference in OS2 between the groups ($\chi^2 = 2.6$, $P = 0.107$). Similarly, for MMPCs, there was a significant difference between patients with an interval of more than 5 years and those with an interval of less than 5 years between the first and second primaries ($\chi^2 = 76.6$, $P < 0.001$). However, there was no statistical difference in OS2 between these groups ($\chi^2 = 1.4$, $P = 0.236$). Some reports have examined the OS1 of patients with MPCs, but the OS2 of these patients has never been reported. Based on our findings, we believe that the difference in OS1 may be related to the staging and tumor location of the first cancer. Female patients with an initial cancer of Stage I-II and an interval between the first and second primaries of more than 5 years have a better prognosis. The OS of MPCs mainly depends on the tumor with the highest stage, and is not associated with the number of multiple primary tumors. Thus, although some patients suffer multiple tumors, they can survive for a long time.

In summary, our findings provide crucial information on the risk of MPCs. New guidance is necessary on the care of cancer survivors at high risk of MPCs that includes screening and prevention strategies. In clinical practice, long-term follow-up of cancer survivors must be strengthened and more attention paid to differentiation of second primary cancers from metastatic carcinomas. Once diagnosed with MPCs, second primary cancers should be treated similarly to first primary cancers with radical therapy. Finally, further basic research is needed on the detailed mechanisms underlying the development of MPCs.

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Disclosure of conflict of interest

None.

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