Clinicopathological features and prognostic analysis of 77 patients with multiple primary cancers

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Summary

Purpose: The purpose of this study was to analyze the characteristics, diagnosis and treatment principles and prognosis of multiple primary cancers (MPC).

Methods: A total of 77 patients with MPC admitted in the Central Hospital of Changsha from December 2013 to December 2018 were enrolled in this retrospective analysis. The survival of these 77 patients with complete follow-up data was calculated.

Results: There were 77 patients with multiple primary cancers, including 70 patients with double primary cancers, 6 patients with three primary cancers, and 1 patient with four primary cancers. Among the 77 MPC patients, there were 4 synchronous carcinomas (SC), 58 metachronous carcinomas (MC), and 15 unknown cases. The 3, 5, and 10-year overall survival rates of 77 patients with follow-up data were 86.5%, 18.2%, and 12.9%, respectively. The median survival time of

4 SC and 58 MC patients was 12 months and 108 months, respectively. The median survival time was 48.5 months in 23 patients with an interval of less than 5 years, and 108 months in 29 patients with first and second primary cancers whose interval was more than 5 years. The median survival time of 26 patients with second primary lung cancer was 84 months, and that of 23 patients with second primary non-lung cancer was 156 months.

Conclusions: MPCs are more likely to occur in the colorectum, and the prognosis of patients with metachronous cancer is better than that of patients with synchronous cancer. The longer the interval between two cancers, the better the prognosis will be. The prognosis of the second primary non-lung cancer patients is better than that of the lung cancer patients.

Key words: multiple primary carcinomas, clinical analysis, prognosis

Introduction

Multiple primary carcinomas (MPC) is a multi-factor, multi-gene and multi-step process by which an individual has two or more primary malignant tumors simultaneously or successively. In recent years, with the continuous enrichment of medical means and the continuous extension of life expectancy, the total survival period of cancer patients has been extended, and the related reports of multiple primary cancers have been increasing. Synchronous carcinoma (SC) and metachronous carcinoma

(MC) can be classified according to the interval of diagnosis. The 77 cases of multiple primary cancers collected in our hospital were analyzed, and the clinical characteristics, etiology, diagnosis, treatment and prognosis of multiple primary cancers are discussed.

Methods

Clinical data

All cases were retrieved from the computer medical record management system of Changsha central Hospital from December 2013 to December 2018. Patients with malignant tumors were excluded from repeated inpatients. Seventy-seven patients with multiple primary cancers were screened out according to the diagnostic criteria, accounting for 1.3% of patients with malignant tumors admitted and treated in the same period. Data were extracted from medical records. All cases were confirmed pathologically, and most of them were pathologically diagnosed by surgical biopsy specimens, and the rest were confirmed by fibroendoscopy or fine-needle biopsy. Combined with tumor marker results and imaging data, recurrence and metastasis of cancers were clearly excluded. This study was approved by the Ethics Committee of the Affiliated Dongguan People's Hospital, Southern Medical University. Signed informed consents were obtained from all participants before the study entry.

Diagnostic criteria

The diagnostic criteria for multiple primary cancers formulated by Warren and Gate are [1]: (1) each type of cancer must be pathologically proved to be malignant; (2) each type of malignant tumor must have a unique pathological morphology; (3) metastasis or recurrence must be excluded. Multiple primary cancers can be classified into simultaneous and asynchronous cancers according to the interval of diagnosis. SC refers to more than two malignant tumors occurring simultaneously or within 6 months, and MC occurs at intervals of more than 6 months.

Follow-up

Follow-up was performed by telephone and outpatient and inpatient visits. Seven cases (9.1%) were lost to follow-up in December 2018.

Statistics

The starting point was the time of diagnosis of the first primary cancer, and the end point was the date of death, lost to follow-up or last follow-up. SPSS 18.0 soft-

Table 1. Interval time between primary and secondary cancers in 70 patients with double primary cancers

Interval time (years)	Number of cases	Percent
≤1	18	25.7
1 -3	12	17.1
3-5	11	15.7
>5	29	41.4

Table 2. Distribution and prognosis of multiple primary cancers in 77 cases

System	Position	First primary carcinoma	Second primary carcinoma	Third primary carcinoma	Fourth primary carcinoma	Subtotal	Median survival time (months)	Average survival time (months)
Digestive	Esophagus	4	3	1	1	9		
	Colorectal	16	11	1	-	28	90	106.7
	Liver	2	1	-	-	3		
	Stomach	2	2	-	-	4		
	Gallbladder	-	1	-	-	1		
Respiratory	Lung	6	38	1	-	46	114	115.3
Head and neck	Head and neck	15	6	2	-	22	108	102.4
Breast Female reproductive system	Breast	11	5	-	-	16	131	143.4
	Ovary	2	-	-	-	2		
	Cervical	12	4	-	-	16	110.5	129.9
	endometrium	1	-	-	-	1		
Urogenital	Kidney	2	-	-	-	2		
	Ureter	-	1	-	-	1		
	Bladder	2	-	-	-	2	139	139
	Prostatitis	1	2	-	-	3		
Blood	Blood	1	1	1	-	3	96	96
Skin	Skin	-	2	-	-	2	-	-
Total		77	77	6	1	161	-	-

ware (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Kaplan-Meier method was used for survival curves and Log-rank test was used for survival comparison between two groups.

Results

Characteristics of onset

Among 77 cases of multiple primary cancers, 70 cases were double primary cancers, 6 were triple primary cancers, 1 was four primary cancer. Forty-one cases were male and 36 were female (male:female=1.4:1). Four cases were SC, 58 were MC, and 15 were unknown. The age at the first primary cancer ranged between 27 and 84 years (median 55 years and average 56.3 years). The age range of the second primary cancer was 39-89 years (median 61 years and average 61.6 years). The age range of the third primary cancer was 41-89 years (median 60 years and average 60.4 years). Among the 70 patients with double primary carcinomas, the interval of onset within 5 years after the first cancer was about 41 cases (58.5%). The mean interval between the first cancer and the second cancer ranged from 0 to 240 months (Table 1); The mean interval between the first cancer and the third cancer in 6 patients with three primary cancers was 108-180 months. The longest interval between the third and fourth cancer in one patient with four primary cancers was 240 months.

Location of disease

Among 77 patients, the digestive system was the most common primary cancer location. The top four high-risk organs were colorectum, head and neck, cervix and breast, accounting for 20.8% (16 cases), 19.5 % (15 cases), 5.6% (12 cases) and 4.3% (11 cases), respectively. The top four high-risk organs of multiple primary cancer were lung, esophagus, ovary and bladder, accounting for 49.4% (38 cases), 14.3% (11 cases), 6.5% (5 cases) and 14.3% (11 cases), respectively. The location of the first and multiple primary cancers is shown in Table 2. Sixteen patients with colorectal cancer had the highest incidence of secondary cancer in the lung (10 cases); 15 patients with head and neck cancer had the highest incidence of secondary cancer in

the lung (4 cases); 12 patients with cervical cancer had the highest incidence of secondary cancer in the lung (11 cases); of 6 patients with three primary cancers, 1 was primary breast cancer, and multiple primary cancers occurred in the other side of the breast and lung; 1 was primary rectal cancer, and multiple primary cancers occurred in the lung and larynx; 1 was primary nasopharyngeal cancer, and multiple primary cancers occurred in the skull base and frontal lobe; 1 was primary tongue cancer, and multiple primary cancers occurred in the esophagus and lung; 1 was primary lung cancer, and multiple primary cancers occurred in the tibia and testis; 1 was primary bladder cancer, and multiple primary cancers occurred in the rectum and esophagus. Four primary cancers were ovarian cancer as the first cancer, and multiple primary cancers occurred in breast, rectum and esophagus, respectively.
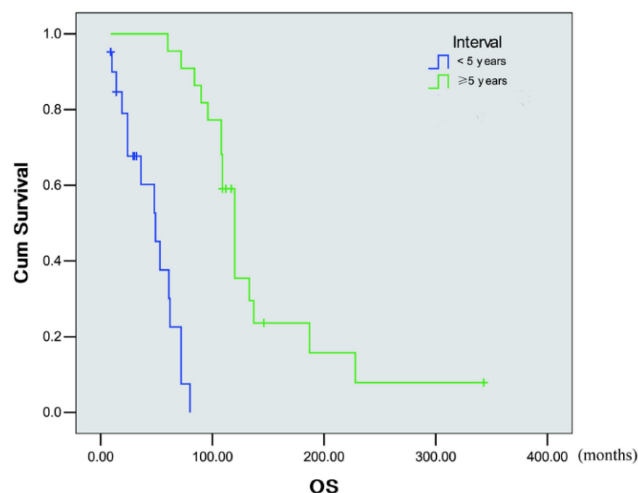

Figure 1. Survival curves of patients with interval less than 5 years and more than 5 years between two cancers (p<0.001).
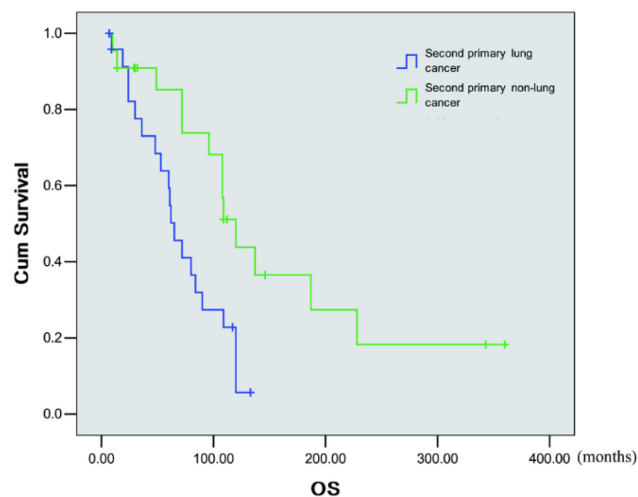

Figure 2. Survival curves of second primary lung cancer group and second primary non-lung cancer group (p<0.05).

Table 3. Survival time of 77 patients with multiple primary cancers

Survival time	Number of cases	Percent
Exceed 3 years	45	86.5
Exceed 5 years	42	18.2
Exceed 10 years	17	12.9

Table 4. Treatments between primary and secondary cancers in 77 patients with multiple primary cancers

Treatments	First primary cancers n	Second primary cancers n
surgery alone	29	11
surgery plus chemotherapy	17	5
surgery plus radiotherapy	2	1
surgery plus chemotherapy plus radiotherapy	12	3
radiotherapy and chemotherapy	6	16
radiotherapy	4	4
chemotherapy	4	13
palliative conservative treatment	3	24

Prognostic analysis

The survival time of 77 patients with multiple primary cancers with complete follow-up data was calculated. The longest survival time was 143.4 months in breast cancer patients, followed by 139 months in urogenital system and 129.9 months in female reproductive system. Among them, 35 patients died, and the mean survival time of 31 patients who could be followed-up was 9-228 months (median 84 months). The overall survival rates for 3, 5 and 10 years were 86.5%, 18.2% and 12.9%, respectively (Table 3). Of 62 patients with multiple primary cancers with follow-up data, 4 patients with SC had a survival time of 10-19 months (median 12 months), 58 patients with MC had a mean survival time of 9-408 (median 108 months). The 5 and 10 year survival rates were 78.9% and 30.8%, respectively. The mean survival time of 29 patients with primary and secondary cancers whose interval of onset was more than 5 years was 72-360 months (median 108 months). The median survival time was 48.5 months in 23 patients whose interval between two cancers was less than 5 years. The survival time of patients whose interval between two cancers was more than 5 years was significantly prolonged (p<0.001, Figure 1). The median survival time of 26 patients with second primary lung cancer was 84 months (average survival time 90.4 months), which was significantly longer than that of 23 patients with second primary non-lung cancer (p<0.05, Figure 2).

Treatments performed

First-episode cancer treatment: 60 of 77 patients with multiple primary cancers received surgical treatment (29 cases were treated by surgery alone, 17 cases by surgery plus chemotherapy, 2 cases by surgery plus radiotherapy, 12 cases by surgery plus chemotherapy plus radiotherapy), 6 cases by radiotherapy and chemotherapy, 4 cases by radiotherapy, 4 cases by chemotherapy, 3 cases by palliative conservative treatment. Of the secondary cancers, 20 received surgical treatment (11 cases were treated by surgery alone, 5 cases by surgery plus chemotherapy, 1 case by surgery plus radiotherapy, 3 cases by surgery plus chemotherapy plus radiotherapy), 16 cases by radiotherapy and chemotherapy, 4 cases by radiotherapy, 13 cases by chemotherapy, 24 cases by palliative conservative treatment. Of 77 patients, 60 underwent radical resection. The surgical treatment rate of multiple primary cancer was significantly lower than that of primary cancer. Multiple primary cancers are often treated by chemoradiotherapy or palliative conservative treatment for late stage, complicated with other diseases or economic reasons (Table 4).

Discussion

Multiple primary malignant tumors, also known as duplicate and multiple cancers, refer to two or more primary malignant tumors occurring simultaneously or continuously in the same patient. Nowadays, Warren and other diagnostic criteria [1] have been widely used to the diagnosis of multiple primary cancers, which are also classified into MC and SC according to the interval of onset. Multiple primary cancers are rare malignant tumors, but in recent years, with the progress of medical technology, the incidence and diagnostic rate of multiple primary cancers has also increased. More and more cases have been reported at home and abroad, however the etiology and pathogenesis of multiple primary cancers have been less reported. The incidence of multiple primary cancers tends to increase, but the proportion of malignant tumors reported in literature [2] at home and abroad varies greatly during the same period. The incidence of multiple primary cancers reported in the literature abroad is mainly 2.3%-10.6%, compared with 2.4% [3] at home, which is related to the

lack of awareness of clinical workers or misdiagnosis as metastatic cancer or recurrence. Among them, double primary cancers were more common, but the incidence of triple cancers and above decreased significantly. The proportion of multiple primary cancers found by Rosso et al [4] was about 6.3% in the same period, and triple cancers and above accounted for 2%-12%.

In this study, multiple primary cancers accounted for 1.3% of patients with malignant tumors in the same period. Seventy-seven patients with multiple primary cancers were retrospectively analyzed, including 70 cases of double primary cancers, 6 cases of three primary cancers and 1 case of four primary cancers. Among 77 cases, 41 were males and 36 females. (Male:female=1.4:1). The ratio of males to females was similar to that of literature on duplicate cancer [5]. The age distribution of patients with first-episode cancer ranges from 27 to 84 years, with a median age of 55 years. People of this age group should be vigilantly reviewed. This study shows that malignant tumors of the digestive system are the most common primary cancers, followed by head and neck, cervix and breast. The most common organs of multiple primary cancers are lung, esophagus and ovary [6]. Isochronous cancers are significantly more than synchronous cancers. Both primary and multiple cancers occur mainly in the digestive system tumors, which are the most common malignant tumors in multiple primary cancers reported by Salem et al [7], followed by head, neck and upper respiratory tract. The causes are related to similar tissue sources, chronic exposure to food and air, and cell mutation leading to tumor regionalization, which is the "regionalized cancer" theory. Close surveillance should be strengthened for the peripheral cancerization of the first cancer, especially for colorectal cancer, which is closely related to colorectal polyps. Early detection, early diagnosis and early treatment should be strived for, and carcinogenic stimulation should be removed in time to delay the progress of cancer. In addition, the most common multiple primary cancers in women are breast cancer and ovarian cancer, both of which are female reproductive organs with estrogen effect, have the same embryonic source and are related to hormone effect.

The etiology of multiple primary cancers is still unclear. At present, it is agreed that genetic susceptibility [8] and environmental factors [9] are important factors leading to multiple primary cancers, Other factors include unhealthy lifestyle, tumor immunity, precancerous lesions, age, endocrine and metabolic diseases, radiotherapy and chemotherapy. Age is an independent risk factor for cancer, especially in the elderly. The age at diagnosis of primary cancer varies greatly [10]. The reason may be related to the accumulation of stimulation of carcinogenic factors with the prolongation of survival time and the decline of immune surveillance ability. It is necessary to pay attention to the continuous development of radiotherapy and chemotherapy as a means of cancer treatment, because the number of patients with second primary cancer induced by radiotherapy and chemotherapy is also increasing, which is closely related to the use of immunosuppressive agents and glucocorticoids in the course of cancer treatment, and the interference of DNA synthesis by radiation [11].

In this study, 77 patients with complete data were used to calculate the overall survival rates of 3, 5 and 10 years, which were 86.5%, 18.2% and 12.9%, respectively. The median survival time (12 months) of 4 patients with SC was much shorter than the 108 months of 58 patients with MC, and the analysis showed that the median survival time of patients with first and second primary cancers whose interval between two cancers was more than 5 years was significantly longer than that of patients whose interval between two cancers was less than 5 years, suggesting that the prognosis of MC is much better than that of SC, and the longer the interval between two cancers, the better the prognosis. Relevant literature reports [12] agree with this view. MC occurs in the follow-up period of treatment after the first cancer. It is found early, the stage of the cancer is early, the treatment is positive, and the prognosis is generally better [13]. In addition, the lung was the most common site of the second primary cancer in this study. It is necessary to consider the influence of the large number of lung clinics and patients with respiratory diseases. The median survival time of second primary non-lung cancer patients was 156 months, which is significantly longer than that (84 months) of the second primary lung cancer patients.

As for the treatment of multiple primary cancers, surgery is the preferred treatment for patients with early stage, just like single cancer. The key to the prognosis of multiple primary cancers is to differentiate them from the recurrence and metastasis of tumors. Early diagnosis, early detection and early treatment can significantly improve the prognosis of patients [14-16]. The majority of researchers believe that the prognosis of multiple primary cancers is not worse than that of single malignant tumors, and even the survival time of multiple primary cancers is significantly longer than that of single malignant tumors [17]. There are many reports suggesting long-term survival of patients with multiple primary cancers [18,19].

In this study, a female patient with quadruple cancer was diagnosed as stage III ovarian cancer at the age of 48, then she underwent radical surgery and chemotherapy after operation. Breast cancer, rectal cancer and esophageal cancer occurred at the age of 55, 60 and 72, respectively. All tumors underwent radical surgery and chemotherapy except a patient with esophageal radiotherapy. At present, the patient is 76 years old, generally in good condition, and the lesion is stable, which may be related to patient better awareness and condition of medical monitoring, early staging of secondary tumors, small lesions, radical surgery, radiotherapy and chemotherapy. It is suggested that the prognosis of multiple primary cancers depends largely on the most malignant tumors and the staging of the tumors. In addition, primary cancers improve the immune clearance ability of the body to tumor cells and also help delay the progress of the tumors [20].

Conclusions

We believe that the understanding of multiple primary cancers should be strengthened. For primary cancers, we should strive for surgical resection, give priority to the treatment of tumors with high malignant potential and great impact on the patient survival, supplemented by chemotherapy, radiotherapy, immunotherapy, targeted therapy and other treatments. Vigilance of multiple primary cancers should be enhanced during the follow-up period after treatment, and enhance the ability to distinguish the recurrence and metastasis of tumors. We should continue to optimize and improve cancer treatment programs, control high-risk factors such as endocrine and metabolic diseases, smoking and alcohol abuse, and strengthen the ability of screening precancerous lesions [21].

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Conflict of interests

The authors declare no conflict of interests.

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