

World Journal of *Clinical Cases*

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OPINION REVIEW

- 10392** Regulating monocyte infiltration and differentiation: Providing new therapies for colorectal cancer patients with COVID-19
Bai L, Yang W, Qian L, Cui JW

REVIEW

- 10400** Role of circular RNAs in gastrointestinal tumors and drug resistance
Xi SJ, Cai WQ, Wang QQ, Peng XC

MINIREVIEWS

- 10418** Liver injury associated with acute pancreatitis: The current status of clinical evaluation and involved mechanisms
Liu W, Du JJ, Li ZH, Zhang XY, Zuo HD
- 10430** Association between celiac disease and vitiligo: A review of the literature
Zhang JZ, Abudoureyimu D, Wang M, Yu SR, Kang XJ
- 10438** Role of immune escape in different digestive tumours
Du XZ, Wen B, Liu L, Wei YT, Zhao K

ORIGINAL ARTICLE**Basic Study**

- 10451** Magnolol protects against acute gastrointestinal injury in sepsis by down-regulating regulated on activation, normal T-cell expressed and secreted
Mao SH, Feng DD, Wang X, Zhi YH, Lei S, Xing X, Jiang RL, Wu JN

Case Control Study

- 10464** Effect of Nephritis Rehabilitation Tablets combined with tacrolimus in treatment of idiopathic membranous nephropathy
Lv W, Wang MR, Zhang CZ, Sun XX, Yan ZZ, Hu XM, Wang TT

Retrospective Cohort Study

- 10472** Lamb's tripe extract and vitamin B₁₂ capsule plus celecoxib reverses intestinal metaplasia and atrophy: A retrospective cohort study
Wu SR, Liu J, Zhang LF, Wang N, Zhang LY, Wu Q, Liu JY, Shi YQ
- 10484** Clinical features and survival of patients with multiple primary malignancies
Wang XK, Zhou MH

Retrospective Study

- 10494** Thoracoscopic segmentectomy and lobectomy assisted by three-dimensional computed-tomography bronchography and angiography for the treatment of primary lung cancer
Wu YJ, Shi QT, Zhang Y, Wang YL
- 10507** Endoscopic ultrasound fine needle aspiration *vs* fine needle biopsy in solid lesions: A multi-center analysis
Moura DTH, McCarty TR, Jirapinyo P, Ribeiro IB, Farias GFA, Madruga-Neto AC, Ryou M, Thompson CC
- 10518** Resection of bilateral occipital lobe lesions during a single operation as a treatment for bilateral occipital lobe epilepsy
Lyu YE, Xu XF, Dai S, Feng M, Shen SP, Zhang GZ, Ju HY, Wang Y, Dong XB, Xu B
- 10530** Improving rehabilitation and quality of life after percutaneous transhepatic cholangiography drainage with a rapid rehabilitation model
Xia LL, Su T, Li Y, Mao JF, Zhang QH, Liu YY
- 10540** Combined lumbar muscle block and perioperative comprehensive patient-controlled intravenous analgesia with butorphanol in gynecological endoscopic surgery
Zhu RY, Xiang SQ, Chen DR
- 10549** Teicoplanin combined with conventional vancomycin therapy for the treatment of pulmonary methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* infections
Wu W, Liu M, Geng JJ, Wang M
- 10557** Application of narrative nursing in the families of children with biliary atresia: A retrospective study
Zhang LH, Meng HY, Wang R, Zhang YC, Sun J

Observational Study

- 10566** Comparative study for predictability of type 1 gastric variceal rebleeding after endoscopic variceal ligation: High-frequency intraluminal ultrasound study
Kim JH, Choe WH, Lee SY, Kwon SY, Sung IK, Park HS
- 10576** Effects of WeChat platform-based health management on health and self-management effectiveness of patients with severe chronic heart failure
Wang ZR, Zhou JW, Liu XP, Cai GJ, Zhang QH, Mao JF
- 10585** Early cardiopulmonary resuscitation on serum levels of myeloperoxidase, soluble ST2, and hypersensitive C-reactive protein in acute myocardial infarction patients
Hou M, Ren YP, Wang R, Lu LX

Prospective Study

- 10595** Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia
Tang F, Yi JM, Gong HY, Lu ZY, Chen J, Fang B, Chen C, Liu ZY

Randomized Clinical Trial

- 10604** Effects of lower body positive pressure treadmill on functional improvement in knee osteoarthritis: A randomized clinical trial study
Chen HX, Zhan YX, Ou HN, You YY, Li WY, Jiang SS, Zheng MF, Zhang LZ, Chen K, Chen QX

SYSTEMATIC REVIEWS

- 10616** Effects of hypoxia on bone metabolism and anemia in patients with chronic kidney disease
Kan C, Lu X, Zhang R

META-ANALYSIS

- 10626** Intracuff alkalinized lidocaine to prevent postoperative airway complications: A meta-analysis
Chen ZX, Shi Z, Wang B, Zhang Y

CASE REPORT

- 10638** Rarely fast progressive memory loss diagnosed as Creutzfeldt-Jakob disease: A case report
Xu YW, Wang JQ, Zhang W, Xu SC, Li YX
- 10645** Diagnosis, fetal risk and treatment of pemphigoid gestationis in pregnancy: A case report
Jiao HN, Ruan YP, Liu Y, Pan M, Zhong HP
- 10652** Histology transformation-mediated pathological atypism in small-cell lung cancer within the presence of chemotherapy: A case report
Ju Q, Wu YT, Zhang Y, Yang WH, Zhao CL, Zhang J
- 10659** Reversible congestive heart failure associated with hypocalcemia: A case report
Wang C, Dou LW, Wang TB, Guo Y
- 10666** Excimer laser coronary atherectomy for a severe calcified coronary ostium lesion: A case report
Hou FJ, Ma XT, Zhou YJ, Guan J
- 10671** Comprehensive management of malocclusion in maxillary fibrous dysplasia: A case report
Kaur H, Mohanty S, Kochhar GK, Iqbal S, Verma A, Bhasin R, Kochhar AS
- 10681** Intravascular papillary endothelial hyperplasia as a rare cause of cervicothoracic spinal cord compression: A case report
Gu HL, Zheng XQ, Zhan SQ, Chang YB
- 10689** Proximal true lumen collapse in a chronic type B aortic dissection patient: A case report
Zhang L, Guan WK, Wu HP, Li X, Lv KP, Zeng CL, Song HH, Ye QL
- 10696** Tigecycline sclerotherapy for recurrent pseudotumor in aseptic lymphocyte-dominant vasculitis-associated lesion after metal-on-metal total hip arthroplasty: A case report
Lin IH, Tsai CH

- 10702** Acute myocardial infarction induced by eosinophilic granulomatosis with polyangiitis: A case report
Jiang XD, Guo S, Zhang WM
- 10708** Aggressive natural killer cell leukemia with skin manifestation associated with hemophagocytic lymphohistiocytosis: A case report
Peng XH, Zhang LS, Li LJ, Guo XJ, Liu Y
- 10715** Chronic lymphocytic leukemia/small lymphocytic lymphoma complicated with skin Langerhans cell sarcoma: A case report
Li SY, Wang Y, Wang LH
- 10723** Severe mediastinitis and pericarditis after endobronchial ultrasound-guided transbronchial needle aspiration: A case report
Koh JS, Kim YJ, Kang DH, Lee JE, Lee SI
- 10728** Obturator hernia - a rare etiology of lateral thigh pain: A case report
Kim JY, Chang MC
- 10733** Tracheal tube misplacement in the thoracic cavity: A case report
Li KX, Luo YT, Zhou L, Huang JP, Liang P
- 10738** Peri-implant keratinized gingiva augmentation using xenogeneic collagen matrix and platelet-rich fibrin: A case report
Han CY, Wang DZ, Bai JF, Zhao LL, Song WZ

ABOUT COVER

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Retrospective Cohort Study

Clinical features and survival of patients with multiple primary malignancies

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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 patients with two malignancies, 51 (23.0%) had synchronous MPM, and 171 (77.7%) had metachronous 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%). 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 had a 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.

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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 ensure early detection and treatment of the subsequent cancer.

Key Words: Multiple primary malignancies; Overall survival; Prognostic factor; Distant metastasis; Age

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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. In clinical procedure and follow-up of initial cancer, the occurrence of second or more cancer should be paid great attention to.

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INTRODUCTION

Multiple primary malignancies (MPM) are characterized by two or more different primary malignancies in the same patient, excluding relapse or metastases of prior cancer[1]. An increased incidence of MPM has been observed with the rapid development of medical techniques and 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 cancer have 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 patients with synchronous MPM[7,9], while this survival 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 3 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.

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%) had synchronous MPM, and 171 patients (77.7%) had metachronous 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%).

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](#)).

Prognostic factors of OS in patients with two malignancies

The univariate and multivariate analyses of prognostic factors for OS in patients 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

Table 1 The characteristics of patients with two malignancies, *n* (%)

Characteristics	Synchronous MPM	Metachronous MPM	Total
Patients	51 (23.0)	171 (77.0)	222 (100)
Gender			
Male	32 (62.7)	87 (50.9)	119 (53.6)
Female	19 (37.3)	84 (49.1)	103 (46.4)
Age in yr, median (range)			
First cancer	62 (32-84)	55 (19-87)	56 (19-87)
Second cancer	62 (32-84)	64 (28-90)	64 (28-90)
The most common sites in first primary cancers			
1 st	Esophagus, 9 (17.6)	Breast, 31 (18.1)	Breast, 33 (14.9)
2 nd	Colorectum, 8 (15.7)	Colorectum, 23 (13.7)	Colorectum, 31 (14.0)
3 rd	Bladder/thyroid/hypopharynx, 4 (7.8), respectively	Stomach, 14 (8.2)	Stomach, 17 (7.7)
The most common sites in second primary cancers			
1 st	NSCLC, 12 (23.5)	NSCLC, 54 (31.6)	NSCLC, 66 (29.7)
2 nd	Stomach, 9 (17.6)	Stomach, 15 (8.8)	Stomach, 24 (10.8)
3 rd	Esophagus/kidney, 6 (11.8), respectively	Liver, 13 (7.6)	Esophagus/liver, 16 (7.2), respectively
Median interval (range) between the first and second cancers (mo)	0.2 (0-5.9)	73.2 (6.3-536.8)	43.6 (0-536.8)
Metastasis	16 (31.4)	83 (48.5)	99 (44.6)
Median overall survival in mo	36.4	35.3	35.4

MPM: Multiple primary malignancies; NSCLC: Non-small cell lung cancer.

Table 2 The most common multiple primary malignancies in patients with two malignancies

Malignancies	Total	Synchronous MPM	Metachronous MPM	Median OS in mo
NSCLC and breast cancer	12	2	10	79.8
NSCLC and gastric cancer	10	0	10	16.7
Colorectal cancer and gastric cancer	10	3	7	Not reached
Esophageal cancer and gastric cancer	9	6	3	36.2
NSCLC and bladder cancer	7	2	5	31.2
NSCLC and cervical cancer	6	1	5	35.5
NSCLC and thyroid cancer	6	2	4	Not reached
NSCLC and colorectal cancer	6	1	5	Not reached
NSCLC and esophageal cancer	6	3	3	Not reached

MPM: Multiple primary malignancies; NSCLC: Non-small cell lung cancer; OS: Overall survival.

significantly different. However, patients aged > 65 years at the second cancer diagnosis had a 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

Table 3 Univariate analysis and multivariate analysis of the prognostic factors of overall survival in patients with two malignancies

Factors	Cases	Univariate analysis		Multivariate analysis		
		Median OS in mo	P	HR	95%CI	P
Gender			0.114			
Male	119	31.2				
Female	103	37.1				
Age at second cancer (yr)			0.038	1.016	1.000-1.032	0.046
≤ 65	128	36.4				
> 65	94	28.4				
Metastasis			0.000	4.291	2.743-6.710	0.000
No	123	86.9				
Yes	99	20.4				
MPM			0.809			
Synchronous	51	36.4				
Metachronous	171	35.3				

MPM: Multiple primary malignancies; OS: Overall survival.

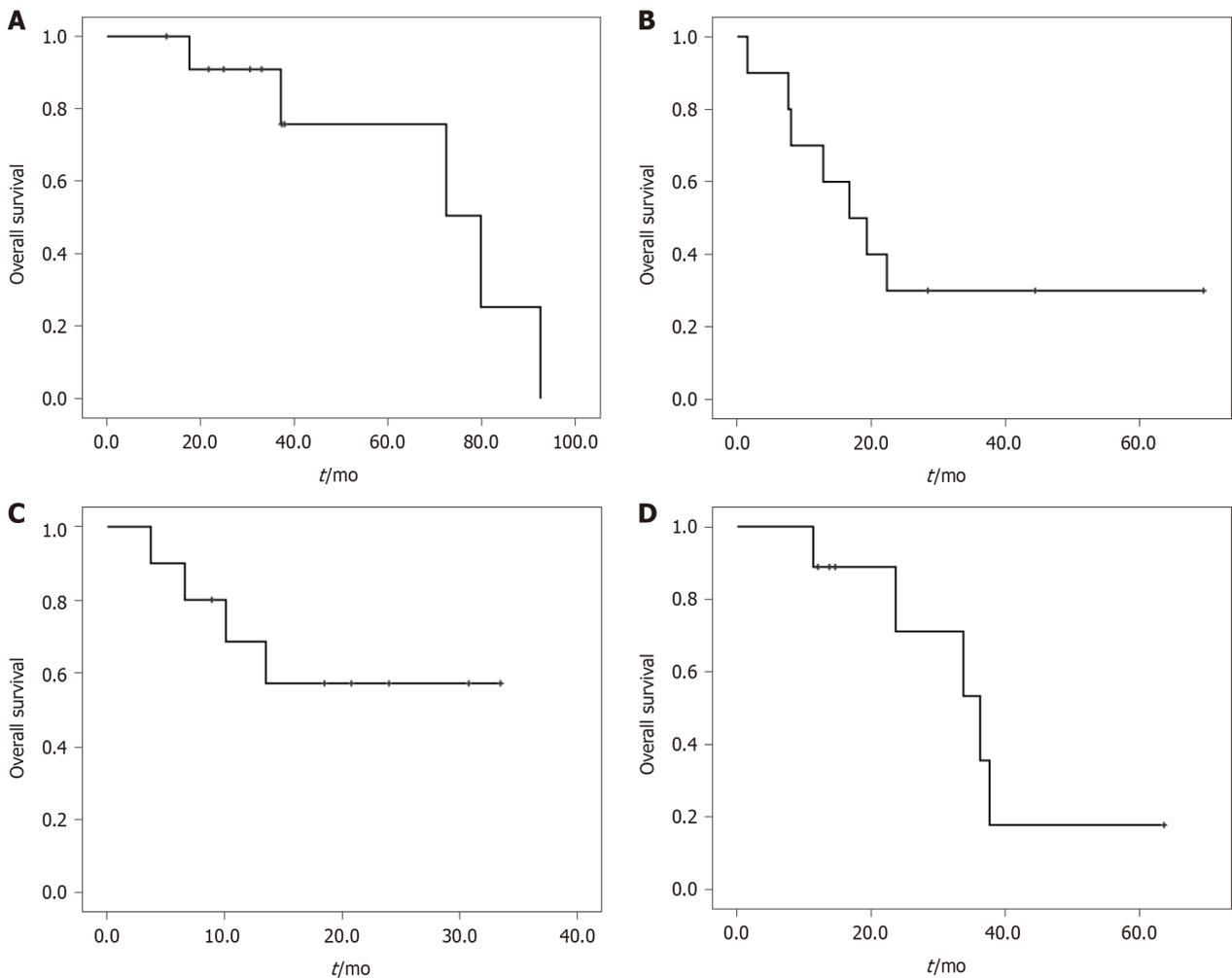


Figure 1 Overall survival of patients with different cancers. A: Twelve patients with non-small cell lung cancer and breast cancer; B: Ten patients with non-small cell lung cancer and gastric cancer; C: Ten patients with colorectal cancer and gastric cancer; D: Nine patients with esophageal cancer and gastric cancer.

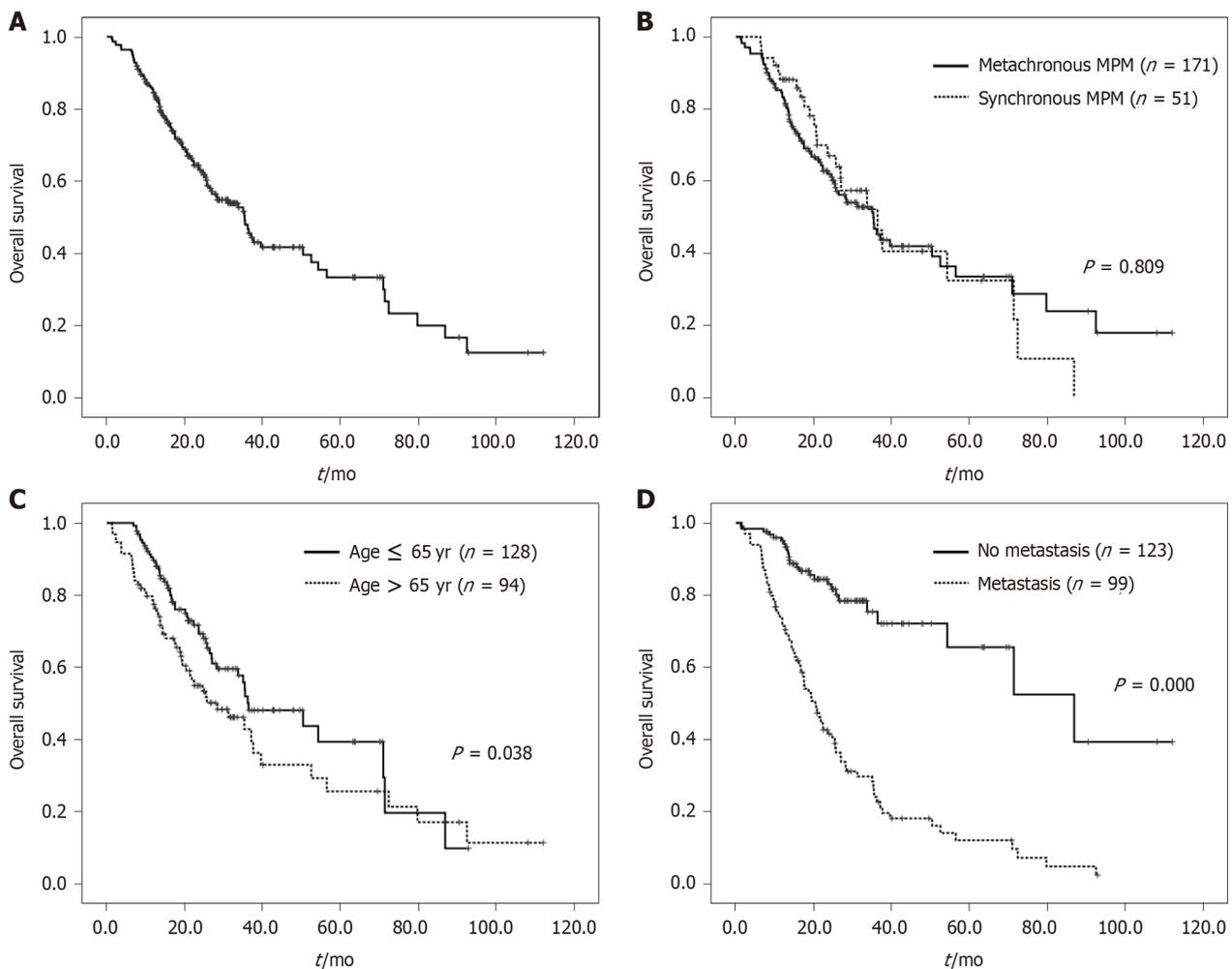


Figure 2 Overall survival of patients with two malignancies. A: Two hundred and twenty-two patients with two primary malignancies; B: Metachronous multiple primary malignancies (MPM) patients vs synchronous MPM patients; C: Patients ≤ 65 years vs patients > 65 years; D: Patients with metastasis vs patients without metastasis. MPM: Multiple primary malignancies.

factors for OS.

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

Table 4 The clinical features of 21 patients with three malignancies

Case	Sex	First cancer	Second cancer	Third cancer	Metastases	Outcome	OS since third cancer in mo
1	M	Parotid cancer	Colon cancer	Penile cancer	Yes	Dead	0.6
2	F	Small cell lung cancer	Colon cancer	Soft tissue sarcoma	No	Dead	14.4
3	M	Gastric cancer	Liver cancer	Rectal cancer	Yes	Dead	14.0
4	M	Rectal cancer	Renal cancer	Colon cancer	No	Alive	23.1
5	M	Colon cancer	Bladder cancer	Renal pelvis cancer	No	Alive	67.5
6	F	Soft tissue sarcoma	Colon cancer	Bladder cancer	Yes	Dead	4.8
7	F	Colon cancer	Endometrial cancer	Breast cancer	Yes	Alive	23.8
8	F	Breast cancer	Parotid cancer	Neuroendocrine carcinoma	Yes	Dead	9.5
9	M	Bladder cancer	Thyroid cancer	Ureteral cancer	No	Alive	18.9
10	M	Rectal cancer	Colon cancer	Cholangiocarcinoma	Yes	Dead	6.0
11	M	Laryngeal cancer	Esophageal cancer	Non-small cell lung cancer	No	Alive	21.5
12	M	Thyroid cancer	Laryngeal cancer	Rectal cancer	Yes	Dead	10.2
13	M	Bladder tumor	Colon cancer	Non-small cell lung cancer	No	Dead	12.7
14	M	Laryngeal cancer	Renal pelvis cancer	Bladder cancer	No	Dead	12.9
15	F	Rectal cancer	Thyroid cancer	Breast cancer	Yes	Dead	95.4
16	F	Skin squamous cell carcinoma	Skin basal cell carcinoma	Endometrial cancer	Yes	Alive	57.7
17	F	Gallbladder cancer	Endometrial cancer	Rectal cancer	No	Alive	15.4
18	F	Endometrial cancer	Rectal cancer	Pancreatic cancer	Yes	Dead	6.0
19	F	Breast cancer	Thymic cancer	Choriocarcinoma	No	Alive	18.8
20	F	Breast cancer	Thyroid cancer	Liver cancer	Yes	Alive	9.0
21	M	Prostate cancer	Gastric cancer	Colon cancer	Yes	Dead	7.9

F: Female; M: Male; OS: Overall survival.

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 in our 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, and in 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 and 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

Table 5 The characteristics of patients with three malignancies, *n* (%)

Characteristics	<i>n</i> (%)
Total	21
Gender	
Male	11 (52.4)
Female	10 (47.6)
Age in yr, median (range)	
First cancer	47 (18-74)
Second cancer	54 (33-87)
Third cancer	57 (34-89)
The most common cancers	
Colon cancer	9 (14.3)
Rectal cancer	7 (11.1)
Breast cancer	5 (7.9)
Bladder/endometrial/thyroid cancer	4 (6.3), respectively
Laryngeal cancer	3 (4.8)
Metastasis	12 (57.1)
Median OS since third cancer in mo	14.4

OS: Overall survival.

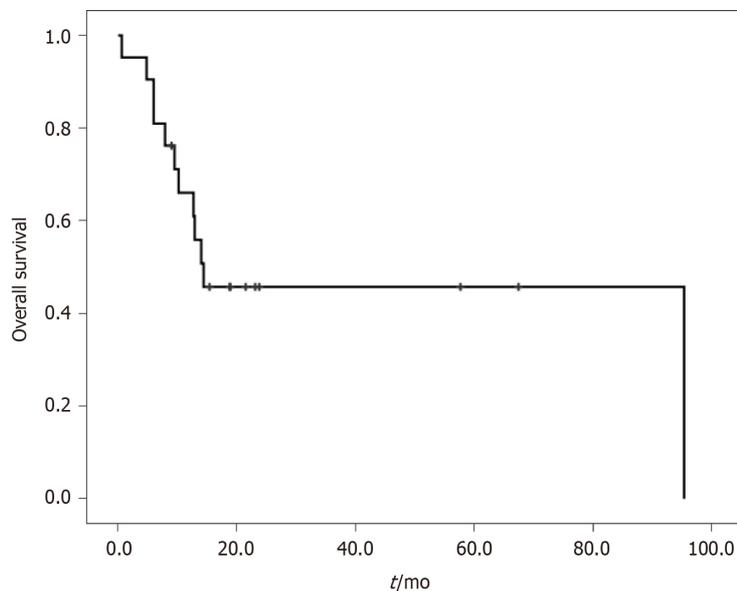


Figure 3 Overall survival of 21 patients with three malignancies.

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 showed no differences in survival. However, Wang *et al*[11] 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. 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 6 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 patient 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.

ARTICLE HIGHLIGHTS

Research background

Multiple primary malignancies (MPM) are characterized by two or more primary malignancies in the same patient, excluding relapse or metastasis of prior cancer.

Research motivation

The clinical features and survival of MPM patients are not clear.

Research objectives

We aimed to elucidate the clinical features and survival of MPM patients.

Research 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.

Research results

A total of 243 patients with MPM, including 222 patients with two malignancies and 21 patients with three malignancies. Following multivariate analyses, age > 65 years

and distant metastasis were independent adverse prognostic factors for OS.

Research conclusions

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.

Research perspectives

For common MPM pairs, such as NSCLC and breast/gastric cancer, colorectal and gastric cancer, the risk of concomitant MPM should be closely monitored, to ensure early detection and treatment of the subsequent cancer.

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