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Original Research

Clinical characteristics and prognostic outcomes of gynaecological multiple primary malignant neoplasms

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Objective: To investigate the clinical characteristics and the prognostic outcomes of patients with gynaecological multiple primary malignant neoplasms (MPMN). *Materials and methods*: For a period of ten years, from January 2008 to December 2018, patients with gynaecological MPMN were enrolled for this study. The clinical characteristics and survival outcomes were collected and analyzed. *Results*: A total of 126 patients with gynaecological MPMN were included, comprising 15 synchronous MPMN and 111 metachronous MPMN. The average age of the patients with gynaecological MPMN was 57.6 $\pm$ 10.8 years, and the probability of overall survival (OS) at 1, 2, 3, and 5 years was 88.6%, 82.6%, 76.9% and 68.7%, respectively. The OS of patients with gynaecological cancer as the first neoplasm was worse than those with non-gynaecological cancer as the first neoplasm (HR: 2.2, P = 0.049); the OS of patients accompanied by breast cancer was better than those accompanied by other cancers (HR: 0.346, P = 0.033). Univariate regression analysis showed that "age", "FIGO stage" and "gynaecological cancer as the first neoplasm" were the factors for poor survival; "Accompanied by breast cancer" and "surgery for first or second neoplasm" were the factors for favourable survival. *Conclusions*: "Gynaecological cancer as the first neoplasm" is a factor for poor survival in patients with gynaecological MPMN, and "FIGO stage" is the independent risk factor (HR: 2.339, P = 0.001). "Accompanied by breast cancer" and "surgery for the neoplasm" are factors for favourable survival. Mostly, "surgery for the second neoplasm" was the independent protective factor (HR: 0.212, P = 0.005) for gynaecological MPMN.

Keywords

Gynaecological cancer; Multiple primary malignant neoplasms (MPMN); Breast cancer

1. Introduction

With the development in diagnostic and therapeutic approaches for malignant neoplasms, the life expectancy and long-term survival of patients with malignant neoplasms have increased, thus contributing to recent increases in the frequency of multiple primary malignant neoplasms (MPMNs) [1, 2]. The term MPMNs refers to two or more unrelated primary malignant neoplasms that originate from single or different organs and occur in one patient; the incidence of these conditions is 0.7%–11.7% [1–3]. MPMNs have been divided into synchronous (10%) and metachronous (90%) based on whether all the neoplasms develop within six months (synchronous) or at least six months after the first primary tumor (metachronous). Double MPMNs are relatively common, but triple and quadruple MPMNs are rare [1–4].

Gynaecological malignant neoplasms threaten the health and quality of life of female patients worldwide [5–8]. Despite this fact, few studies have assessed the clinical characteristics and prognoses of gynaecological cancer-associated MPMNs (gynaecological MPMNs). Only isolated case reports and clinical investigations conducted using small sample sizes have been published [9]. The present study aimed to investigate the clinical characteristics and prognostic outcomes of a cohort of patients with gynaecological MPMNs.

2. Materials and methods

2.1 Patient enrollment

We evaluated records of gynaecological malignant neoplasm patients hospitalized in the First Affiliated Hospital of Nanjing Medical University between January 2008 and December 2018. Final analyses only included those patients who met the diagnostic criteria for MPMN.

2.2 Study design

This retrospective study conformed to the provisions of the Declaration of Helsinki; additionally, the ethical committee of the First Affiliated Hospital of Nanjing Medical University approved this work. Considering the retrospective and non-interventional nature of this study, we obtained verbal informed consent for data analysis and publication directly from patients or their immediate family members in cases where the patient was deceased. This strategy was approved by the ethics committee (2018-SRFA-052). To analyze the characteristics of gynaecological MPMNs, we collected relevant clinical data, including the age of onset, organ/tissue involvement, FIGO stage of gynaecological malignant neoplasms, as well as the time interval (see next) and treatment of multiple neoplasms. If the time elapsing before multiple neoplasm development was shorter than six months, the condition was defined as synchronous MPMN (sMPMN). Alternatively, it was defined as metachronous MPMN (mMPMN). Survival follow-ups were conducted *via* telephone or "face-to-face" interviews, and each participating patient's survival

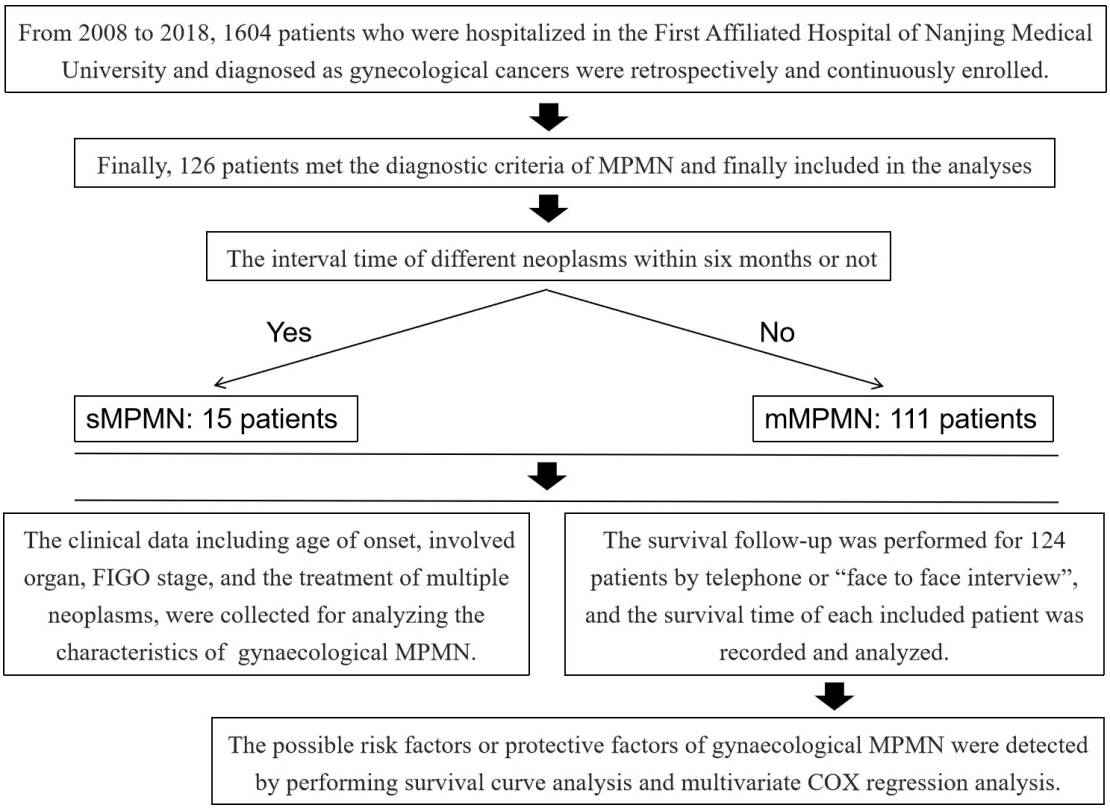

Fig. 1. The workflow diagram for the study. MPMN, multiple primary malignant neoplasms; sMPMN, synchronous multiple primary malignant neoplasms; mMPMN, metachronous multiple primary malignant neoplasms.

time was recorded. We utilized our previously reported follow-up interview guide [9]. The workflow diagram for the study is depicted in Fig. 1.

2.3 Statistical analyses

We identified potential risk factors and protective factors for gynaecological MPMNs by performing survival and multivariate COX regression analyses. We used SPSS Statistics 23.0 (IBM, New York, NY, USA) for statistical analyses and Graph Pad Prism 5 Demo for graph generation. Data were expressed as mean difference (MD) ± standard error (SE). Kaplan-Meier survival analyses and multivariate COX regression analyses with a hazard ratio (HR) and 95% confidence interval (CI) were performed to identify risk factors and protective factors; a two-sided $P < 0.05$ was considered statistically significant.

3. Results

We enrolled a total of 126 patients diagnosed with gynaecological MPMNs; 15 patients (12%) had sMPMNs, and 111 patients (88%) had mMPMNs. The incidence of sMPMNs and mMPMNs relative to non-MPMNs was 0.094% and 6.9%, respectively (Fig. 1). The average ages of all study patients, patients with sMPMNs, and patients with mMPMNs were 57.6 ± 10.8, 50.3 ± 7.7, and 59.0 ± 11 years. Table 1 shows the age distribution of gynaecological MPMN patients.

Double MPMNs were diagnosed in all sMPMN patients included in this study. In the mMPMN group, 103 patients had double MPMNs, seven patients had triple MPMNs, and only one patient was diagnosed with quadruple MPMN. For patients with mMPMNs, the average and median time intervals for multiple neoplasms were 84.3 months and 60 months, respectively.

Table 1. The distribution of age in patients with gynaecological MPMN.

Age	sMPMN	mMPMN	Sum
30–39	0	3	3
40–49	7	22	29
50–59	7	39	46
60–69	0	27	27
≥70	1	20	21
Sum	15	111	126

MPMN, multiple primary malignant neoplasms; sMPMN, synchronous multiple primary malignant neoplasms; mMPMN, metachronous multiple primary malignant neoplasms.

Our group of 126 gynaecological MPMN patients included 59 (46.8%) cases who had endometrial cancer-associated MPMNs, 29 (23%) who had ovarian cancer-associated MPMNs, 46 (36.5%) who had cervical cancer-associated MPMNs, and 62 (49.2%) patients whose first neoplasm was gynaecological cancer.

In terms of the neoplasms that accompanied gynaecological MPMNs, 45 (35.7%) cases were breast cancers, 37 (29.4%) were gastrointestinal cancers, 14 (11.1%) were lung cancers,

and less than 10% were other neoplasms. Tables 2 and 3 list the onset sites of sMPMNs and mMPMNs, respectively.

Lastly, 124 of 126 patients completed the survival follow-up evaluations, and 27 patients reached the endpoint (death). Among the deaths, five occurred in the sMPMN group, and 22 occurred in the mMPMN group. The follow-up time ranged from 1 month to 136 months, and the median survival time was 28 months. The overall survival (OS) of all gynaecological MPMN patients was 88.6%, 82.6%, 76.9%, and 68.7% at 1, 2, 3, and 5 years, respectively. The OS of patients with sMPMNs at 1, 2, and 3 years was 74.5%, 60.6%, and 55.6%, while that of patients with mMPMNs at 1, 2, 3, and 5 years was 90.0%, 84.5%, 79.6%, and 70.3%. While the OS of mMPMNs patients appeared higher than that of sMPMNs patients, the difference was not statistically significant (Fig. 2; HR: 0.509, 95% CI: 0.192–1.348, $P = 0.17$).

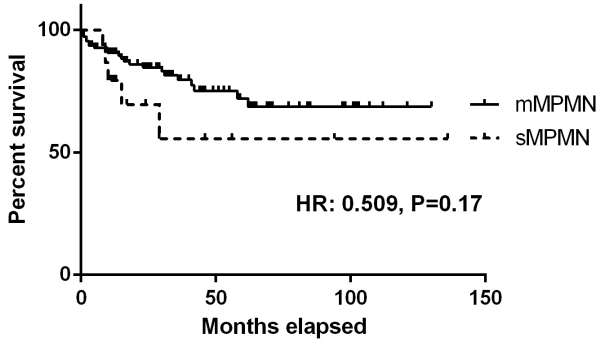

Fig. 2. The overall survival of sMPMN and mMPMN. sMPMN, synchronous multiple primary malignant neoplasms; mMPMN, metachronous multiple primary malignant neoplasms.

The OS of patients with gynaecological cancer as the first neoplasm was worse than that of patients with other non-gynaecological cancers as the first neoplasm (Fig. 3; HR: 2.2, 95% CI: 1.002–4.829, $P = 0.049$). There was no statistically significant difference of OS in the endometrial, ovarian, and cervical cancer subgroups (Fig. 4; $P = 0.39$). However, the endometrial cancer subgroup appeared to fare better than the other two subgroups based on the survival curve. The OS of patients whose gynaecological MPMN was accompanied by breast cancer was longer than that of patients with other accompanying cancers (Fig. 5; HR: 0.346, 95% CI: 0.131–0.915, $P = 0.033$). This OS difference was not observed when other common neoplasms, such as gastrointestinal and lung cancers, accompanied gynaecological MPMNs ($P > 0.05$).

Using univariate regression analyses we found that factors contributing to poor survival of patients with gynaecological MPMNs included "age" (HR: 1.409, 95% CI: 1.012–1.087, $P = 0.01$), "FIGO stage" (HR: 1.812, 95% CI: 1.241–2.647, $P = 0.002$), "gynaecological cancer as first neoplasm" (HR: 2.2, 95% CI: 1.002–4.829, $P = 0.049$) and "accompanied by other uncommon neoplasms (not breast/gastrointestinal/lung cancers)" (HR: 3.374, 95% CI: 1.569–7.254, $P = 0.002$). Favorable prognostic factors included "accompanied by breast cancer"

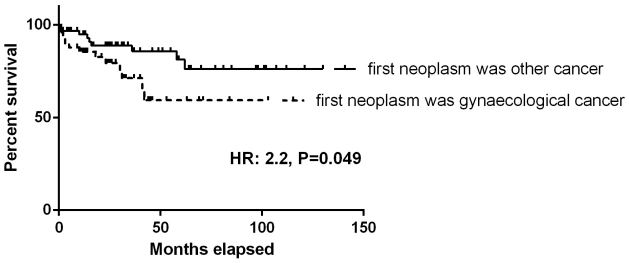

Fig. 3. The overall survival of patients "with" versus "without" gynaecological cancer as the first neoplasm.

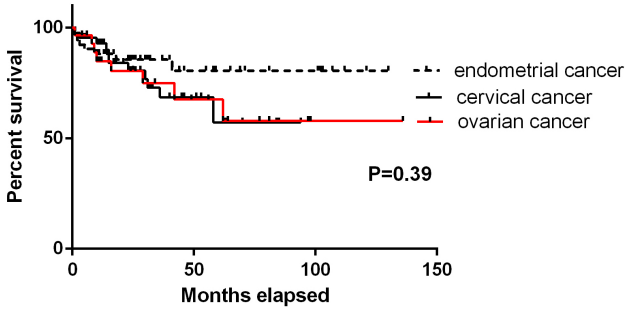

Fig. 4. The overall survival of endometrial cancer, ovarian cancer and cervical cancer.

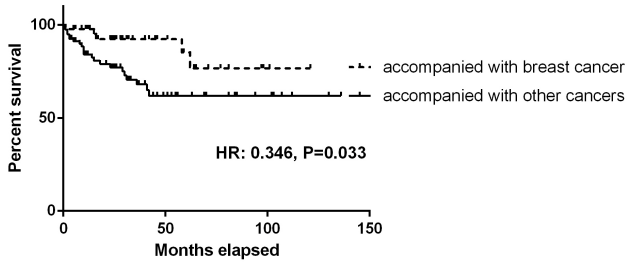

Fig. 5. The overall survival of patients accompanied by breast cancer and those accompanied by other cancers.

(HR: 0.346, 95% CI: 0.131–0.915, $P = 0.033$), "surgery for the first neoplasm" (HR: 0.219, 95% CI: 0.074–0.648, $P = 0.006$) and "surgery for the second neoplasm" (HR: 0.108, 95% CI: 0.047–0.247, $P = 0.000$). Multivariate COX regression analyses showed that "FIGO stage" was an independent risk factor (HR: 2.339, 95% CI: 1.449–3.776, $P = 0.001$) and that "surgery for the second neoplasm" was an independent protective factor for gynaecological MPMNs (HR: 0.212, 95% CI: 0.073–0.622, $P = 0.005$).

4. Discussion

This study evaluated 126 gynaecological MPMN cases assessed at the First Affiliated Hospital of Nanjing Medical University. Previous studies evaluated radiotherapy, chemotherapy, and hormonal therapy for the first neoplasm, individual immune status, and environmental-genetic factors as potential risk factors for MPMN development [3, 10, 11]. In this study, there were 64 (50.8%) and 34 (27%) patients who re-

ceived chemotherapy and radiotherapy to treat the first neoplasm, respectively.

Homologous tissues sharing a common embryonic origin, such as ovarian, uterine, and cervical tissues, are vulnerable to carcinogenic factors [12]. Dragoumis *et al.* [12] reported a 2.9% probability of simultaneous ovarian and malignant uterine neoplasm development. In our study, eight of 15 sMPMN cases occurred in the female reproductive system. It is important to emphasize that mammary glands, ovaries, and endometria are sex hormone-sensitive organs; additionally, colonic tissues express estrogen receptors. Estrogen stimulation is associated with the occurrence of endometrial and breast cancer and may also correlate with the incidence of colorectal cancer [13–17]. In this study, 45 (35.7%) gynaecological MPMN cases were accompanied by breast cancer, and 28 (22.2%) MPMN cases were accompanied by colorectal cancer.

On the other hand, some primary cancers originating from other sites tend to be accompanied by gynaecological cancer. For example, Lynch syndrome (also known as hereditary non-polyposis colorectal cancer) is characterized by mutations in mismatch repair genes and is an example of genetic predisposition to MPMN development and increased risk of endometrial and ovarian cancer [13, 14]. The endometrium is the second target of Lynch syndrome; 40%–60% of patients with Lynch syndrome develop endometrial cancer [13, 14]. Hereditary breast and ovarian cancer (HBOC) is another syndrome related to MPMN; *BRCA1/2* mutations increase the risk of both breast and ovarian cancer [6, 15]. In our study, 12 patients had ovarian cancer after breast cancer, and one patient had ovarian cancer and breast cancer simultaneously. Among these 12 patients, two were tested and found to harbor *BRCA1/2* mutations. These observations suggest that, following a first neoplasm, it is essential to monitor the potential development of gynaecological MPMN, particularly in patients harboring *BRCA1/2* mutations. Genomic mutations in other genes that participate in homologous recombination (HR) pathways have also been investigated. These include Fanconi anemia genes (*BRIP1*, *PALB2*), the core *RAD* genes (*RAD51C*, *RAD51D*), and other genes that are directly (*CHEK2*, *BARD1*, *NBN*, *ATM*) or indirectly (*CDK12*) involved in HR pathways. Mutations in moderate- and high-penetrance HR pathway susceptibility genes are associated with a lifetime risk of epithelial ovarian cancer that ranges between 5% and 60%, approximately [16]. Patients who have ovarian cancer accompanied by breast cancer are likely to benefit from PARP inhibitors due to their mutations in *BRCA1/2*, leading to better prognoses, as shown in this study. PARP inhibitors selectively kill malignant cells deficient in homologous recombination, and they do so in the absence of an exogenous DNA damaging agent. Six available PARP inhibitors include olaparib, rucaparib, niraparib, talazoparib, pamiparib, and veliparib. The FDA has approved olaparib, rucaparib, and niraparib for clinical use. The efficacy of talazoparib in ovarian cancer treatment is still under investigation, whereas veliparib has not yet been approved and has been investigated mostly in combination with chemotherapeutic and targeted agents [17].

It has been reported that MPMNs develop with high incidence in patients aged 50–59 years [1–3]. Aydiner *et al.* [18] found that 72.6% of MPMN patients had an onset age of over 50 years. The mean age of the patients in the present study was 57.6 years old, consistent with previous reports. However, the preferred site of MPMN development differed among studies. Gursel *et al.* [1] reported that, overall, the top three sites of MPMNs were larynx, bladder, and breast; in women, breast, uterine adnexa, and intestine were the main MPMN sites. We found that out of 126 gynaecological MPMN cases, 59 (46.8%), 29 (23%), 46 (36.5%), and 45 (35.7%) were accompanied by endometrial, ovarian, cervical, and breast cancers, respectively. Gynaecological MPMNs accompanied by breast cancer had a better prognosis than other combinations. While we found no statistically significant differences in prognosis among the endometrial, ovarian, and cervical cancer subgroups, the endometrial cancer subgroup appeared to fare better based on survival analyses. We considered the possibility that CA-125 levels and ascites could be associated with prognostic value, especially for ovarian cancer patients. Unfortunately, we were unable to obtain initial CA-125 levels for this patient group due to our study's retrospective nature. FIGO staging, which included ascites and other relevant clinical parameters, was utilized for stratification purposes in the survival analyses of gynaecological cancer patients.

Tichansky *et al.* [19] reported that second neoplasms typically developed within 1–3 years following treatment for the first neoplasm (average 5–7 years); moreover, shorter time intervals were associated with worse prognoses [19]. Our results agree with several studies suggesting that sMPMNs have worse prognoses than mMPMNs [1, 2, 9, 19]. However, the differences we observed did not reach statistical significance, possibly due to the small sample size of our sMPMN cohort.

MPMNs are currently viewed as diseases of multiple independent malignant neoplasms instead of late-stage malignant conditions. This observation is important because the latter diseases are associated with better prognoses than metastatic disease resulting from malignant neoplasms [9]. Durmus *et al.* [2] reported that the 2-, 3-, and 5-year OS of patients with sMPMNs was 86%, 75%, 63%, respectively, and the OS of mMPMN patients was 92%, 88%, 80%. This trend is similar to our results in gynaecological MPMN cases (sMPMNs: 74.5%, 60.6%, 55.6%, and mMPMNs: 90.0%, 84.5%, 79.6%, 70.3%). Our study also showed that both "surgery for the first neoplasm" and "surgery for the second neoplasm" were protective factors and that "surgery for the second neoplasm" was an independent protective factor for gynaecological cancer MPMNs. These observations suggest that active clinical interventions, including surgery combined with cancer stage and pathological grade considerations, can be utilized to treat MPMNs as individual malignant neoplasms.

Table 2. The onset sites of sMPMN.

	Ovary	Uterus	Cervix	Oviduct	Breast	Colorectum	Kidney	Sum
First neoplasm	4	5	3	0	3	0	0	15
Second neoplasm	3	4	3	1	1	2	1	15

sMPMN, synchronous multiple primary malignant neoplasms.

Table 3. The onset sites of mMPMN.

	Ovary	Uterus	Cervix	Oviduct	Breast	Colorectum	Urinary	Stomach	Lung	Esophagus	Liver	Cholecyst	Pancreas	Omentum	Hemic	Thyroid	Bone and soft tissue	Nasopharynx	Sum
First neoplasm	2	21	27	0	34	13	1	4	1	0	1	0	2	0	1	3	0	1	111
Second neoplasm	17	27	13	1	7	11	3	3	10	2	2	4	1	1	5	2	2	0	111
Third neoplasm	0	2	0	1	0	1	0	0	3	0	0	0	0	0	0	0	0	0	7
Fourth neoplasm	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1

mMPMN, metachronous multiple primary malignant neoplasms.

Finally, our study discovered for the first time that patients whose first MPMN neoplasm is gynaecological cancer tend to have poor prognoses. This observation underscores the importance of monitoring potential MPMN development following a gynaecological cancer diagnosis.

5. Conclusions

Gynaecological MPMNs, including sMPMNs (12%) and mMPMNs (88%), were characterized by overall survivals of 88.6%, 82.6%, 76.9% and 68.7% at 1, 2, 3, and 5 years, respectively. mMPMN patients may have better prognoses compared with those diagnosed with sMPMN. "Age" and "gynaecological cancer as the first neoplasm" were predictive of poor survival, and "FIGO stage" was identified as an independent risk factor. "Accompanied by breast cancer", "surgery for the first neoplasm" and "surgery for the second neoplasm" predicted favourable outcomes. "t1Surgery for the second neoplasm" was the only independent factor for improved survival of gynaecological MPMN patients.

Author contributions

YS, HD, and WC conceived and designed the study; YS and XY performed follow-ups; YS, YJ, and JL analyzed the data; YS, YJ, JR, XC, and WC wrote and revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective study conformed to the provisions of the Declaration of Helsinki; additionally, the ethical committee of the First Affiliated Hospital of Nanjing Medical University approved this work. Considering the retrospective and non-interventional nature of this study, we obtained verbal informed consent for data analysis and publication directly from patients or their immediate family members in cases where the patient was deceased. This strategy was approved by the ethics committee (2018-SRFA-052).

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Conflict of interest

The authors declare no conflict of interest.

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