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*Original Article*

# Multiple primary malignant neoplasms with endometrial carcinoma: a clinicopathological study of cases

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**Abstract:** Objective: To improve the prognosis and patient survival rate through clinicopathological features analysis of multiple primary neoplasms (MPMNs) with endometrial carcinoma. Method: In this study, 31 patients suffering from multiple primary neoplasms among 397 cases of endometrial carcinomas that were operated on in our hospital from 2003 to 2015 were examined. The tumor distribution, clinical and pathological features, and survival rate were studied, respectively. Results: The incidence of multiple primary neoplasms was 7.8% among those with endometrial carcinoma with the median age of 50.3 years old. The major organs involved were the colon, rectum, ovary, breast, and lung. The 5-year survival rate of endometrial carcinomas with MPMN is 22.6%, and the median survival time is 70 ± 26.86 months. However, the cumulative survival rate at 5 years is 55.8% which is below the 5-year survival rate of any primary malignant neoplasm. The median interval time from the first primary cancer diagnosis to the second cancer diagnosis exceeding 3 years will prolong life time. Conclusion: The major primary malignant neoplasms associated with endometrial carcinoma include those of the colon, rectum, ovary, breast, and lung. The 5-year survival rate is lower than any primary neoplasms. The median interval time from the first primary cancer diagnosis to the second cancer diagnosis exceeding 3 years will prolong life time.

**Keywords:** Endometrial carcinoma, multiple primary malignant neoplasms, tumor distribution, clinical and pathological features, survival

## Introduction

Multiple primary malignant neoplasms (MPMNs) are defined as two or more unrelated malignancies in an individual that occur in the body at the same time or one after another [1]. Second primary tumors were most common, whereas third, fourth, and higher primary tumors were relatively uncommon [2].

Recently, it has been revealed that the occurrence of certain types of malignant tumors was related, such as Lynch syndrome which is associated with double primary cancers of the colorectum and endometrium [3]. However, the clinical features and prognosis are still not fully understood. Therefore, case studies of MPMNs should facilitate diagnosis and treatment.

In this study, we analyzed the clinicopathological features of MPMNs associated with endometrial carcinoma. We found the incidence of multiple primary neoplasms was 7.8% among those with endometrial carcinoma. The median age of endometrial carcinomas patients was 50.3 years old. The major organs involved in were the colon, rectum, ovary, breast, and lung. In addition, the 5-year survival rate of endometrial carcinomas with MPMN was 22.6%, and the median survival time was 70 ± 26.86 months. However, the cumulative survival rate in 5 years was 55.8% which is below the 5-year survival rate of any primary malignant neoplasm, and the median interval between the first and the second primary neoplasm exceeding 3 years will prolong life time. Our studies add another layer to facilitate the prognosis and treatment of the patients with MPMNs and associated with endometrial carcinoma.

## Materials and methods

### *Tumor tissues*

Patients of MPMNs with endometrial carcinoma were diagnosed between January 2003 and

March 2015 from the Gynecology Department of China-Japan Friendship Hospital. All patients were pathologically diagnosed by surgery, curettage, or endoscopy. The age at onset and duration, location of tumors, clinical features, pathological data, family history, treatment outcome, and prognosis of patients were collected through medical records and telephone calls.

*Diagnostic criteria*

The diagnostic principles of MPMN are based on the following standards provided by Warren (Warren and Gates, 1932): 1) there are two unrelated primary malignant tumors that originate from different organs; 2) each tumor is malignant; 3) each tumor has its own metastatic pathway and the diagnosis of metastatic or recurrent tumors can be excluded.

Definitions and classifications for MPMNs, proposed by Moertel in 1977. SMPMNs are defined if the tumors occur simultaneously or within 6 months of one another, whereas MMPMNs are indicated if the interval time is more than 6 months. In this study, 31 cases of MPMNs with endometrial carcinoma were assessed according to the above diagnostic criteria.

Overall survival and median survival period are the main indicators for clinical evaluation of survival. The overall survival time of patients with SMPMN is calculated according to the confirmed date of first primary cancer, whereas for patients with MMPMN, the overall survival time is calculated from the confirmed date of the last diagnosis of cancer. The patients were followed up with the deadline of May 1st, 2015, by either telephone or in-patient. The total following up time is 3-336 months.

*Statistical analysis*

An unpaired Student's t-test was used for comparison between two groups and one-way analysis of variance test followed by Tukey's multiple comparison test was used to compare the significance of differences between the means of multiple groups. IBM SPSS Statistics 21 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Kaplan-Meier analysis was used to generate the survival curve for the median survival time. $P < 0.05$ was considered to indicate a statistically significant difference.

## Results

*Tumor distribution*

All 31 patients were assessed according to the diagnostic criteria for MPMN developed by Warren and Gates. There were unrelated primary tumors, and all cases were diagnosed by pathology except the metastasis. Among them, 27 cases had double primary malignant tumors, 3 cases had three primary malignant tumors, and 1 case had six primary malignant tumors. In summary, there were 69 primary malignant tumors and involve multiple organs such as internal reproductive system, digestive tract, mammary glands, respiratory system, etc. (**Table 1**). All primary cancers are treated according to the surgery principal, chemotherapy, radiation or alleviative treatment.

For the patients with six primary malignant tumors, the treatment included surgery and chemotherapy for the highly differentiated adenocarcinoma of the sigmoid colon in September 1992. Pancreatoduodenectomy was performed for those with poorly differentiated adenocarcinoma of the lower bile duct in December, 1992. The translational cell carcinoma of the bladder (II-III) was found in July, 1993. After then, the multiple papillary transitional cell carcinoma (II-III) in the lower ureteral segment was excised in 1996. For the high-grade urothelial carcinoma of the renal pelvis, radical surgery was performed in October, 2009. The highly differentiated endometrioid carcinoma (stage Ib) was found in January, 2004.

*Clinical and pathological features*

The average age of the first primary tumor was 53.6 ± 10.28 years old (30-79 years old). Of the 31 patients, 25 cases (83.8%) patients had vaginal bleeding and/or vaginal discharge, and 11 (41.9%) had one of the triads of endometrial cancer. 32.26% of the 31 patients had family history. For 19 patients with CA125, two cases (10.5%) were > 35 U/L. For patients with breast cancer, endometrial cancer was found in two patients after surgery. These two patients took tamoxifen for 2 years or 4 years and 9 months, respectively.

Endoscopic biopsy, diagnostic curettage, or pathological diagnosis after surgery is the interval time between different tumors. There were

**Table 1.** Tumor distribution

| Category (n tumor) | Uterus | Transverse colon | Ascending colon | Sigmoid colon | Rectum | Duodenum | Breast | Lung | Kidney | Bile duct | Bladder | Ureter | Ovarian | Renal pelvis | Appendix | Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 15 | 3 | 2 | 4 | 1 | 1 | 3 | 1 | | | | | 2 | | | 33 |
| 2 | 14 | 4 | 2 | 3 | 3 | 2 | 0 | | | 1 | | | | | | 29 |
| 3 | 1 | | | | | | | 1 | 1 | | 1 | | | | 1 | 5 |
| 4 | | | | | | | | | | | | 1 | | | | 1 |
| 5 | | | | | | | | | | | | | | 1 | | 1 |
| 6 | 1 | | | | | | | | | | | | | | | 1 |
| Summary | 31 | 7 | 4 | 7 | 4 | 3 | 3 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 69 |

n: the primary tumors in chronological order.

**Table 2.** SMPMN clinical pathological features

| | First primary cancer | Age | Interval time from the previous cancer | Treatment | Subsequent primary cancer | Results |
|---|---|---|---|---|---|---|
| Endometrioid adenocarcinoma Ia G1-G2 | 49 | 0 | Surgery + chemotherapy | Ovarian Endometrioid G2 | Surgery + chemotherapy | Survival |
| Endometrial differentiated adenocarcinoma stage Ia | 79 | 0 | Surgery + chemotherapy | Right ovary junction malignant papillary serous cystadenoma stage Ia | Surgery + chemotherapy | Death |
| Highly differentiated adenocarcinoma of sigmoid colon | 47 | 3 | Surgery + chemotherapy | Lower bile duct poorly differentiated adenocarcinoma | Surgery | |
| | | | | Transitional cell carcinoma of the bladder (I-II) | Surgery | |
| | | | | Lower ureter polypapillary transitional cell carcinoma (Grade II-III) | Surgery | |
| | | | | High-grade papillary urothelial carcinoma of the renal pelvis | Surgery | |
| | | | | Highly differentiated endometrioid carcinoma in uterus (stage Ib) | Surgery | Survival |
| Duodenal adenocarcinoma | 60 | 5 | Surgery | Endometrial poorly differentiated adenocarcinoma III | Surgery + chemotherapy | Death |
| Differentiated adenocarcinoma T4N3 in sigmoid colon | 50 | 0 | Surgery + chemotherapy | Endometrial severe dysplasia, focal canceration | Surgery + chemotherapy | Survival |

**Table 3.** Clinicopathological features of MMPMN (endometrial cancer as the first cancer)

| Cases | First primary cancer | Age | Interval time from the previous cancer | Subsequent primary cancer | Results |
|---|---|---|---|---|---|
| 1 | Endometrial highly differentiated adenocarcinoma stage Ib | 34 | 36 | Differentiation of adenocarcinoma in the transverse colon | Survival |
| 2 | Endometrial moderately differentiated adenocarcinoma stage Ia | 41 | 36 | Transverse colon differentiated adenocarcinoma T3N0 | Survival |
| 3 | Endometrioid adenocarcinoma | 59 | 36 | Ascending colon adenocarcinoma stage IV | Death |
| 4 | Endometrioid adenocarcinoma Ia G2 | 51 | 28 | Duodenum | Survival |
| 5 | Endometrioid adenocarcinoma stage IC | 70 | 96 | Duodenal papillary adenocarcinoma | Death |
| 6 | Endometrioid adenocarcinoma II | 67 | 76 | Sigmoid adenocarcinoma | Death |
| 7 | Endometrial adenocarcinoma | 53 | 34 | Sigmoid transverse colon adenocarcinoma T3N0 | Survival |
| 8 | Endometrial differentiated adenocarcinoma TisN0M0 | 72 | 57 | Moderately differentiated adenocarcinoma T4 in sigmoid colon N12 | |
| 9 | Endometrial differentiated adenocarcinoma stage Ib | 57 | 18 | Rectal moderately differentiated adenocarcinoma, ulcer type T2N0 | Survival |
| 10 | Endometrial carcinoma stage Ia, G2. Clear cell carcinoma, papillary carcinoma and adenosquamous carcinoma | 51 | 94 | Left lung adenocarcinoma, papillary glands | Death |
| 11 | Endometrioid adenocarcinoma (moderately differentiation), partial clear cell differentiation | 59 | 29 | Transthoracic bulk adenocarcinoma T3N0 | |
| | | | 9 | Right lobar resection: lung adenocarcinoma, consistent with bronchioloalveolar carcinoma | Survival |
| 12 | Endometrial clear cell carcinoma | 50 | 24 | Rectal adenocarcinoma | Death |
| 13 | Endometrial adenosquamous carcinoma | 54 | 20 | Moderately differentiated adenocarcinoma in the transverse colon | Survival |

**Table 4.** Clinicopathological features of MMPMN (endometrial cancer is the second or third primary cancer)

| | First primary cancer | Age | Interval time from the previous cancer | Subsequent primary cancer | Results |
|---|---|---|---|---|---|
| 1 | Moderately differentiated adenocarcinoma in sigmoid colon | 62 | 144 | Endometrioid adenocarcinoma III G1-G2 | Death |
| 2 | Sigmoid adenocarcinoma | 64 | 24 | Endometrioid adenocarcinoma | Death |
| 3 | Highly differentiated adenocarcinoma of the transverse colon | 46 | 30 | Highly differentiated endometrioid adenocarcinoma stage Ib | Survival |
| 4 | Rectal Adenocarcinoma A1 | 56 | 60 | Moderately differentiated endometrial adenocarcinoma stage Ib | Survival |
| 5 | Right ascending colon in differentiated adenocarcinoma B stage | 63 | 26 | Endometrioid adenocarcinoma III | Death |
| 6 | Right ascending colon, moderately differentiated adenocarcinoma, stage B ascending colon polyp, local canceration | 38 | 78 | Moderately differentiated endometrioid adenocarcinoma, localized, without the exception of adenocarcinoma | Survival |
| 7 | Ascending colon adenocarcinoma | 47 | 30 | Highly differentiated endometrioid adenocarcinoma, phase Ib Survival | |
| 8 | Moderately differentiated adenocarcinoma in the transverse colon | 45 | 21 | Endometrial serous adenocarcinoma | Survival with tumor |
| 9 | Right breast ductal papillary carcinoma | 62 | 146 | Endometrial Carcinoid Adenocarcinoma IaG1 | Survival |
| 10 | Lobular adenocarcinoma of the breast | 50 | 72 | Moderately differentiated adenocarcinoma stage Ib | Survival |
| 11 | Lung adenocarcinoma | 68 | 36 | Moderately differentiated endometrial adenocarcinoma with scale | Death |
| 12 | Transverse colon adenocarcinoma | 31 | 96 | Renal cell carcinoma | |
| | | | 24 | Endometrial adenocarcinoma | |
| | | | 120 | l Colon cancer (recurrence) | Death |
| 13 | Left breast lobular carcinoma in situ | 60 | 70 | Moderately differentiated rectal adenocarcinoma T4N2 | |
| | | | 25 | Endometrial adenocarcinoma, moderately differentiated | Survival |

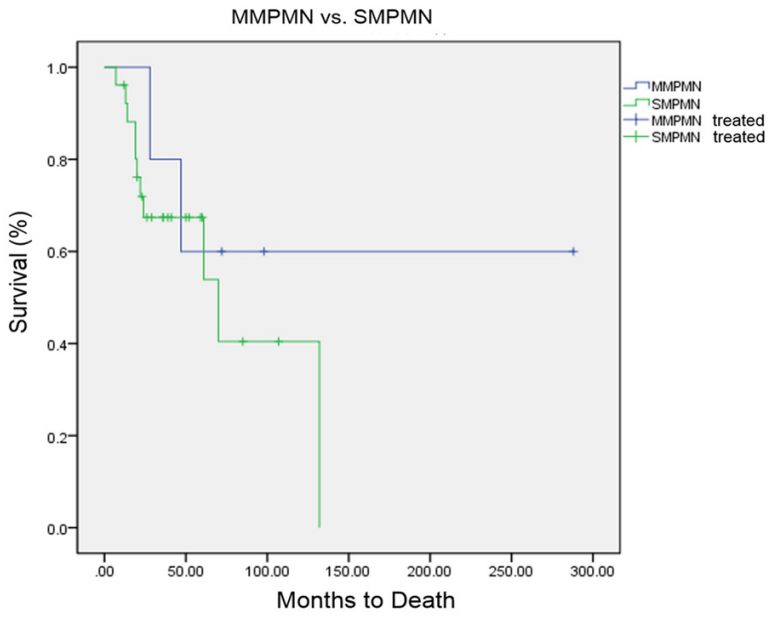


**Figure 1.** Kaplan-Meier curve depicting survival patients grouped according to the MMMPMN and SMPMN. Green line: MMPMN; blue line: SMPMN (P = 0.36).


**Figure 2.** Kaplan-Meier curve depicting survival patients grouped according to the interval time between the first tumor and second tumor. Green line: the recurrence time was ≥ 3 years; blue line: the recurrence time was < 3 years (P < 0.05).

5 patients with SMPNM and 26 patients with MMPMN in the 31 patients. In the MMPMN groups, the interval time between the first and second tumor was 51.27 months (16-146 months). Among them, 17 patients had an interval time ≤ 60 months, whereas 10 patients had internal time > 60 months. For patients with 3 malignant tumors, the interval time between the first and third tumors was up to 240 months (**Tables 2**-**4**).

*Survival analysis*

Of the 31 patients, 13 patients died. The average survival time of the 31 patients was 119.21 ± 33.08 months, and the median survival time was 70 ± 28.86 months. The 5-year survival rate after the last cancer was 7 of 31 (22.6%), the 5-year cumulative survival rate was 55.8%, and the 10-year survival rate was 1 of 31 (3%).

Patients are at a greater risk (~6 times) of developing a second malignancy after the initial primary malignancy tumors. The second primary cancer occurs most often within 1 to 3 years after the treatment of the first tumor, with an average of 5 to 7 years, with shorter intervals correlating with worse prognosis [4]. In this study, the interval between the first tumor and the second tumor of MMPMN was 51.27 months (16 to 146 months). The cumulative survival rate was 60% in the MMPMN patients, whereas the survival rate was 53.9% in the SMPMN patients. The survival curve of the patients with SMPNM and MPMN had no significant difference (**Figure 1**, P = 0.36). The survival curve of the patients with < 3 years and ≥ 3 years interval was significantly different, which is indicating that the survival time was prolonged with the recurrence time was ≥ 3 than the < 3 years (**Figure 2**, P < 0.05). However, the survival curve of the patients with

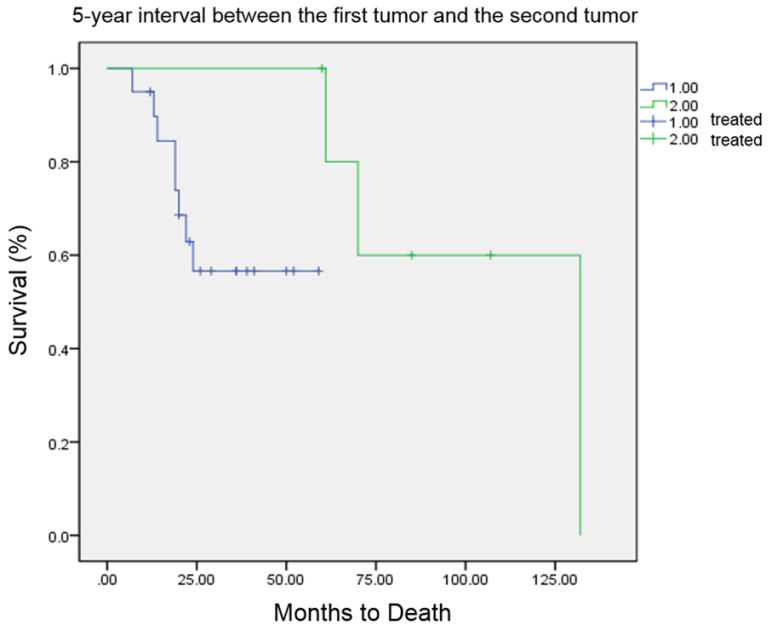


**Figure 3.** Kaplan-Meier curve depicting survival patients grouped according to the interval time between the first tumor and second tumor. Green line: the recurrence time was ≥ 5 years; blue line: the recurrence time was < 5 years (P = 0.07).

≥ 5 years interval was different but not significant (**Figure 3**, P = 0.07), which is indicating that the survival time was not significantly prolonged in the patients with ≥ 5 years interval than patients with the 3~5 years interval. Although these results suggested that there might a correlation between the 3-year interval time and the prognosis of patients with multiple primary malignant tumors, it still need to increase sample size to increase the validity.

## Discussion

MPMNs causally associated with environmental factors (smoking, occupational exposure, contamination, ultraviolet radiation), genetic susceptibility, diet, radiotherapy and chemotherapy history, gender, endocrinology, and the interaction within these factors [5, 6]. SMPMNs are relatively rare (~10%), whereas MMPMN is relatively frequent (90%). The incidence of patients diagnosed with endometrial cancer associated with the second primary tumor is around 10~23%. In this study, more than 2% of patients with multiple primary cancers accounted for 6.8% of patients with endometrial cancer at the same time. The median age of the 31 patients diagnosed as primary endometrial cancer was 50.3 years old, which was younger than the endometrial cancer alone.

In this study, in addition to the endometrial cancer, multiple primary cancers involved the female reproductive organs such as colon, breast, respiratory system, etc. Among these organs, colon (22/61) was the most common and accounting for 36.06%. It is more common to find the endometrial cancer with colorectal malignancy which is causally associated with lynch syndrome [3, 7]. Lynch syndrome belongs to the chromosomal dominant hereditary disease which caused by a mutation of the DNA mismatch repair (MMR) gene in germ cells [8]. The lifetime cumulative risk of endometrial cancer for women with lynch syndrome is 40~60%, which equals or exceeds their risk of colorectal cancer (49%) [9]. Currently, Lynch syndrome has been given more attention by clinical investigators. In our study, 12 patients were diagnosed and needed the further genetic testing for MMR gene mutation. In addition, the primary cancer outside the endometrial cancer is found in the colorectal, and most of them are adenocarcinomas. Those patients without Lynch syndrome deserve further study. Possibly, the colorectal area contains more ER, which is associated with the stimulation of the same carcinogenic factors. The female reproductive system is one of the most common systems for secondary primary cancer from primary endometrial cancer, such as ovaries, mammary glands, homologous tissues, or pathological changes under the same carcinogenic factors. If the pathological change has been found in one organ, such as ovary, the pathological changes were found in other organs, such as the fallopian tubes, the uterus, or the cervix, by either the metaplasia, or neoplasia lesions. It has been reported that there was a 2.9% possibility of the simultaneous occurrence of ovarian cancer and uterine cancer [10]. In our study, 6 patients had been diagnosed with cancers occurred in the ovary or mammary gland MPMN, which is consistent with the report.

In this study, there were several cases of rectal cancer after endometrial cancer, endometrial cancer after breast cancer. One patient had been diagnosed with 6 primary tumors, and three patients had 3 primary tumors. It is indicated that radiotherapy, chemotherapy, and other drug treatment, DNA synthesis that affects normal cells in the body, resulting in the immune resistance, has a correlation with the subsequent occurrence of the secondary primary cancer. It has been reported that the occurrence of the secondary tumor may be related to radiotherapy [11]. It has been also shown that about 8% of MPMN and 5% of gynecological malignancies are related to the history of radiotherapy of the first tumor [12]. This leaves us with a worthy direction to think about how to avoid iatrogenic causes or promote the occurrence of follow-up primary cancer.

In this study, 22 patients (71.0%) were diagnosed with endometrial cancer accounted in stage I. All patients were selected for surgical treatment and those who did not undergo surgery during the late period did not count. 24 patients (77.4%) have been diagnosed with histologic types of endometrioid adenocarcinoma, but the 5-year survival rate after the last malignant tumor was only 22.6%, the median of survival time was 70 ± 26.86 months, and the 5-year cumulative survival rate was 55.8%. This 5-year cumulative survival rate is lower than for patients with endometrial cancer (stage II, or type II), colon cancer (stage III), or breast cancer (stage III). This group of patients were treated with radiotherapy and chemotherapy, but the survival rate was still low. These results indicate that the prognosis of patients with endometrial cancer with multiple primary cancers is worse than that of patients with a single primary cancer.

Treatment of MPMN is different from metastatic malignancy and recurrent malignancy. In our study with a small size group, 32.2% patients with family history had no significant difference from patients with the initial primary tumor in the clinical manifestation and pathological types, but not the prognosis. Therefore, it is important to increase the patient size of endometrial cancer with multiple primary cancer for screening such cancers to identify the second primary tumor earlier, and eventually to improve the prognosis and patient survival rate.

## Disclosure of conflict of interest

None.

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