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Research

Clinical characteristics and survival of breast cancer patients with extramammary malignancies in a single Asian center over the past 23 years

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Abstract

Background The rise of multiple primary malignant neoplasms (MPMNs) necessitates exploration. MPMNs represent 18% of U.S. cancers. Breast cancer is the predominant malignancy among female Americans. However, most studies on breast cancer with MPMNs are confined to case reports with small sample sizes. Hence, this article scrutinizes 280 patients diagnosed with breast cancer and extramammary primary malignancies via long-term follow-up.

Methods We reviewed 280 breast cancer cases with extramammary primary malignancies from January 2000 to December 2022 at our institute, excluding those diagnosed with stage IV breast cancer. The double primary malignant neoplasms (DPMNs) were used as focal points and segregated into the first primary breast cancer (FPBC) and second primary breast cancer (SPBC) subgroups. With a median follow-up period of 107 months (8.9 years), we examined the characteristics of these diseases in various patients.

Results Concerning breast cancer patients with extramammary primary malignancies, DPMNs were predominant, comprising 77.1% (216/280). Among these DPNMs, gynecology, thyroid, and lung were the primary site of extramammary tumors, predominantly. Nearly all (93.9%) of FPBC patients exhibited metachronous cancer whereas 55.9% of SPBC patients experienced this. The median interval between the onset of breast cancer and extramammary malignancy in metachronous FPBC and metachronous SPBC patients was 60 months and 48 months, respectively. Over time, both metachronous FPBC and metachronous SPBC patients demonstrated a diminishing prevalence of second tumors. The distinction lay in that in the metachronous FPBC group, second tumors ceased to occur after 300 months, whereas in the metachronous SPBC group, their emergence persisted. Synchronous cancer, negative ER/PR status, and advanced extramammary malignancy stage portend poor prognosis among patients with DPMNs.

Conclusions Careful monitoring of MPMNs necessitates precise guidelines, differing amongst FPBC and SPBC patients. Synchronous cancer, ER/PR-negative, and advanced extramammary malignancy stage indicate poor prognosis in DPMNs patients.

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Keywords Multiple primary malignant neoplasms · Double primary malignant neoplasms · Breast cancer · Extramammary malignancy

Abbreviations

MPMNs	Multiple primary malignant neoplasms
DPMNs	Double primary malignant neoplasms
FPBC	First primary breast cancer
SPBC	Second primary breast cancer
OS	Overall survival
ER	Estrogen receptor,
PR	Progesterone receptor,
HER-2	Human epidermal growth factor receptor 2

1 Introduction

Multiple Primary Malignant Neoplasms (MPMNs) are defined as two or more tumors with disparities in histologic origin coexisting in the same patient, excluding metastases and recurrence [1]. MPMNs was initially described by Billroth at the end of nineteenth century [2]. Several cases of double or triple primary malignancies have been reported since been [2, 3]. The phenomenon of MPMNs has been associated with underlying immunodeficiency, genetic susceptibility, exposure to carcinogens, and prior exposure to chemoradiotherapy [4, 5]. MPMNs can present synchronously or metachronously. As per Moertel [3], synchronous MPMNs refers to malignancies that materialize within six months subsequent to the initial diagnosis of malignancy, while metachronous tumors are those that occur six months post-diagnosis of the preceding primary malignancy.

Evolution in the diagnosis and management of cancer have instigated an augmentation in the number of cancer survivors and prolonged survival necessitating a second malignancy [6–9]. Currently, cancer survivors constitute 3.5% of the overall US population, with approximately 10% of newly diagnosed malignancies occurring among cancer survivors [10]. Breast cancer is the predominant malignancy among American women [11]. Some studies have reported features of patients with breast cancer and extramammary malignancies [12, 13]. However, few have attempted to pool and evaluate malignancies before and after breast cancer. Herein, we characterized extramammary malignancies preceding and subsequent to breast cancer over extended follow-up.

2 Methods

From January 2000 to December 2022, 80,351 patients with new-onset breast cancer were admitted to Tianjin Medical University Cancer Institute & Hospital. Of these, 290 cases harbored primary malignancies prior to or subsequent to breast cancer. The diagnosis of all cancers were histologically verified. Inclusion criteria: Among the patients newly diagnosed with breast cancer (unilateral or bilateral) in our center, those who have one or more primary extramammary malignancies before or after the diagnosis of breast cancer in the same individual were included. Exclusion criteria: Patients with unilateral breast cancer; patients with only bilateral breast cancer without any primary extramammary malignancies; patients with stage IV breast cancer at the time of diagnosis. Following the exclusion of 10 stage IV breast cancer patients at diagnosis, a total of 280 breast cancer patients with extramammary primaries were retained for analysis. Clinical, pathological, and prognostic characteristics were analyzed retrospectively.

Out of the 280 patients with multiple primary malignancies, 216 exhibited double primary malignant neoplasms (DPMNs). DPMNs were classified into first primary breast cancer (FPBC) and second primary breast cancer (SPBC) groups contingent on the chronological sequence of breast cancer and extramammary primary malignancies. They were further categorized into synchronous (interval within 6 months) and metachronous (interval longer than 6 months) groups [14] in relation to the intervals of breast and non-breast cancers occurrences. The order and span of occurrence of breast cancer on the survival of patients with DPMNs was scrutinized and analyzed. Overall survival (OS) was defined as the date from the first cancer diagnosis to the date of death from any cause or the follow-up endpoint (October 2023). Family cancer history is defined as cancer diagnoses among the patient's first-degree relatives. The study received approval from the Medical Ethics Committee of Tianjin Medical University Cancer Institute & Hospital.

Categorical data comparisons employed the chi-square or Fisher's exact tests. Patients' OS was analyzed via the Kaplan–Meier method and multivariate survival analysis using the Cox regression model. Statistical significance was accepted at $p < 0.05$. Analyses were conducted using SPSS 27.0, Graphpad Prism 9.5, and R software (version 4.2.2).

3 Results

3.1 Cancer occurrence of entire cohort

As shown in Table 1, of the total 280 patients, double primary malignant neoplasms (DPMNs) were the predominant entity, comprising 216 patients (77.1%). Triple primary malignant neoplasms consisted of 58 individuals (20.7%), with quadruple—and quintuple primary malignant neoplasms being 5 (1.8%) and 1 (0.4%), respectively. In terms of the order of appearance of breast cancer (in the event of bilateral breast cancer, it is determined accordingly to the initial breast cancer), the first primary breast cancer (FPBC) was predominant, with 142 cases (50.7%), followed by the second primary breast cancer (SPBC), with 128 cases (45.7%). The third primary breast cancer and the fourth primary breast cancer were scarce, with 9 cases (3.2%) and 1 case (0.4%), respectively. A collective total of 37 patients exhibited bilateral primary breast cancer coexisting with extramammary malignant tumors, representing 13.2% (37/280).

A total of 631 primary malignancies arose in 280 patients, including 317 breast glands and 314 extramammary organs. Extramammary primary malignant tumors' organ frequencies were: thyroid gland (69), lung (54), ovary (43), endometrium (22), colon (21), stomach (18), cervix (17), kidney (11), rectum (9), liver (7), lymphoma (6), pancreas (4), leukemia (4), glioma (4), fallopian tube (3), esophagus (3), gallbladder (3), ureter (2), bladder (2), bone tumor (2), tonsil (2), multiple myeloma (1), skin (1), vulva (1), hypopharynx (1), mediastinal mesothelial sarcoma (1), polycythemia vera (1), peritoneum (1), uterine body (1).

4 Extramammary malignancies in patients with DPMNs

The sites and quantity of extramammary malignancies in patients with DPMNs are delineated in Table 2. The majority (65.3%) of extramammary malignancies took place in the gynecological system, thyroid gland, and lungs, representing 25.5% (55/216), 22.2% (48/216), and 17.6% (38/216), respectively; digestive system is also prevalent, accounting for 23.2% (9.3% + 7.9% + 6.0%), whilst hematologic system, urinary system, nervous system, and bone & soft tissues are comparably infrequent. Thyroid cancers were observed more prevalent in SPBC compared to FPBC (14.3% *vs.* 28.8%, $p = 0.011$).

Table 1 Cancer occurrence in patients with breast cancer(s) and primary extramammary malignancies (n = 280)

	Double Primary Malignant Neoplasms	Triple Primary Malignant Neoplasms	Quadruple Primary Malignant Neoplasms	Quintuple Primary Malignant Neoplasms	Total
1st primary breast cancer	98	42	2	0	142
2nd primary breast cancer	118	8	1	1	128
3rd primary breast cancer	0	8	1	0	9
4th primary breast cancer	0	0	1	0	1
5th primary breast cancer	0	0	0	0	0
Total	216	58	5	1	280

Patients with bilateral breast cancer were calculated based on the time of the earlier one

Table 2 Sites and numbers of extramammary malignancies in patients with DPMNs (n = 216) n (%)

Sites	Total	FPBC (n = 98)		SPBC (n = 118)		*P*
	N = 216	Synchronous (n = 6)	Metachronous (n = 92)	Synchronous (n = 52)	Metachronous (n = 66)	
Gynecologic system	55(25.5)	3(3.1)	25(25.5)	8(7.6)	19(16.1)	0.339
Thyroid gland	48(22.2)	0	14(14.3)	14(11.9)	20(16.9)	0.011*
Lung	38(17.6)	1(1.0)	19(19.4)	12(10.1)	6(5.1)	0.322
Colon & rectum	20(9.3)	0	9(9.2)	4(3.4)	7(5.9)	0.972
Stomach & esophagus	17(7.9)	0	11(11.2)	5(4.2)	1(0.8)	0.095
Hepatobiliary & pancreas	13(6.0)	1(1.0)	6(6.1)	4(3.4)	2(1.7)	0.527
Hematologic system	9(4.2)	0	2(2.0)	2(1.7)	5(4.2)	0.188
Urinary system	8(3.7)	0	3(3.1)	1(0.8)	4(3.4)	0.731
Nervous system	3(1.4)	1(1.0)	0	1(0.8)	1(0.8)	1.000
Bone & soft tissue	2(0.9)	0	1(1.0)	1(0.8)	0	1.000
Others						
Tonsil	2(0.9)	0	1(1.0)	0	1(0.8)	1.000
Peritoneum	1(0.5)	0	1(1.0)	0	0	0.454

P represents the site distribution comparison for FPBC and SPBC

FPBC: First primary breast cancer, SPBC: Second primary breast cancer

*: *P* value < 0.05

5 Clinical and pathological characteristics of patients with DPMNs

As shown in Table 3, of the total 216 patients with DPMNs, 98 were FPBC and 118 were SPBC. The median age at breast cancer diagnosis was 53 years (range 29–87 years). The median interval time between two cancers was 26 months (range 0–436 months), with majority (73.1%) being metachronous. 75% patients were ER/PR positive and 33.3% overexpressed HER-2. Smoking history and family history of cancers were found in 6.0% and 37.5% of patients, respectively. With regard to extramammary primary malignancies, 38.9% were diagnosed at an advanced stage.

Substantial majority (93.9%) of FPBC were metachronous, contrasting with 55.9% of SPBC, indicating a notable statistical contrast. In addition, FPBC patients typically manifested at an earlier age of breast cancer diagnosis (51 vs. 55 years) and exhibited a higher frequency of advanced extramammary primary malignancies (50% vs. 29.7%) than SPBC patients.

6 Intervals between breast cancer and extramammary malignancy

The median time interval between the onset of breast cancer and extramammary malignancy in patients with DPMNs was 26 months (range 0–436 months), specifically, FPBC demonstrated a median of 52 months (range 0–296), while SPBC presented a median of 8 months (range 0–436), as illustrated in Table 3.

A total of 158 patients presented with metachronous DPMNs, of which FPBC and SPBC represented 92 cases (92/98 93.9%) and 66 cases (66/118 55.9%), respectively. Figure 1 outlines the timeline of breast cancer and extramammary malignancies development in these patients. The median interval duration between the occurrence of two cancers in patients with metachronous FPBC and metachronous SPBC was 60 months and 48 months, respectively. As time elapses, the risk of secondary primary malignancies in metachronous FPBC and metachronous SPBC patients exhibited a diminishing trend. Notably, in the metachronous FPBC cohort, no extramammary malignancies surfaced beyond 300 months (25 years), whereas in the metachronous SPBC group, the incidence of subsequent breast cancers persisted, with the longest observed interval reaching 436 months (36.3 years).

Table 3 Clinical and pathological characteristics of patients with DPMNs (n = 216) n (%)

	Total (n = 216)	FPBC(n = 98)	SPBC(n = 118)	*p*
Sex				1.000
Male	3(1.4)	1(1.0)	2(1.7)	
Female	213(98.6)	97(99.0)	116(98.3)	
Age at diagnosis of breast cancer (years)				**0.011***
≤ 45	51(23.6)	31(31.6)	20(16.9)	
> 45	165(76.4)	67(68.4)	98(83.1)	
Median	53	51	55	
Range	29–87	31–73	29–87	
Interval time(months)				**< 0.001***
Synchronous	58(26.9)	6(6.1)	52(44.1)	
Metachronous	158(73.1)	92(93.9)	66(55.9)	
Median	26	52	8	
Range	0–436	0–296	0–436	
ER/PR status				0.636
Positive	162(75.0)	72(73.5)	90(76.3)	
Negative	54(25.0)	26(26.5)	28(23.7)	
HER-2 status				0.122
Positive	72(33.3)	38(38.8)	34(28.8)	
Negative	144(66.7)	60(61.2)	84(71.2)	
T staging				0.307
Tis-T1	58(26.9)	23(23.5)	35(29.7)	
T2-4	158(73.1)	75(76.5)	83(70.3)	
N staging				0.418
N0	132(61.1)	57(58.2)	75(63.6)	
N1-3	84(38.9)	41(41.8)	43(36.4)	
Stage of extramammary malignancy				**0.002***
I/II	132(61.1)	49(50.0)	83(70.3)	
III/IV	84(38.9)	49(50.0)	35(29.7)	
Smoking history				0.606
Yes	13(6.0)	5(5.1)	8(6.8)	
No	203(94.0)	93(94.9)	110(93.2)	
Family history of cancers				0.180
Yes	81(37.5)	32(32.7)	49(41.5)	
No	135(62.5)	66(67.3)	69(58.5)	
Follow-up[#], median (range), mo	107(1–509)	126(12–385)	104(1–509)	

Bold indicates that the *P*-value has statistical significance ($P<0.05$)

ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor 2

*: *P* value < 0.05

[#]: Only patients who were followed up were included (n = 200)

7 Survival and prognostic factors of patients with DPMNs

Table 4 presents the univariate survival analysis of patients with DPMNs. Of 216 DPMNs patients, 200 were followed, yielding a follow-up rate of 92.6%. The median follow-up duration was 107 months (8.9 years). Median overall survival of FPBC and SPBC patients amounted to 126 and 104 months, respectively. As illustrated in Fig. 2, the prognosis of patients with synchronous DPMNs were inferior to that of metachronous ones. Figure 3A–E depicts additional prognostic factors for patients with DPMNs. The findings revealed that advanced extramammary malignancy stage, age ≥ 60 at extramammary tumor diagnosis, age > 45 at breast cancer diagnosis, and negative ER/PR status predict poor DMPNs patient outcomes, while FPBC or SPBC status did not affect prognosis significantly (p = 0.572). Figure 4

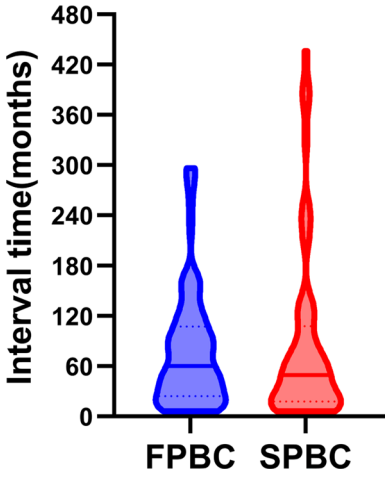

Fig. 1 Distribution of time intervals between the development of breast cancer and extramammary malignancy in metachronous DPMNs (n = 158)

illustrates that synchronous cancer, negative ER/PR status, and advanced extramammary malignancy stage portend poor prognosis among patients with DPMNs.

8 Discussion

Annual incidences of MPMNs is variable, estimated between 0.73% to 11.7%, depending on study cohorts [15]. Of cancer diagnoses in the USA, second and higher-order malignancies constitute about 18% [16]. It is projected that by 2040, there will be 26.10 million US cancer survivors [17]. Those with a primary tumor have a 10% higher risk of developing a second tumor than the general population [18, 19]. Estimates indicate one-third of 60 + year old cancer survivors harbor another primary malignancy [15]. The incidence ratio of developing MPMNs among female cancer survivors is 1.17 to 1.6 [20]. Notably, in female breast cancer survivors, the incidence ratio increases to 1.96 (95% CI, 1.48–2.44), based on initial breast cancer diagnosis age [20]. Multiple studies have explored primary breast cancer associations with non-breast primaries [12, 13, 21–28]; while comprehensive, these focus primarily on secondary tumors post-breast cancer. This study consolidated pre- and post-breast primary malignancies and examined their correlations.

Compared to the general population, elevated MPMNs risk in cancer survivors appears multifactorial, linked to four main influences: genetic factors, intrinsic factors, extrinsic factors, and therapeutic factors [29, 30]. To date, genome-wide association studies have revealed 72 loci linked to breast malignancy susceptibility, 17 of which correspond to MPMTs associations [31]. BRCA gene mutation carriers have elevated risks of early-onset breast and ovarian cancer [32]. Immune status, susceptibility, endocrine, and embryonic development comprise intrinsic factors. Reduction in immune defense and immune surveillance facilitate MPMNs development [30]. Environmental factors and personal lifestyle choices such as prolonged industrial pollution and occupational diseases feature among extrinsic factors [30]. In addition, lack of physical activity, alcohol consumption, and smoking can act as significant carcinogens. Therapy-related factors primarily include radiotherapy and chemotherapy in cancer patients, significantly increasing risk of MPMNs [33]. Also, paradoxically, chemo drugs may augment cancer patient survival while inducing acquired immunodeficiency. Research [33] indicates some chemo drugs like topoisomerase II inhibitors, alkylating agents, and radiotherapy can substantially enhance the risk of secondary tumors in cancer survivors, primarily due to acquired immunodeficiency. These cytotoxins and immunosupressants may instigate second tumor onset either directly as carcinogens or indirectly as cofactors [33].

Some studies have confirmed the probable links between breast cancer and non-breast malignancies. In the present study, the most prevalent malignancies in breast cancer patients were gynecological tumors. The considerable correlation between breast cancer and gynecological tumors, specifically ovarian cancer, is well-established. They often share risk factors like obesity, low number of pregnancies/nulliparity, early menarchy, and a high-fat diet exceeding 38% of daily caloric intake [34–37]. Hereditary tumor syndromes display a high cancer risk due to inherited mutations in single genes [38]. Individuals with breast cancer exhibit an elevated potential for the development of sporadic ovarian cancer, which is augmented further when they harbor an amalgamation of genetic syndromes, like hereditary BRCA1 and BRCA2 gene mutations [32, 38, 39]. Thyroid cancer emerged as the second most frequent extramammary tumor in our study. Survivors of thyroid cancer exhibit an enhanced risk of developing a second

Table 4 Univariate survival analysis of patients with DPMNs (n = 200)

Variable	n	*p*
Sex		0.611
Male	3	
Female	197	
Age at diagnosis of breast cancer (years)		**0.042***
≤ 45	49	
> 45	151	
Group		0.572
FPBC	96	
SPBC	104	
Interval time(months)		**< 0.001***
Synchronous	51	
Metachronous	149	
ER/PR status		**0.041***
Positive	151	
Negative	49	
HER-2 status		0.745
Positive	66	
Negative	134	
T staging		0.126
Tis-T1	53	
T2-4	147	
N staging		0.681
N0	124	
N1-3	76	
Stage of extramammary malignancy		**0.039***
I/II	121	
III/IV	79	
Age at diagnosis of extramammary malignancy (years)		**0.045***
< 60	130	
≥ 60	70	
Smoking history		0.138
Yes	13	
No	187	
Family history of cancers		0.625
Yes	76	
No	124	

Bold indicates that the *P*-value has statistical significance ($P<0.05$)

ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor 2.

*: *P* value < 0.05

tumor, most notably breast cancer [40–43], which was also proved in our prior study [44]. For patients with MPMNs, the breast gland is the second most common site [41], with an elevated risk if thyroid cancer is detected before the age of 50 years [45]. Breast and thyroid carcinomas parallel numerous molecular mechanisms. One of the mechanism might be observing elevated ER levels in thyroid carcinoma cases, exceeding the sex steroid receptor density present in the thyroid parenchyma of the general populace [46, 47]. Moreover, Thyroid receptor mutations contribute significantly to the development of breast hyperplasia [48]. Additionally, in genetic syndromes like Cowden syndrome or Cowden-like syndrome, a close association between breast and thyroid cancers is evident [49]. Our data show thyroid cancer prevalence is greater in SPBC than FPBC (14.3% vs 28.8%, p = 0.011), suggesting additional vigilance towards breast cancer surveillance during thyroid cancer treatment and targeted follow-up. Lung cancer is another prevalent tumor within breast cancer patients in our study. Exclusion of metastases is always necessary if

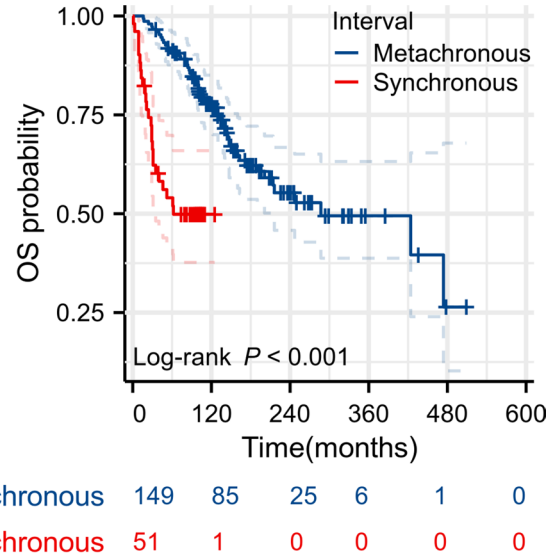

Fig. 2 Overall survival curve of patients with synchronous DPMNs and metachronous DPMNs (n = 200)

breast cancer patients display suspicious lung lesions, as this is the secondary most frequent site of breast carcinoma metastasis after bone [50]. However, coexistence of these two malignancies as primary tumors is not infrequent [23, 51–62]. This may be attributed to high incidences of both cancers coupled with extended survival of breast cancer patients, heightening risk of secondary tumors [63–65]. Moreover, this article underscores the significant correlation between breast cancer and gastrointestinal malignancies. Some studies suggest a sporadic association between high gastrointestinal cancers (such as gastric, esophageal, liver) with breast cancer [26, 52, 66–71]. Others contend that the coexistence of these two cancers could be related to patients' elevated smoking rates compared to the general

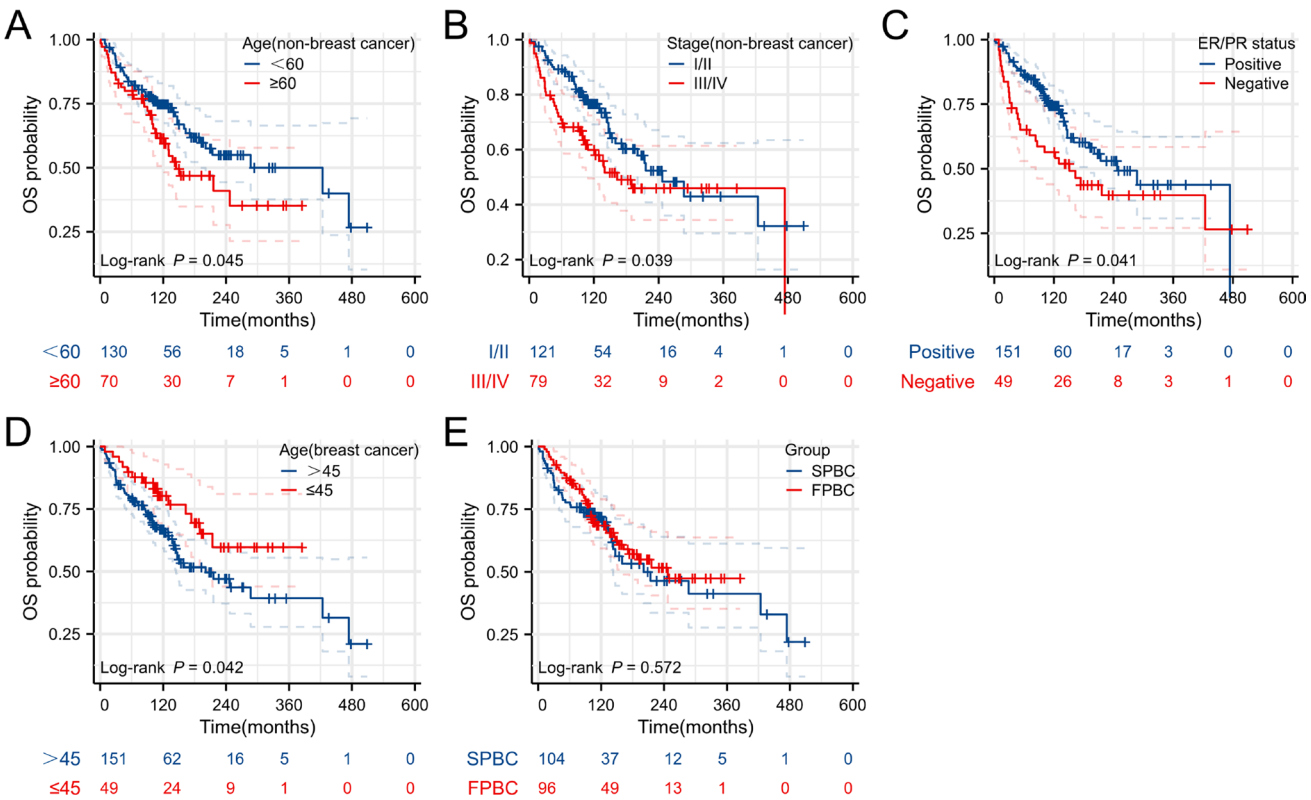

Fig. 3 Univariate survival analysis of patients with DPMNs (n = 200). (**A-E**) Survival curves showed correlations between clinical characteristics and OS

populace [72]. Regrettably, only 6% of patients smoked in this study, impeding further analysis of the relationship between smoking and these two cancers.

In our study, the prognosis of synchronous DPMNs is inferior to that of metachronous DPMNs, which may be due to the superposition of tumor burden caused by two or more malignant tumors occurring in the same individual in a short period of time, which will make body suffer a severe blow, while metachronous DPMNs patients have a certain recovery period. However, cellular and molecular studies need to be further explored. As shown in the study, synchronous DPMNs refer to two primary cancers occur within 6 months, which means that two tumors do not necessarily occur at the same time. In fact, there are not many patients who have a second tumor at the same time in the first diagnosis of breast cancer. Patients with two primary cancers diagnosed at the same time are usually divided into two situations: the first is that if both tumors are very aggressive, we usually choose chemotherapy drugs or treatment methods that have an effect on both tumors; the second situation is that if one of the tumors is indolent, we usually treat the aggressive tumor first, and sometimes we are surprised to find that the indolent tumor shrinks as the treatment progresses, which makes it possible to treat the indolent tumor at a later date. More often, the occurrence of the two tumors is separated by a period of time, such as 2 months. Patient may develop new symptoms, or may be told to have a second cancer through the follow-up examination during the treatment of the first tumor. Unfortunately, this often indicates that the treatment of the first tumor has no effect on the second tumor and may even stimulate the progress of the second tumor. The condition of these patients is usually more complex and requires comprehensive judgment through means such as multi-disciplinary treatment. The prognosis of synchronous DPMNs is very poor, multi-disciplinary treatment usually play an important role in the treatment, and standardized treatment provides a guarantee for improving the prognosis of patients. In addition, based on the findings of this study, 44.1% of patients with primary extramammary malignancies suffer from second breast cancer within 6 months after the diagnosis of the first tumor, which is a high proportion. The occurrence of second breast cancer is mostly occurred in the 0 months to 4 years after the diagnosis of the first tumor, so standardizing follow-up play a great role in the early detection of disease, which could improve the prognosis of these patients.

Many cancer survivors manifest secondary tumors within the initial 5 years post-diagnosis. An analysis of 10,822 patients by Sandi et al. demonstrated that 46.3% of cancer survivors developed breast cancer within 5 years of diagnosis [73]. Our findings align, moreover, we found that the risk of secondary tumors among cancer survivors diminishes over time. To investigate further, we sub-classified DPMNs patients as FPBC or SPBC group. Analysis indicated that nearly all breast cancer survivors (93.9%) manifested a second tumor as a metachronous cancer in FPBC cohort. By 60 months post-diagnosis of breast cancer, half of the metachronous FPBC patients exhibited a second tumor, and no second tumor transpired beyond 300 months. However, the scenario of SPBC patients was distinct. A noteworthy number (44.1%) of survivors of extramammary malignancies presented a second breast cancer within 6 months of diagnosis. The median time interval between the detection of extramammary malignancy and breast cancer in metachronous SPBC patients was 48 months. Moreover, the occurrence of second breast cancer was relentless, without any observable plateau. These results offer clinicians precise follow-up guidelines: i) For initial breast cancer patients, active surveillance is necessary within 6 months to 5 years post-diagnosis to detect extramammary malignancies. Following this period, the frequency can be gradually

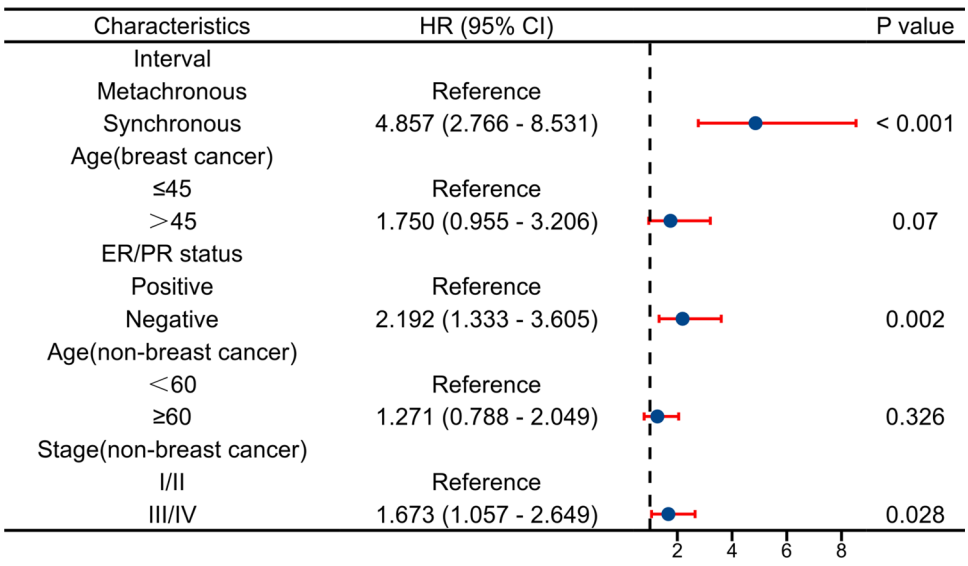

Fig. 4 Multivariable survival analysis of patients with DPMNs (n = 200)

reduced up to 25 years post-diagnosis, at which point follow-up may cease. ii) For extramammary malignancy patients, intensive monitoring is necessary within 0 months to 4 years post-diagnosis to prompt the detection of second breast cancer. Post-4 years, surveillance frequency can be lessened, though it should never cease. Urgent vigilance for secondary primary breast cancer remains imperative.

There are still some limitations in this study. First, this is a retrospective, single-center study in Asia, which may lead to recall bias and selection bias. Second, patients with certain gene mutations (such as BRCA1, BRCA2) are at increased risk of developing secondary malignancies. Unfortunately, most patients in this study are not tested for gene mutations due to their economic constraints, which makes it impossible to obtain mutation data for genes such as BRCA in these patients. Third, stage IV breast cancer patients were excluded, which led to selection bias, while stage IV patients with extramammary malignancies were not excluded, which reduced the rigor of study design. In addition, our study found that breast cancer patients have different probabilities of developing primary extramammary malignancies, which greatly increases the need to explore the molecular mechanisms behind the development of secondary malignancies in breast cancer survivors.This will be the focus of our subsequent research to identify potential risk characteristics and improve patient monitoring in the analysis of genetic or environmental factors leading to these malignancies. In future studies, we plan to progressively incorporate these analyses to enhance our study. At the same time, domestic multi-center and international cooperation should be carried out to eliminate the bias of different genetic backgrounds, environmental exposures and races. In future studies, we plan to gradually incorporate these analyses to enhance our research At the same time, we will carry out multi-center studies in China and international cooperation to eliminate the bias of different genetic backgrounds, environmental exposure and races.

9 Conclusions

In conclusion, MPMNs are not uncommon. Follow-up strategies for FPBC and SPBC patients differ. Synchronous cancer, ER/PR-negative, and advanced stage of non-breast malignancies predict adverse outcomes in DPMNs patients.

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Author contributions BS contributed to the conception of the study. YJ performed the analysis and wrote the manuscript. YJ modified the article. YW,XZ, HW, JZ, and FH collected the data. All authors examined and accredited the final manuscript. All authors contributed to the article and approved the submitted version.

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Data availability All data supporting the findings of this study are available within the paper.

Declarations

Ethics approval and consent to participate Studies involving human participants were approved and reviewed by the Medical Ethics Committee of Tianjin Medical University Cancer Institute & Hospital. Informed consent has been obtained from the patients for the study. The research was carried out following the guidelines of the ethics committee listed in the ethics statement.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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