Clinical characteristics of second primary malignancies among first primary malignancy survivors: A single-center study, 2005-2020

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Abstract. The cancer survivor population is growing due to advances in detection and treatment. For improved long-term patient management, it is critical to examine the clinical characteristics and outcomes of second primary malignancies (SPMs). An SPM is defined as a second distinct pathological diagnosis, with the same or different origin as the first primary malignancy (FPM). In the present retrospective study, categorical clinical variables were compared between subgroups and the impact on overall survival was evaluated. A total of 1,188 patients with an FPM were included, of which 102 experienced an SPM (8.59%). When compared with the patients who did not develop an SPM, patients with an SPM were significantly older at first diagnosis, had a higher pathological stage and higher rates of biliary tract disease and thyroid disease. In addition, patients with an SPM were more likely to have received postoperative chemotherapy (28.43 vs. 12.16%, P<0.0001) and to be long-term consumers of cigarettes and alcohol (25.00 vs. 8.95%, P<0.05). In addition, an increase in the number of regimens received but not in the number of courses of chemotherapy was associated with a reduction in the time interval to SPM development. Non-small cell lung cancer (NSCLC) was the most common type of FPM (18.27%). In patients with NSCLC the occurrence of SPMs was relatively low (5.07%) and the SPM-associated mortality rate was 2.30%. Breast cancer was the second common type of FPM (12.09%). Patients with breast cancer had a relatively high likelihood of developing an SPM (9.30%), for which family history of malignancy and postoperative chemotherapy were identified as potential risk factors. Patients with stomach cancer were the most vulnerable to SPM (17.95%) and patients with digestive tract cancer had the longest time interval between the FPM and SPM development. In addition, thyroid adenoma was identified as a potential risk factor for SCLC. The findings of the present study may provide valuable guidance for the short- and long-term monitoring of FPM survivors.

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Introduction

Population aging and exposure to carcinogenic factors from industry and lifestyle choices, in addition to improvements in detection have resulted in the reported cancer incidence increasing in China (1). Due to advances in cancer treatment, including molecular targeted therapy, immunotherapy and heavy ion radiotherapy, the 5-year survival rate of most types of cancer has improved substantially over the past two decades, with an increase for all cancers combined from 30.9% during 2003-2005 to 40.5% during 2012-2015 (2). In parallel with the prolonged survival and growth of the first primary

malignancy (FPM) survivor population (3), the occurrence of second primary malignancies (SPMs) has increased markedly over recent decades in the USA (4) and other countries (5-8). Big data analysis has revealed the clinical characteristics of SPMs in the US population (9-11), which has aided in clinical decisions and healthcare policies.

In China, case reports (12) and retrospective analyses (13,14) have examined SPMs derived from first primary non-hematological malignancies, but most of these have focused on one or more cases of a single cancer type. Therefore, essential issues such as risk factors for SPM, the FPM-SPM time interval for specific types of cancer and the long-term efficacy of FPM treatment remain unclear for the Chinese population. Therefore, the present retrospective cohort study was conducted at a single center to assess the clinical characteristics of Chinese patients with an SPM, focusing on the site distributions of the FPM and SPM, the influence of cancer treatment and pathological stage on the FPM-SPM interval, the impact of SPM on the overall survival (OS) of patients with lung or breast cancer, and the potential impacts of continued alcohol consumption, biliary tract diseases and benign FPM on SPM risk.

Materials and methods

Patient cohort. A retrospective patient cohort from the Oncology Department of The Hospital of 81st Group Army PLA (Zhangjiakou, China), a former national military center for the treatment of cancer using integrated Chinese and Western medical methods, was examined. A total of 1,423 patients with malignancy were enrolled and 235 cases were excluded due to the lack of a pathological diagnosis, according to clinical records dating from June 1, 2005 to December 30, 2020.

To ensure the quality of the data, inpatient cases were selected and associated information was gathered from inpatient records and from the medical staff via telephone. All patients who did not meet the exclusion criteria were excluded. The exclusion criteria were as follows: i) Patients with hematological malignances, who were enrolled mainly in the Hematology Department; ii) patients receiving outpatient chemo- or radiotherapy in this hospital, with no access to long term follow-up; iii) patients without histopathological confirmation of malignancy or whose detailed follow-up was not available; and iv) patients at high risk of the development of SPMs due to hereditary cancer syndromes.

The cohort was then established according to the following inclusion criteria: i) Patients diagnosed with FPM and SPM confirmed pathologically; ii) patients receiving at least one course of inpatient radio- or chemotherapy; iii) patients who developed SPM at an interval of ≥6 months, which is considered to be the standard for distinguishing between synchronous malignancy and SPM in the cohort of patients with breast or gastric cancer, the two main types of cancer that were separately analyzed in the present study (13,15); and iv) patients with regular follow up (recorded every ~2 months during the course of therapy, and at least every 3 months for 2 years, then every 6 months after the first 2 years).

Data collection. The clinical data collected included the age of the patient at diagnosis, the time interval between the FPM and SPM, treatment of the FPM, sites of the FPM and SPM, complications of diabetes, hypertension and biliary tract diseases, family history of cancer, cigarette use, alcohol consumption and OS. The age of the participants ranged from 20 to 78 years. As the average age of FPM diagnosis was ~60 years, and drinking and smoking are not common among teenagers, 40 years was regarded as the standard for long-term consumption when investigating the association of long-term tobacco use and excessive alcohol intake with the occurrence of SPM. Data on family history of cancer and the presence of thyroid and biliary tract diseases, namely cholecystolithiasis, cholecystitis and cholecystectomy, were mainly obtained from the records at first admission. Patients diagnosed with hypertension or diabetes by an endocrinologist or cardiologist before the first diagnosis of malignancy were regarded as patients with hypertension while those who developed hypertension during cancer treatment were not. Diabetes and hypertension were mostly controlled during cancer treatment, with the exception of two female patients with esophageal cancer, who developing uncontrolled hypertension prior to lethal upper gastrointestinal bleeding, and three patients with lung squamous cell carcinoma (LUSC) and one patient with lung adenocarcinoma (LUAD) who were treated with anti-angiogenic therapy and suffered from uncontrolled hypertension, which eased with the withdrawal of the therapy. The prescription of chemotherapy and intensity-modulated radiation therapy was administered by colleagues in the oncology department mainly according to guidelines from the National Comprehensive Cancer Network (16).

Bioinformatics analysis. Gene profiles of SCLC cell populations were investigated through the online database SynEcoSys (version V1.1.0; Singleron Biotechnologies). The access numbers of the three datasets involved in this paper were GSE129299, GSE150766 and GSE161570. All datasets are visualized with UMAP plots in 2D. The 'Explore gene expression' tab plots the expression of a single gene using UMAP. DEGs with log transformed fold change >1, expressed in >10% of the cells and with $P \leq 0.05$ are considered significant in this database.

Statistical analysis. GraphPad Prism 8.0 software (GraphPad Software, Inc.) was used to analyze the data. Basic characteristics were summarized as counts and frequencies and comparisons of categorical characteristics were made using Chi-square or Fisher's exact tests. For continuous characteristics, analysis was performed using an unpaired t-test or one-way ANOVA (with Turkey's multiple comparisons test for the pairwise comparison of groups). The odds ratio (OR) of each variable and the corresponding 95% confidence interval (CI) were calculated using univariate analysis. OS was defined as the period between the date of FPM diagnosis and the last known date of follow-up or the date of death. Cumulative survival was evaluated by Kaplan-Meier analysis and differences in survival curves between groups of patients were assessed using the log-rank (Mantel-Cox) test. The hazard ratio (HR) was calculated using the Mantel-Haenszel test. A two-tailed $P<0.05$ was considered to indicate a statistically significant result for all tests.

Results

Baseline characteristics. A total of 1,188 patients were diagnosed with an FPM between June 1, 2005 and December 30, 2020 and 102 (8.59%) of these patients subsequently developed

an SPM. The 1,086 patients who did not develop an SPM were designated as the FPM group. In the comparison of baseline characteristics between the SPM and FPM groups (Table I), the patients with an SPM presented at a significantly older age at diagnosis (59.72±10.22 vs. 57.22±11.17 years, P<0.05), higher rate of biliary tract disease (14.71 vs. 7.73, P<0.05) and thyroid disease (7.84 vs. 1.01%, P<0.0001), lower rate of receiving radiochemotherapy (14.71 vs. 34.90%, P<0.0001) and higher rate of receiving post-operative chemotherapy (28.43 vs. 12.16%, P<0.0001). In addition, no significant differences were detected between the FPM and SPM groups in sex ratio, family history of cancer and metabolic syndromes, including diabetes and hypertension. Notably, the results on cigarette and/or alcohol consumption revealed that the proportion of patients with ≥40 years' consumption of both cigarettes and alcohol in the SPM group was much higher than that in the FPM group (25.00 vs. 8.95%, P<0.05), while the long-term use of either cigarette or alcohol alone was not found to be significantly different between the SPM and FPM groups (Table II).

Clinical characteristics of the SPM cohort. To visualize the characteristics of the SPM cohort, the distribution of the primary and second cancer sites in the SPM group was analyzed as a heat map (P=0.0014; Fig. 1A), and significant differences were identified (Table I). Non-small cell lung cancer (NSCLC; 13.73%) and breast cancer (15.69%) were the two most common types of cancer for the first diagnosis in the SPM group, followed by digestive tract malignancies (stomach cancer, 6.86%; esophageal cancer, 4.90%; and colorectal cancer, 4.90%) for which details are shown in Tables SI-SIII. In addition, the occurrence rate of SPM development in patients with primary NSCLC was 5.07%, which was much lower than that of stomach cancer (17.95%), esophageal cancer (8.33%) and breast cancer (9.30%). Moreover, the results suggest potential associations between the distributions of FPM and SPM. For example, patients with first primary colorectal tumors were prone to SPM in the colon and rectum (6/18), while patients with an FPM in the breast frequently developed reproductive system tumors as the SPM (6/17). Due to the diverse OS times of different types of cancers and the markedly different constitution of the FPM and SPM cohorts, a comparison of the OS between SPM and FPM groups was not performed. However, it was observed that the TNM stage of the SPMs was more advanced than that of the FPMs (P=0.0061; Fig. 1C). This establishes an SPM as a life-threatening event, which was subjected to further examination in specific types of cancer. These results confirm that breast cancer is a common type of FPM with high likelihood of SPM development, and SPMs tend to be more advanced than FPMs.

The time interval between the FPM and SPM among cancer types was investigated. A broad distribution of intervals was observed for different types of cancer, among which the mean time interval for digestive tract cancers was the longest (79.00 months, 95% CI: 40.71-117.3), while that for lung cancer was the shortest (33.36 months, 95% CI: 8.121-58.61) without statistical significance (P=0.2705; Fig. 1B). Thus, patients with digestive tract cancer were not only the most vulnerable to SPM, but also had the longest time interval for the development of SPM in the present study population.

Although it has been reported that cancer treatment increases the risk of SPM development (17,18), no impact of radiotherapy, chemotherapy or surgical resection alone on the risk of SPM was found in the present study. However, adjuvant chemotherapy after surgery significantly increased the risk of developing an SPM (OR, 2.871; 95% CI: 1.804-4.518, Table I). Furthermore, the results showed that chemotherapy significantly reduced the FPM-SPM interval to 46.86±8.355 months compared with 85.15±12.66 months for patients who received no chemo- or radiotherapy (P<0.05; Fig. 2A). However, no difference in the FPM-SPM time interval was observed between patients receiving radiotherapy or radiochemotherapy and those who received no chemo- or radiotherapy. To explore the factors responsible for the chemotherapy-associated reduction of the FPM-SPM time interval, the impact of the numbers of chemotherapy regimens (Fig. 2B) and courses (Fig. 2C) on the time interval were then investigated. The results revealed that an increase in the number of regimens but not in the number of courses reduced the FPM-SPM time interval. Given the ubiquity of platinum-based chemotherapy as the first-line treatment for cancers, the effect of platinum-based treatment was analyzed separately, but no significant difference was detected among different numbers of courses (Fig. 2D). These results indicate that the chemotherapy regimen, with the exception of platinum-based chemotherapy, accelerated the occurrence of SPM, particularly in postoperative patients.

Separate analysis of patients with NSCLC or breast cancer. Lung and breast cancers were the most two common FPMs in the present study; therefore, they were subjected to further analysis. A total of 109 cases of LUSC, 96 cases of LUAD and 103 cases of small cell lung cancer (SCLC), together with 28 cases of other types, including neuroendocrine, carcinoid and sarcomatoid cancers, formed the cohort of lung cancer patients (Table SIV). There were 11 patients among the 217 patients with NSCLC who developed a SPM (Table SV), while none of the patients with SCLC did so. In patients with NSCLC, when the clinical characteristics were compared between patients with and without an SPM (Table III), no significant difference was identified in family history of malignancy, the consumption of alcohol or cigarettes, treatment strategy or biliary tract disease. In addition, the proportion of cases with a pathological stage of ≥IIIA was significantly higher for patients without an SPM than for those with an SPM (81.55 vs. 54.55%, P<0.05). Furthermore, the results of Kaplan-Meier analysis revealed a significant reduction in OS for patients with NSCLC without an SPM compared with those with an SPM, with a markedly reduced median survival time (15 vs. 52 months, P<0.001; Fig. 3A). However, the proportion of SPM-associated deaths was only 45.45% (5/11) for the SPM group and 2.30% for the entire NSCLC cohort. The impact of pathological stage (Fig. 3B) and type (Fig. 3C) on the time interval of SPM development in patients with an NSCLC FPM was further analyzed and no significant difference was detected. In addition, no significant difference in the time of survival with SPM was detected between patients with LUSC and LUAD FPMs (Fig. 3D). Therefore, the improved OS of the SPM group may largely be associated with the early stage at which the primary NSCLC

Table I. Clinical characteristics of patients with and without SPM.

Characteristics	Total (n=1,188)	Patients with SPM (n=102)	Patients without SPM (n=1,086)	P-value
Age, years, mean ± SD (range)	57.43±11.11 (31-84)	59.72±10.22 (41-74)	57.22±11.17 (31-84)	0.0299
Female, n (%)	577 (48.57)	50 (49.02)	527 (48.53)	>0.9999
DM, n (%)	50 (4.21)	4 (3.92)	46 (4.24)	>0.9999
HP, n (%)	146 (12.29)	14 (13.73)	132 (12.15)	0.6370
DM and HP, n (%)	29 (2.44)	2 (1.96)	27 (2.49)	>0.9999
Family history of cancer, n (%)	116 (9.76)	11 (10.78)	105 (9.67)	0.7266
Biliary tract disease, n (%)	99 (8.33)	15 (14.71)	84 (7.73)	0.0228
Thyroid disease, n (%)	19 (1.60)	8 (7.84)	11 (1.01)	<0.0001
Cancer type, n (%)				
NSCLC	217 (18.27)	11 (13.73)	206 (18.97)	0.0438
SCLC	103 (8.67)	0	103 (9.48)	NA
Other types of lung cancer	31 (2.61)	3 (2.94)	28 (2.58)	0.7443
Breast cancer	172 (12.09)	16 (15.69)	156 (11.81)	0.6616
Esophageal cancer	60 (5.05)	5 (4.90)	55 (5.06)	>0.9999
Stomach cancer	39 (3.283)	7 (6.863)	32 (2.947)	0.0717
Colorectal cancer	88 (7.41)	5 (4.90)	83 (7.64)	0.4279
Other	478 (40.24)	55 (53.92)	423 (38.95)	0.0042
Treatment, n (%)				
None	26 (2.19)	3 (2.94)	23 (2.12)	0.4835
RT	56 (4.71)	4 (3.92)	52 (4.79)	>0.9999
CT	144 (12.12)	8 (7.84)	136 (12.52)	0.204
RCT	394 (33.16)	15 (14.71)	379 (34.90)	<0.0001
ST	32 (2.69)	4 (3.92)	28 (2.58)	0.3469
SRT	46 (3.87)	4 (3.92)	42 (3.87)	>0.9999
SCT	161 (13.55)	29 (28.43)	132 (12.16)	<0.0001
SRCT	329 (27.69)	35 (34.31)	294 (27.07)	0.1322

SPM, second primary malignancy; DM, diabetes mellitus; HP, hypertension; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; RT, radiotherapy; CT, chemotherapy; RCT, radiochemotherapy; ST, surgical resection; SRT, post-surgical RT; SCT, post-surgical CT; SRCT, post-surgical chemotherapy; NA, not applicable.

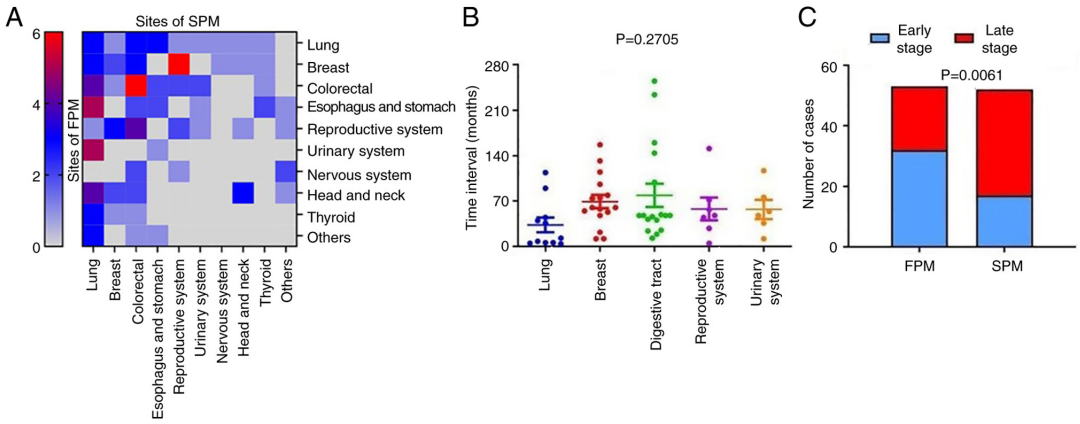

Figure 1. Clinical characteristics of the SPM cohort. (A) Heat map showing the distribution of the sites of FPM and SPM, including 7 cases of thyroid adenoma as the FPM. (B) Comparison of FPM-SPM intervals for different cancer types. (C) Comparison of pathological stages between FPMs and SPMs, where early stage is defined as TNM I/II and late stage is defined as TNM III/IV. SPM, second primary malignancy; FPM, first primary malignancy.

was treated with the SPM itself showing limited impact on the OS of the NSCLC cohort.

In contrast with NSCLC, a family history of malignancy was screened out as a risk factor of the development of an

Table II. Influence of long-term cigarette or/and alcohol consumption on the risk of developing an SPM for male FPM patients.

	A_0		A_{10}		A_{20}		A_{30}		A_{40}	
Consumption	SPM	No SPM	SPM	No SPM	SPM	No SPM	SPM	No SPM	SPM	No SPM
C_{40}	3 (5.77)	74 (13.24)	0 (0.00)	5 (0.89)	1 (1.92)	11 (1.97)	3 (5.77)	15 (2.68)	13 (25.00)[a]	50 (8.95)
C_{30}	6 (11.54)	56 (10.02)	0 (0.00)	1 (0.18)	3 (5.77)	14 (2.50)	1 (1.92)	56 (10.02)	0 (0.00)	5 (0.89)
C_{20}	2 (3.85)	38 (6.80)	0 (0.00)	3 (0.54)	0 (0.00)	23 (4.11)	0 (0.00)	6 (1.07)	1 (1.92)	0 (0.00)
C_{10}	0 (0.00)	6 (1.07)	1 (1.92)	3 (0.54)	0 (0.00)	3 (0.54)	0 (0.00)	0 (0.00)	0 (0.00)	00 (0.00)
C_0	13 (25.00)	157 (28.09)	3 (5.77)	3 (0.54)	1 (1.92)	6 (1.07)	1 (1.92)	6 (1.07)	0 (0.00)	8 (1.43)

[a]P<0.05 for $C_{40}A_{40}$ vs. C_0A_0. SPM, second primary malignancy; FPM, first primary malignancy; C, cigarette; A, alcohol; C/A_{30}, regular cigarette/alcohol consumption for 30-39 years.

SPM in patients with breast cancer (OR, 6.167; 95% CI: 1.819-22.68). The proportion of patients with an SPM that received post-operative chemotherapy was significantly higher than of patients without an SPM and was accompanied by a reduction in the proportion of patients that received radiochemotherapy after surgery (Table IV). Moreover, although no difference in OS was detected between the FPM and SPM groups (Fig. 3E), the mortality rate for patients with breast cancer who did not develop an SPM was only 22.44% and 13/16 (81.25%) patients with an SPM succumbed to the second malignancy. The pathological stage exhibited no significant effect on the occurrence of an SPM in patients with breast cancer (Table IV), whereas a higher stage (≥IIIA) in the SPM group was found to be associated with a significant reduction in the time interval for SPM development (Fig. 3F). Differences among the sites at which an SPM occurred showed no significant impact on the time interval for SPM development (Fig. 3G) or the time of survival with an SPM (Fig. 3H) in patients with breast cancer. These results support the idea that patients with breast cancer who have a family history of malignancy or have received postoperative chemotherapy are more vulnerable to the development of an SPM and a shortened time interval for SPM development is expected for patients with late-stage breast cancer.

Thyroid adenoma maybe a sign of SCLC development. In the present study, patients with an SPM presented a higher rate of biliary tract or thyroid disease than those without an SPM, as shown in Table I. Excluding one case with hypothyroidism, the present study included 7 patients with thyroid adenoma, all of whom received excision surgery and also developed an SPM (Fig. 4A). Of these SPMs, SCLC was the most common type (42.86%) and the FPM-SPM interval was relatively short at 40.67±2.91 months. However, only one of the 5 patients with thyroid carcinoma who subsequently had an SPM developed SCLC. This indicates that benign tumors may also increase the risk of subsequent malignancy at a different site.

To clarify this potential association, the thyroid adenoma signaling-associated gene profiles of SCLC cell populations from three different studies were investigated using bioinformatics analysis. The differentially expressed genes (DEGs) of thyroid adenoma are reported to be insulin-like growth factor 2 (IGF2), von Willebrand factor (VWF), complement factor D (CFD) and multimerin 1 (MMRN1), which are involved in the regulation of IGF and the complement and collagen systems (19). Therefore, an investigation of the corresponding receptors for DEG-mediated signaling [the IGF2 receptor (IGF2R) for IGF2, complement C5a receptor 1 (C5AR1) for CFD and coagulation factor V (F5) for MMRN1] and the VMF expression profile was performed using a dataset from an orthotopic SCLC mouse model available on SynEcoSys, with the commonly used SCLC biomarker thyroid transcription factor 1 as the reference (20). The results showed that the expression of IGF2R and VWF was relatively high in cancer cells, while the expression of F5 and C5AR1 was high in the surrounding immune cells. In addition, the expression profiles of integrin subunit α V (ITGAV), integrin subunit β 3, solute carrier family 16 member 2/10 (SLC16A2/10) and thyroid hormone

Table III. Clinical and pathological characteristics of patients with NSCLC.

Characteristics	Total (n=217)	Patients with SPM (n=11)	Patients without SPM (n=206)	P-value
Age, years, mean ± SD (range)	60.91±0.45 (31-77)	59.71±2.84 (41-71)	60.95±0.45 (31-77)	0.6406
Sex, n (%)				0.2451
Female	45 (20.74)	4 (36.36)	41 (19.90)	
Male	172 (79.26)	7 (63.64)	165 (80.10)	
Cigarette and alcohol consumption, n (%)				
None	23 (10.60)	4 (36.36)	19 (9.22)	
C_{30}	26 (11.98)	2 (18.18)	24 (11.65)	0.4002
$C_{30}A_{30}$	41 (18.89)	5 (45.45)	36 (17.48)	0.6972
Treatment, n (%)				
RT	8 (3.69)	1 (9.09)	7 (3.40)	0.5517
CT	32 (14.75)	1 (9.09)	31 (15.05)	0.6431
RCT	48 (22.12)	4 (36.36)	44 (21.36)	
SCT	16 (7.37)	1 (9.09)	15 (7.28)	>0.9999
SRT	33 (15.21)	1 (9.09)	32 (15.53)	0.5892
SRCT	28 (12.90)	2 (18.18)	26 (12.62)	
Family history of malignancy, n (%)	36 (16.59)	4 (36.36)	32 (15.53)	0.0889
DM, n (%)	12 (5.53)	1 (9.09)	11 (5.34)	0.4733
Biliary tract disease, n (%)	15 (6.91)	2 (18.18)	13 (6.31)	0.1707
TNM stage, n (%)				0.0442
≤IIB	43 (29.82)	5 (45.45)	38 (18.45)	
≥IIIA	174 (80.18)	6 (54.55)	168 (81.55)	
Median survival in months, n (%)	15.5, 120 (55.30)	52, 11 (100)	15, 109 (52.91)	0.0007
Succumbed to SPM, n (%)	5 (2.30)	5 (45.45)	NA	NA

NSCLC, non-small cell lung cancer; SPM, second primary malignancy; C_{30}, regular cigarette consumption for 30-39 years; $C_{30}A_{30}$, regular cigarette and alcohol consumption for 30-39 years; RT, radiotherapy; CT, chemotherapy; RCT, radiochemotherapy; ST, surgical resection; SRT, post-surgical RT; SCT, post-surgical CT; SRCT, post-surgical chemotherapy; DM, diabetes mellitus; NA, not applicable.

receptor α/β (THRA and THRB) were explored, as these molecules function as transporters or receptors of thyroid hormones and regulate the thyroid hormone signaling pathway. The cancer cells were positive for SLC16A2, SLC16A10 and THRA while the other genes were enriched in paracancerous cells (Fig. 4B).

Further analysis of single cell RNA sequencing (scRNA-Seq) datasets from another two independent studies was conducted. The first dataset revealed that IGF2R, ITGAV or THRA positive cancer cells gradually increase over time at a similar rate to that at which SCLC cells evolve from being neurogenic differentiation factor 1 positive to being Yes1 associated transcriptional regulator positive (Fig. 5A and B) (21). The second dataset revealed that despite their abundant expression in orthotopic SCLC cells, relatively high expression levels of IGF2R, ITGAV and THRA were also detected in liver metastases, whereas THRB was absent (Fig. 5C and D) (22). These results suggest that thyroid adenoma signals via IGF, the complement system, collagen system and thyroid hormones, and SCLC cells are well-prepared to receive these signals. Moreover, this potential connection may affect the evolution, metastasis and immunotherapy of SCLC.

Discussion

To the best of our knowledge, this is the first description of SPM characteristics in Chinese patients with diverse non-hematological malignancies (23). The study population comprised only patients with solid tumors as those with hematological malignances were treated by other departments. Furthermore, due to the relatively small number of FPM cases, it was not possible to describe SPMs following less common types of primary tumor. However, the distribution of FPMs was sufficient to examine cancers of the lung, breast, colon and rectum, esophagus and stomach, reproductive system, urinary system, nervous system, head and neck and thyroid. The results of this study provide valuable information on the potential sites and time to recurrence of SPMs for specific FPMs in Chinese patients.

The relative incidences of common types of cancer in China, including lung, colorectal and female breast cancer, are comparable to those in the USA (24). Therefore, it is rational to compare differences in SPM characteristics from the present study to US data. In a previous study it was reported that nearly 1 in 12 patients (8.1%) diagnosed with a common cancer in the US develop a second malignancy, with

Table IV. Clinical and pathological characteristics of patients with breast cancer.

Characteristics	Total (n=172)	Patients with SPM (n=16)	Patients without SPM (n=156)	P-value
Age, years, mean ± SD (range)	50.90±0.70 (24-72)	52.00±2.86 (24-67)	50.78±0.71 (28-72)	0.6131
Treatment, n (%)				0.0371
SCT	48 (27.91)	8 (50.00)	40 (25.64)	
SRCT	119 (69.19)	7 (43.75)	112 (71.79)	
Family history of malignancy, n (%)	12 (6.98)	4 (25.00)	8 (5.13)	0.0159
Biliary tract disease, n (%)	14 (8.14)	3 (18.75)	11 (7.05)	0.1271
DM, n (%)	9 (5.23)	1 (6.25)	8 (5.13)	0.5938
HP, n (%)	16 (9.30)	3 (18.75)	13 (8.33)	0.1737
TNM stage, n (%)				0.5508
≤IIB	61 (35.47)	9 (56.25)	57 (36.54)	
≥IIIA	65 (37.79)	7 (43.75)	61 (39.10)	
Median survival in months, n (%)	80.50, 48 (27.91)	82, 13 (81.25)	67, 35 (22.44)	0.3526
Succumbed to SPM, n (%)	13 (7.56)	13 (81.25)	NA	NA

SPM, second primary malignancy; SCT, post-surgical CT; SRCT, post-surgical chemotherapy; DM, diabetes mellitus; HP, hypertension; NA, not applicable.

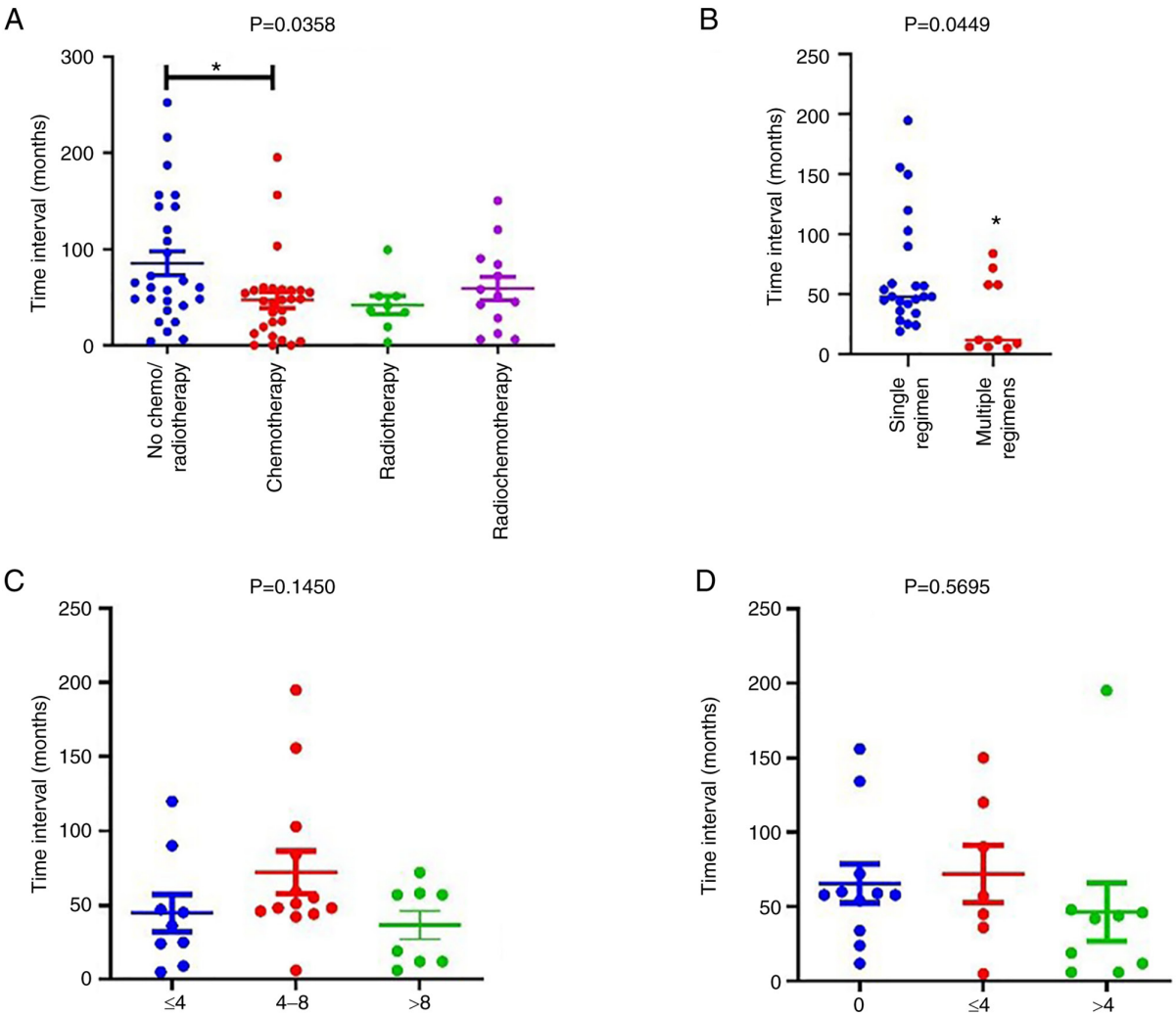

Figure 2. Impact of therapy on the FPM-SPM time interval. Influence of the (A) anticancer treatment modality, specifically chemotherapy, radiotherapy, both or neither, (B) number of chemotherapy regimens, (C) number of chemotherapy courses and (D) number of platinum-based chemotherapy courses on the FPM-SPM interval. FPM, first primary malignancy; SPM, second primary malignancy.

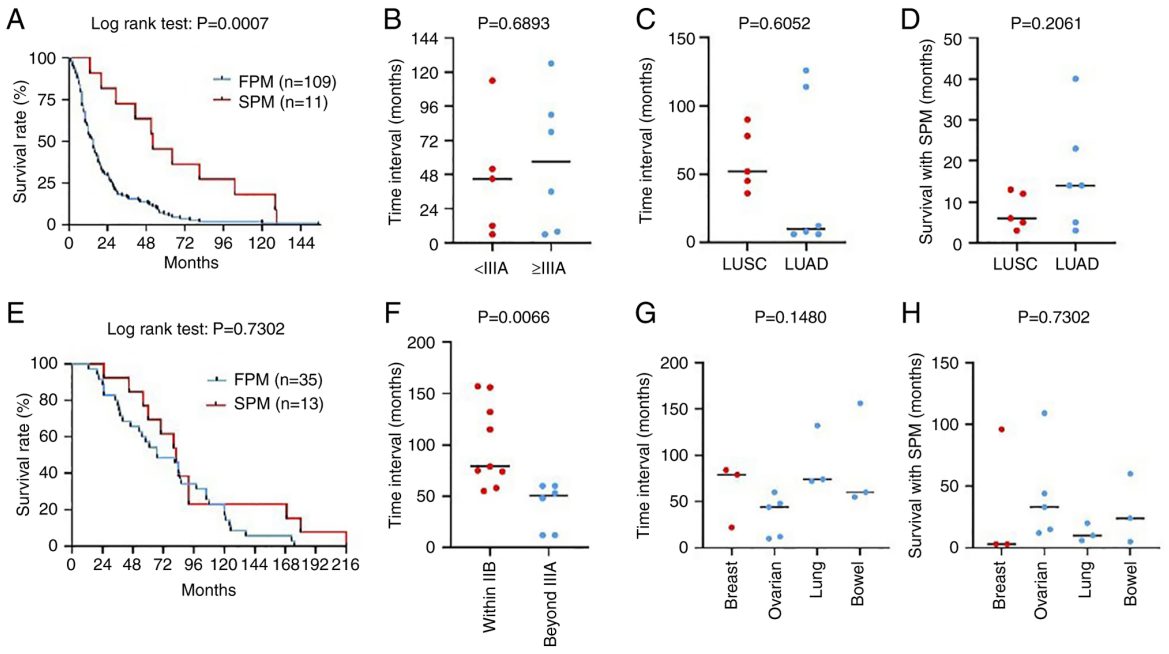

Figure 3. Influence of SPMs on the OS of patients with lung or breast cancer. (A) Kaplan-Meier curves comparing the impacts of SPMs and FPMs on the OS of patients with NSCLC. (B) Effect of TNM stage on the FPM-SPM interval of patients with NSCLC. Influence of NSCLC tumor type on the (C) FPM-SPM interval and (D) survival time of patients with an SPM. (E) Kaplan-Meier curves comparing the impacts of SPMs and FPMs on the OS of patients with breast cancer. (F) Effect of TNM stage on the FPM-SPM interval of patients with breast cancer. Influence of the pathological type of SPM on the (G) interval time and (H) survival time of patients with an SPM following a breast cancer FPM. SPM, second primary malignancy; OS, overall survival; FPM, first primary malignancy; NSCLC, non-small cell lung cancer; LUSC lung squamous cell carcinoma; LUAD, lung adenocarcinoma.

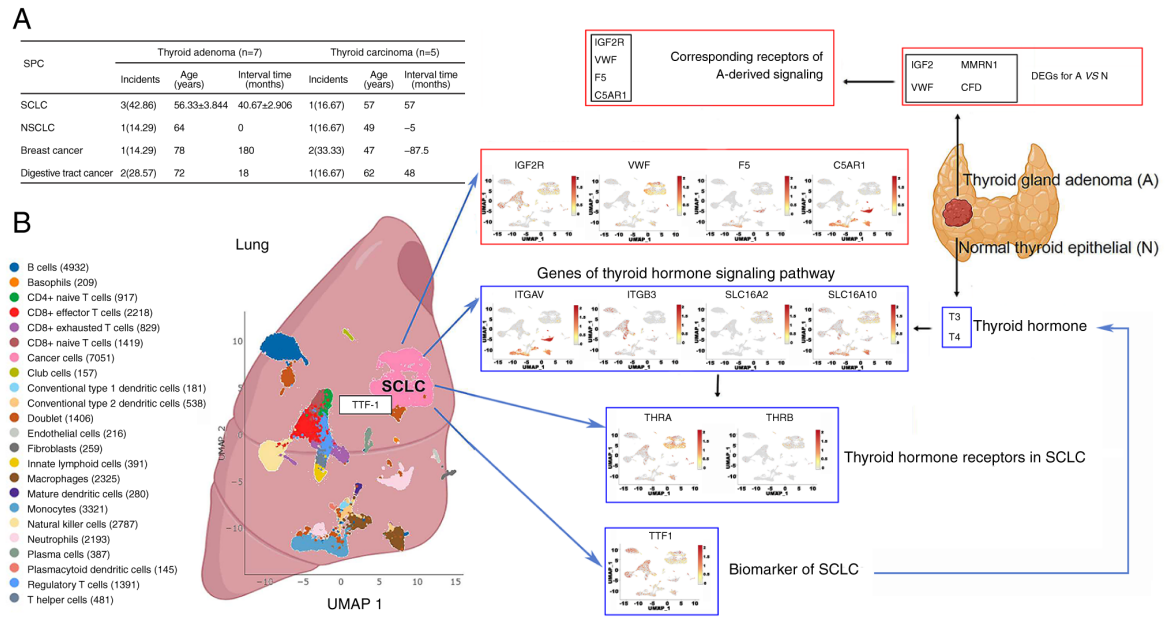

Figure 4. Potential association between thyroid gland adenoma and SCLC. (A) Summary of the clinical characteristics of the SPMs for thyroid gland adenoma and thyroid carcinoma. (B) Analysis of the expression profiles of the receptors corresponding to the DEG-mediated signaling from thyroid gland adenoma. Vital genes involved in the thyroid hormone signaling pathway and TTF-1 in SCLC cells, based on a reported single cell RNA-sequencing dataset analyzed using SynEcoSys (Singeron). SCLC, small cell lung cancer; NSCLC, non-SCLC; SPM, second primary malignancy; DEG, differentially expressed gene; TTF-1, thyroid transcription factor 1; IGF2, insulin-like growth factor 2; IGF2R, IGF2 receptor; VWF, von Willebrand factor; MMRN1, multimerin 1; F5, coagulation factor V; CFD, complement factor D; C5AR1, complement C5a receptor 1; ITGAV, integrin subunit α V; ITGB3, integrin subunit β 3; SLC16A2/10, solute carrier family 16 member 2/10; THRA, thyroid hormone receptor α; THRB, thyroid hormone receptor β; T3, triiodothyronine; T4, thyroxine.

the majority of the patients with an SPM being >65 years old (60%) and significantly older than those without an SPM, with a well differentiated or moderately differentiated first cancer (55%) (4). In the present study, the SPM rate at 8.59% was comparable with and within the range of previous reports (5.5-16%) (25,26). In addition, the median age at first diagnosis of the SPM cohort was significantly older than that of patients without an SPM (59.72±10.22 vs. 57.22±11.17 years,

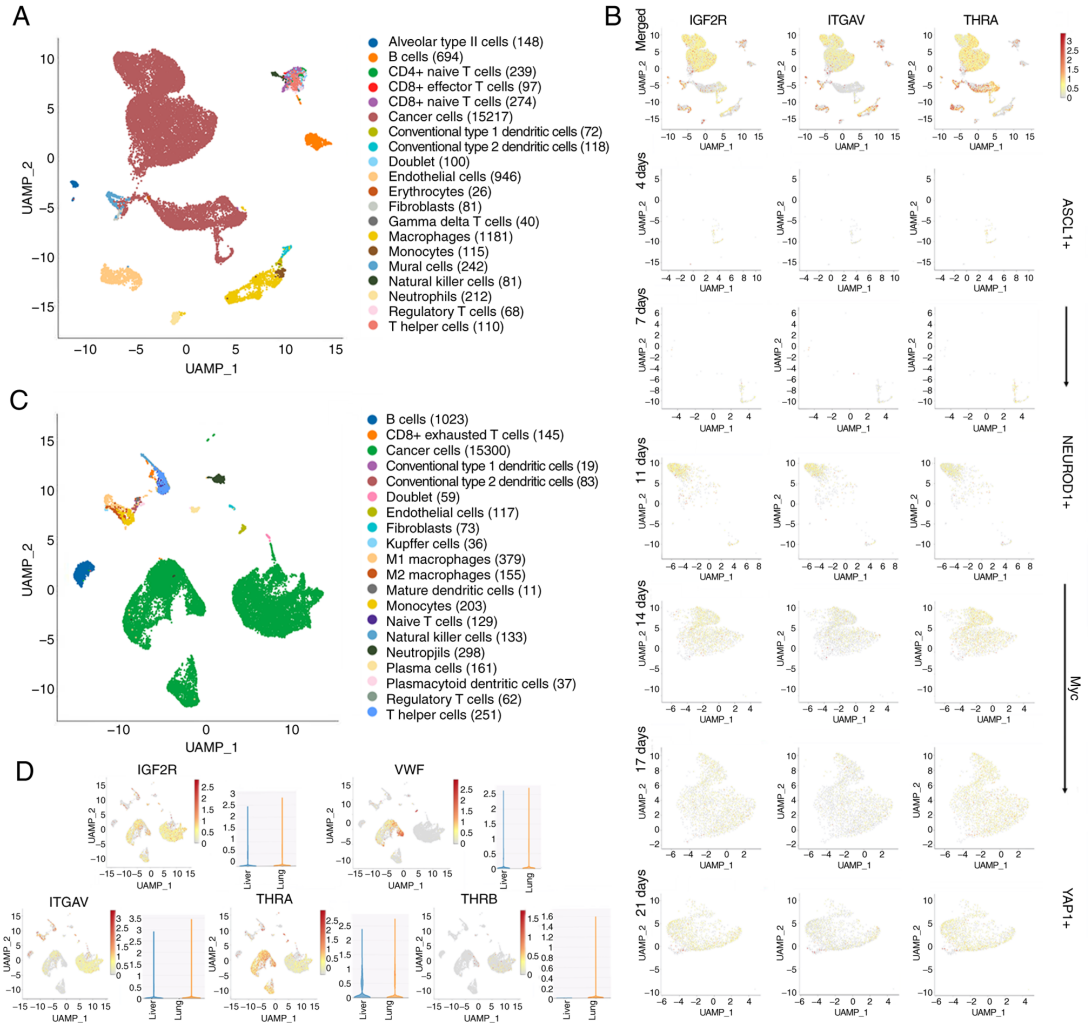

Figure 5. Signaling associated with thyroid gland adenoma affects the evolution and metastasis of SCLC. (A) The UAMP projection of main clusters in human SCLC samples. (B) Investigation of the changes of IGF2R, ITGAV and THRA expression over time in the Myc-driven evolution of SCLC, through SynEcoSys based on scRNA-Seq of human SCLC samples. (C) The UAMP projection of main clusters in orthotopic and metastatic SCLC tissues from mice. (D) Analysis of expression profiles of genes responsive for signaling from thyroid gland adenoma in orthotopic and metastatic SCLC tissues, through SynEcoSys based on scRNA-Seq of mouse SCLC samples. SCLC, small cell lung cancer; IGF2R, insulin-like growth factor 2 receptor; ITGAV, integrin subunit α V; THRA, thyroid hormone receptor α; scRNA-Seq, small conditional RNA-sequencing; VWF, von Willebrand factor; THRB, thyroid hormone receptor β; ASCL1, achaete-scute homolog 1; NEUROD1, neurogenic differentiation factor 1; YAP1, Yes1 associated transcriptional regulator.

P<0.05). Consistent with previous reports (4,9,21), a relatively large proportion of the SPMs were lung cancer, and none of the SCLC cases developed SPM; however, the proportion of cases of SCLC rose markedly to 15.69% (16/102) as the second diagnosis of the SPM cohort.

In contrast to previous reports (9,27,28), prostate cancer was rare as the FPM in the present study. Also, the present study demonstrated that patients with gastrointestinal malignances were most vulnerable to SPM and had a relatively long FPM-SPM interval. In addition, a longer OS of patients with an SPM was observed for the NSCLC cohort. However, patients with a FPM who have a longer survival time are more likely to develop an SPM. Notably, the TNM stage of 6/11 NSCLC patients with an SPM was ≥IIIA, while 168/206 of those without an SPM were in a relatively late stage in terms of the diagnosis at first admission. Furthermore, 16 patients with breast cancer developed an SPM and 13 of them succumbed to the SPM (81.25%). By contrast, the mortality rate for patients with breast cancers without an SPM was only 35/156 (22.44%). Thus, having an early-stage cancer allows for longer survival and the development of an SPM, which results in a relatively longer OS for patients with an SPM than those without an SPM. However, the SPM itself increases the risk of death. In light of these distinct characteristics of Chinese SPM cases, larger scale studies including patients from different regions, with different FPM types, FPM treatments and comorbidity/complication profiles are required.

Treatment- (26,29), syndrome- and exposure-related risk factors, particularly tobacco and excessive alcohol intake, are regarded as the three major etiological factors for SPMs (25). Ionizing radiation is carcinogenic and it has been reported that ~8% of SPMs may be attributed to previous radiotherapy, although the proportion of cases varies according to the age at diagnosis, FPM site and exposure dose (30). However, the present study observed little effect of radiotherapy on SPM risk. This discrepancy from previous findings may stem from the shorter and later follow-up period compared with that in the previous study (31), which was ~30 years starting from 1978.

Modern radiotherapeutic technology has developed to mitigate excessive damage to non-target tissues and thus reduce the delayed carcinogenic effects of radiation. Chemotherapy can also increase the risks of hematologic and solid malignancies, particularly chemotherapy using platinum-based drugs and alkylating agents (32,33). In the present study, postoperative chemotherapy not only increased the SPM risk but also shortened the FPM-SPM interval. Moreover, the results revealed that the number of chemotherapy regimens but not the number of courses affected the FPM-SPM interval. Furthermore, platinum-based chemotherapy, ubiquitously used as the first line treatment against cancers, showed a limited impact on the FPM-SPM interval. Given the number of new anticancer agents, drug combinations and radiation techniques, larger-scale studies with long-term follow-up are required to further assess the treatment-associated risk factors for SPM.

Through analysis of the SEER database, Adjei Boakye *et al* (34) found that 1/12 of patients who survived a smoking-associated cancer developed an SPM, a large proportion of which were lung cancers However, in the current study, the influence of long-term smoking (≥40 years) on SPM development was limited for the entire cohort and among patients with lung cancer. Alcohol intake has been linked to an increased risk of SPM among patients with upper aerodigestive tract cancer (35) and female patients with keratinocyte carcinoma (36). However, relatively few females in China regularly smoke tobacco or consume alcohol, so the effects of these behaviors on the occurrence of SPM after breast cancer were not analyzed in the present study. However, the long-term consumption of alcohol and cigarettes was observed to significantly increase the risk of SPM (OR, 3.140, 95% CI: 1.346-7.298, P=0.0089).

Diabetes, hypertension and family history of malignancy were also analyzed in the present study and, in contrast to previous studies (37,38), no differences were observed in these factors according to whether the patients had an SPM or not. However, the proportion of patients with a biliary tract or thyroid disease was significantly higher for patients with an SPM than those without. In addition, data from the separate analysis of patients with breast cancer supported the proposition that a family history of malignancy is a risk factor of SPM. Together, these findings indicate that long-term alcohol and cigarette consumption as well as dysfunction of the biliary tract or thyroid increased the risk of developing SPM. Furthermore, postoperative chemotherapy appeared to accelerate the development of SPMs in the whole patient population. However, larger multiple-center studies are necessary to assess the effects of treatment, syndromes and environmental risk factors for SPM.

Multiple malignancies in different site are not uncommon; however, it is unclear whether benign tumors predict SPMs at other sites. The patient population in the present study included 7 cases of thyroid adenoma with an SPM at a different site, most frequently cancer of the lung, including 3 patients with SCLC and a single NSCLC case. Thus, thyroid adenoma may predict future lung cancer, although there is as yet no direct evidence for such an association. It has been reported that higher free thyroxine 4 levels are associated with greater lung cancer risk (HR, 2.33; 95% CI, 1.39-3.92) (39). Furthermore, elevated thyrotropin levels suggestive of hyperthyroid function were also shown to be associated with increased risks of lung and prostate cancer in another prospective population study (40). Together with the bioinformatics analysis based on scRNA-Seq datasets, we hypothesize that thyroid adenoma could be a potential risk factor for lung cancer. In the present study, the FPM-SPM interval between a thyroid adenoma FPM and SCLC SPM was 3-3.5 years. Therefore, a longer follow-up for patients with thyroid adenoma is recommended to ensure the early detection of SCLC. Further study is required on this issue to guide the follow-up of patients with thyroid adenoma and certain other benign tumors.

The present study is a single-center study and due to the limited number of cases, some malignancies were categorized according to the system affected, i.e., the reproductive system, which covered different pathological types. Therefore, it was only possible to analyze the relationships between the site distributions of FPM and SPM, and not to determine the risk factors and influence of SPMs on OS in specific systems. Further analysis was only performed for patients with BC and NSCLC, the two most common types of FPM. The results revealed the influence of chemotherapy on the interval of diagnosis; however, it was not possible to investigate each regimen. Only the role of platinum-based chemotherapy was observed, since it is ubiquitously used in chemotherapy, and the exact regimen was not definite (gemcitabine, taxol or some other agents in company with platinum). In addition, some results in the present study may be affected by the small sample size. The study did not evaluate whether a reduction in OS occurred for patients with an SPM in general, and no influence of radiotherapy on the occurrence of an SPM was detected, which may conflict with previous studies (17,18). A larger sample size including patients from multiple centers is necessary to understand whether these differences are due to the patients being from different regions or the limited number of cases.

The present study is a retrospective study and thus selection bias is inevitable. Based on the exclusion criteria, only solid malignancies were included and information on SPMs associated with hematological FPMs was not gathered. In addition, the included cases are mostly low- and middle-income patients who mainly accepted primary examination and chemo- and/or radiotherapy. Therefore, the roles of genetic testing, immunotherapy and other targeted therapies on SPM were not investigated. Advanced diagnosis and treatment methods should improve the prognosis of malignancies and their role in SPMs merits further attention.

In conclusion, the present single-center retrospective study showed that the malignancy of SPMs was higher than that of FPMs and post-surgical chemotherapy shortened the time taken for SPM development. Furthermore, the sites at which SPMs developed were demonstrated to be associated with the site of the FPM. Moreover, certain potential independent risk factors for SPM were screened out, namely biliary tract disease, thyroid disease and long-term cigarette and alcohol consumption through general analysis, and a family history of malignancy for patients with breast cancer. In addition, clinical and experimental evidence for the potential connection between thyroid adenoma and SCLC was obtained. These findings may provide valuable guidance for the close monitoring of cancer survivors. However, a comprehensive investigation based on a larger population is necessary to develop long-term screening programs for SPM.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Authors' contributions

JZ and JY were responsible for the concept and design of the study. FL, YG, JYZ, JS, LG and SW collected the data. ST and JC analyzed the data. JC and CY performed the literature review. FG and ML interpreted the data and wrote the manuscript. YW revised the statistical analysis and CY helped with the bioinformatics analysis. All authors read and approved the final version of the manuscript. JZ and FG confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This study was approved by The Hospital of 81st Group Army PLA, Human Research Ethics Committee. Written informed consent was obtained from all individual participants involved in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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