Clinical characteristics and overall survival nomogram of second primary malignancies after prostate cancer, a SEER population-based study

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Prostate cancer (PCa) is the most prevalent cancer among males and the survival period of PCa has been significantly extended. However, the probability of suffering from second primary malignancies (SPMs) has also increased. Therefore, we downloaded SPM samples from the SEER database and retrospectively analyzed the general characteristics of 34,891 PCa patients diagnosed between 2000 and 2016. After excluding cases with unknown clinical information, 2203 patients were used to construct and validate the overall survival (OS) nomogram of SPM patients after PCa. We found that approximately 3.69% of PCa patients were subsequently diagnosed with SPMs. In addition, the three most prevalent sites of SPM were respiratory and intrathoracic organs, skin, and hematopoietic system. The top three histological types of SPMs were squamous cell carcinoma, adenoma and adenocarcinoma, nevi and melanoma. Through univariate and multivariate Cox regression analysis, we found that the site of SPM, age, TNM stage, SPM surgery history, and PCa stage were associated with the OS of SPM. By virtue of these factors, we constructed a nomogram to predict the OS of SPM. The C-index in the training set and validation set were 0.824 (95CI, 0.806–0.842) and 0.862 (95CI, 0.840–0.884), respectively. Furthermore, we plotted the receiver operating characteristic curve (ROC) and the area under curve (AUC) which showed that our model performed well in assessing the 3-year (0.861 and 0.887) and 5-year (0.837 and 0.842) OS of SPMs in the training and validation set. In summary, we investigated the general characteristics of SPMs and constructed a nomogram to predict the prognosis of SPM following PCa.

Prostate cancer (PCa) is the most prevalent cancer among men, and it is estimated that 3.6 million men in the United States have a history of PCa in 2019. In addition, in 2020, approximately 191,930 new PCa cases have been registered and 33,330 people have died of PCa in the United States in 2020. Owing to prostate-specific antigen (PSA) screening, digital rectal examination (DRE), and transrectal ultrasound (TRUS) followed by ultrasound-guided biopsy, PCa can be diagnosed at its early stage. Treatment options for PCa, such as, prostatectomy, androgen deprivation therapy (ADT), chemotherapy, and radiotherapy (RT) have also greatly improved the survival rate of PCa. Due to early diagnosis and treatment, the 5-year relative survival rate of PCa has increased to 98%. Moreover, the death rate of PCa has dropped by 52% from its peak.

Despite the extended survival period of cancer, some people may suffer from the second primary malignancies (SPMs). Previous research demonstrated that about 11.3% of PCa patients were diagnosed with SPMs. According to two large-scale studies in Sweden and Germany, the most frequently detected SPMs originated from PCa patients, accounting for 22.5% and 16.9% of all SPMs, respectively. However, mechanisms of triggering conversion to SPMs are unclear, resulting in diagnostic uncertainty and delays in the diagnosis and treatment of SPMs. The underlying causes of SPMs may include environmental and lifestyle-related factors.

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(e.g., smoking)\textsuperscript{10}, genetic factors\textsuperscript{11} and treatment-related exposures (e.g., radiotherapy (RT))\textsuperscript{12,13}. Although the mechanism of SPMs is vague, the survival period of patients will be shortened once they are diagnosed with SPMs, and a former study has proved that adolescents and young adults with SPMs have worse survival than those with only primary cancer\textsuperscript{14}.

Nomogram created by regression analysis has been widely employed to predict the prognosis of diverse cancers\textsuperscript{15} because of its simplicity, intuitiveness, and practicality. It has been used for bladder cancer\textsuperscript{16}, cervical cancer\textsuperscript{17}, primary gliosarcoma\textsuperscript{18}, and many other diseases. The efficiency of nomogram has been proved and has even become a new standard.

We have realized that it is of great significance for treatment providers and PCa survivors to understand the incidence and prognosis of SPMs after PCa. Therefore, in this study, we aimed to investigate the general characteristics of SPMs and construct a nomogram to predict the 3-year and 5-year survival of SPMs following PCa.

Materials and methods

Data source and study design. We extracted SPM cases from 18 population-based registries (2000–2016) in the Surveillance, Epidemiology, and End Results (SEER) database using SEER\textsuperscript{*} Stat version 8.3.6. Clinicopathological data of interest were extracted, including age, race, TNM stage, site of SPM, histological type of SPM and PCa, surgery history of SPM and PCa, marital status, follow-up time, and latency time between PCa and SPM. To make our results more accurate, we adopted the Warren criterion to identify SPM. SPMs were identified as cancers histologically different from the initial primary cancer (IPC), with a latency period of not less than 6 months to exclude errors caused by metastasis and recurrence\textsuperscript{19}.

First, we downloaded a total of 68,954 PCa cases from the SEER database. The inclusion criteria were as follows: 1. diagnosed age greater than 18 years; 2. A record of malignant behavior; 3. patients with complete survival data and follow-up information. The exclusion criteria were as below: 1. latency period between IPC and SPM shorter than 6 months; 2. patients with only autopsy or death certificate records. Then, after excluding 33,702 patients with the same histology as PCa, there remained 34,891 patients diagnosed with SPM. Patients with unknown information were also excluded, including no TNM stage: n = 24,452, unknown history of surgery: n = 184, unknown marital status: n = 121, unknown lymph node removed (LNR): n = 10, and no stage of PCa: n = 7921. Ultimately, we identified 2203 qualified cases, which were then divided into the training set (n = 1543) and the validation set (n = 660). The training set was used to identify prognostic factors and built a nomogram based on these factors. The training set and validation set were used for internal and external validation, respectively.

The study cohort comprised patients with the following International Classification of Diseases for Oncology, Third Edition (ICD-O-3), morphology codes: 8000/3, 8010/3, 8140/3, 8255/3, 8480/3, 8481/3 and 8490/3, and the site codes: C61.9. The detailed flow chart for patient screening was presented in Fig. 1.

Statistical analysis. To explore the association between clinicopathological variables and OS of SPM, we performed univariate and multivariate Cox proportional hazards regression analysis in the training set to identify the significant factors. Using these screened factors, we calculated the risk score of each patient according to the following formula: \textit{risk score} = β\textsubscript{1} \times X\textsubscript{1} + β\textsubscript{2} \times X\textsubscript{2} + \cdots + β\textsubscript{n} \times X\textsubscript{n} (β, regression coefficient; X, prognostic factor)\textsuperscript{18}. According to the median score of the risk score, patients were divided into the high-risk group and low-risk group. Next, we chose factors with \textit{p} value < 0.001 to develop a nomogram to predict the 3- and 5-year survival rates of SPM patients. To evaluate the prognostic ability of our model, we calculated the concordance index (C-index). Meanwhile, the receiver operating characteristic curve (ROC) was plotted and the area under the curve (AUC) was assessed. The calibration curves were drawn to estimate whether the actual result was consistent with the predicted probability. Each cohort was divided into three groups according to sample size. Bootstrapping with 1,000 resamples was used to evaluate discrimination and calibration. Kaplan–Meier curves were plotted and Log-rank analysis was applied to compare the OS on account of different prognostic factors.

All statistical analyses were performed in SPSS 24.0 (SPSS Inc., Chicago, IL, USA) or the R software (version 3.6.1; \textit{http://www.r-project.org/}) using the following packages: ‘rms’, ‘survival’, and ‘survivalROC’. All tests were two-sided and \textit{p} < 0.05 was considered statistically significant.

Ethical statement. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Institutional review board approval was waived for this study because SEER database is a public anonymized database. The author Y Liu has gotten the access to the SEER database (accession number: 16704-Nov2018). The authors are accountable for all aspects of the work.

Results

Characteristics of SPM. We downloaded 68,954 PCa patients diagnosed during 2000–2016 from the SEER database. In order to exclude the bias caused by PCa recurrence and metastasis, we ruled out cases with the same histological type as PCa. Cases with a latency period of less than 6 months between PCa and SPMs were also excluded. Finally, a total of 34,891 patients diagnosed with SPMs were identified. Using the SEER database, we found that 945,196 men were diagnosed during 2000–2016 and approximately 3.69% of PCa patients were subsequently diagnosed with SPMs in this period. We concluded that the median interval between diagnosis of PCa and SPM was 57.0 months and the median diagnosed age of SPM was 74.0 years. We listed the sites and histological types of SPM that exceeded 1% in Fig. 2A,B. The three most prevalent sites of SPM were respiratory and intrathoracic organs, skin, and hematopoietic system (Table 1). In addition, bronchial and lung cancers accounted for the majority of cancers in respiratory and intrathoracic organs (Table S1). As shown in Table 2,
the top three histological types of SPMs were squamous cell carcinoma, adenoma and adenocarcinoma, nevi and melanoma.

Baseline characteristics of patients. A total of 34,891 cases diagnosed with SPMs were identified from the original data downloaded from the SEER database. After excluding patients with unknown clinical information, 2203 cases were ultimately enrolled for further analysis. These cases were randomly divided into the training set (n = 1543) and the validation set (n = 660). There were no significant differences (p > 0.05) in the site of SPM, SPM histology, age, race, T stage, M stage, LNR, PCa surgery, PCa stage, and marital status (Table 3). The training set was used to construct nomogram and validate the model internally, while the validation set was used for external validation. In the entire cohort, we found that approximately 32.73% (n = 721) of SPM patients died after a median follow-up of 56 months.

Prognostic factors for the overall survival of SPM. Intending to reveal the associated factors with the OS of SPM, we applied univariate and multivariate Cox regression analysis. The results were listed in Table 4. Univariate Cox regression analysis demonstrated that age (p < 0.001), race (p < 0.001), TNM stage (p < 0.001), LNR (p < 0.001), histology of SPM (p < 0.001), site of SPM (p < 0.001), marital status (p < 0.001), SPM surgical history (p < 0.001), PCa surgical history (p < 0.001), and PCa stage (p < 0.001) were associated with the OS of SPM. Next, using the factors identified by univariate Cox regression analysis, multivariate Cox regression analysis revealed that age (p < 0.001), TNM stage (p < 0.001), histology of SPM (p = 0.002), site of SPM (p < 0.001), marital status (p = 0.038), PCa surgical history (p < 0.001), and PCa stage (p < 0.001) were independent prognostic factors for the OS of SPM.

Kaplan–Meier analysis for prognostic factors. We first calculated the risk score of each case according to the following formula: \( \text{risk score} = \beta_1 \times X_1 + \beta_2 \times X_2 + \cdots + \beta_n \times X_n \) (\( \beta \), regression coefficient; \( X \), prognostic factor). Then, we divided samples into the high-risk group and low-risk group based on the media risk score. Kaplan–Meier (K–M) analysis showed significant differences in the prognosis between these two groups in the training set and validation set (Fig. 3A,B) and patients with high risks tended to have worse survival than those with low risk (p < 0.001). Significant differences were also observed in site of SPM (p < 0.001), age, TNM stage (p < 0.001), SPM surgery history (p < 0.001), and PCa stage (p < 0.001). Patients with higher age, TNM stage, PCa stage...
Figure 2. Features of second primary malignancies (SPMs) after prostate cancer (PCa). (A) Sites of SPMs that over than 1%, (B) Histology types of SPMs that more than 1%.

| Site of SPMs                              | N   | N% (%) |
|------------------------------------------|-----|--------|
| All                                      | 34,891 | 100    |
| Respiratory and intrathoracic organs     | 6866  | 19.68  |
| Skin                                     | 6711  | 19.23  |
| Hematopoietic system                     | 5717  | 16.39  |
| Digestive organs                         | 4523  | 12.96  |
| Lymph nodes                              | 2872  | 8.23   |
| Urinary tract                            | 2343  | 6.72   |
| Lip, oral cavity and pharynx             | 1985  | 5.69   |
| Eye, brain and other parts of central nervous system | 1331  | 3.81   |
| Thyroid and other endocrine glands       | 917   | 2.63   |
| Conn, subcutaneous, other soft tissue    | 563   | 1.61   |
| Unknown primary site                     | 348   | 1.00   |
| Male genital organs                      | 283   | 0.81   |
| Bone, joints and articular cartilage     | 210   | 0.60   |
| Retropertitoneum and peritoneum          | 125   | 0.36   |
| Other and ill-defined sites              | 55    | 0.16   |
| Breast                                   | 33    | 0.09   |
| Peripheral nerves and autonomic nervous system | 9    | 0.03   |

Table 1. Site of SPMs after PCa. Abbreviations: SPMs: second primary malignancies; PCa: prostate cancer.
had better survival (Fig. 3C,G). Also, patients who received surgery for SPM tended to have increased survival (Fig. 3H). SPM of skin had significantly better survival than other kinds of SPM (Fig. 3I).

**Construction and validation of OS nomogram.** According to the results of univariate and multivariate Cox analysis, we chose the factors with *p* value < 0.001 to establish a nomogram to predict the 3-year and 5-year survival rate (Fig. 4). Seven clinical indicators, including site of SPM, age, TNM stage, SPM surgical history, and PCa stage were enrolled in our nomogram. In order to evaluate the discriminative ability of the nomogram constructed by us, we calculated the C-index in the training set (0.824, 95% CI: 0.806–0.842) and validation set.

| Histology type of SPMs                  | N    | N% (%) |
|----------------------------------------|------|--------|
| All                                    | 34,891| 100    |
| Squamous cell neoplasms                | 6686  | 19.16  |
| Adenomas and adenocarcinomas           | 6634  | 19.01  |
| Nevi and melanomas                     | 5996  | 17.18  |
| Hodgkin and non-Hodgkin lymphoma       | 4203  | 12.05  |
| Leukemias                              | 3214  | 9.21   |
| Epithelial neoplasms                   | 2064  | 5.92   |
| Plasma cell tumors                     | 2011  | 5.76   |
| Gliomas                                | 994   | 2.85   |
| Mesothelial neoplasms                  | 479   | 1.37   |
| Myelodysplastic syndromes              | 278   | 0.80   |
| Fibromatous neoplasms                  | 259   | 0.74   |
| Complex epithelial neoplasms           | 234   | 0.67   |
| Complex mixed and stromal neoplasms    | 227   | 0.65   |
| Lipomatous neoplasms                   | 214   | 0.61   |
| Soft tissue tumors and sarcomas        | 174   | 0.50   |
| Transitional cell papillomas and carcinomas | 145 | 0.42   |
| Immunoproliferative diseases           | 136   | 0.39   |
| Blood vessel tumors                    | 132   | 0.38   |
| Adnexal and skin appendage neoplasms   | 130   | 0.37   |
| Ductal, lobular and medullary neoplasms| 102   | 0.29   |
| Chronic myeloproliferative disorders   | 96    | 0.28   |
| Osseous and chondromatous neoplasms    | 95    | 0.27   |
| Mucoepidermoid neoplasms               | 71    | 0.20   |
| Thymic epithelial neoplasms            | 46    | 0.13   |
| Germ cell neoplasms                    | 46    | 0.13   |
| Cystic, mucinous and serous neoplasms  | 29    | 0.08   |
| Neoplasms                              | 25    | 0.07   |
| Meningiomas                            | 25    | 0.07   |
| Myxomatous neoplasms                   | 23    | 0.07   |
| Nerve sheath tumors                    | 20    | 0.06   |
| Miscellaneous tumors                   | 17    | 0.05   |
| Other hematologic disorders            | 14    | 0.04   |
| Paragangliomas and glomus tumors       | 12    | 0.03   |
| Neuroepitheliomatous neoplasms         | 11    | 0.03   |
| Myxomatous neoplasms                   | 10    | 0.03   |
| Neoplasms of histiocytes and accessory lymphoid cells | 8 | 0.02 |
| Synovial-like neoplasms                | 6     | 0.02   |
| Odontogenic tumors                     | 6     | 0.02   |
| Basal cell neoplasms                   | 5     | 0.01   |
| Miscellaneous bone tumors              | 4     | 0.01   |
| Mast cell tumors                       | 4     | 0.01   |
| Choriocarcinoma                        | 2     | 0.01   |
| Lymphatic vessel tumors                | 2     | 0.01   |
| Giant cell tumors                      | 2     | 0.01   |

**Table 2.** Histology types of SPMs after PCa. Abbreviations: SPMs: second primary malignancies; PCa: prostate cancer.
| Characteristics                      | Training set (n = 1543) | Validation set (n = 660) | $X^2$ | $p$  |
|--------------------------------------|-------------------------|--------------------------|-------|------|
| Site of SPMs                         |                         |                          |       |      |
| Skin                                 | 439 28.5 188 28.5       |                          | 4.91  | 0.423|
| Bronchus and lung                    | 298 19.3 111 16.8       |                          |       |      |
| Renal                                | 145 9.4 71 10.8         |                          |       |      |
| Liver                                | 85 5.5 48 7.3           |                          |       |      |
| Thyroid gland                        | 87 5.6 38 5.8           |                          |       |      |
| Others                               | 489 31.7 204 30.9       |                          |       |      |
| **Histology of SPMs**                |                         |                          | 7.47  | 0.188|
| Squamous cell cancer                 | 426 27.6 159 24.1       |                          |       |      |
| Melanomas                            | 413 26.8 173 26.2       |                          |       |      |
| Papillary adenocarcinoma             | 118 7.6 62 9.4          |                          |       |      |
| Hepatocellular carcinoma             | 75 4.9 44 6.7           |                          |       |      |
| Renal cell carcinoma                 | 79 5.1 29 4.4           |                          |       |      |
| Others                               | 432 28.0 193 29.2       |                          |       |      |
| Age                                  |                         |                          | 3.40  | 0.334|
| <= 60                                | 205 13.3 98 14.8        |                          |       |      |
| 61–70                                | 589 38.2 268 40.6       |                          |       |      |
| 71–80                                | 588 38.1 226 34.2       |                          |       |      |
| > 80                                 | 161 10.4 68 10.3        |                          |       |      |
| Race                                 |                         |                          | 0.71  | 0.703|
| White                                | 1261 81.7 532 80.6      |                          |       |      |
| Black                                | 220 14.3 103 15.6       |                          |       |      |
| Others                               | 62 4.0 25 3.8           |                          |       |      |
| **Stage_T**                          |                         |                          | 1.22  | 0.875|
| Ta                                   | 71 4.6 27 4.1           |                          |       |      |
| T1                                   | 673 43.6 301 45.6       |                          |       |      |
| T2                                   | 344 22.3 149 22.6       |                          |       |      |
| T3                                   | 279 18.1 111 16.8       |                          |       |      |
| T4                                   | 176 11.4 72 10.9        |                          |       |      |
| **Stage_N**                          |                         |                          | 9.37  | 0.035|
| N0                                   | 1131 73.3 511 77.4      |                          |       |      |
| N1                                   | 164 10.6 67 10.2        |                          |       |      |
| N2                                   | 203 13.2 58 8.8         |                          |       |      |
| N3                                   | 45 2.9 24 3.6           |                          |       |      |
| **Stage_M**                          |                         |                          | 1.52  | 0.218|
| M0                                   | 1359 88.1 594 90.0      |                          |       |      |
| M1                                   | 184 11.9 66 10.0        |                          |       |      |
| **LNR**                              |                         |                          | 0.41  | 0.521|
| No                                   | 1214 78.7 528 80.0      |                          |       |      |
| Yes                                  | 329 21.3 132 20.0       |                          |       |      |
| **SPM surgical history**             |                         |                          | 0.79  | 0.374|
| Yes                                  | 521 33.8 210 31.8       |                          |       |      |
| No                                   | 1022 66.2 450 68.2      |                          |       |      |
| **Histology of PCa**                 |                         |                          | 1.27  | 0.260|
| Other                                | 13 0.8 9 1.4           |                          |       |      |
| Ade                                  | 1530 99.2 651 98.6      |                          |       |      |
| **PCa surgical history**             |                         |                          | 0.07  | 0.792|
| Yes                                  | 977 63.3 414 62.7       |                          |       |      |
| No                                   | 566 36.7 246 37.3       |                          |       |      |
| **PCa stage**                        |                         |                          | 2.73  | 0.440|
| I                                    | 431 27.9 194 29.4       |                          |       |      |
| II                                   | 905 58.7 373 56.5       |                          |       |      |
| III                                  | 139 9.0 55 8.3          |                          |       |      |
| IV                                   | 68 4.4 38 5.8           |                          |       |      |
| Continued                            |                         |                          |       |      |
improving the prognosis of PCa. Recently, the use of ADT in combination with second-generation AR target-
tors for castration-resistant prostate cancer (CRPC), such as enzalutamide, also show significant capacities of using ADT alone. Two clinical trials have shown that, compared with alone, ADT plus docetaxel can significantly prolong the longevity of metastatic hormone sensitive prostate cancer (mCRPC) patients. The addition of abiraterone acetate to ADT has shown a survival advantage compared with SPMs. In order to explore the outcome of SPM following PCa, we identified 7 parameters, including the genetic mutations, may be the reasons for this trend. The top three histological types of SPM were squamous cell carcinoma, adenoma and adenocarcinoma, nevi and melanoma, consistent with the histology of epidemic sites. These results indicated that these prone sites should be cautiously monitored.

As a result of the extended survival period of PCa patients, recurrence, metastasis, and SPMs are expected to increase. In clinical practice, SPMs or multiple primary malignancies are very frequently indistinct from the metastasis of initial malignancy, leading to misdiagnosis and improper treatment of patients. In contrast to multiple primary malignancies, SPMs can affect the same organ but are anatomically distinct from the primary tumor, and represent neither a metastatic nor recurrent tumor from the initial malignancy. Via a strict screening process, we distinguished between SPMs from multiple primary malignancies, metastasis, and recurrence. After accurate identification, 3.69% of PCa patients were diagnosed with SPMs, which was much lower than previous observations for 3-year and 5-year OS.

Discussions
As the most common cancer among males, the survival time of PCa patients has been significantly extended due to early detection and effective therapeutic strategies. PSA screening is helpful for early diagnosis, and can significantly reduce the mortality rate of PCa. For decades, ADT through surgical or medical castration has been part of the standard treatment for PCa. Newly launched second-generation androgen receptor (AR) inhibitors for castration-resistant prostate cancer (CRPC), such as enzalutamide, also show significant capacities of improving the prognosis of PCa. Recently, the use of ADT in combination with second-generation AR targeting agents or chemotherapy has significantly prolonged the longevity of metastatic hormone sensitive prostate cancer (mCRPC) patients. The addition of abiraterone acetate to ADT has shown a survival advantage compared to using ADT alone. Two clinical trials have shown that, compared with alone, ADT plus docetaxel can improve the survival rate for adequately fit men. All these advanced treatments have together contributed to the prolonged survival of PCa patients. Previous studies have shown that patients with in situ melanoma have an increased risk of developing PCa and young men among colorectal cancer survivors have an excessively high risk of developing SPMs. These evidences indicate that cancer patients and Taiwan show that compared to the general population, PCa patients have a lower risk of SPMs, but once they got SPMs, the survival time of PCa patients will be greatly shortened. For the reason of better insight into SPMs after PCa, we investigated the characteristics of SPM following PCa, and constructed a model based on clinicopathologic characteristics to predict the prognosis of SPM following PCa.

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| Characteristics                      | Univariate analysis |                      | Multivariate analysis |                      |
|--------------------------------------|---------------------|----------------------|-----------------------|----------------------|
|                                      | HR                  | CI95                 | p                     | HR                  | CI95                 |

### Site of SPM

| Site of SPM                  | HR                  | CI95                 | p                     | HR                  | CI95                 |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| Skin                        | Reference           |                      |                       | Reference           |                      |
| Bronchus and lung           | 8.385               | 6.294–11.171         | 0.000                 | 1.952               | 0.995–3.831          | 0.052 |
| Renal                       | 1.973               | 1.313–2.964          | 0.001                 | 1.240               | 0.401–3.828          | 0.799 |
| Liver                       | 9.024               | 6.308–12.909         | 0.000                 | 7.265               | 2.834–18.623         | 0.000 |
| Thyroid gland               | 1.008               | 0.543–1.871          | 0.979                 | 0.595               | 0.242–1.463          | 0.258 |
| Others                      | 2.671               | 1.990–3.585          | 0.000                 | 0.978               | 0.513–1.866          | 0.947 |

### Histology of SPM

| Histology of SPM            | Reference           |                      |                       | Reference           |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| Squamous cell neoplasms     | Reference           |                      |                       | Reference           |                      |
| Melanomas                   | 0.199               | 0.147–0.269          | 0.000                 | 0.549               | 0.278–1.085          | 0.085 |
| Papillomas                  | 0.292               | 0.186–0.458          | 0.000                 | 0.921               | 0.412–2.058          | 0.841 |
| Hepatocellular carcinoma    | 1.742               | 1.277–2.375          | 0.000                 | 0.576               | 0.268–1.242          | 0.159 |
| Adenocarcinomas             | 0.553               | 0.362–0.845          | 0.006                 | 1.072               | 0.382–3.011          | 0.895 |
| Others                      | 0.815               | 0.666–0.997          | 0.047                 | 1.364               | 1.084–1.717          | 0.008 |

### Age

| Age                          |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| < 60                        | Reference           |                      |                       | Reference           |                      |
| 61–70                       | 1.211               | 0.885–1.657          | 0.231                 | 1.130               | 0.818–1.561          | 0.458 |
| 71–80                       | 1.861               | 1.373–2.521          | 0.000                 | 1.692               | 1.224–2.340          | 0.001 |
| > 80                        | 2.465               | 1.734–3.504          | 0.000                 | 2.354               | 1.619–3.424          | 0.000 |

### Race

| Race                         |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| White                       | Reference           |                      |                       | Reference           |                      |
| Black                       | 1.605               | 1.287–2.001          | 0.000                 | 1.040               | 0.821–1.317          | 0.747 |
| Other                       | 1.003               | 0.640–1.571          | 0.991                 | 0.817               | 0.515–1.297          | 0.392 |

### Stage_T

| Stage_T                     |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| T1                           | Reference           |                      |                       | Reference           |                      |
| Ta                          | 1.381               | 0.873–2.186          | 0.167                 | 1.443               | 0.878–2.372          | 0.148 |
| T2                           | 2.108               | 1.665–2.669          | 0.000                 | 1.334               | 1.034–1.721          | 0.026 |
| T3                           | 2.930               | 2.309–3.719          | 0.000                 | 1.626               | 1.242–2.127          | 0.000 |
| T4                           | 3.825               | 2.952–4.956          | 0.000                 | 1.871               | 1.386–2.526          | 0.000 |

### Stage_N

| Stage_N                     |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| N0                          | Reference           |                      |                       | Reference           |                      |
| N1                           | 2.710               | 2.128–3.450          | 0.000                 | 2.028               | 1.552–2.65           | 0.000 |
| N2                           | 3.516               | 2.838–4.357          | 0.000                 | 1.493               | 1.152–1.934          | 0.002 |
| N3                           | 4.299               | 2.913–6.346          | 0.000                 | 1.739               | 1.128–2.679          | 0.012 |

### Stage_M

| Stage_M                     |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| M0                          | Reference           |                      |                       | Reference           |                      |
| M1                           | 7.664               | 6.305–9.315          | 0.000                 | 2.893               | 2.292–3.651          | 0.000 |

### LNR

| LNR                         |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| No                           | Reference           |                      |                       | Reference           |                      |
| Yes                          | 0.600               | 0.474–0.760          | 0.000                 | 0.757               | 0.555–1.033          | 0.079 |

### SPM surgical history

| SPM surgical history        |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| No                           | Reference           |                      |                       | Reference           |                      |
| Yes                          | 0.198               | 0.165–0.236          | 0.000                 | 0.597               | 0.452–0.790          | 0.000 |

### Histology of PCa

| Histology of PCa            |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| Other                       | Reference           |                      |                       | Reference           |                      |
| Adenocarcinomas             | 0.538               | 0.240–1.203          | 0.131                 |                      |                      |

### PCa surgical history

| PCa surgical history        |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| Yes                          | Reference           |                      |                       | Reference           |                      |
| No                           | 0.600               | 0.495–0.726          | 0.000                 | 0.930               | 0.751–1.151          | 0.503 |

### PCa Stage

| PCa Stage                   |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| I                            | Reference           |                      |                       | Reference           |                      |
| II                           | 1.143               | 0.934–1.399          | 0.193                 | 1.046               | 0.85–1.288           | 0.668 |
| III                          | 0.745               | 0.512–1.086          | 0.126                 | 0.856               | 0.571–1.281          | 0.449 |
| IV                           | 2.411               | 1.704–3.410          | 0.000                 | 2.419               | 1.684–3.476          | 0.000 |

### Marital status

| Marital status              |                      |                      |                       |                      |                      |
|------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|
| Continued                    |                      |                      |                       |                      |                      |
Table 4. Univariate and multivariate Cox analysis of SPMs patients after PCa in the training and validation set. Abbreviations: SPM: second primary malignancy; PCa: prostate cancer, LNR: lymph node removed.

| Characteristics      | Univariate analysis | Multivariate analysis |
|----------------------|---------------------|-----------------------|
|                      | HR  | CI95 | p     | HR  | CI95 | p     |
| Married              | Reference          | Reference             |
| Previously married   | 1.391 | 1.141–1.696 | 0.001 | 1.120 | 0.914–1.372 | 0.275 |
| Never married        | 1.477 | 1.126–1.939 | 0.005 | 1.469 | 1.104–1.955 | 0.008 |

Figure 3. Kaplan–Meier analysis for overall survival (OS) of second primary malignancy (SPM) after prostate cancer (PCa) based on risk score in the training set ($p < 0.001$) (A) and the validation set ($p < 0.001$) (B), age ($p < 0.001$) (C), stage T ($p < 0.001$) (D), stage N ($p < 0.001$) (E), stage M ($p < 0.001$) (F), PCa stage ($p < 0.001$) (G), SPM surgery history ($p < 0.001$) (H), and site of SPMs ($p < 0.001$) (I).
Figure 4. Nomogram to predict 3- and 5-year survival for second primary malignancy (SPM) patients.

Figure 5. Receiver operating characteristic (ROC) analysis to assess 3-year (A) and 5-year (B) survival for second primary malignancy (SPM) patients in the training set; The ROC curve to assess 3-year (C) and 5-year (D) survival in the validation set.
outcome of SPM, which might suggest that SPM mainly accounted for the death of SPM following PCa. Besides, researchers also found that most causes of death were caused by SPM not PCa\textsuperscript{11,35}. PCa stage was enrolled in our nomogram, and was used to construct a predicting model for metastatic PCa together with TNM stage\textsuperscript{36,37}. We could conclude that PCa still had its impact on the OS of SPM.

However, we did not investigate the relationship between RT and SPM. According to earlier reports, PCa patients receiving RT have a higher risk of getting SPMs\textsuperscript{38–40}. A meta-analysis also reveals that PCa patients receiving RT had an increasing risk of developing SPM of the bladder, colon, and rectum\textsuperscript{41}. Some studies have shown that there is no difference in the incidence of SPM among patients receiving RT or other therapies\textsuperscript{13,42}. The role of RT in the initiation of SPM still needs more exploration and the effect of RT on the survival of PCa patients remains unclear. Gene is another important internal factor of tumorigenesis of SPM, but the genotype–phenotype correlation of SPMs is still unclear. A significantly increased risk of SPM has been observed in survivors of hereditary retinoblastoma with high RB1 mutations\textsuperscript{43}. P53 gene whose polymorphisms are associated with an increased risk of SPM is another gene extensively researched\textsuperscript{44–46}. On the contrary, Anette. E et.al believed the correlation between P53 mutation and the incidence of SPM was doubtful\textsuperscript{47}. Only limited evidence about the SPM genotype were explored and more studies are needed to explain the relationship between SPMs and gene mutations. Some other factors, such as smoking and obesity, were not investigated due to the nature of the SEER database. We are trying to explore the association between cancer-specific survival and clinicopathologic characteristics, but the causes of tumor death in many patients are still vague. Despite these limitations, our study still has its implications for PCa survivors.

In conclusion, we described the general characteristics of SPM following PCa and identified 7 clinical indicators to build a nomogram to predict the survival of SPM. The model we constructed performed well in assessing the prognosis of SPM but its actual efficiency should be evaluated with more large-scale researches. In addition, more studies should focus on the initiation, development, and prognosis of SPM.

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References
1. Miller, K. D. et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J. Clin. https://doi.org/10.3322/caac.21565 (2019).
2. Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2020. CA Cancer J. Clin. 70(1), 7–30. https://doi.org/10.3322/caac.21590 (2020).
3. Teo, M. Y., Rathkopf, D. E. & Kantoff, P. Treatment of advanced prostate cancer. Annu. Rev. Med. 70, 479–499. https://doi.org/10.1146/annurev-med-051517-011947 (2019).
39. Kendal, W. S., Eapen, L., Macrae, R., Malone, S. & Nicholas, G. Prostatic irradiation is not associated with any measurable increase in the risk of subsequent rectal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **65**, 661–668. https://doi.org/10.1016/j.ijrobp.2005.11.013 (2006).
40. Pickles, T. & Phillips, N. The risk of second malignancy in men with prostate cancer treated with or without radiation in British Columbia, 1984–2000. *Radiother. Oncol.* **65**, 145–151. https://doi.org/10.1016/s0167-8140(02)00307-9 (2002).
41. Wallis, C. J. et al. Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. *BMJ* **352**, i851. https://doi.org/10.1136/bmj.i851 (2016).
42. Hinnen, K. A. et al. Prostate brachytherapy and secondary cancer risk: a competitive risk analysis. *J. Clin. Oncol.* **29**, 4510–4515. https://doi.org/10.1200/JCO.2011.35.0991 (2011).
43. Dommering, C. J. et al. RB1 mutations and second primary malignancies after hereditary retinoblastoma. *Fam. Cancer* **11**, 225–233. https://doi.org/10.1007/s10689-011-9505-3 (2012).
44. Zhang, Y. et al. Genetic variants of the p53 and p73 genes jointly increase risk of second primary malignancies in patients after index squamous cell carcinoma of the head and neck. *Cancer* **118**, 485–492. https://doi.org/10.1002/cncr.26222 (2012).
45. Gasparotto, D. et al. Recurrences and second primary tumours in the head and neck region: differentiation by p53 mutation analysis. *Ann. Oncol.* **6**, 933–939. https://doi.org/10.1093/oxfordjournals.annonc.a059362 (1995).
46. Chung, K. Y. et al. Discordant p53 gene mutations in primary head and neck cancers and corresponding second primary cancers of the upper aerodigestive tract. *Cancer Res.* **53**, 1676–1683 (1993).
47. Escher, A., Piotet, E., Waridel, F., Iggo, R. & Monnier, P. p53 Mutation in histologically normal mucosa of the aero-digestive tract is not a marker of increased risk for second primary carcinoma in head and neck cancer patients. *Eur. Arch. Otorhinolaryngol.* **266**, 547–551. https://doi.org/10.1007/s00405-008-0780-z (2009).

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