Estimating the risk of developing secondary hematologic malignancies in patients with T1/T2 prostate cancer undergoing diverse treatment modalities: A large population-based study

Xiaofei Mo1,2 | Mingge Zhou1,2 | Hui Yan1,2 | Xueqin Chen1,2 | Yuetao Wang1,2

Background: Patients with prostate cancer (PC) are at a high risk of developing secondary hematologic malignancies (SHMs) after radiation therapy (RT), while no study has assessed the relationship of different treatment modalities with the occurrence of SHMs after PC at early stage. This study aimed to investigate the risks of developing SHMs in patients with T1/T2 PC undergoing different treatment modalities.

Methods: Patients with T1/T2 PC were identified from the Surveillance, Epidemiology, and End Results database. Competing risk regression (CRR) model was performed to evaluate the hazard ratios (HRs) of developing SHMs. As SHMs scarcely occur, the relative risk (RR) analysis was employed to compare the risks of different treatment modalities associating with the development of SHMs.

Results: The CRR analysis showed that undergoing RT was associated with a higher risk of developing SHMs (external beam radiation therapy [EBRT]: HR = 1.21, 95% confidence interval [CI]: 1.10–1.34; radioactive implant [RI]: HR = 1.20, 95% CI: 1.06–1.36). As for different types of SHMs, EBRT, and RI were correlated with decreased risks of developing CLL (RR = 0.67, 0.72; 95% CI: 0.53–0.85, 0.54–0.96, respectively), but with the increased risks of developing NHL (RR = 1.18, 1.23; 95% CI: 1.02–1.35, 1.05–1.44, respectively); EBRT also showed increased risks of developing acute/chronic myeloid leukemia (AML/CML, RR = 1.54, 1.56; 95% CI: 1.16–2.03, 1.05–2.33, respectively); No increased risk of developing SHMs was detected in patients who only underwent prostatectomy.

Conclusions: Although RT was found to be associated with the increased risks of developing SHMs in patients with T1/T2 PC, this finding cannot be extended to diverse types of SHMs. RT was correlated with the increased risks of the development of NHL, AML, and CML, but with the decreased risk of developing CLL. Prostatectomy did not increase the risk of developing SHMs.

Keywords: hematologic malignancy, prostate cancer, prostatectomy, radiation therapy
1 INTRODUCTION

Prostate cancer (PC) is the most common malignancy in middle-aged and elderly men, accounting for 10% of cancer-related deaths in the United States according to the statistics published by the American Cancer Society. For patients with T1/T2 PC, radiation therapy (RT) and prostatectomy are the main therapeutic options, including external beam radiation therapy (EBRT), radioactive implant (RI), and combination of RT with prostatectomy. The PC-specific survival of patients who underwent RT has markedly attracted scholars’ attention. However, it was frequently reported that RT is associated with a high risk of secondary hematologic malignancies (SHMs) in patients with diverse types of cancer. This can be related to the fact that RT enhances the fitness of clonal hematopoietic stem cells, which can influence outcome through progression to hematologic malignancies and through cell nonautonomous effects on solid tumors.

Although a number of scholars have concentrated on the association between RT and development of SHMs in patients with early-stage PC, few researches have investigated the risk of developing SHMs in such patients undergoing various therapies. The present study aimed to assess the risk of developing SHMs in patients with T1/2 PC who underwent different treatment modalities.

2 METHODS

2.1 Data collection

The Surveillance, Epidemiology, and End Results (SEER) database covers approximately 30% of the US population and provides complete cancer patient data, including demographic, clinical information, and follow-up data. This database is updated annually by the National Center for Health Statistics. It also provides incidence, survival, and mortality data for histopathologic cancer subtypes. We chose 18 registry research datasets (2000–2015, with additional treatment fields; November 2017) in the SEER database to identify cases with T1/T2 PC.

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) PC was the first primary cancer, performing diagnosis according to the International Classification of Diseases for Oncology, third edition (ICD-O-3; particularly C61.9) and with T1-T2M0 stage according to the American Joint Committee on Cancer (AJCC) stage system; (b) conducting diagnosis between 2004 and 2010.

2.3 Statistical analysis

After data entry, data were manually and statistically checked as a part of the data cleaning process. Then, descriptive statistics were calculated for patients’ demographic and clinical data at baseline. The Chi-square test was utilized to analyze categorical variables; the skewness and kurtosis were used to evaluate the distribution of continuous data, and the Kruskal–Wallis test was employed to analyze those data. A two-sided p-value <0.05 was considered statistically significant.

2.4 Competing risk regression model

We used a competing risk regression (CRR) model to evaluate the hazard ratios (HRs) of SHMs. Patients’ demographic and clinical data were imported into the model, which included patients’ age at the time of diagnosis of PC, marital status, race, T and N stages of the AJCC staging system, prostate-specific antigen (PSA) level, receiving chemotherapy or not, Gleason’s score and treatment modality. Among them, age at the time of diagnosis was considered as a continuous variable, and the PSA level and the Gleason’s score were categorized by their clinical implications (i.e., PSA level at the range of 0–4 is normal; a Gleason’s score of <7 represents a low-grade cancer, a Gleason’s score equal to 7 indicates a medium-grade cancer, and a Gleason’s score of >7 represents a high-grade cancer). The variable of treatment modality included EBRT, RI, combination of EBRT and RI, prostatectomy, and combination of RT and prostatectomy, whereas no RT or prostatectomy was taken as reference into account. Patients who were alive at the last follow-up were regarded as censored patients, and the development of other malignancies and death before the occurrence of SHMs were considered as competing risks. Cases from autopsy/death certification reports and not in active follow-up were lack of survival periods, we assigned their survival time as the mean values of the corresponding outcomes in our study.

All the variables were firstly imported into the univariate CRR analysis, and then, the variables with significant differences were imported into the multivariate CRR analysis. After that, multicollinearity was assessed using variance inflation factor (VIF), measuring the inflation in the variances.
of the parameter estimates due to multicollinearity potentially caused by the correlated predictors.

**2.5 Relative risk regression analysis of the risks of different treatment modalities associating with the development of SHMs**

As SHMs scarcely occur, the relative risk (RR) regression analysis was employed to compare the risks of different treatment modalities associating with the development of SHMs. In the present study, therapeutic methods were taken as exposure, SHMs as outcomes, and RR was calculated as follows,\textsuperscript{16,17}

\[
RR = \frac{O_1/N_1}{O_2/N_2} \times 100\% ,
\]

where \(O\) represents the number of observations in each cohort and \(N\) denotes the person-year at risk in each cohort.

As the incidence rate was significantly different in each cohort, \(O\) was adjusted to eliminate the difference with the reference cohort,\textsuperscript{16} which was formulated as follows,

\[
\frac{O_1}{O_{a}} = \frac{E_1/N_1}{E_{R}/N_{R}} \times 100\% ,
\]

where \(E\) represents the number of expectations in each cohort.

The subscripts “a” and “R” denote “adjusted” and “reference cohort,” respectively.

We utilized multiple primary-standardized incidence ratios (MP-SIRs) in the SEER database to calculate the RR value. The values of \(E\) parameter could be achieved according to patients’ age, race, gender, and calendar time-specific incidence rate by stratum-specific person-years of follow-up. The 95% confidence intervals (CIs) and SIRs were derived from SEER*stat with the quantile approximation of the Chi–square distribution.\textsuperscript{18,19} A RR value with 95% CI >1 or <1 was considered statistically significant. Data, in the present study, were analyzed by the R 3.6.3 programming language. The cmprsk package in the R 3.6.3 programming language was used to establish the competing risk model.

**3 RESULTS**

**3.1 Patients’ demographic and clinical data**

A total of 288,400 patients with T1/T2 PC met the defined criteria, of whom 3479 patients experienced development of SHMs (Table 1). Among them, 1597 (45.9%) patients experienced development of SHMs into NHL, 723 (20.8%) into MM, 485 (13.9%) into CLL, 335 (9.6%) into AML, 164 (4.7%) into CML, and 175 (5.0%) into other SHMs. Therefore, NHL, MM, and CLL were the top three frequently developed SHMs in patients with T1/2 PC.

According to the treatment modality, patients were divided into 6 groups, including no RT or prostatectomy (n = 66132, 22.93%), only EBRT (n = 64020, 22.20%), only RI (n = 29115, 10.23%), combination of EBRT/RI/radioisotopes (n = 15695, 5.44%), only prostatectomy (n = 108305, 37.55%), and combination of RT and prostatectomy (n = 4737, 1.64%). The patients’ characteristics in each group are summarized in Table 1.

**3.2 CRR analysis of the development of SHMs**

As shown in Table 2, age at the time of diagnosis of PC, marital status, and RT were associated with the risk of the development of SHMs by multivariate CRR analysis. More specifically, elderly patients were at a higher risk of the development of SHMs than non-elderly patients (HR = 1.03, 95% CI: 1.02–1.04); married patients were at a higher risk of the development of SHMs compared with unmarried patients (HR = 1.30, 95% CI: 1.19–1.42). Besides, patients who received EBRT, RI, combination of EBRT and RI, and combination of prostatectomy and RT were at a higher risk of the development of SHMs than those who did not receive RT or prostatectomy (HR = 1.21, 95% CI: 1.10–1.34; HR = 1.20, 95% CI: 1.06–1.36; HR = 1.27, 95% CI: 1.10–1.48 and HR = 1.36, 95% CI: 1.07–1.74, respectively). However, patients who underwent prostatectomy were not at a higher risk of development of SHMs than those who did not undergo RT or prostatectomy. The VIFs of the variables are presented in Table 2, and a VIF <2 indicated that multicollinearity was not existed among these factors. The results of univariate CRR analysis are presented in Data S1.

**3.3 RRs of the development of SHMs in patients with T1/T2 PC undergoing diverse treatment modalities**

Table 3 presents the RRs of the development of SHMs in patients with T1/T2 PC undergoing diverse treatment modalities. It was found that undergoing EBRT was associated with a higher risk of NHL, AML, and CML with RRs of 1.18 (95% CI: 1.02–1.35), 1.54 (95% CI: 1.16–2.03), and 1.56 (95% CI: 1.05–2.33), respectively, while that was correlated with an attenuated risk of CLL (RR = 0.67, 95% CI: 0.53–0.85). In addition, undergoing RI was associated with a higher risk of NHL with RR of 1.23 (95% CI: 1.05–1.44) and with a lower risk of CLL (RR = 0.72, 95% CI: 0.54–0.96), and undergoing...
| Variable                      | Subgroup                      | Overall cohort (n = 288,400) | No RT or prostatectomy (n = 66,132, 22.93%) | Only EBRT (n = 64,020, 22.20%) | Only RI (n = 29,115, 10.23%) | Combination of EBRT/RI/radioisotopes (n = 15,695, 5.44%) | Only prostatectomy (n = 108,305, 37.55%) | Prostatectomy with RT (n = 4737, 1.64%) | p-value |
|-------------------------------|-------------------------------|-------------------------------|---------------------------------------------|------------------------------|-------------------------------|-------------------------------------------------------------|------------------------------------------|------------------------------------------|---------|
| Age at diagnosis              |                              | 66.0 (9.32)                   | 70.0 (10.07)                                | 68.8 (7.85)                  | 65.7 (7.83)                   | 65.9 (7.97)                                                  | 62.0 (8.55)                               | 65.6 (8.79)                               | <0.001  |
| Race                          | White                        | 226888 (78.67)                | 49293 (74.54)                               | 48552 (75.84)                | 24343 (82.49)                 | 11683 (74.44)                                                | 89347 (82.50)                            | 3670 (77.48)                             | <0.001  |
|                              | Black                        | 42283 (14.66)                 | 10570 (15.98)                               | 10794 (16.86)                | 3717 (12.60)                  | 3217 (20.50)                                                 | 13201 (12.19)                            | 784 (16.55)                              |         |
|                              | Asian or Pacific Islander    | 13225 (4.59)                  | 3034 (4.59)                                 | 3568 (5.57)                  | 1161 (3.93)                   | 689 (4.39)                                                   | 4518 (4.17)                              | 255 (5.38)                               |         |
|                              | American Indian/Alaska Native| 857 (0.30)                    | 252 (0.38)                                  | 200 (0.31)                   | 73 (0.25)                     | 33 (0.21)                                                    | 285 (0.26)                               | 14 (0.30)                                |         |
|                              | Unknown                      | 5147 (1.78)                   | 2983 (4.51)                                 | 906 (1.420)                  | 217 (0.74)                    | 73 (0.47)                                                    | 954 (0.88)                               | 14 (0.30)                                |         |
| Marital status               | Single/divorce/widow         | 59646 (20.68)                 | 14598 (22.07)                               | 14957 (23.36)                | 5945 (20.18)                  | 3144 (20.03)                                                 | 19953 (18.42)                            | 1040 (21.95)                             | <0.001  |
|                              | Married                      | 196066 (67.98)                | 33159 (50.14)                               | 43481 (67.92)                | 21723 (73.61)                 | 11593 (73.86)                                                | 82635 (76.30)                            | 3475 (73.36)                             |         |
|                              | Unknown                      | 32688 (11.33)                 | 18375 (27.76)                               | 5582 (8.72)                  | 1834 (6.21)                   | 958 (6.10)                                                   | 5717 (5.28)                              | 222 (4.69)                               |         |
| T (AJCC 6th) status          | I                            | 120013 (41.61)                | 36371 (55.00)                               | 40224 (62.83)                | 20498 (69.46)                 | 9902 (63.09)                                                 | 11054 (10.21)                            | 1964 (41.46)                             | <0.001  |
|                              | II                           | 168387 (58.39)                | 29761 (45.00)                               | 23796 (37.17)                | 9013 (30.54)                  | 5793 (36.91)                                                 | 97251 (89.79)                            | 2773 (58.54)                             |         |
| N (AJCC 6th) status          | 0                            | 283882 (98.43)                | 64640 (97.74)                               | 62931 (98.30)                | 29192 (98.92)                 | 15541 (99.02)                                                | 107008 (98.80)                           | 4570 (96.47)                             | <0.001  |
|                              | I                            | 1557 (0.54)                   | 466 (0.70)                                  | 391 (0.61)                   | 17 (0.06)                     | 44 (0.28)                                                    | 528 (0.49)                               | 111 (2.34)                               |         |
|                              | X                            | 2961 (1.03)                   | 1026 (1.55)                                 | 698 (1.09)                   | 302 (1.02)                    | 110 (0.70)                                                   | 769 (0.71)                               | 56 (1.18)                                |         |
| Chemotherapy                 | No/Unknown                   | 287635 (99.73)                | 65924 (99.69)                               | 63765 (99.60)                | 29467 (99.85)                 | 15638 (99.64)                                                | 108145 (99.85)                           | 4696 (99.13)                             | <0.001  |
|                              | Yes                          | 765 (0.27)                    | 208 (0.31)                                  | 255 (0.40)                   | 44 (0.15)                     | 57 (0.36)                                                    | 160 (0.15)                               | 41 (0.87)                                |         |

(Continues)
| Variable            | Subgroup        | Overall cohort (n = 288,400) | No RT or prostatectomy (n = 66,132, 22.93%) | Only EBRT (n = 64,020, 22.20%) | Only RI (n = 29,115, 10.23%) | Combination of EBRT/RI/radioisotopes (n = 15,695, 5.44%) | Only prostatectomy (n = 108,305, 37.55%) | Prostatectomy with RT (n = 4737, 1.64%) | p-value |
|---------------------|-----------------|------------------------------|---------------------------------------------|--------------------------------|-----------------------------|-----------------------------------------------------------|------------------------------------------|---------------------------------------|---------|
| PSA, ng/mL (IQR)    |                 | 6.1 (4.6–9.2)               | 7.1 (4.9–12.1)                              | 7.1 (5.1–11.1)                | 5.7 (4.5–7.6)              | 6.3 (4.7–9.9)                                              | 5.4 (4.2–7.5)                            | 6.6 (4.6–11)                           | <0.001  |
| 0–4                 |                 | 38718 (13.43)               | 6372 (9.64)                                 | 5918 (9.24)                   | 4348 (14.73)              | 1906 (12.14)                                              | 19448 (17.96)                           | 726 (15.33)                            | <0.001  |
| >4                  |                 | 214345 (74.32)              | 45711 (69.12)                               | 55452 (86.62)                 | 23473 (79.54)             | 12960 (82.57)                                              | 73291 (67.67)                           | 3458 (73.00)                           |         |
| Unknown             |                 | 35337 (12.25)               | 14069 (21.24)                               | 2650 (4.14)                   | 1690 (5.73)               | 829 (5.28)                                                | 15566 (14.37)                           | 553 (11.67)                            |         |
| Gleason's score (IQR) |                 | 6 (6–7)                     | 6 (6–7)                                     | 7 (6–7)                       | 6 (6–7)                   | 7 (6–7)                                                    | 7 (6–7)                                 | <0.001                               |         |
| 0–4                 |                 | 2440 (0.85)                 | 1020 (1.54)                                 | 276 (0.43)                    | 224 (0.76)                | 49 (0.31)                                                  | 831 (0.77)                              | 40 (0.84)                             | <0.001  |
| 5–7                 |                 | 203118 (70.43)              | 41441 (62.66)                               | 41727 (65.18)                 | 24141 (81.80)             | 11016 (70.19)                                              | 81733 (75.47)                           | 3060 (64.60)                           |         |
| 7–10                |                 | 25123 (8.71)                | 6779 (10.25)                                | 8649 (13.51)                  | 899 (3.05)                | 2211 (14.09)                                               | 5820 (5.37)                             | 765 (16.15)                           |         |
| Unknown             |                 | 57719 (20.01)               | 16892 (25.54)                               | 13368 (20.88)                 | 4255 (14.7)               | 2419 (15.41)                                               | 19921 (18.39)                           | 872 (18.41)                           |         |
| Outcomes            | Alive           | 21723 (73.41)               | 40389 (61.07)                               | 43830 (68.46)                 | 22474 (76.15)             | 11705 (74.58)                                              | 90002 (83.10)                           | 3323 (70.15)                           | <0.001  |
| Other second cancer |                 | 29031 (10.07)               | 6874 (10.39)                                | 7806 (12.19)                  | 3384 (11.47)              | 1797 (11.45)                                               | 8635 (7.97)                             | 535 (11.29)                           |         |
| Death               |                 | 44342 (15.38)               | 18100 (27.37)                               | 11414 (18.1)                  | 3267 (11.07)              | 1979 (12.61)                                               | 8663 (8.00)                             | 813 (17.16)                           |         |
| NHL                 |                 | 1597 (0.55)                 | 343 (0.52)                                  | 411 (0.64)                    | 201 (0.68)                | 95 (0.61)                                                  | 516 (0.48)                              | 31 (0.65)                             |         |
| MM                  |                 | 723 (0.25)                  | 178 (0.27)                                  | 187 (0.29)                    | 76 (0.26)                 | 49 (0.31)                                                  | 219 (0.20)                              | 14 (0.30)                             |         |
| CLL                 |                 | 485 (0.17)                  | 153 (0.23)                                  | 101 (0.16)                    | 52 (0.18)                 | 26 (0.17)                                                  | 150 (0.14)                              | 3 (0.06)                              |         |
| AML                 |                 | 335 (0.12)                  | 67 (0.10)                                   | 110 (0.17)                    | 36 (0.12)                 | 34 (0.22)                                                  | 76 (0.07)                               | 12 (0.25)                             |         |
| CML                 |                 | 164 (0.06)                  | 28 (0.04)                                   | 55 (0.09)                     | 21 (0.07)                 | 10 (0.06)                                                  | 44 (0.04)                               | 6 (0.13)                              |         |

Note: The PSA value and Gleason's score is presented as median (IQR), age at diagnosis is mean (SD), while other variables are frequency (%).

Abbreviations: AJCC, American Joint Committee on Cancer; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; EBRT, external beam radiation; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PSA, prostate-specific antigen; RI, radioactive implants; RT, radiation therapy; SHM, second hematological malignancy.
combination of EBRT/RI/radioisotopes was correlated with a higher risk of AML (RR = 2.03, 95% CI: 1.40–2.93). Moreover, patients who underwent prostatectomy was associated with an attenuated risk of CLL (RR = 0.80, 95% CI: 0.66–0.98) and did not show correlation with developing other types of SHMs. The SIRs of each cohort are presented in Data S2.

### DISCUSSION

RT remains an important component of cancer treatment with approximately 50% of all cancer patients receiving RT during their course of disease. A number of scholars pointed out that RT is effective for improving cancer-specific survival rate in various malignancies, especially in T1/2 PC. However, it has been frequently reported that the risk of the development of SHMs after RT is noteworthy and whether RT can attenuate the risk of the development of SHMs remains controversial. In the present study, a large population-based database was used to analyze the association between RT and the development of SHMs in patients with T1/2 PC.

Regarding the development of SHMs in patients with T1/2 PC, it was noted that NHL, MM, and CLL were the top three frequently developed SHMs. While some studies have showed thyroid cancer was noticeably enhanced the development of AML and CML after radioiodine treatment, and breast cancer could significantly intensify the development of AML and NHL after RT. According to the report of the American Cancer Society published in 2020, the most frequently occurred SHMs in the United States were NHL, MM, and CLL, which was consistent with the result of the current research, but not totally coincide with thyroid cancer and breast cancer as mentioned above. Therefore, it is necessary to focus on the incidence of NHL, MM, and CLL in T1/T2 PC patients. As mentioned earlier, RT was found to be associated with a high incidence of secondary AML and CML in some malignancies, a number of scholars demonstrated that genotoxic stress, ribosome biogenesis stress, and inflammation from RT might increase the risk of transformation from clonal hematopoiesis to a myeloid malignancy included AML and CML, which highlighted the necessity of estimation of the risks of development of AML and CML in T1/T2 PC patients.

| Variables                  | HR   | 95% CI lower-upper | p-value | VIF |
|----------------------------|------|--------------------|---------|-----|
| Age at diagnosis           | 1.03 | 1.02–1.04          | <0.001  | 0.867 |
| Marital status             |      |                    |         |     |
| Single/divorce/widow       | 1.00 |                    |         |     |
| Married                    | 1.30 | 1.19–1.42          | <0.001  | 0.722 |
| Unknown                    | 1.16 | 1.02–1.32          |         | 0.697 |
| Race                       |      |                    |         |     |
| White                      | 1.00 |                    |         |     |
| Black                      | 0.98 | 0.89–1.09          | 0.752   |     |
| Asian or Pacific Islander  | 0.87 | 0.74–1.03          | 0.105   |     |
| American Indian/Alaska Native | 0.70 | 0.33–1.56          | 0.337   |     |
| Unknown                    | 0.05 | 0.01–0.16          | <0.001  |     |
| T (AJCC 6th) status        |      |                    |         |     |
| I                          | 1.00 |                    |         |     |
| II                         | 1.02 | 0.95–1.10          | 0.615   |     |
| Therapy modality           |      |                    |         |     |
| No RT or prostatectomy     | 1.00 |                    |         |     |
| Only EBRT                  | 1.21 | 1.10–1.34          | <0.001  | 0.628 |
| Only RI                    | 1.20 | 1.06–1.36          | 0.003   | 0.733 |
| Combination of EBRT/RI/ radioisotopes | 1.27 | 1.10–1.48          | 0.002   | 0.829 |
| Only prostatectomy         | 1.02 | 0.92–1.12          | 0.755   | 0.505 |
| RT with prostatectomy      | 1.36 | 1.07–1.74          | 0.012   | 0.937 |

**Abbreviations**: AJCC, American Joint Committee on Cancer; CRR, competing risk regression analysis; EBRT, external beam radiation; HR, hazard ratio; RI, radioactive implants; VIF, variance inflation factor.

**TABLE 2** The results of multivariable competing risk regression analysis of developing SHMs in patients with T1/2 PC.
Although a number of previous studies have shown that RT was associated with a higher risk of the development of SHMs, the models and factors included in those studies were not comprehensive, and we, in the present research, used CRR analysis to assess the risk of the development of SHMs, which included factors related to PC patients’ demographic and clinical characteristics. We found that the risk of developing SHMs was elevated with the increase of age, married patients were at a higher risk compared with unmarried ones, and undergoing RT was also associated with the increased risk of developing SHMs. It has reported that age-related clonal hematopoiesis was a common condition that was associated with increases in the risk of hematologic cancer, where a single mutant hematopoietic stem or progenitor

| SHMs         | Therapy modality                              | O   | E     | Person-year at risk | Oa     | RR   | 95% CI lower-upper |
|--------------|-----------------------------------------------|-----|-------|---------------------|--------|------|-------------------|
| NHL          | No prostatectomy or RT                        | 368 | 427.81| 412709.81           | Reference |
|              | Only EBRT                                     | 463 | 458.05| 441002.69           | 462.072| 1.18 | 1.02–1.35         |
|              | Only RI                                       | 226 | 213.59| 226584.32           | 248.521| 1.23 | 1.05–1.44         |
|              | Combination of EBRT/RI/radioisotopes         | 99  | 102.85| 111976.09           | 111.728| 1.12 | 0.91–1.38         |
|              | Only Prostatectomy                            | 550 | 605.05| 799191.88           | 753.058| 1.06 | 0.93–1.20         |
|              | RT with prostatectomy                         | 11  | 12.83 | 38705.21            | 34.39867| 1.10 | 0.70–1.41         |
| MM           | No prostatectomy or RT                        | 187 | 181.01| 412709.81           | Reference |
|              | Only EBRT                                     | 207 | 198.48| 441002.69           | 201.72 | 1.01 | 0.83–1.23         |
|              | Only RI                                       | 82  | 87.77 | 226584.32           | 92.84  | 0.90 | 0.71–1.16         |
|              | Combination of EBRT/RI/radioisotopes         | 50  | 46.41 | 111976.09           | 52.91  | 1.04 | 0.77–1.41         |
|              | Only prostatectomy                            | 245 | 245.64| 799191.88           | 349.60 | 0.97 | 0.81–1.15         |
|              | RT with prostatectomy                         | 6   | 8.14  | 38705.21            | 12.51  | 0.71 | 0.40–1.26         |
| CLL          | No prostatectomy or RT                        | 159 | 144.82| 412709.81           | Reference |
|              | Only EBRT                                     | 112 | 152.44| 441002.69           | 113.70 | 0.67 | 0.53–0.85         |
|              | Only RI                                       | 56  | 70.8  | 226584.32           | 62.89  | 0.72 | 0.54–0.96         |
|              | Combination of EBRT/RI/radioisotopes         | 29  | 34.13 | 111976.09           | 33.39  | 0.77 | 0.53–1.12         |
|              | Only prostatectomy                            | 174 | 197   | 799191.88           | 247.70 | 0.80 | 0.66–0.98         |
|              | RT with prostatectomy                         | 3   | 3.43  | 38705.21            | 11.87901| 0.44 | 1.44             |
| AML          | No prostatectomy or RT                        | 80  | 95.08 | 412709.81           | Reference |
|              | Only EBRT                                     | 132 | 102.15| 441002.69           | 131.29 | 1.54 | 1.16–2.03         |
|              | Only RI                                       | 49  | 45.5  | 226584.32           | 56.22  | 1.28 | 0.91–1.80         |
|              | Combination of EBRT/RI/radioisotopes         | 38  | 22.3  | 111976.09           | 43.96  | 2.03 | 1.40–2.93         |
|              | Only prostatectomy                            | 102 | 122.05| 799191.88           | 153.87 | 0.99 | 0.86–1.30         |
|              | RT with prostatectomy                         | 9   | 6.15  | 38705.21            | 13.04912| 1.74 | 0.97–3.12         |
| CML          | No prostatectomy or RT                        | 38  | 38.84 | 412709.81           | Reference |
|              | Only EBRT                                     | 63  | 41.16 | 441002.69           | 63.52  | 1.56 | 1.05–2.33         |
|              | Only RI                                       | 27  | 18.65 | 226584.32           | 30.87  | 1.48 | 0.92–2.38         |
|              | Combination of EBRT/RI/radioisotopes         | 11  | 9.1   | 111976.09           | 12.74  | 1.24 | 0.65–2.33         |
|              | Only prostatectomy                            | 47  | 51.47 | 799191.88           | 68.68  | 0.93 | 0.63–1.38         |
|              | RT with prostatectomy                         | 0   | 0.64  | 38705.21            | 0      | /   | /                |

Bold fonts: \( p < 0.05 \).

Abbreviations: AML, acute myeloid leukemia; CI, confidence intervals; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; E, expectations; EBRT, external beam radiation; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; O, observations; Oa, observations(adjusted); RI, radioactive implants; RR, relative risk; RT, radiation therapy; SHM, second hematological malignancy.
cell contributes to a significant, measurable clonal proportion of mature blood lineages. Evolution of mutant clonal hematopoiesis with age predisposes the elderly to myelodysplastic syndromes (MDS), AML, and other aging-associated diseases. As for marital status of patients with PC, some scholars have reported that married patients had better prognosis than unmarried, but for the development of SHMs, this result was opposite in our study, and it is expected that further researches could explain these results.

Several previously conducted studies have demonstrated that RT was associated with a high incidence of AML and CML, and we therefore attempted to estimate the risks of developing these SHMs in patients with T1/2 PC. The RR is the ratio of risk of an event in one group (e.g., exposed group) to the risk of the event in the other group (e.g., nonexposed group). Adjustment for baseline covariates in the analysis of randomized controlled trials can lead to a substantial increase in power when the covariates are highly prognostic. In the present study, values of $E$ parameter could be achieved according to the patients’ age, race, and calendar time-specific incidence rate by stratum-specific person-years of follow-up.

Regarding the RRs in the current study, RT was found to be associated with a significantly increased risk of developing AML and CML and a slightly increased risk of developing NHL than those who did not receive RT or prostatectomy, whereas patients who only underwent prostatectomy did not show the correlations of increased risk of developing SHMs. Although a large population-based database was utilized in the current study, it was revealed that the influence of RT on the development of SHMs was different, the incidence of AML and CML was more sensitive to RT, and the decreased risk of developing CLL might be attributed to the treatment for PC.

Some limitations existed in the present study should be presented. First, the RT protocols for PC patients were not existed in the SEER database, thus, we could not take the radiation dosage into account. Second, some patients’ demographic and clinical data were unidentifiable and the present retrospective study was therefore vulnerable to ascertainment bias. Third, the selection bias was found due to the retrospective nature of this study. Despite the above-mentioned limitations, utilization of a large population-based database enhanced the reliability of the results. However, further research is warranted to eliminate these limitations and to confirm our findings.

5 | CONCLUSIONS

In summary, NHL, MM, and CLL were the top three frequently developed SHMs in patients with T1/2 PC. Besides, undergoing RT was associated with the increased incidence of NHL, AML, and CML, while with the decreased incidence of CLL, and no significant association was detected between undergoing RT and the incidence of MM. Moreover, prostatectomy did not significantly correlate with the increased risk of developing SHMs.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

We received permission from the National Cancer Institute, US to access the research data file in the SEER program (reference number 13610-Nov2019). Ethics approval was not applicable because SEER data is publicly available and without specific identifiers.

DATA AND MATERIAL AVAILABILITY STATEMENT

The datasets analyzed during the current study are available in the SEER repository (https://seer.cancer.gov/). The databases are public access.

ACKNOWLEDGMENTS

The authors acknowledge the efforts of the SEER Program tumor registries in providing high-quality open resources for researches, and thank TopEdit (www.topeditsci.com) for its linguistic assistance during the preparation of this manuscript.

CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

XM, MZ, and YW conceived the study design and analytical concept. XM conducted the data acquisition, performed the statistical analyses and drafted the manuscript. HY assisted with collection of data and interpretation. XC participated in data interpretation and revision of manuscript. XM and MZ contributed to the interpretation of the results and the critical revision of the manuscript. The authors participated in the revision of the manuscript and approved the final manuscript.

ORCID

Xiaofei Mo https://orcid.org/0000-0002-8633-4188

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. Cancer J Clin. 2018;68(1):7-30.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. Cancer J Clin. 2019;69(1):7-34.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. Cancer J Clin. 2020;70(1):7-30.
4. Litwin MS, Tan HJ. The diagnosis and treatment of prostate cancer: a review. JAMA. 2017;317:2532-2542.
5. Guo Y, Mao S, Zhang A, et al. Survival significance of patients with low prostate-specific antigen and high-grade prostate cancer...
after radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy. Front Oncol. 2019;9:638.
6. Muralidhar V, Mahal BA, Butler S, et al. Combined external beam radiation therapy and brachytherapy versus radical prostatectomy with adjuvant radiation therapy for Gleason 9–10 prostate cancer. J Urol. 2019;202:973-978.
7. Molenaar RJ, Sidana S, Radiovoyevitch T, et al. Risk of hematologic malignancies after radiiodine treatment of well-differentiated thyroid cancer. J Clin Oncol. 2018;36:1831-1839.
8. Radiovoyevitch T, Sachs RK, Gale RP, et al. Defining AML and MDS second cancer risk dynamics after diagnoses of first cancers treated or not with radiation. Leukemia. 2016;30:285-294.
9. Ohnoshi T, Hiraki S, Ueda N, et al. Long-term results of combination chemotherapy with or without irradiation in small cell lung cancer: a 5- to 11-year follow-up. Internal Med (Tokyo, Japan). 1993;32:215-220.
10. Jabagi MJ, Goncalves A, Vey N, Le Tri T, Zureik M, Dray-Spira R. Risk of hematologic malignant neoplasms after postoperative treatment of breast cancer. Cancer. 2019;11(10):1463.
11. Fan C-Y, Huang W-Y, Lin C-S, et al. Risk of second primary malignancies among patients with prostate cancer: a population-based cohort study. PLoS One. 2017;12:e0175217.
12. Wang C, King CR, Kamrava M, et al. Pattern of solid and hematopoietic second malignancy after local therapy for prostate cancer. Radiother Oncol. 2017;123:133-138.
13. Shuryak I, Sachs RK, Hlatky L, Little MP, Hahnfeldt P, Brenner DJ. Radiation-induced leukemia at doses relevant to radiation therapy: modeling mechanisms and estimating risks. J Natl Cancer Inst. 2006;98:1794-1806.
14. Coombs CC, Zehir A, Devlin SM, et al. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and associated with adverse clinical outcomes. Cell Stem Cell. 2017;21:374-82.e4.
15. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist. 2007;12:20-37.
16. Simon SD. Understanding the odds ratio and the relative risk. J Androl. 2001;22:533-536.
17. Andrade C. Understanding relative risk, odds ratio, and related terms: as simple as it can get. J Clin Psychiatry. 2015;76:1749.e857-e861.
18. Olsen RJ. Risk of second cancer after cancer in childhood. Cancer. 1986;57(11):2250-2254.
19. Wei JL, Jiang YZ, Shao ZM. Survival and chemotherapy-related risk of second primary malignancy in breast cancer patients: a SEER-based study. Int J Clin Oncol. 2019;24:934-940.
20. Baskar R, Lee KA, Yeo R, Yeoh KW. Cancer and radiation therapy: current advances and future directions. Int J Med Sci. 2012;9:193-199.
21. Zhou X, Ning Q, Jin K, Zhang T, Ma X. Development and validation of a preoperative nomogram for predicting survival of patients with locally advanced prostate cancer after radical prostatectomy. BMC Cancer. 2020;20:97.
22. Sahota RA, Nesslinger NJ, Ludgate C, et al. Hormone and radiation therapy induce tumor-specific immune responses in prostate cancer. 2006;66.
23. Kamran SC, D’Amico AV. Radiation therapy for prostate cancer. Hematol Oncol Clin North Am. 2020;34:45-69.
24. Curtis RE, Boice JD Jr, Stovall M, Flannery JT, Moloney WC. Leukemia risk following radiotherapy for breast cancer. J Clin Oncol. 1989;7:21-29.
25. Alldodi RS, Tucker MA, Hawkins MM, et al. Role of radiotherapy and chemotherapy in the risk of leukemia after childhood cancer: an international pooled analysis. Int J Cancer. 2021;148(9):2079-2089.
26. Abalo KD, Rage E, Leuraud K, et al. Early life ionizing radiation exposure and cancer risks: systematic review and meta-analysis. Pediatr Radiol. 2021;51:45-56.
27. Warren JT, Link DC. Clonal hematopoiesis and risk for hematologic malignancy. Blood. 2020;136:1599-1605.
28. Desai P, Hassane D, Roboz GJ. Clonal Hematopoiesis and risk of Acute Myeloid Leukemia. Best Practice Res Clin Haematol. 2019;32:177-185.
29. Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. Science. 2019;366(6465):eaan4673.
30. Zheng Z, Zhou Z, Yan W, et al. Tumor characteristics, treatments, and survival outcomes in prostate cancer patients with a PSA level <4 ng/ml: a population-based study. BMC Cancer. 2020;20:340.
31. Guo Z, Gu C, Li S, et al. Association between marital status and prognosis in patients with prostate cancer: a meta-analysis of observational studies. Urol J. 2020;16(7):6917.
32. Zhang J, Yu KF. What’s the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998;280:1690-1691.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Mo X, Zhou M, Yan H, Chen X, Wang Y. Estimating the risk of developing secondary hematologic malignancies in patients with T1/T2 prostate cancer undergoing diverse treatment modalities: A large population-based study. Cancer Med. 2021;00:1–9. https://doi.org/10.1002/cam4.4087