Survival in Patients With Metastatic Prostate Cancer Undergoing Radiotherapy: The Importance of Prostate-Specific Antigen-Based Stratification

Zijian Tian1,2†, Lingfeng Meng1,2†, Xin Wang1, Xuan Wang1, Tianming Ma1,2, Miao Wang1,2, Qiuzi Zhong†, Yaquon Zhang1,2* and Ming Liu1,2*

1 Department of Urology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China, 2 Graduate School of Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

Objectives: To explore the effectiveness of radiotherapy in mPCa patients with different PSA stratiﬁcations based on the cancer database of a large population.

Background: Screening criteria for patients with metastatic prostate cancer, who are candidates for radiotherapy, are rarely reported.

Patients and Methods: We identiﬁed 22,604 patients with metastatic prostate cancer in the Surveillance, Epidemiology, and End Results database and divided them into a radiotherapy group and a control group. Patients with metastatic prostate cancer were divided into subgroups according to their levels of prostate-speciﬁc antigen to evaluate the efﬁcacy of radiotherapy. They were also divided into six subgroups according to their prostate-speciﬁc antigen levels. We used multivariate Cox analysis to evaluate overall survival and cancer-speciﬁc survival. After 1:1 propensity score matching, Kaplan-Meier analysis was used to explore the difference in overall survival and cancer-speciﬁc survival in the radiotherapy and control group.

Results: In all, 5,505 patients received radiotherapy, compared to 17,099 in the control group. In the multivariate Cox analysis, radiotherapy improved overall survival (hazard ratio [HR]: 0.730, 95% conﬁdence interval [CI]: 0.636–0.838; P<0.001) and cancer-speciﬁc survival (HR: 0.764, 95% CI: 0.647–0.903; P=0.002) in patients with a PSA level of 4–10 ng/mL. Similar results were obtained by Kaplan-Meier analysis after 1:1 propensity score matching. In patients with prostate-speciﬁc antigen levels between 4–10 ng/mL, the overall survival (P<0.001) and cancer-speciﬁc survival (P<0.05) in the radiotherapy group was signiﬁcantly better than those in the control group.

Conclusion: The result of this large population-based study shows that rigorous selection of appropriate metastatic prostate cancer patients for radiotherapy can beneﬁt prognosis signiﬁcantly. This can be the basis for future prospective trials.

Keywords: prostate-speciﬁc antigen, metastatic prostate cancer, SEER, survival analysis, radiotherapy
INTRODUCTION

The incidence of prostate cancer (PCa) has been increasing annually, ranking first among male malignant tumors in the United States. It is estimated that there were 191,930 new cases of PCa in 2020, with 33,330 patients dying from PCa (1). PCa can present in different stages, and metastasis is an important stage adversely affecting prognosis (2, 3). Although the widespread use of prostate-specific antigen (PSA) testing has reduced the incidence of metastatic prostate cancer (mPCa) (4), 6% of PCa patients in the United States and 15.8% in the Netherlands still have metastatic disease at diagnosis (3, 5). The incidence can be as high as 50–64% in Asian countries (6, 7).

Two recent, prominent randomized controlled trials, HORRAD and STAMPEDE, have shown that radiotherapy has no survival benefit in overall unscreened cohorts of mPCa. In the HORRAD trial, 432 mPCa patients with PSA > 20 ng/mL were divided into a radiotherapy and a control group. The results revealed that radiotherapy did not significantly prolong the overall survival (OS) of patients with mPCa [hazard ratio (HR), 0.90; 95% confidence interval (CI): 0.70–1.14; P=0.4] (8). In the STAMPEDE trial of 2,061 mPCa patients with PSA > 30 ng/mL, there were no survival benefits of radiotherapy in the general population (HR: 0.92, 95% CI 0.80–1.06; P=0.27) (9). This was similar to the HORRAD results. However, in the subgroup analysis based on metastatic burden, radiotherapy was found to prolong the OS of patients with oligometastatic PCa. A meta-analysis combining data from the HORRAD and STAMPEDE studies revealed that radiotherapy could increase the absolute value of 3-year OS by 7% if the number of metastases was less than 4 (10). At present, radiotherapy for oligometastatic PCa has become a routine recommendation (11). Patient selection is important for radiotherapy, with clinicians trying to define further clinical parameters for optimal patient selection. However, no study has reported the efficacy of radiotherapy in patients with mPCa under different PSA subgroups.

PSA levels reflect the load of tumor cells. PCa with a higher PSA level is more aggressive and carries a higher risk of death due to cancer. However, recent studies have reported that PSA levels in patients with mPCa are not linearly related to prognosis. Patients with lower PSA levels (≤ 4 ng/mL) exhibited poorer prognoses than patients with higher PSA levels (12). The HORRAD and STAMPEDE studies also included only mPCa patients with PSA levels greater than 20 and 30 ng/mL, respectively. Previous retrospective studies (13–15) did not stratify mPCa patients according to PSA levels to explore the efficacy of radiotherapy. Therefore, the purpose of this study was to explore the effectiveness of radiotherapy in mPCa patients with different PSA stratifications based on the cancer database of a large population.

MATERIALS AND METHODS

Study Population

The Surveillance, Epidemiology, and End Results (SEER) database is the authoritative cancer statistics database in the United States. It covers about 28% of the clinical cancer patients in the United States and records the morbidity, mortality, and illness of these patients among other clinical information. In the SEER database (2004–2015), we identified 22,604 mPCa patients who met our inclusion criteria. The inclusion criteria were as follows: pathological diagnosis of prostate cancer, metastatic disease at the time of diagnosis, age > 18 years, and having received radiotherapy. The exclusion criteria were as follows: those who underwent radical prostatectomy, patients whose radiotherapy details were incomplete, patients whose PSA information was unrecorded, and patients whose survival time information was lacking. Age, race, Gleason score, T stage, N stage, M stage, and PSA level were recorded for patients who met the criteria.

Statistical Analysis

This study’s main outcome index is OS; the secondary outcome index is cancer-specific survival (CSS). Pearson’s chi-square analysis was used to determine the variables between different treatment groups. We stratified the data according to PSA levels (< 4.0, 4.1–10.0, 10.1–20.0, 20.1–40.0, 40.1–80.0, > 80.1 ng/mL). Covariates were included in univariate and multivariate Cox regression analyses to determine the prognostic HR and 95% CI of the treatment group. In the multivariate analysis, PSA (4.1–10.0 ng/mL) was used as a reference to explore the relative HR of other subgroups. To balance covariance and reduce deviation in the evaluation of therapeutic effect, we measured OS and CSS using the Kaplan-Meier (KM) method at 1:1 propensity score matching in the radiotherapy group and control group of each PSA subgroup. We designed the analysis for two-sided tests using IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp., Armonk, NY). Statistical significance was set at P < 0.05.

RESULTS

Demographics and Pathological Characteristics

A total of 22,604 mPCa patients who met the inclusion criteria were identified from the SEER database. There were 5,505 patients in the radiotherapy group and 17,099 participants in the control group. Patient characteristics are shown in Table 1.

Statistical Analysis

Univariate and multivariate analysis were used to determine whether there was a statistical correlation between the PSA subgroups and the prognosis of patients within each subgroup. With each PSA subgroup, we included age, race, Gleason score, treatment groups, T stage, N stage, and M stage in a univariate Cox analysis. The univariate Cox analysis showed that the PSA group with the highest OS was the PSA 4.1–10.0 ng/mL subgroup (P < 0.001), while the PSA groups correlated with CSS were the PSA 4.1–10.0 ng/mL and PSA > 80.1 ng/mL subgroups (P<0.05) (Supplementary Table 1). All significant factors in the univariate Cox analysis (e.g., 4.1–10.0 ng/mL, 40.1–80.0 ng/mL, and > 80.1 ng/mL subgroups) were included in the multivariate Cox regression analysis. The results showed that
radiotherapy could significantly improve OS (HR: 0.730, 95% CI: 0.636–0.838; P < 0.001) and CSS (HR: 0.764, 95% CI: 0.647–0.903; P=0.002) of mPCa in the PSA 4.1–10.0 ng/mL subgroup (Table 2). In the PSA > 80.1 ng/mL subgroup, the radiotherapy group was associated with worse CSS (HR: 1.065, 95% CI: 1.009–1.124; P=0.023) (Supplementary Table 2).

In the multivariate analysis, using the PSA 4.1–10.0 ng/mL subgroup as the reference, the distribution of OS in the SEER cohort showed a U-shaped distribution relative to PSA (Figure 1), the HRs of the PSA < 4.0, 10.1–20.0, 20.1–40.0, 40.1–80.0, and > 80.1 ng/mL groups were 1.331, 1.136, 1.211, 1.379, and 1.544, respectively (Supplementary Table 3). When CSS was used as the outcome index, KM analysis showed that radiotherapy was most beneficial in mPCa patients with PSA levels of 4.1–10.0 ng/mL. In the PSA > 80.1 ng/mL subgroup, the CSS of the radiotherapy group was inferior to that of the control group (P < 0.05), but there was no significant difference in the improvement of prognosis among other PSA subgroups (Figure 3).

DISCUSSION

Large-scale population-based cohort analyses of PCa patients can provide important guidelines for clinical treatment and further prospective studies. At present, a stratified analysis of 22,604 patients with mPCa in the SEER database was conducted to

### TABLE 1 | Clinicopathological characteristics of the cohort by treatment groups.

| Characteristics | Radiotherapy (n=5505; %) | Control (n=17099; %) | P value* |
|-----------------|--------------------------|----------------------|---------|
| **Age**         |                          |                      |         |
| ≤65             | 2303 (41.8%)             | 5564 (32.5%)         | <0.001  |
| >65             | 3202 (58.2%)             | 11535 (67.5%)        |         |
| **Race**        |                          |                      | 0.672   |
| Caucasians      | 4106 (74.6%)             | 12761 (74.6%)        |         |
| African Americans| 1044 (19.0%)             | 3185 (18.6%)         |         |
| Other/unknown   | 355 (6.4%)               | 1153 (6.7%)          |         |
| **Gleason**     |                          |                      | <0.001  |
| ≤6              | 193 (3.5%)               | 501 (2.9%)           |         |
| 7               | 750 (13.6%)              | 2384 (13.9%)         |         |
| 8-10            | 3092 (56.2%)             | 10385 (60.7%)        |         |
| Unknown         | 1470 (26.7%)             | 3829 (22.4%)         |         |
| **T**           |                          |                      | 0.006   |
| ≤T1             | 1334 (24.2%)             | 4305 (25.2%)         |         |
| T2              | 1662 (30.2%)             | 5480 (32.0%)         |         |
| T3              | 569 (10.3%)              | 1610 (9.4%)          |         |
| T4              | 749 (13.6%)              | 2154 (12.6%)         |         |
| Tx              | 1191 (21.6%)             | 3550 (20.8%)         |         |
| **N**           |                          |                      | <0.001  |
| N0              | 2959 (53.8%)             | 8901 (52.1%)         |         |
| N1              | 1396 (25.4%)             | 4128 (24.1%)         |         |
| Nx              | 1150 (20.9%)             | 4070 (23.8%)         |         |
| **M**           |                          |                      | <0.001  |
| M1a             | 228 (4.1%)               | 1043 (6.1%)          |         |
| M1b             | 3996 (72.6%)             | 12256 (71.7%)        |         |
| M1c             | 1142 (20.7%)             | 3275 (19.2%)         |         |
| M1x             | 139 (2.5%)               | 525 (3.1%)           |         |
| **PSA**         |                          |                      | <0.001  |
| <4 ng/ml        | 154 (2.8%)               | 403 (2.4%)           |         |
| 4.1–10 ng/ml    | 551 (10.0%)              | 1146 (6.7%)          |         |
| 10.1–20 ng/ml   | 596 (10.8%)              | 1645 (9.6%)          |         |
| 20.1–40 ng/ml   | 622 (11.3%)              | 2019 (11.8%)         |         |
| 40.1–80 ng/ml   | 666 (12.1%)              | 2134 (12.5%)         |         |
| >80.1 ng/ml     | 2916 (53.0%)             | 9752 (57.0%)         |         |

Data are present as n (%).

PSA, prostate-specific antigen.

*Chi-square test as appropriate.

1:1 Propensity Score Matching

After matching with a 1:1 tendency score, there was no significant difference in age, race, Gleason score, T stage, N stage, and M stage between the radiotherapy and control group in each PSA subgroup (Tables 3–8). KM analysis showed that radiotherapy could significantly improve OS only in patients of the PSA 4.1–10.0 ng/mL subgroup (P < 0.001). There was no significant difference in OS between the radiotherapy and control groups in other PSA subgroups (Figure 2). When CSS was used as the outcome index, KM analysis showed that radiotherapy was most beneficial in mPCa patients with PSA levels of 4.1–10.0 ng/mL. In the PSA > 80.1 ng/mL subgroup, the CSS of the radiotherapy group was inferior to that of the control group (P < 0.05), but there was no significant difference in the improvement of prognosis among other PSA subgroups (Figure 3).
determine whether PSA grouping would affect the efficacy of radiotherapy.

The direct cytotoxic effects of local radiotherapy for PCa have been widely reported (16). The biological mechanism of radiotherapy may be related to tumor cell death and changes in the tumor microenvironment (TME) induced by radiation (17). In short, radiation directly damages the TME, triggering the release of immunostimulatory factors, such as heat shock protein 70,
| Characteristics | Radiotherapy (n=154) | Control (n=403) | P value<sup>a</sup> | Propensity score adjusted radiotherapy (n=103) | Propensity score adjusted control (n=103) | P value<sup>b</sup> |
|-----------------|----------------------|----------------|---------------------|-----------------------------------------------|------------------------------------------|---------------------|
| **Age**         |                      |                |                     |                                               |                                          |                     |
| ≤65             | 55 (35.7%)           | 123 (30.5%)    | 0.240               | 29 (28.2%)                                    | 28 (27.2%)                               | 0.876               |
| >65             | 99 (64.3%)           | 280 (69.5%)    |                     | 74 (71.8%)                                    | 75 (72.8%)                               |                     |
| **Race**        |                      |                |                     |                                               |                                          |                     |
| Caucasians      | 128 (83.1%)          | 337 (83.6%)    | 0.632               |                                               |                                          |                     |
| African Americans| 21 (13.6%)           | 47 (11.7%)     |                     | 6 (5.8%)                                      | 6 (5.8%)                                 | 1.000               |
| Other/unknown   | 5 (3.2%)             | 19 (4.7%)      |                     | 2 (1.9%)                                      | 2 (1.9%)                                 |                     |
| **Gleason**     |                      |                |                     |                                               |                                          |                     |
| ≤8              | 8 (5.2%)             | 20 (5.0%)      | 0.003               | 2 (1.9%)                                      | 2 (1.9%)                                 | 0.953               |
| >7              | 99 (64.3%)           | 280 (69.5%)    |                     | 9 (8.7%)                                      | 7 (6.8%)                                 |                     |
| 8-10            | 85 (55.2%)           | 274 (68.0%)    |                     | 69 (67.0%)                                    | 72 (69.9%)                               |                     |
| Unknown         | 32 (20.8%)           | 75 (18.6%)     |                     | 23 (22.3%)                                    | 22 (21.4%)                               |                     |
| **T**           |                      |                |                     |                                               |                                          |                     |
| ≤T1             | 27 (17.5%)           | 107 (26.6%)    | 0.014               |                                               |                                          | 1.000               |
| T2              | 54 (35.1%)           | 144 (35.7%)    |                     | 34 (33.0%)                                    | 34 (33.0%)                               |                     |
| T3              | 22 (14.3%)           | 60 (14.9%)     |                     | 13 (12.6%)                                    | 13 (12.6%)                               |                     |
| T4              | 32 (20.8%)           | 80 (19.4%)     |                     | 21 (20.4%)                                    | 21 (20.4%)                               |                     |
| Tx              | 19 (12.3%)           | 62 (15.4%)     |                     | 15 (14.6%)                                    | 16 (15.5%)                               |                     |
| **N**           |                      |                |                     |                                               |                                          |                     |
| N0              | 101 (65.6%)          | 229 (56.8%)    | 0.065               |                                               |                                          | 1.000               |
| N1              | 25 (16.2%)           | 102 (25.3%)    |                     | 15 (14.6%)                                    | 15 (14.6%)                               |                     |
| Nx              | 28 (18.2%)           | 72 (18.6%)     |                     | 16 (15.5%)                                    | 16 (15.5%)                               |                     |
| **M**           |                      |                |                     |                                               |                                          |                     |
| M1a             | 8 (5.2%)             | 39 (9.7%)      | 0.374               |                                               |                                          | 0.784               |
| M1b             | 95 (61.7%)           | 243 (60.3%)    |                     | 70 (66.0%)                                    | 65 (63.1%)                               |                     |
| M1c             | 43 (27.9%)           | 104 (25.8%)    |                     | 28 (27.2%)                                    | 30 (29.1%)                               |                     |
| M1x             | 8 (5.2%)             | 17 (4.2%)      |                     | 1 (1.0%)                                      | 1 (1.0%)                                 |                     |

Data are present as n (%).

<sup>a</sup>Comparing radiotherapy versus control group (unmatched).

<sup>b</sup>Comparing radiotherapy versus control group (propensity score-adjusted cohorts).

---

**TABLE 4** | Clinicopathological characteristics of the PSA 4.1-10 ng/ml subgroup stratified according to treatment modality with and without propensity score matching.

| Characteristics | Radiotherapy (n=551) | Control (n=1146) | P value<sup>a</sup> | Propensity score adjusted radiotherapy (n=441) | Propensity score adjusted control (n=441) | P value<sup>b</sup> |
|-----------------|----------------------|-----------------|---------------------|-----------------------------------------------|------------------------------------------|---------------------|
| **Age**         |                      |                 |                     |                                               |                                          |                     |
| ≤65             | 188 (34.1%)          | 328 (28.6%)     | 0.210               | 124 (28.1%)                                    | 121 (27.4%)                               | 0.822               |
| >65             | 363 (65.9%)          | 818 (71.4%)     |                     | 317 (71.9%)                                    | 320 (72.6%)                               |                     |
| **Race**        |                      |                 |                     |                                               |                                          |                     |
| Caucasians      | 445 (80.8%)          | 930 (81.2%)     | 0.663               |                                               |                                          | 0.967               |
| African Americans| 73 (13.2%)           | 138 (12.0%)     |                     | 45 (10.2%)                                    | 43 (9.8%)                                 |                     |
| Other/unknown   | 33 (6.0%)            | 78 (6.8%)       |                     | 24 (5.4%)                                      | 25 (5.7%)                                 |                     |
| **Gleason**     |                      |                 |                     |                                               |                                          |                     |
| ≤8              | 74 (13.4%)           | 104 (9.1%)      | <0.001              |                                               |                                          | 0.997               |
| >7              | 128 (23.2%)          | 193 (16.8%)     |                     | 90 (20.4%)                                    | 92 (20.9%)                                |                     |
| 8-10            | 304 (55.2%)          | 730 (63.7%)     |                     | 277 (62.8%)                                    | 277 (62.8%)                               |                     |
| Unknown         | 45 (8.2%)            | 119 (10.4%)     |                     | 29 (6.6%)                                      | 28 (6.3%)                                 |                     |
| **T**           |                      |                 |                     |                                               |                                          |                     |
| ≤T1             | 227 (41.2%)          | 391 (34.1%)     | 0.006               |                                               |                                          | 0.993               |
| T2              | 185 (33.6%)          | 413 (36.0%)     |                     | 162 (36.7%)                                    | 162 (36.7%)                               |                     |
| T3              | 49 (8.9%)            | 117 (10.2%)     |                     | 37 (8.4%)                                      | 35 (7.9%)                                 |                     |
| T4              | 59 (10.7%)           | 112 (9.8%)      |                     | 41 (9.3%)                                      | 44 (10.0%)                                |                     |
| Tx              | 31 (5.6%)            | 113 (9.9%)      |                     | 23 (5.2%)                                      | 21 (4.8%)                                 |                     |
| **N**           |                      |                 |                     |                                               |                                          |                     |
| N0              | 386 (70.1%)          | 741 (64.7%)     | 0.077               |                                               |                                          | 0.988               |
| N1              | 90 (16.3%)           | 211 (18.4%)     |                     | 69 (15.6%)                                    | 68 (15.4%)                                |                     |
| Nx              | 75 (13.6%)           | 194 (16.9%)     |                     | 50 (11.3%)                                    | 49 (11.1%)                                |                     |
| **M**           |                      |                 |                     |                                               |                                          |                     |
| M1a             | 29 (5.3%)            | 76 (6.6%)       | 0.350               |                                               |                                          | 0.939               |
| M1b             | 401 (72.8%)          | 814 (71.0%)     |                     | 352 (79.8%)                                    | 350 (79.4%)                               |                     |
| M1c             | 109 (19.8%)          | 217 (18.9%)     |                     | 66 (15.0%)                                    | 66 (15.0%)                                |                     |
| M1x             | 12 (2.2%)            | 39 (3.4%)       |                     | 4 (0.9%)                                      | 6 (1.4%)                                  |                     |

Data are present as n (%).

<sup>a</sup>Comparing radiotherapy versus control group (unmatched).

<sup>b</sup>Comparing radiotherapy versus control group (propensity score-adjusted cohorts).
### TABLE 5 | Clinicopathological characteristics of the PSA 10.1-20 ng/ml subgroup stratified according to treatment modality with and without propensity score matching.

| Characteristics | Radiotherapy (n=596) | Control (n=1645) | P value<sup>a</sup> | Propensity score adjusted radiotherapy (n=520) | Propensity score adjusted control (n=520) | P value<sup>b</sup> |
|-----------------|----------------------|------------------|----------------------|-----------------------------------------------|---------------------------------------------|----------------------|
| Age | | | | | | |
| ≤65 | 202 (33.9%) | 463 (28.1%) | 0.009 | 164 (31.5%) | 162 (31.2%) | 0.894 |
| >65 | 394 (66.1%) | 1182 (71.9%) | | 356 (68.5%) | 358 (68.8%) | |
| Race | | | | | | |
| Caucasians | 477 (80.0%) | 1300 (79.0%) | 0.407 | 434 (83.5%) | 440 (84.6%) | 0.651 |
| African Americans | 88 (14.8%) | 234 (14.2%) | | 61 (11.7%) | 61 (11.7%) | |
| Other/unknown | 31 (5.2%) | 111 (6.7%) | | 25 (4.8%) | 19 (3.7%) | |
| Gleason | | | | | | |
| ≤6 | 36 (6.0%) | 111 (6.7%) | 0.558 | 26 (5.0%) | 27 (5.2%) | 0.979 |
| >6 | 394 (66.1%) | 1182 (71.9%) | | 356 (68.5%) | 358 (68.8%) | |
| T0-10 | | | | | | |
| 8-10 | 371 (62.2%) | 1027 (62.4%) | 0.056 | 340 (65.4%) | 335 (64.4%) | |
| Unknown | 76 (12.8%) | 231 (14.0%) | | 58 (11.2%) | 57 (11.0%) | |
| T | | | | | | |
| ≤T1 | 198 (33.2%) | 536 (32.6%) | 0.066 | 177 (34.0%) | 174 (33.5%) | 0.999 |
| T2 | 203 (34.1%) | 571 (34.7%) | | 188 (36.2%) | 189 (36.3%) | |
| T3 | 68 (11.4%) | 139 (8.4%) | | 47 (9.0%) | 46 (8.8%) | |
| T4 | 71 (11.9%) | 187 (11.4%) | | 62 (11.9%) | 63 (12.1%) | |
| Tx | 56 (9.4%) | 212 (12.9%) | | 46 (8.8%) | 48 (9.2%) | |
| N | | | | | | |
| N0 | 410 (68.8%) | 1001 (60.9%) | <0.001 | 378 (72.7%) | 378 (72.7%) | 1.000 |
| N1 | 118 (19.8%) | 311 (18.9%) | | 84 (16.2%) | 84 (16.2%) | |
| Nx | 68 (11.4%) | 333 (20.2%) | | 58 (11.2%) | 58 (11.2%) | |
| M | | | | | | |
| M1a | 33 (5.5%) | 118 (7.2%) | 0.024 | 15 (2.9%) | 19 (3.7%) | 0.896 |
| M1b | 430 (72.1%) | 1192 (72.5%) | | 412 (79.2%) | 411 (79.0%) | |
| M1c | 118 (19.8%) | 294 (17.9%) | | 88 (16.9%) | 86 (16.5%) | |
| M1x | 15 (2.5%) | 41 (2.5%) | | 5 (1.0%) | 4 (0.8%) | |

Data are present as n (%).
<sup>a</sup>Comparing radiotherapy versus control group (unmatched).
<sup>b</sup>Comparing radiotherapy versus control group (propensity score-adjusted cohorts).

### TABLE 6 | Clinicopathological characteristics of the PSA 20.1-40 ng/ml subgroup stratified according to treatment modality with and without propensity score matching.

| Characteristics | Radiotherapy (n=622) | Control (n=2019) | P value<sup>a</sup> | Propensity score adjusted radiotherapy (n=564) | Propensity score adjusted control (n=564) | P value<sup>b</sup> |
|-----------------|----------------------|------------------|----------------------|-----------------------------------------------|---------------------------------------------|----------------------|
| Age | | | | | | |
| ≤65 | 224 (36.0%) | 587 (29.1%) | 0.001 | 186 (33.0%) | 189 (33.5%) | 0.850 |
| >65 | 398 (64.0%) | 1432 (70.9%) | | 378 (67.0%) | 375 (65.5%) | |
| Race | | | | | | |
| Caucasians | 491 (78.9%) | 1623 (80.4%) | 0.552 | 467 (82.8%) | 466 (82.6%) | 0.991 |
| African Americans | 89 (14.3%) | 255 (12.6%) | | 69 (12.1%) | 68 (12.1%) | |
| Other/unknown | 42 (6.8%) | 141 (7.0%) | | 29 (5.1%) | 30 (5.3%) | |
| Gleason | | | | | | |
| ≤6 | 24 (3.9%) | 62 (3.1%) | 0.024 | 14 (2.5%) | 17 (3.0%) | 0.919 |
| >6 | 91 (14.6%) | 362 (17.9%) | | 83 (14.7%) | 84 (14.9%) | |
| T0-10 | | | | | | |
| 8-10 | 396 (63.7%) | 1317 (65.2%) | 0.063 | 372 (66.0%) | 374 (66.3%) | 0.906 |
| Unknown | 111 (17.8%) | 278 (13.8%) | | 95 (16.8%) | 89 (15.8%) | |
| T | | | | | | |
| ≤T1 | 167 (26.8%) | 600 (29.7%) | 0.074 | 158 (28.0%) | 160 (28.4%) | 0.869 |
| T2 | 204 (32.8%) | 705 (34.9%) | | 186 (33.0%) | 181 (32.1%) | |
| T3 | 78 (12.5%) | 230 (11.4%) | | 69 (12.2%) | 77 (13.7%) | |
| T4 | 64 (10.3%) | 214 (10.6%) | | 54 (9.6%) | 47 (8.3%) | |
| Tx | 109 (17.5%) | 270 (13.4%) | | 97 (17.2%) | 99 (17.6%) | |
| N | | | | | | |
| N0 | 367 (59.0%) | 1213 (60.1%) | 0.704 | 345 (61.2%) | 344 (61.0%) | 0.642 |
| N1 | 126 (20.3%) | 418 (20.7%) | | 113 (20.0%) | 108 (19.1%) | |
| Nx | 129 (20.7%) | 388 (19.2%) | | 106 (18.6%) | 112 (19.9%) | |
| M | | | | | | |
| M1a | 40 (6.4%) | 146 (7.2%) | 0.905 | 33 (5.9%) | 32 (5.7%) | |
| M1b | 452 (72.7%) | 1449 (71.8%) | | 427 (75.7%) | 414 (73.4%) | |
| M1c | 111 (17.8%) | 366 (18.1%) | | 92 (16.3%) | 108 (19.1%) | |
| M1x | 19 (3.1%) | 58 (2.9%) | | 12 (2.1%) | 10 (1.8%) | |

Data are present as n (%).
<sup>a</sup>Comparing radiotherapy versus control group (unmatched).
<sup>b</sup>Comparing radiotherapy versus control group (propensity score-adjusted cohorts).
### Table 7 | Clinicopathological characteristics of the PSA 40.1-80ng/ml subgroup stratified according to treatment modality with and without propensity score matching.

| Characteristics | Radiotherapy (n=666) | Control (n=2134) | P value<sup>a</sup> | Propensity score adjusted radiotherapy (n=588) | Propensity score adjusted control (n=588) | P value<sup>b</sup> |
|-----------------|----------------------|------------------|---------------------|---------------------------------------------|---------------------------------------------|------------------|
| Age             | 261 (39.2%)          | 661 (31.0%)      | <0.001              | 217 (36.9%)                                 | 215 (36.6%)                                 | 0.904            |
| ≤65             |                      |                  |                     |                                             |                                             |                  |
| >65             | 405 (60.8%)          | 1473 (69.0%)     |                     | 371 (63.1%)                                 | 373 (63.4%)                                 |                  |
| Race            | 0.160                |                  |                     | 477 (81.1%)                                 | 475 (80.8%)                                 | 0.988            |
| Caucasians      | 511 (76.7%)          | 1684 (78.9%)     |                     | 747 (12.8%)                                 | 76 (12.9%)                                  |                  |
| African Americans| 98 (14.7%)          | 313 (14.7%)      |                     | 75 (12.8%)                                  | 76 (12.9%)                                  |                  |
| Other/unknown   | 57 (8.6%)            | 137 (6.4%)       |                     | 36 (6.1%)                                   | 37 (6.3%)                                   |                  |
| Gleason         | 0.022                |                  |                     | 5 (0.9%)                                    | 5 (0.9%)                                    | 1.000            |
| ≤8              | 11 (1.7%)            | 43 (2.0%)        |                     | 5 (0.9%)                                    | 5 (0.9%)                                    |                  |
| >8              | 108 (16.2%)          | 336 (15.7%)      |                     | 81 (13.8%)                                  | 80 (13.6%)                                  |                  |
| 8-10            | 406 (61.0%)          | 1409 (66.0%)     |                     | 389 (66.2%)                                 | 389 (66.2%)                                 |                  |
| Unknown         | 141 (21.2%)          | 346 (16.2%)      |                     | 113 (19.2%)                                 | 114 (19.4%)                                 |                  |

Data are present as n (%).

<sup>a</sup>Comparing radiotherapy versus control group (unmatched).

<sup>b</sup>Comparing radiotherapy versus control group (propensity score-adjusted cohorts).

### Table 8 | Clinicopathological characteristics of the PSA >80.1 ng/ml subgroup stratified according to treatment modality with and without propensity score matching.

| Characteristics | Radiotherapy (n=2916) | Control (n=9752) | P value<sup>a</sup> | Propensity score adjusted radiotherapy (n=2823) | Propensity score adjusted control (n=2823) | P value<sup>b</sup> |
|-----------------|----------------------|------------------|---------------------|---------------------------------------------|---------------------------------------------|------------------|
| Age             | 1372 (47.1%)         | 3402 (34.9%)     | <0.001              | 1301 (46.1%)                                 | 1307 (46.3%)                                 | 0.873            |
| ≤65             |                      |                  |                     |                                             |                                             |                  |
| >65             | 1543 (52.9%)         | 6350 (65.1%)     |                     | 1522 (53.9%)                                 | 1516 (53.7%)                                 |                  |
| Race            | 0.611                |                  |                     | 2024 (71.7%)                                 | 2028 (71.8%)                                 | 0.990            |
| Caucasians      | 2054 (70.4%)         | 6887 (70.6%)     |                     | 2024 (71.7%)                                 | 2028 (71.8%)                                 |                  |
| African Americans| 675 (23.1%)        | 2198 (22.5%)     |                     | 636 (22.5%)                                  | 634 (22.5%)                                  |                  |
| Other/unknown   | 187 (6.4%)           | 667 (6.8%)       |                     | 163 (5.8%)                                   | 161 (5.7%)                                   |                  |
| Gleason         | 0.205                |                  |                     | 19 (3.2%)                                    | 19 (3.2%)                                    | 0.991            |
| ≤8              | 40 (1.4%)            | 161 (1.7%)       | <0.001              | 27 (1.0%)                                    | 29 (1.0%)                                    |                  |
| >8              | 281 (9.6%)           | 1183 (12.1%)     |                     | 267 (9.5%)                                   | 271 (9.6%)                                   |                  |
| 8-10            | 1530 (52.5%)         | 5628 (57.7%)     |                     | 1513 (53.6%)                                 | 1511 (53.5%)                                 |                  |
| Unknown         | 1065 (36.5%)         | 2780 (28.5%)     |                     | 1016 (36.0%)                                 | 1012 (35.8%)                                 |                  |
| T               |                      |                  | <0.001              |                                             |                                             | 1.000            |
| ≤T1             | 539 (18.5%)          | 2067 (21.2%)     |                     | 518 (18.3%)                                  | 518 (18.3%)                                  |                  |
| T2              | 821 (28.2%)          | 2970 (30.5%)     |                     | 807 (28.6%)                                  | 810 (28.7%)                                  |                  |
| T3              | 269 (9.2%)           | 881 (8.8%)       |                     | 252 (9.9%)                                   | 251 (9.9%)                                   |                  |
| T4              | 434 (14.9%)          | 1319 (13.5%)     |                     | 409 (14.5%)                                  | 406 (14.4%)                                  |                  |
| Tx              | 853 (29.3%)          | 2535 (26.0%)     |                     | 837 (29.6%)                                  | 838 (29.7%)                                  |                  |
| N               |                      |                  | <0.001              |                                             |                                             | 1.000            |
| ≤N0             | 1335 (45.8%)         | 4560 (46.8%)     |                     | 1301 (46.1%)                                 | 1302 (46.1%)                                 |                  |
| N1              | 875 (30.0%)          | 2557 (26.2%)     |                     | 845 (29.9%)                                  | 844 (29.9%)                                  |                  |
| N2              | 706 (24.2%)          | 2635 (27.0%)     |                     | 677 (24.0%)                                  | 677 (24.0%)                                  |                  |
| M               |                      |                  | <0.001              |                                             |                                             | 0.998            |
| ≤M1a            | 86 (2.9%)            | 514 (5.3%)       |                     | 75 (2.7%)                                    | 77 (2.7%)                                    |                  |
| M1b             | 2136 (73.3%)         | 7028 (72.1%)     |                     | 2103 (74.5%)                                 | 2105 (74.6%)                                 |                  |
| M1c             | 630 (21.6%)          | 1908 (19.6%)     |                     | 598 (21.2%)                                  | 594 (21.0%)                                  |                  |
| M1x             | 64 (2.2%)            | 302 (3.1%)       |                     | 47 (1.7%)                                    | 47 (1.7%)                                    |                  |

Data are present as n (%).

<sup>a</sup>Comparing radiotherapy versus control group (unmatched).

<sup>b</sup>Comparing radiotherapy versus control group (propensity score-adjusted cohorts).
enhancing the anti-tumor activity of immune cells (18, 19). Radiotherapy also changes the vascular endothelial cells of the tumor bed and promotes the release of chemokines, thus promoting the recruitment and entry of activated immune cells to tumors (20, 21). These synergistic effects eventually lead to the invasion of CD8+ T cells and other effector cells into the TME, resulting in a strong local anti-tumor immune response (22). The release of immunomodulatory factors, activation of dendritic cells, and increased antigen presentation mediated by MHC I in tumor cells, induced by radiotherapy, can promote tumor-associated

![Kaplan-Meier survival analysis](image-url)

**FIGURE 2** | Kaplan-Meier survival analysis of overall survival in (A) PSA <4 ng/mL, (B) PSA 4.1–10 ng/mL, (C) PSA 10.1–20 ng/mL, (D) PSA 20.1–40 ng/mL, (E) PSA 40.1–80 ng/mL, and (F) PSA >80.1 ng/mL subgroups.
antigens’ immune recognition initiating anti-tumor T cells (23–25). Subsequently, tumor-associated antigen-specific cytotoxic T cells can attack tumor cells not only in irradiated local tumors but also in distant metastatic tumors (26).

Interestingly, this study showed that radiotherapy only significantly improved OS in mPCa patients with PSA levels of 4.1–10.0 ng/mL. Radiotherapy for mPCa with PSA < 4.0 ng/mL did not improve the survival rate. In the multivariate analysis, PSA was
identified as an independent prognostic factor for mPCa, and the prognosis of the PSA in the < 4.0 ng/mL subgroup was lower than that of the PSA in the 4.1–10.0 ng/mL subgroup, which may explain why the curative effect of radiotherapy in the PSA < 4.0 ng/mL subgroup was not as good as that of the PSA in the 4.1–10.0 ng/mL subgroup. Wang et al. also pointed out that low PSA (< 4 ng/mL) is a unique entity that represents more invasive disease in mPCa and indicates a poor prognosis (12). It is reported that about 5–10% of PCa show low PSA (27); this may be due to the potential biological characteristics of dedifferentiation where epithelial cells lose the expression of PSA-coding genes (28), and patients with this type of PCa may have a higher incidence of non-organ-limiting diseases (29). In a study of 183 patients with mPCa, low PSA secretors’ molecular characteristics and clinical results were described. Compared with normal secretors, RB1 and TP53 gene deletions were more common in low PSA secretors. More importantly, similar to our results, patients with low PSA secretion had a shorter OS (30). Therefore, a low PSA level is an indicator of poorly differentiated aggressive tumor behavior, while a very high PSA level is an indicator of a high tumor burden (31). We believe that poor differentiation and a high tumor load may have a negative impact on the survival rate and efficacy of radiotherapy in patients with mPCa.

Boeve et al. provided important data for evaluating the quality of life in patients with mPCa after radiotherapy. In their recent study, they reported that patients who received radiotherapy had more diarrhea, urinary, and intestinal symptoms than those in the control group. Although the differences in urinary symptoms and diarrhea disappeared, the intestinal symptoms were still higher than those in the control group after two years (5). Therefore, the choice of radiotherapy for patients with mPCa should be carefully considered to avoid unnecessary complications.

There are some limitations to our study. Since it is a retrospective study, it is inevitably affected by some potential biases. Second, the database lacks detailed information on systemic treatments, androgen deprivation therapy, and radiation doses. The variables available in the SEER database may be inadequate to account for all the variation in treatment selection. Third, our data was obtained only from the SEER database since there are very few mPCa patients with low PSA levels in the clinic; consequently, there is no real-world data verification. Our results need to be verified by high-quality prospective randomized trials.

CONCLUSIONS

In this assessment of a large, population-based dataset, we found that therapeutic effects in mPCa patients after radiotherapy varied depending on PSA level. This study shows that radiotherapy is most beneficial for mPCa patients with PSA levels of 4.1–10.0 ng/mL. We not only confirmed that radiotherapy provides no added benefit when the tumor load is high, but also proposed for the first time that radiotherapy for poorly differentiated mPCa patients does not significantly improve the prognosis. Our study provides direction to prospective clinical trials and clinical treatment in the future and is expected to change the existing treatment strategies for mPCa.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

Study concept & design: ZT and ML. Data acquisition or data analysis/interpretation: LM, QZ, and YZ. Manuscript drafting or manuscript revision for important intellectual content: ZT and XinW. Approval of final version of submitted manuscript: ML and XuanW. Literature research: TM and MW. All authors contributed to the article and approved the submitted version.

FUNDING

This study was financially supported by the Beijing Municipal Science and Technology Project (Z201100005620007), the Beijing Hospital Clinical Research 121 Project (BJ-2018-090), and the Fundamental Research Funds for the Central Universities (3332020069).

ACKNOWLEDGMENTS

The results published here are based on data in the SEER database (https://seer.cancer.gov/data/).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.706236/full#supplementary-material
With and Without Concurrent Radiation Therapy to the Prostate in a Prospective Randomised Clinical Trial; Data from the HORIZON Trial. Eur Urol (2021) 79:188–97. doi: 10.1016/j.eururo.2020.08.023

6. Chen R, Ren S Chinese Prostate Cancer Consortium, Yuu MK, Fai NC, Cheng WS, et al. Prostate Cancer in Asia: A Collaborative Report. Asian J Urol (2014) 1:15–29. doi: 10.1016/j.ajur.2014.08.007

7. Uemura H, Ye D, Kanesvaran R, Chiong E, Lojanapiwat B, Pu YS, et al. Large, Multi-Centre, Prospective, Longitudinal Cohort Study of Advanced Prostate Cancer in Asia. BJU Int (2020) 125:541–52. doi: 10.1111/bju.14980

8. Boeve LMS, Huishof MCMC, Vis AN, Zwijnderman AH, Twisk JWR, Witjes WPJ, et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined With Concurrent Radiation Therapy to the Prostate in Patients With Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data From the HORIZON Trial. Eur Urol (2019) 75:410–8. doi: 10.1016/j.eururo.2018.11.030

9. Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the Primary Tumour for Newly Diagnosed, Metastatic Prostate Cancer (STAMPEDE): A Randomised Controlled Phase 3 Trial. Lancet (2018) 392:2353–66. doi: 10.1016/S0140-6736(18)32486-3

10. Burdett S, Boeve LM, Ingleby FC, Fisher DJ, Rydzewska LH, Vale CL, et al. Prostate Radiotherapy for Metastatic Hormone-Sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-Analysis. Eur Urol (2019) 76:115–24.

11. Conford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, et al. Prostate Radiotherapy for Metastatic Hormone-Sensitive Prostate Cancer-Impact of Baseline PSA and Metastatic Substages. Prostate (2018) 78:753–7. doi: 10.1002/pros.23519

12. Wang J, Abudurexiti M, Shao N, Wei Y, Zhu Y, Ye DW. The U Shape of Prostate-Specific Antigen and Prostate Cancer-Specific Mortality in High-Grade Metastatic Prostate Adenocarcinoma. Eur Urol Focus (2020) 6:53–62. doi: 10.1016/euf.2018.08.024

13. Pompe RS, Tilki D, Preisser F, Leyh-Bannurah SR, Bandini M, Marchioni M, et al. Survival Benefit of Local Versus No Local Treatment for Metastatic prostate cancer-Impact of Baseline PSA and Metastatic Substages. Prostate (2018) 78:753–7. doi: 10.1002/pros.23519

14. Stolzenbach LF, Deuker M, Colla-Ruvolo C, Nocera I, Mansour M, Tian Z, et al. External Beam Radiation Therapy Improves Survival in Low-Volume Metastatic Prostate Cancer Patients: A North American Population-Based Study. Prostate Cancer Prostatic Dis (2020) 24:235–60. doi: 10.1038/s41391-020-00276-2

15. Stolzenbach LF, Rosiello G, Deuker M, Martin T, Knipper S, Tian Z, et al. External Beam Radiation Therapy Improves Survival in Elderly Metastatic Prostate Cancer Patients With Low PSA. Urol Oncol (2021) 39:131.e–7. doi: 10.1016/j.urolonc.2020.10.011

16. Vilalta M, Rafat M, Graves EE. Effects of Radiation on Metastasis and Tumor Cell Migration. Cell Mol Life Sci (2016) 73:2999–3007. doi: 10.1007/s00018-016-2210-5

17. Brooks ED, Chang JY. Time to Abandon Single-Site Irradiation for Inducing Abscopal Effects. Nat Rev Clin Oncol (2019) 16:123–35. doi: 10.1038/s41571-018-0119-7

18. Levy A, Chargari C, Marabelle A, Perfetti JL, Magne N, Deutsch E. Can Immunostimulatory Agents Enhance the Abscopal Effect of Radiotherapy? Eur J Cancer (2016) 62:36–45. doi: 10.1016/jeca.2016.03.067

19. Gehrmann M, Marienhagen J, Eichholz-Wirth F, Fritz E, Ellwart J, Ja¨ytteli M, et al. Dual Function of Membrane-Bound Heat Shock Protein 70 (Hsp70), Bag-4, and Hsp40: Protection Against Radiation-Induced Effects and Target Structure for Natural Killer Cells. Cell Death Differ (2005) 12:38–51. doi: 10.1038/sj.jdd.4401510

20. Hellevik T, Martinez-Zubialle A, Radiotherapy and the Tumor Stroma: The Importance of Dose and Fractionation. Front Oncol (2014) 4:1. doi: 10.3389/fonc.2014.00001

21. Matsumura S, Wang B, Kawashima N, Braunstein S, Badura M, Cameron TO, et al. Radiation-Induced CXCL16 Release by Breast Cancer Cells Attracts Effector T Cells. J Immunol (2008) 181:3099–107. doi: 10.4049/jimmunol.181.5.3099

22. Liang H, Deng L, Chmura S, Burnette S, Liadis N, Darga T, et al. Radiation-Induced Equilibrium is a Balance Between Tumor Cell Proliferation and T Cell-Mediated Killing. J Immunol (2013) 190:5874–81. doi: 10.4049/jimmunol.1202612

23. Gameiro SR, Jammeh ML, Wattenberg MM, Tsang KY, Ferrone S, Hodge JW. Radiation-Induced Immunomodulatory Effects of Tumor Enhances Antigen Processing and Calreticulin Exposure, Resulting in Enhanced T-cell Killing. Oncotarget (2014) 5:403–16. doi: 10.18632/oncotarget.1719

24. Golden EB, Frances D, Pellicciotta I, Demaria S, Helen Barcellos-Hoff M, Formenti SC. Radiation Fosters Dose-Dependent and Chemotherapy-Induced Immunogenic Cell Death. Oncoimmunology (2014) 3:e28518. doi: 10.4161/onci.28518

25. Filatentsev A, Baker J, Mueller AMS, Kenkel J, Ahn GO, Dutt S, et al. Ablative Tumor Radiation can Change the Tumor Immune Cell Microenvironment to Induce Complete Durability: Rms. Cancer Res (2015) 21:3727–39. doi: 10.1186/1078-0432-CCR-14-2824

26. Siva S, MacManus MP, Martin RF, Martin OA. Abscopal Effects of Radiation Therapy: A Clinical Review for the Radiobiologist. Cancer Lett (2015) 356:82–90. doi: 10.1016/j.canlet.2013.09.018

27. Genega EM, Hutchinson B, Reuter VE, Gaudin PR. Immunophenotype of High-Grade Prostatic Adenocarcinoma and Urothelial Carcinoma. Mod Pathol (2000) 13:1186–91. doi: 10.1038/modpathol.3880220

28. Weir EG, Partin AW, Epstein JL. Correlation of Serum Prostate Specific Antigen and Quantitative Immunohistochemistry. J Urol (2000) 163:1739–42. doi: 10.1016/S0022-5347(05)67532-5

29. Berglund RD, Stephenson AJ, Cronin AM, Vickers AJ, Eastham JA, Klein EA, et al. Comparison of Observed Biochemical Recurrence-Free Survival in Patients With Low PSA Values Undergoing Radical Prostatectomy and Predictions of Preoperative Nomogram. Urology (2009) 73:1098–103. doi: 10.1016/j.urology.2008.07.052

30. Aggarwal R, Romero GR, Friedl V, Weinstein A, Foye A, Huang J, et al. Clinical and Genomic Characterization of Low PSA Secretors: A Unique Subset of Metastatic Castration Resistant Prostate Cancer. Prostate Cancer Prost (2020) 24:2481–7. doi: 10.1038/s41391-020-0228-0

31. Song P, Yang B, Peng Z, Zhou J, Ren Z, Fang K, et al. Reduced Cancer-Specific Survival of Low Prostate-Specific Antigen in High-Grade Prostate Cancer: A Population-Based Retrospective Cohort Study. Int J Surg (2020) 76:664–8. doi: 10.1016/j.ijsu.2020.02.024

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Tian, Meng, Wang, Wang, Ma, Wang, Zhong, Zhang and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.