Immunohistochemical analysis of PD-L1 and tumor-infiltrating immune cells expression in the tumor microenvironment of primary signet ring cell carcinoma of the prostate

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Primary signet ring cell carcinoma (SRCC) of the prostate is a rare neoplasm. However, its potential tumorigenic mechanism, clinicopathological features, and prognostic outcome have not been systematically described. To determine the pathogenic mechanism, we detected distributions of programmed cell death-ligand 1 (PD-L1), programmed death 1 (PD-1), and cellular components in the tumor microenvironment, including tumor-infiltrating lymphocytes (CD4 and CD8), tumor-associated macrophages (TAMs; CD163 and CD68), and tumor-associated fibroblasts (vimentin and alpha-smooth muscle actin (α-SMA)), in tumor tissues from four patients with primary prostatic SRCC compared with corresponding adjacent tissues and tumor tissues from 30 patients with prostate adenocarcinoma (PCa) by immunohistochemical staining. We found higher expression of PD-L1, CD163, and CD68 in primary SRCC specimens than that in both corresponding adjacent nontumor specimens and PCa specimens with different Gleason scores, indicating that TAMs may participate in the malignant biological behavior of primary SRCC of the prostate. For further analysis, we searched electronic journal databases and Surveillance, Epidemiology, and End Results (SEER) to identify 200 eligible patients including our four cases. According to Kaplan–Meier survival curve analysis, patients <68 years old, with radical prostatectomy (RP), Gleason score of 7–8, and lower clinical stage had longer overall survival (OS). Moreover, Cox multivariate analysis indicated that race (hazard ratio [HR] = 1.422), surgical approach (HR = 1.654), and Gleason score (HR = 2.162) were independent prognostic factors for OS. Therefore, primary SRCC of the prostate represents a distinct and aggressive subtype of prostate cancer associated with a higher distribution of PD-L1 and TAMs, which warrants further clinical investigation.

INTRODUCTION

Approximately 1.4 million new cases of prostate cancer, the second most prevalent cancer and fifth leading cause of tumor-related death among men globally, were reported in 185 countries worldwide in 2020, accounting for 14.1% of the 36 cancer diagnoses in men. Incidence rates differ from 6.3 to 83.4 per 100 000 men across regions, with the highest rates in Northern and Western Europe and the lowest rates in Asia and Northern Africa.1 Moreover, an estimated 248 530 new cases of prostate cancer and 34 130 deaths were reported in the United States in 2021.2 As a rare histological variant of prostate cancer, primary signet ring cell carcinoma (SRCC) of the prostate is characterized by an intracytoplasmic vacuole that compresses the cell nucleus into a crescent shape.3,4 Although SRCC mainly occurs in the gastrointestinal (GI) system, it has been detected in the thyroid,1 breast,6 pancreas,7 bladder,8 and prostate.9 The diagnosis requires pathological examination, gastrointestinal examination (consisting of an abdominal computed tomography [CT] scan, esophagogastroduodenoscopy, and colonscopy), and specialized staining processes that facilitate detection of the primary lesion of prostate cancer.10,11 Patients with primary SRCC of the prostate usually have a poor prognosis, and a standard therapy has not been proposed due to the low number of cases. According to electronic resources, 196 cases of primary SRCC of the prostate have been reported to date. Here, we add four patients in China with primary SRCC of the prostate and summarize similar cases in terms of clinical patient-related and tumor-related pathological characteristics and treatment solutions as well as strategies for monitoring prognosis, based on searching electronic journals and databases. Then, we conducted Kaplan–Meier curves and Cox univariate and multivariate regression analyses to clarify independent prognostic factors for patients with primary prostatic SRCC.
Moreover, as the tumor microenvironment (TME), including immune effectors, extracellular matrix, and blood vessels, affects the treatment and prognosis of cancer, crosstalk between cancer cells (neck squamous cell carcinomas,\textsuperscript{12} pancreatic ductal adenocarcinoma,\textsuperscript{13} and colorectal liver metastases\textsuperscript{14}) and the surrounding TME has been investigated. On the one hand, immune cells in the TME may modulate the growth and evolution of cancer cells.\textsuperscript{15,16} On the other hand, tumors affect the TME by secreting proteins to promote angiogenesis, regulate extracellular signaling, and induce immune tolerance.\textsuperscript{17–21} In terms of the mechanism of evasion from host immune responses, programmed cell death-ligand 1 (PD-L1) may interact with programmed death 1 (PD-1) on cytotoxic T lymphocytes, potentially decreasing activation of T cells.\textsuperscript{19–21} Therefore, immunohistochemical staining was performed to detect the distributions of PD-L1, PD-1, and cellular components in the TME, such as CD4+ T lymphocytes, CD8+ T lymphocytes, TAMs, and tumor-associated fibroblasts. We then analyzed the differentially expressed ingredient in tumor tissues from four patients with primary prostatic SRCC compared with corresponding adjacent tissues and tumor tissues from 30 patients with prostate adenocarcinoma (PCa).

**PATIENTS AND METHODS**

Tissues from case 1 of primary SRCC of the prostate: a 75-year-old male patient presented with a high prostate-specific antigen (PSA) value of 49.73 ng ml\textsuperscript{-1}. Transrectal ultrasound (TRUS; HI VISION, Guangzhou, China) and digital rectal examination (DRE) revealed solid and hard nodules in the prostate. Subsequently, prostate biopsy for histopathological examination showed SRCC with a Gleason score of 7 (4+3). No obvious bone metastases were detected by bone scan. GI examination indicated no evidence of tumor. A normal carcinoembryonic antigen (CEA) level was shown by laboratory examination. The patient had an initial diagnosis of primary SRCC of the prostate and stage T2cNxM0 and received hormonal therapy (250 mg of flutamide administered orally three times a day). Ten months later, the patient underwent transurethral resection of a bladder mass due to urothelial cancer. There was no local recurrent disease after a follow-up of 117 months.

Tissues from case 2 of primary SRCC of the prostate: a 70-year-old man was admitted to the hospital with a PSA value of 10.09 ng ml\textsuperscript{-1} and hematuria that had persisted for 2 weeks. Pelvic magnetic resonance imaging (MRI; GE Healthcare, Waukesha, WI, USA) revealed an enlarged prostate and thickened bladder wall, and computed tomography urography (CTU) showed a bladder filling defect, suggestive of prostate space-occupying lesions. Prostate biopsy revealed primary SRCC of the prostate with a Gleason score of 8 (4+4) on the right side of the prostatic apexes, and immunohistochemical staining was positive for PSA and α-methylacyl coenzyme A racemase (P504S). A bone scan of the body revealed potential bone metastases at stage I1N1Mx. After 2 months of hormone therapy (50 mg of bicalutamide administered orally once a day and a subcutaneous injection of 3.6 mg of Zoladex once a month), the patient underwent laparoscopic radical prostatectomy. Postoperative pathological results showed prostatic hyperplasia with a few disordered local glands (suspicious adenocarcinoma), which indicated that hormone therapy may be effective. The patient was still alive without local recurrence after a follow-up of 106 months.

Tissues from case 3 of primary SRCC of the prostate: a 69-year-old man with PSA >100 ng ml\textsuperscript{-1} presented with hydrolephrosis. DRE revealed an enlarged prostate with palpable nodules. TRUS-guided prostate biopsy showed primary SRCC of the prostate with a Gleason score of 7 (4+3). Whole-body bone imaging indicated multiple bone metastases, though the results of GI examination revealed no evidence of tumors. The patient received hormone treatment (250 mg of flutamide administered orally three times a day and a subcutaneous injection of 3.6 mg of Zoladex once a month), and zoledronic acid was used to prevent bone metastasis. In September 2013, palliative transurethral resection of the prostate and bilateral orchietomy were performed due to progressive dysuria. Postoperative pathological results indicated prostate cancer with a Gleason score of 9 (5+4). Because the patient was unable to tolerate the side effects of paclitaxel monotherapy (PTX: 300 mg dl\textsuperscript{-1} per intravenous drip for 21 days), six cycles of docetaxel chemotherapy (docetaxel: 120 mg dl\textsuperscript{-1} per intravenous drip for 21 days) was administered. He continued with subcutaneous injection of 3.6 mg of Zoladex once a month and was still alive after a follow-up of 142 months.

Tissues from case 4 of primary SRCC of the prostate: a 67-year-old man presented with a PSA value of 65.87 ng ml\textsuperscript{-1} and difficulty urinating for 1 week. DRE demonstrated a tenacious prostate with a moderate increase in size. Both ultrasound and CT of a urinary system scan suggested prostate hyperplasia with calcification, and prostate MRI identified multiple diffusely restricted areas of the prostate and vesical diverticulum, which suggested prostate cancer. Subsequently, prostate biopsy revealed primary SRCC of the prostate with a Gleason score of 9 (5+4). Gastrointestinal tumors were not detected using GI or colon fiber endoscopy. The patient refused relevant surgery and medication for economic reasons. The patient was still alive after a follow-up of 20 months.

**Immunohistochemical staining**

Tumor specimens were obtained from 30 PCa patients, which included 10 cases with Gleason scores of 2–4, 10 cases with Gleason scores of 5–7, and 10 cases with Gleason scores of 8–10. The median age was 73 (range: 63–89) years, and PSA values varied from 0.5 to >100 (median: 12.08) ng ml\textsuperscript{-1}. Most patients \((n = 15)\) presented with stage II disease at diagnosis. Twenty-three patients presented with pathological stage T2 cancer, followed by T1/T3 cancer \((n = 3)\). Half of the tissue samples \((n = 15)\) were obtained from radical prostatectomy; the other half were from transurethral resection of prostate (TUR-P). Two patients had perineural invasion; 2 patients had lymph node involvement; 1 patient had lymphovascular emboli; and 5 patients had distant metastasis. All tissue samples were evaluated by two experienced independent pathologists for confirmation of PCa.

Tissues were fixed in formalin (10%) for 48 h, embedded in paraffin after dehydration with ethanol solution, and cut into longitudinal sections (thickness of 4 μm). The tissues were stained with hematoxylin and eosin (HE; PH0516, Phylene Life Sciences Company, Fuzhou, China), periodic acid Schiff (PAS) stain kit (ab150680, Abcam, Cambridge, UK), mucicarmine stain (ab150677, Abcam), and Alcian blue stain kit (ab150662, Abcam).

Four-micrometer sections were stained by immunohistochemistry using a standard protocol. After dewaxing with xylene overnight andsubjecting it to alcohol solutions, the sections were heated in 10 mmol\textsuperscript{-1} citrate buffer (MVS-0066, Maixin Biological Technology Development Company, Fuzhou, China) for 15 min at 120°C for antigen retrieval. Endogenous peroxidases were intercepted using 3% hydrogen peroxide (SP KIT-A3, Maixin Biological Technology Development Company, Fuzhou, China), and Alcian blue stain kit (ab150662, Abcam).

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monoclonal anti-PD-L1 (dilution 2 μg ml⁻¹; ab205921, Abcam), rabbit monoclonal vimentin (dilution 1: 300; ab92547, Abcam), rabbit polyclonal anti-alpha-smooth muscle actin (α-SMA; dilution 1: 3000; 14395-1-AP, ProteinTech Group, Chicago, IL, USA), rabbit monoclonal anti-CD163 (dilution 1: 400; ab182422, Abcam), mouse monoclonal anti-CD68 (dilution 1: 3000; ab955, Abcam), rabbit monoclonal anti-CD4 (dilution 1: 500; ab183685, Abcam), and mouse monoclonal anti-CD8 (dilution 1: 6000; 66868-1-Ig, ProteinTech Group). The sections were then incubated with biotinylated secondary antibodies and avidin-conjugated horseradish peroxidase and developed with diaminobenzidine (DAB; DAB-0031, Maixin Biological Technology Development Company). The level of stromal expression was calculated by two experienced investigators who were double blinded. The staining intensity was scored as follows: 0 (no staining), 1 (weak), 2 (moderate), and 3 (strong). Expression of the aforementioned markers was evaluated by multiplying the score for the percentage by the intensity score, which is presented as each individual column in a heatmap.

Search methods for identification of studies and patients

The PubMed, Google Scholar, Embase, Cochrane Library, and Ovid MEDLINE databases were used to search for studies examining primary SRCC of the prostate from database inception until July 2021. The search terms included “signet ring cell”, “prostate cancer”, “prostate carcinoma”, and “primary cancer”. Additional eligible studies were searched in the bibliographies of Urological Men’s Health: A Guide for Urologists and Primary Care Physicians, Campbell-Walsh Urology, Surgical Procedures for Core Urology Trainees, etc. Bibliographies of the retrieved articles were also hand-searched to identify other potentially eligible studies. No filters were applied regarding the date of publication or language. Our study was performed based on the Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA) statement. The present study has been registered at the International Prospective Register of Systematic Reviews (PROSPERO; registration No. CRD42021269757). A flowchart of the literature search is presented in Figure 1.

Studies were eligible when they satisfied with the following criteria: (i) histopathological examination confirmed the diagnosis of primary prostatic SRCC and (ii) patient-specific and tumor-specific characteristics were reported. The following exclusion criteria were used: (i) patients who had metastasized cancer from other organs or mixed carcinoma; (ii) studies without original data; or (iii) letters to the editor, reviews, or commentaries.

A meticulous procedure was carried out independently by two investigators (QLT and BF) who selected potentially relevant studies according to the predetermined criteria. Any discrepancies in data extraction were assessed by the reviewer (ZYL), who checked the resulting extractions. Data collected from the studies included study type, year of publication, first author, country, number of patients, recruitment period, PSA level, Gleason score, clinical stage, tumor, node, and metastasis (TNM) stage, treatment modalities, tumor characteristics, histological characteristics, follow-up period, and demographics (age and race).

A quality investigation was performed for our study based on the latest version of the risk assessment tool suggested by the ROBINS-I checklist²² to evaluate interventions in eligible studies. The studies were investigated for bias regarding selection bias, confounding, intervention measurement, reporting bias, missing data bias, outcome measurement, and other types of bias (Supplementary Figure 1).

SEER (Incidence-SEER 18 Regs Custom Data with additional treatment fields, November 2018 Sub, 1975-2016 varying and Incidence-SEER Research Plus Data, 18 Registries, November 2020 Sub, 2000–2018) data were used to review prostate cancer subtypes. SEER State version 8.3.6.1 was used to achieve a complete case-listing file. The selected criteria for patients included SRCC of the prostate as the first cancer diagnosis who had been histopathologically diagnosed with SRCC (ICD-O-3 8490/3). Patients diagnosed between 1975 and 1999 from SEER database (1975–2016), and between 2000 and 2018 from SEER database (2000–2018) were selected.

Statistical analyses

SPSS version 19.0 (SPSS Corp., Armonk, NY, USA) and R version 3.6.3 software (R Foundation for Statistical Computing, Vienna, Austria) were used to perform statistical analyses. OS was defined as the interval between the diagnosis and the last follow-up or death. Kaplan–Meier curves were drawn to estimate the effects of race, age, PSA, Gleason score, clinical stage, surgery therapy, hormone therapy, and radiation therapy on OS using a log-rank test. Forest plots for the results of multivariate and univariate Cox regression were completed using the visualization package ggplot2 using R software.²³ In addition, a heatmap for immunohistochemical staining results for PCa tissues with different Gleason scores, primary SRCC specimens and corresponding adjacent nontumor specimens was generated with the visualization package ComplexHeatmap of R software under the clustering method of Euclidean.²⁴ P < 0.05 represented a statistically significant difference.

RESULTS

Immunohistochemistry for identifying the histologic source of primary SRCC of the prostate

Microscopic examination of specimens from the four patients using HE staining revealed that tumor cells were arranged in sheets, with nest-like adenoids and single cells with hyperplastic fibrous tissue between these structures. The tumor cytoplasm was vacuolated, and the nucleus was located on the side of the cell, resembling a signet ring (Figure 2a). However, the surrounding normal prostate tissue exhibited atrophy. Immunohistochemical staining for PSA and PSAP was performed to ensure the prostatic source (Figure 2b and 2c). Positive staining for PSA, mucaricaine, and Alcan blue revealed the presence of intracytoplasmic mucin, which confirmed that the histologic source was signet ring cells of the prostate (Figure 2d–2f).
Immunohistochemistry for detecting components of the tumor microenvironment

Immunohistochemical staining was also applied to analyze the distributions of PD-1 and PD-L1, markers of tumor-associated fibroblasts (vimentin and α-SMA), markers of TAMs (CD163 and CD68), and markers of CD4^+ and CD8^+ T lymphocytes (CD8). As shown in Figure 3 and 4, we found higher expression of PD-L1, CD163, and CD68 in primary SRCC specimens than those in both corresponding adjacent nontumor specimens and conventional PCa specimens with different Gleason scores, indicating that TAMs may participate in the malignant biological behavior of primary SRCC of the prostate. Nevertheless, an obvious difference in the staining distribution of low PD-1, CD4, and CD8 expression was not observed among PCa specimens with different Gleason scores, primary SRCC specimens, and corresponding adjacent nontumor specimens. In contrast, higher levels of vimentin and α-SMA were detected in both primary SRCC specimens and corresponding adjacent nontumor specimens, with no difference in the distribution of cancer-associated fibroblasts. Moreover, levels of vimentin and α-SMA were lower in PCa specimens with different Gleason scores than those in primary SRCC specimens.

Patient-specific characteristics in primary prostatic SRCC

After an initial search of electronic databases to identify studies examining primary SRCC of the prostate based on the title/abstract and full text, thirty-five published articles including 69 cases with primary SRCC of the prostate were identified. A total of 127 eligible patients were selected from the SEER database according to the screening criteria. A summary of the characteristics of all 200 patients with our four cases is shown in Supplementary Table 1. All patients were aged between 44 years and 91 years. Of the eligible patients, 70.4% (102/145) were White, 18.6% (27/145) were Black, and 11.0% (16/145) were Asian or Pacific Islander. PSA values varied substantially between 0.19 ng ml^−1 and 1990.00 ng ml^−1. PSA levels of 72 (92.3%, 72/78) individuals were greater than 4.00 ng ml^−1, and PSA levels of 44 (56.4%, 44/78) individuals were greater than 10.00 ng ml^−1. It should be noted that the SEER database does not provide information about DRE and GI examination. Based on 73 patients in the included studies, 37.0% (27/73) had an abnormal DRE result (Supplementary Figure 2a), and 49.3% (36/73) had a negative GI result (Supplementary Figure 2b).

Tumor-specific characteristics of primary prostatic SRCC

Most patients (30.0%, 60/200) presented with stage T2 cancer, followed by T3 (13.5%, 27/200), T1 (10.0%, 20/200), and T4 (6.0%, 12/200), as shown in Supplementary Figure 3a. The most frequent Gleason score was 9–10 (23.5%, 47/200), followed by 7–8 (12.0%, 24/200), as shown in Supplementary Figure 3b. Most patients (38.0%, 76/200) presented with stage II–III disease at diagnosis. However, the SEER dataset lacks information on immunohistochemical staining. According to the included studies of 73 cases, the most widely used staining method was PSA or PSAP staining (84.2%, 48/57), followed by PAS (63.6%, 28/44) and Alcian blue (50.0%, 17/34) staining (Supplementary Figure 3c).

Treatment-specific characteristics of primary prostatic SRCC

In general, the therapeutic strategy for this malignancy is a combination of surgical, hormonal, and radiation treatments. For 192 patients with available treatment data, the adjuvant therapy was mainly hormone therapy alone (15.1%, 29/192), followed by hormone therapy with radiotherapy (9.9%, 19/192). Notably, radical prostatectomy was performed in 30.7% of patients (59/192), and 8.9% of patients (17/192) occasionally underwent TUR-P. The median OS time was 47.5 months after diagnosis. Among 200 eligible patients, 188 had survival time and outcome after follow-up data available, which was assessed...
by Kaplan–Meier curves and Cox univariate and multivariate regression analyses. The Kaplan–Meier curve showed that younger patients (age < 68 years, OS = 0.010; Figure 5a) had a longer OS than those treated with TUR-P or no surgery (P < 0.001) (Figure 5b). Moreover, patients with a Gleason score of 9–10 and higher clinical stage (IV) experienced a shorter OS than those with a Gleason score of 7–8 (P = 0.037) and lower clinical stage (II–III; P < 0.001), as shown in Figure 5c and 5d. Survival analysis using the multivariate Cox regression model adjusted for age, race, PSA, Gleason score, clinical stage, surgery therapy, hormone therapy, and radiation therapy suggested that race (hazard ratio [HR] = 1.422, 95% confidence interval [CI]: 1.186–1.706; P < 0.001), Gleason score (HR = 2.162, 95% CI: 1.332–3.509; P = 0.002), and surgical approach (HR = 1.654, 95% CI: 1.286–2.128; P < 0.001) were independent prognostic factors for OS for patients with primary prostatic SRCC, as illustrated in Figure 6.

**DISCUSSION**

As a component of the TME in many cancers, TAMs are divided into two main subsets. The first is called proinflammatory (M1) macrophages, which produce a mutagenic microenvironment to participate in the initial process of tumorigenesis. TAMs often differentiate into the second subset called anti-inflammatory (M2) macrophages, which create an immunosuppressive TME for tumor growth promotion. Immunohistochemistry of tissue samples from our four patients with primary prostatic SRCC showed an increase in the staining distribution of CD163 and CD68 in tumor tissues compared with corresponding adjacent non-tumor tissues and PCa tissues. As a marker of TAMs, CD68, a scavenger receptor, is expressed at high levels in tissue macrophages and is considered to be a panmacrophage marker. CD163 is a highly specific marker of the M2 macrophages subset, and TAMs in most tumors present the M2 macrophages phenotype, which produces immunosuppressive factors and expresses PD-L1 to directly inhibit T-cell function to promote tumor invasion, angiogenesis and metastasis. As high CD68 and/or CD163 expression on macrophages is thought to be associated with advanced tumor stage and worse prognosis in breast cancer, ovarian cancer, and cutaneous melanoma, TAMs may participate in the malignant progression of tumors or affect the malignant biological behavior of primary SRCC of the prostate.

In our study, we found higher expression of PD-L1 in tumor samples from four patients with primary SRCC than in corresponding adjacent non-tumor tissues or prostate adenocarcinoma tissues. Many tumor and immune cells express PD-L1, which is thought to play an essential role in decreasing cancer immunity by binding PD-1 and B7.1 (CD80), which are positive regulators of T lymphocyte inactivation. Binding of PD-L1 to PD-1/B7.1 blocks T-cell proliferation, migration and cytotoxic mediator secretion and reduces the killing of tumor cells. In primary gastric SRCC, Jin et al. evaluated PD-1 and PD-L1 expression and infiltration by CD3+ T cells in advanced gastric SRCC and found that PD-1 expression on tumor-infiltrating lymphocytes was significantly related to PD-L1 expression. Another study by Huang et al. found that gastric SRCC...
patients with the AT-rich interacting domain containing protein 1A (ARID1A) mutations had higher PD-L1 expression than counterparts without based on the Cancer Genome Atlas (TCGA). These authors proposed a hypothesis that Epstein–Barr virus (EBV) infection may have an influence on PIK3CA and ARID1A mutations, which may contribute to elevation of PD-L1 expression. For SRCC in the colon, Alvi et al. observed higher CD3 and PD-L1 levels were microsatellite instability cases associated with the hypermethylated genotype, and Tai et al. detected that PD-L1 expression was associated with an improved prognosis, representing a possible ideal target for immune checkpoint-based therapy. Therefore, we speculate that patients with primary SRCC of the prostate presenting with high PD-L1 expression may benefit from treatment with anti-PD-1/PD-L1 antibodies, including nivolumab, pembrolizumab, and durvalumab, though clinical trials with a large sample size are required for verification.

“Signet ring cell” is a term describing the histological pattern of a tumor cell that is identified by compression of the nucleus into a crescent shape and displacement by an intracytoplasmic vacuole. As signet ring cells can more commonly be detected in the gastrointestinal tract, gastrointestinal endoscopy may be useful for distinguishing primary SRCC from metastatic SRCC. As SRCC is commonly present with other patterns of high-grade prostate cancer, Guerin et al. suggested that SRCC is a variant of high-grade adenocarcinoma rather than a histological type. Currently, pathological diagnosis of primary prostatic SRCC must consider these two aspects. (1) The signet ring cell proportion of 20% to 50% of the entire number of tumor cells will usually help establish an SRCC diagnosis. A relatively persuasive indication of the prostatic source is the presence of more typical prostatic adenocarcinoma cells in the specimen. (2) Immunohistochemistry for PSA and PSAP may assist in diagnosis.

In this investigation, 84.2% of patients presented positive staining for PSA and PSAP. Other types of positive staining included PAS in approximately 63.6% of patients and Alcian blue in approximately 50.0% of patients.

Based on our four cases and cases identified in the literature, 68 years is the average age at diagnosis (range: 44–91 years), the same as that in a previous report. As signet ring cells can more commonly be detected in the gastrointestinal tract, gastrointestinal endoscopy may be useful for distinguishing primary SRCC from metastatic SRCC. Among the included patients, only 49.3% underwent a recorded GI examination with a negative result. In terms of the clinicopathological characteristics of the tumor, most patients presented with T2 stage disease and a Gleason score of 9–10. The multivariate Cox model identified race (HR = 1.422; P < 0.001), Gleason score (HR = 2.162; P = 0.002), and surgical approach (HR = 1.654; P < 0.001) as independent prognostic factors for OS. To date, there is no standard treatment for the management of primary SRCC of the prostate. As clinical cases are limited and scattered worldwide, urologists often adopt treatment options for adenocarcinoma of the prostate comprising various combinations of hormone therapy, radiotherapy, and surgery. In terms of chemotherapy, one patient accepted chemotherapy with leucovorin, fluorouracil and oxaliplatin (FOLFOX) and Erbitux, which produced a near-complete response. In addition, combination therapy for primary SRCC of the prostate has received increasing attention. Yoshimura et al. reported a survival period of 100 months for a patient treated with the combination of hormone therapy and radiotherapy, and Lilleby et al. reported a favorable response of a patient with primary SRCC of the prostate to neoadjuvant hormone therapy and radiotherapy after 12 months of follow-up. In terms of controlling increases in PSA level, neoadjuvant hormonal therapy and radical prostatectomy show good therapeutic effects. Regarding surgical treatment, except for radical prostatectomy, which was performed in 30.7% of patients (59/192), 8.9% of patients (17/192) underwent TUR-P. Patients with a normal total PSA level received TUR-P treatment for severe prostatic hyperplasia, but the pathological diagnosis unexpectedly indicated a rare type of cancer. In addition, patients with advanced prostate cancer had a main complaint of acute urinary retention and underwent palliative TUR-P. Of the patients included in our study, the 15 patients who underwent hormone therapy and radiotherapy presented the highest survival rate of 36 months. Overall, based on the treatment characteristics of included studies, patients and aggressive and comprehensive treatment should be considered, which likely will rely on early invasive surgery combined with hormone treatment and adjuvant radiation therapy.

Our study also has some limitations. First, the number of available cases was very limited as a result of the scarcity of this disease, with research spanning almost 30 years. Hence, several patients were probably diagnosed at an advanced stage in the pre-PSA era. Second, although we found that PD-L1 and M2 macrophages were expressed at higher levels in tumor tissues from four patients with primary prostatic SRCC than those in corresponding adjacent non-tumor tissues and prostate adenocarcinoma tissues, the precise mechanism warrants further investigation based on multicentre research, which will help investigate the clinical profile and primary cell culture technology. Genetic alterations of SRCC in prostate cancer should thus be revealed. Furthermore, the staining methods did not use rigorous criteria to diagnose early cases and were different from the methods used currently to exclude a GI source. To date, systematic reviews of primary SRCC of the prostate are limited, and the classification criteria for some clinical information also differ, requiring a careful interpretation.
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The roles of tumor-associated M2 macrophages

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Primary signet ring cell carcinoma of the prostate

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| Reference | Age (year) | Race | PSA at diagnosis (ng ml⁻¹) | Treatment | TNM stage | Clinical stage | Gleason score | Follow-up (month) | Outcome |
|-----------|------------|------|----------------------------|-----------|-----------|---------------|---------------|------------------|---------|
| Gupta and Gulwani 2020³³ | 72 | NR | 6.5 | TURP⁺ | NR | NR | 5+5=10 | 6 | Alive |
| Blas et al. 2019⁴ | 82 | NR | 331 | H | T₁N₂M₁ | 4 | 5+5=10 | 11 | Dead |
| 75 | NR | 10.6 | H+R | T₁N₂M₁ | NR | NR | 5+4=9 | 23 | Alive |
| 79 | NR | 18 | H | T₁N₂M₁ | NR | NR | 5+5=10 | 21 | Alive |
| 79 | NR | 11 | RP+H | T₁N₂M₁ | NR | NR | 4+5=9 | 37 | Alive |
| 74 | NR | 43 | H+R | T₁N₂M₁ | 4 | 4+4=9 | 84 | Dead |
| Gök et al. 2018⁵ | 70 | NR | 7.26 | H+R | NR | NR | 5+5=10 | 16 | Alive |
| Xiao and Unger 2017²⁴ | 74 | White | 6.1 | NR | NR | NR | NR | NR | Alive |
| Tiwari et al. 2017¹⁵ | 65 | NR | 1990 | H | NR | NR | 5+5=10 | 24 | Alive |
| Sáez Barranquero and Herrera Imbroda 2017⁷ | 74 | NR | 10.3 | H | NR | NR | NR | 6 | Alive |
| Kim et al. 2016¹⁶ | 56 | Asian | 0.64 | RP+R+C | NR | NR | NR | 24 | Dead |
| Celik et al. 2014⁶⁷ | 66 | NR | 66.58 | TURP+H+R+C | T₁N₂M₁ | 4 | 5+5=10 | 42 | Dead |
| Haddad et al. 2014³⁸ | 63 | NR | 10 | H+R | T₁N₂M₁ | 2 | 3+4=7 | NR | NR |
| Kwon et al. 2013³⁹ | 61 | Asian | 14.7 | H+C | T₁N₂M₁ | 4 | NR | 11 | Dead |
| Roldán et al. 2012⁴⁸ | 65 | NR | 6.6 | RP+C | T₁N₂M₁ | 3 | 4+5=9 | 23 | Alive |
| Bonetti et al. 2011⁵⁰ | 70 | NR | NR | Hc | NR | NR | NR | 11 | Dead |
| Hashimoto et al. 2011⁵¹ | 61 | Asian | 0.19 | C | T₁N₂M₁ | 4 | NR | 16 | Dead |
| Warner et al. 2010⁴⁷ | 58 | NR | NR | TURP+R | T₁N₂M₁ | NR | NR | 24 | Dead |
| 82 | NR | NR | H | T₁N₂M₁ | 4 | NR | 5 | Dead |
| 68 | NR | NR | H | T₁N₂M₁ | 4 | NR | 12 | Dead |
| 65 | NR | NR | TURP+H | T₁N₂M₁ | 4 | NR | 24 | Dead |
| 67 | NR | NR | RP | T₁N₂M₁ | NR | 3+5=8 | 108 | Dead |
| 67 | NR | 1.9 | H+R | T₁N₂M₁ | NR | 4+5=9 | 48 | Alive |
| 79 | NR | 5.9 | RP | T₁N₂M₁ | NR | NR | 4 | Dead |
| 51 | NR | NR | RP+R | T₁N₂M₁ | NR | NR | 36 | Alive |
| 59 | NR | 4.8 | RP+H | T₁N₂M₁ | NR | 4+4=8 | 12 | Alive |
| Matsuoka et al. 2007⁷¹ | 62 | NR | 364.7 | H | T₁N₂M₁ | 4 | 5+4=9 | 15 | Dead |
| Derouiche et al. 2007³³ | 85 | NR | 9.1 | TURP+R | T₁N₂M₁ | 2 | NR | 18 | Alive |
| Lileby et al. 2007⁵⁰ | 70 | NR | 27 | H+R | T₁N₂M₁ | 3 | 4+4=8 | 12 | Alive |
| Fujita et al. 2004⁴⁴ | 75 | NR | 9.3 | RP+H | T₁N₂M₁ | 2 | NR | 12 | Alive |
| Akagashi et al. 2003⁵² | 72 | NR | 470 | H | T₁N₂M₁ | 4 | NR | 20 | Alive |
| Kuroda et al. 1999⁵⁰ | 81 | Asian | >100 | H | T₁N₂M₁ | 2 | NR | 2 | Alive |
| Torbenson et al. 1998⁴⁴ | 77 | NR | 92.6 | NR | T₁N₂M₁ | 7 | NR | NR | |
| 69 | NR | NR | H+R | T₁N₂M₁ | 4 | 9 | 18 | Dead |
| 82 | NR | 5.2 | H+R | T₁N₂M₁ | NR | 7 | NR | NR |
| 54 | NR | 24 | H | T₁N₂M₁ | 3 | 7 | 34 | Alive |
| 64 | NR | 8.8 | H+R | T₁N₂M₁ | 2 | 9 | NR | NR |
| 67 | NR | 4.4 | NR | T₁N₂M₁ | 2 | 7 | 32 | Alive |
| 63 | NR | 16.7 | R | T₁N₂M₁ | 2 | 7 | 24 | Alive |
| 76 | NR | NR | NR | NR | NR | 9 | NR | NR |
| 67 | NR | 19.9 | H | T₁N₂M₁ | 2 | 8 | 21 | Alive |
| 67 | NR | 15.8 | RP+H+R | T₁N₂M₁ | NR | 8 | 27 | Alive |
| 66 | NR | 29.6 | NR | T₁N₂M₁ | 2 | 6 | NR | NR |
| 71 | NR | 20 | NR | T₁N₂M₁ | 2 | 8 | NR | NR |
| Kanematsu and Hiura 1997²¹ | 76 | NR | 237 | RP+H | T₁N₂M₁ | NR | NR | 36 | Alive |
| Leong et al. 1996⁴⁴ | 71 | NR | 536 | TURP | T₁N₂M₁ | 4 | 5+4=9 | 11 | Dead |
| Yoshimura et al. 1996⁴⁹ | 65 | NR | NR | H+R | T₁N₂M₁ | 3 | NR | 100 | Alive |
| Segawa and Kakehi 1993⁴⁵ | 61 | Asian | Normal | TURP+H+R | NR | 3 | NR | 26 | Dead |
| Skodras et al. 1993⁵⁷ | 57 | Black | Normal | TURP+H+R | T₁N₂M₁ | 4 | NR | NR | NR |
| Guerin et al. 1993⁴⁲ | 84 | NR | NR | TURP+TURBT | NR | ≤2 | NR | 13 | Alive |
| 81 | NR | NR | TURP | NR | ≤2 | NR | 15 | Alive |
| 70 | NR | NR | TURP+H | NR | 4 | NR | 1 | Dead |
| 83 | NR | NR | TURP+H | NR | 4 | NR | 12 | Dead |
| 78 | NR | NR | TURP | NR | ≤2 | NR | 15 | Dead |
| Ben-Izhak and Lichtig 1992²⁸ | 70 | NR | NR | TURP+H+R | NR | 4 | NR | 36 | Dead |

Contd...
| Reference                                      | Age (year) | Race | PSA at diagnosis (ng ml⁻¹) | Treatment | TNM stage | Clinical stage | Gleason score | Follow-up (month) | Outcome |
|------------------------------------------------|------------|------|----------------------------|------------|-----------|---------------|---------------|-------------------|---------|
| Catton et al. 1992⁵⁵                           | 63         | NR   | NR H                       | 4          | 5+5=10    | NR            | NR            | 24                | Dead    |
| Alline and Cohen 1992⁷⁰                        | 53         | NR   | 5.2 TURP+H                 | 4          | 5+5=10    | NR            | NR            | 2                 | Alive   |
| Hejka and England 1989⁵¹                       | 57         | White | NR NR                      | 4          | 5+5=10    | NR            | NR            | 2                | Alive   |
| Remmele et al. 1988⁵²                         | 67         | White | NR H                       | 4          | 5+5=10    | 2             | Alive         | 2                 | Alive   |
| Ro et al. 1988⁴⁶                              | 50         | White | NR d                       | 4          | 5+5=10    | 2             | Alive         | 2                 | Alive   |
| Kums and van Helsingingen 1985⁵³                | 63         | NR   | NR TURP+R                  | 2          | NR        | 48            | 2             | 48                | Dead    |
| Gitman 1981⁴³                                  | 77         | White | NR NR                      | 4          | NR        | 0.5           | 4             | 60                | Dead    |
| Patient 1*                                     | 62         | White | NR RP                      | 4          | NR        | 192           | 4             | 192               | Alive   |
| Patient 2                                      | 67         | White | NR RP+H                    | Tₜₙ Mₜ   | 4          | 111           | 4             | 111               | Alive   |
| Patient 3                                      | 60         | Black | NR RP                      | Tₜₙ Mₜ   | 3          | 127           | 4             | 127               | Alive   |
| Patient 4                                      | 69         | Black | 12.3 H+R                  | Tₜₙ Mₜ   | 4          | 2             | 5+4=9         | 3                 | Dead    |
| Patient 5                                      | 44         | White | ≥98 H+R+C                  | Tₜₙ Mₜ   | 4          | 5+5=10        | 18            | 18                | Dead    |
| Patient 6                                      | 84         | Black | NR H°                      | Tₜₙ Mₙ   | 4          | 5+4=9         | 12            | 12                | Dead    |
| Patient 7                                      | 76         | White | NR NR°                    | NR        | NR        | 195           | NR            | 195               | Dead    |
| Patient 8                                      | 60         | White | NR RP°                    | NR        | NR        | 209           | NR            | 209               | Alive   |
| Patient 9                                      | 74         | White | NR NR°                    | NR        | NR        | 55            | NR            | 55                | Dead    |
| Patient 10                                     | 84         | White | NR NR°                    | NR        | NR        | 1             | NR            | 1                 | Alive   |
| Patient 11                                     | 68         | White | NR NR°                    | NR        | NR        | 157           | NR            | 157               | Dead    |
| Patient 12                                     | 69         | White | NR NR°                    | Tₜₙ Mₘ   | 2          | 178           | 2             | 178               | Alive   |
| Patient 13                                     | 81         | White | NR NR°                    | Tₜₙ Mₘ   | 2          | 125           | 2             | 125               | Dead    |
| Patient 14                                     | 75         | White | NR NR°                    | Tₜₙ Mₘ   | 2          | 84            | 2             | 84                | Dead    |
| Patient 15                                     | 66         | White | 8.7 RP                    | Tₜₙ Mₘ   | 2          | 5+4=9         | 74            | 74                | Alive   |
| Patient 16                                     | 53         | Asian | ≥98 C°                    | NR        | NR        | 35            | NR            | 35                | Dead    |
| Patient 17                                     | 57         | Black | NR RP°                    | NR        | NR        | 219           | NR            | 219               | Alive   |
| Patient 18                                     | 61         | Black | NR RP°                    | NR        | NR        | 191           | NR            | 191               | Dead    |
| Patient 19                                     | 79         | White | NR NR°                    | NR        | NR        | 37            | NR            | 37                | Dead    |
| Patient 20                                     | 82         | White | NR NR°                    | NR        | NR        | 89            | NR            | 89                | Dead    |
| Patient 21                                     | 91         | White | NR R°                     | NR        | NR        | 20            | NR            | 20                | Dead    |
| Patient 22                                     | 65         | White | NR NR°                    | Tₜₙ Mₘ°   | 2          | 11            | 2             | 11                | Alive   |
| Patient 23                                     | 73         | White | NR NR°                    | Tₜₙ Mₘ°   | 2          | 77            | 2             | 77                | Dead    |
| Patient 24                                     | 69         | White | NR RP+H                   | Tₜₙ Mₘ°   | 3          | 99            | 2             | 99                | Dead    |
| Patient 25                                     | 81         | Black | ≥98 NR°                   | Tₜₙ Mₘ°   | 2          | 25            | 5+3=8         | 25                | Dead    |
| Patient 26                                     | 65         | White | 6.5 NR°                   | Tₜₙ Mₘ°   | 2          | 37            | 4+4=8         | 37                | Alive   |
| Patient 27                                     | 83         | White | NR NR°                    | Tₜₙ Mₘ°   | 2          | 13            | 4             | 13                | Dead    |
| Patient 28                                     | 84         | White | NR NR°                    | Tₜₙ Mₘ°   | 4          | NR            | 4             | NR                | Dead    |
| Patient 29                                     | 58         | NR   | NR RP+H+R                 | Tₜₙ Mₘ°   | 4          | 134           | 4             | 134               | Alive   |
| Patient 30                                     | 63         | White | NR RP                    | Tₜₙ Mₘ°   | 2          | 118           | 2             | 118               | Alive   |
| Patient 31                                     | 64         | White | 32.2 RP                   | Tₜₙ Mₘ°   | 2          | 5+5=10        | 53            | 53                | Alive   |
| Patient 32                                     | 63         | White | 28 NR°                   | Tₜₙ Mₘ°   | NR         | 39            | 5+4=9         | 39                | Alive   |
| Patient 33                                     | 49         | White | 19 RP                    | NR        | NR        | 11            | 4+5=9         | 11                | Alive   |
| Patient 34                                     | 79         | White | NR NR°                    | NR        | NR        | 219           | NR            | 219               | Alive   |
| Patient 35                                     | 71         | NR   | NR NR°                    | NR        | NR        | 116           | NR            | 116               | Dead    |
| Patient 36                                     | 72         | White | NR NR°                    | Tₜₙ Mₘ°   | 2          | 90            | 4+4=8         | 90                | Alive   |
| Patient 37                                     | 83         | Asian | NR NR°                    | Tₜₙ Mₘ°   | 2          | 10            | NR            | 10                | Dead    |
| Patient 38                                     | 80         | White | NR NR°                    | Tₜₙ Mₘ°   | 2          | 68            | NR            | 68                | Dead    |
| Patient 39                                     | 65         | White | NR RP                    | Tₜₙ Mₘ°   | 4          | 91            | NR            | 91                | Dead    |
| Patient 40                                     | 73         | White | NR NR°                    | Tₜₙ Mₘ°   | 2          | 119           | 2             | 119               | Dead    |
| Patient 41                                     | 76         | White | NR NR°                    | Tₜₙ Mₘ°   | 2          | 118           | NR            | 118               | Alive   |

Contd...
| Reference | Age (year) | Race | PSA at diagnosis (ng ml$^{-1}$) | Treatment | TNM stage | Clinical stage | Gleason score | Follow-up (month) | Outcome |
|-----------|------------|------|-------------------------------|-----------|-----------|---------------|---------------|-----------------|---------|
| Patient 52 | 82 White | 20 | NR | T$_{N}{M}_{0}$ | 2 | 5+4=9 | 106 | Alive |
| Patient 53 | 48 White | | | | | | | |
| Patient 54 | 54 Black | 98 | 2+5=8 | 90 | Alive |
| Patient 55 | 58 Black | | | | | | | |
| Patient 56 | 61 Black | 69 | 3+4=7 | 103 | Alive |
| Patient 57 | 59 Black | 4.1 | NR | T$_{N}{M}_{i}$ | 2 | 4+4=8 | 85 | Alive |
| Patient 58 | 62 White | 12.7 | RP | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 34 | Alive |
| Patient 59 | 66 White | ≥98 | RP+H | T$_{N}{M}_{i}$ | 4 | 4+5=9 | 74 | Alive |
| Patient 60 | 72 Black | 37.4 | H$^+$ | NR | NR | 5+4=9 | 16 | Dead |
| Patient 61 | 79 Black | 9 | RP | NR | NR | 5+4=9 | 17 | Alive |
| Patient 62 | 81 White | 4 | RP | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 40 | Alive |
| Patient 63 | 84 Black | 8 | RP | NR | NR | 5+4=9 | 14 | Alive |
| Patient 64 | 85 Black | 4.1 | RP+H | NR | NR | 4+4=8 | 27 | Alive |
| Patient 65 | 87 Black | 9 | RP | NR | NR | 4+4=8 | 19 | Alive |
| Patient 66 | 90 White | 4 | RP | NR | NR | 5+4=9 | 19 | Alive |
| Patient 67 | 94 White | 3 | RP | NR | NR | 5+4=9 | 19 | Alive |
| Patient 68 | 95 White | 1c | RP | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 45 | Alive |
| Patient 69 | 62 White | 20 | NR | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 76 | Alive |
| Patient 70 | 59 White | 98 | 2+5=8 | 90 | Alive |
| Patient 71 | 61 White | 9 | RP | NR | NR | 5+4=9 | 16 | Dead |
| Patient 72 | 63 White | 4 | RP | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 34 | Alive |
| Patient 73 | 66 White | 8 | RP | NR | NR | 5+4=9 | 14 | Alive |
| Patient 74 | 69 White | 4 | RP | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 74 | Alive |
| Patient 75 | 72 White | 37.4 | H$^+$ | NR | NR | 5+4=9 | 16 | Dead |
| Patient 76 | 79 Black | 9 | RP | NR | NR | 5+4=9 | 17 | Alive |
| Patient 77 | 81 White | 4 | RP | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 40 | Alive |
| Patient 78 | 84 Black | 8 | RP | NR | NR | 5+4=9 | 14 | Alive |
| Patient 79 | 87 Black | 4.1 | RP+H | NR | NR | 4+4=8 | 27 | Alive |
| Patient 80 | 90 White | 9 | RP | NR | NR | 4+4=8 | 19 | Alive |
| Patient 81 | 94 White | 4 | RP | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 45 | Alive |
| Patient 82 | 95 White | 8 | RP | NR | NR | 5+4=9 | 16 | Dead |
| Patient 83 | 62 White | 20 | NR | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 76 | Alive |
| Patient 84 | 59 White | 98 | 2+5=8 | 90 | Alive |
| Patient 85 | 61 White | 9 | RP | NR | NR | 5+4=9 | 16 | Dead |
| Patient 86 | 63 White | 4 | RP | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 40 | Alive |
| Patient 87 | 66 White | 8 | RP | NR | NR | 5+4=9 | 14 | Alive |
| Patient 88 | 69 White | 4 | RP | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 74 | Alive |
| Patient 89 | 72 White | 37.4 | H$^+$ | NR | NR | 5+4=9 | 16 | Dead |
| Patient 90 | 79 Black | 9 | RP | NR | NR | 5+4=9 | 17 | Alive |
| Patient 91 | 81 White | 4 | RP | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 45 | Alive |
| Patient 92 | 84 Black | 8 | RP | NR | NR | 5+4=9 | 16 | Dead |
| Patient 93 | 87 Black | 4.1 | RP+H | NR | NR | 4+4=8 | 27 | Alive |
| Patient 94 | 90 White | 9 | RP | NR | NR | 4+4=8 | 19 | Alive |
| Patient 95 | 94 White | 8 | RP | NR | NR | 5+4=9 | 14 | Alive |
| Patient 96 | 62 White | 20 | NR | T$_{N}{M}_{i}$ | 2 | 4+5=9 | 76 | Alive |
| Patient 97 | 59 White | 98 | 2+5=8 | 90 | Alive |

*Contd...*
| Reference | Age (year) | Race | PSA at diagnosis (ng ml\(^{-1}\)) | Treatment | TNM stage | Clinical stage | Gleason score | Follow-up (month) | Outcome |
|-----------|-----------|------|----------------------------------|-----------|-----------|---------------|---------------|------------------|---------|
| Patient 98 | 69        | Asian | 13.4                             | RP        | T\(_{2}\) N\(_{0}\) M\(_{0}\) | 3             | 5+4=9         | 102                | Alive   |
| Patient 99 | 69        | White | 27.3                             | NR\(^e\)  | T\(_{3a}\) N\(_{0}\) M\(_{0}\) | 4             | 5+5=10         | 62                 | Alive   |
| Patient 100 | 67       | White | 14.9                             | NR        | NR        | NR            | NR            | 28                 | Alive   |
| Patient 101 | 62       | White | 5.4                              | RP        | NR        | NR            | NR            | 6                  | Alive   |
| Patient 102 | 77       | White | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | 3             | NR            | 186                | Dead    |
| Patient 103 | 57       | White | NR                               | RP        | T\(_{3a}\) N\(_{0}\) M\(_{0}\) | 3             | NR            | 4                  | Dead    |
| Patient 104 | 80       | White | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | 2             | NR            | 12                 | Dead    |
| Patient 105 | 73       | Black | NR                               | RP        | T\(_{3a}\) N\(_{0}\) M\(_{0}\) | 3             | NR            | 91                 | Dead    |
| Patient 106 | 81       | White | NR                               | NR\(^e\)  | T\(_{3a}\) N\(_{0}\) M\(_{0}\) | NR            | NR            | 117                | Alive   |
| Patient 107 | 71       | White | ≥98                              | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | 2             | 5+5=10         | 77                 | Alive   |
| Patient 108 | 61       | White | 5.5                              | NR        | NR        | NR            | 4+5=9         | 6                  | Dead    |
| Patient 109 | 64       | White | 64.7                             | RP+H+R+C  | NR        | NR            | 5+5=10         | 21                 | Alive   |
| Patient 110 | 77       | White | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | NR            | NR            | 202                | Alive   |
| Patient 111 | 73       | White | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | 4             | NR            | 35                 | Dead    |
| Patient 112 | 82       | Black | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | NR            | NR            | 2                  | Dead    |
| Patient 113 | 75       | White | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | 2             | NR            | 37                 | Dead    |
| Patient 114 | 66       | White | 4.3                              | RP        | T\(_{3b}\) N\(_{0}\) M\(_{0}\) | 3             | 4+5=9         | 88                 | Alive   |
| Patient 115 | 49       | Black | 8                                | RP+H+R    | T\(_{3b}\) N\(_{0}\) M\(_{0}\) | 3             | 3+5=8         | 86                 | Alive   |
| Patient 116 | 58       | Black | 4.6                              | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | 2             | 4+5=9         | 40                 | Alive   |
| Patient 117 | 79       | White | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | NR            | NR            | 92                 | Dead    |
| Patient 118 | 75       | White | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | 2             | NR            | 150                | Alive   |
| Patient 119 | 67       | White | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | 4             | 4+4=8         | 88                 | Alive   |
| Patient 120 | 57       | White | NR                               | R\(^e\)   | NR        | NR            | NR            | 209                | Alive   |
| Patient 121 | 52       | Black | NR                               | RP+R      | NR        | NR            | NR            | 192                | Alive   |
| Patient 122 | 75       | White | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | NR            | NR            | 80                 | Dead    |
| Patient 123 | 58       | White | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | 2             | NR            | 173                | Alive   |
| Patient 124 | 60       | Black | NR                               | NR\(^e\)  | T\(_{1}\) N\(_{0}\) M\(_{0}\) | 2             | NR            | 141                | Dead    |
| Patient 125 | 74       | Black | 6                                | RP        | T\(_{3a}\) N\(_{0}\) M\(_{0}\) | 4             | 5+5=10         | 76                 | Alive   |
| Patient 126 | 50       | Black | 3.9                              | RP+H      | T\(_{3a}\) N\(_{0}\) M\(_{0}\) | 3             | 5+4=9         | 75                 | Alive   |
| Patient 127 | 65       | White | <1                              | RP+H+R+C  | T\(_{3a}\) N\(_{0}\) M\(_{0}\) | 4             | 5+4=9         | 142                | Alive   |
| Our study  | 75       | Asian | 49.73                            | H         | T\(_{1}\) N\(_{0}\) M\(_{0}\) | NR            | 4+3=7         | 117                | Alive   |
|           | 70       | Asian | 10.09                            | RP+H      | T\(_{3a}\) N\(_{0}\) M\(_{0}\) | NR            | 4+4=8         | 106                | Alive   |
|           | 69       | Asian | >100                             | TURP+H+R+C| T\(_{3a}\) N\(_{0}\) M\(_{0}\) | 4             | 5+4=9         | 20                 | Alive   |

\(^{a}\) Data were available for 127 patients from SEER database; \(^{b}\) The patient underwent TURP but the study did not specify whether postoperative treatment was radiation, hormonal treatment, or both; \(^{c}\) The patient underwent hormonotherapy but the study did not specify the surgical approach; \(^{d}\) This study did not specify the individual treatment; \(^{e}\) The specific surgical approach information of these patients was not available of SEER database; \(^{f}\) These patients did not undergo surgery. C: chemotherapy; H: hormonotherapy; R: radiotherapy; RP: radical prostatectomy; NR: not reported; PSA: prostate-specific antigen; TURBT: transurethral resection of bladder tumor; TURP: transurethral resection of the prostate.
Supplementary Figure 1: Methodological quality graph for our study of the incidence. The authors’ judgments about each methodological quality item of ROBINS-I are presented as different colors across all included studies. The red, yellow, and green colors represent critical, moderate, and low bias, respectively.

Supplementary Figure 2: (a) Pie chart showing an abnormal result of digital rectal examination in 37.0% of patients with SRCC of the prostate. (b) Pie chart showing the proportion of patients undergoing gastrointestinal endoscopy. SRCC: signet ring cell carcinoma; NR: not reported.

Supplementary Figure 3: (a) Pie chart showing the distribution of the clinical stages of patients with primary prostatic SRCC. The proportions of patients with clinical stage T1–T4 disease were 10.0%, 30.0%, 13.5%, and 6.0%, respectively. (b) Pie chart showing the distribution of the Gleason scores of patients with SRCC of the prostate. The proportions of patients with Gleason scores of 7–8 and 9–10 were 12.0% and 23.5%, respectively. (c) Bar chart showing the proportions of patients with positive immunohistochemical staining for PSA or PSAP, CEA, mucicarmine, Alcian blue, and PAS, which may assist in determining a definitive diagnosis of primary prostatic SRCC. SRCC: signet ring cell carcinoma; NR: not reported; PSA: prostate-specific antigen; PSAP: prostatic-specific acid phosphatase; CEA: carcinoembryonic antigen; PAS: periodic acid Schiff.