



# Neuroendocrine Carcinoma as an Independent Prognostic Factor for Patients With Prostate Cancer: A Population-Based Study

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**Background:** Neuroendocrine carcinoma (NEC) is a rare and highly malignant variation of prostate adenocarcinoma. We aimed to investigate the prognostic value of NEC in prostate cancer.

#### **OPEN ACCESS**

#### Edited by:

Antongiulio Faggiano, Sapienza University of Rome, Italy

#### Reviewed by:

Franz Sesti, Sapienza University of Rome, Italy Marta Opalińska, University Hospital in Krakow, Poland

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#### Specialty section:

This article was submitted to Cancer Endocrinology, a section of the journal Frontiers in Endocrinology

Received: 17 September 2021 Accepted: 17 November 2021 Published: 08 December 2021

#### Citation:

Yao J, Liu Y, Liang X, Shao J, Zhang Y, Yang J and Zheng M (2021) Neuroendocrine Carcinoma as an Independent Prognostic Factor for Patients With Prostate Cancer: A Population-Based Study. Front. Endocrinol. 12:778758. doi: 10.3389/fendo.2021.778758 **Methods:** A total of 530440 patients of prostate cancer, including neuroendocrine prostate cancer (NEPC) and adenocarcinoma from 2004 to 2018 were obtained from the national Surveillance, Epidemiology, and End Results (SEER) database. Propensity score matching (PSM), multivariable Cox proportional hazard model, Kaplan-Meier method and subgroup analysis were performed in our study.

**Results:** NEPC patients were inclined to be older at diagnosis (Median age, 69(61-77) vs. 65(59-72), P< 0.001) and had higher rates of muscle invasive disease (30.9% vs. 9.2%, P < 0.001), lymph node metastasis (32.2% vs. 2.2%, P < 0.001), and distal metastasis (45.7% vs. 3.6%, P < 0.001) compared with prostate adenocarcinoma patients. However, the proportion of NEPC patients with PSA levels higher than 4.0 ng/mL was significantly less than adenocarcinoma patients (47.3% vs. 72.9%, P<0.001). NEPC patients had a lower rate of receiving surgery treatment (28.8% vs. 43.9%, P<0.001), but they had an obviously higher rate of receiving chemotherapy (57.9% vs. 1.0%, P<0.001). A Cox regression analysis demonstrated that the NEPC patients faced a remarkably worse OS (HR = 2.78, 95% Cl = 2.34–3.31, P < 0.001) and CSS (HR = 3.07, 95% Cl = 2.55–3.71, P < 0.001) compared with adenocarcinoma patients after PSM. Subgroup analyses further suggested that NEPC patients obtained significantly poorer prognosis across nearly all subgroups.

**Conclusion:** The prognosis of NEPC was worse than that of adenocarcinoma among patients with prostate cancer. The histological subtype of NEC is an independent prognostic factor for patients with prostate cancer.

Keywords: neuroendocrine prostate cancer, prostate adenocarcinoma, clinicopathological characteristics, prognosis, SEER, survival

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# INTRODUCTION

Prostate cancer, has the highest incidence of malignancy among men in the United States in 2021, which accounts for 26% of diagnoses (1, 2). Furthermore, it is also the second leading cause of cancer related deaths, only behind lung cancer (1). The predominant pathological type of prostate cancer is adenocarcinoma, and the assessment regarding incident rates, survival outcomes and therapeutic methods for prostate cancer are primarily according to this single histology (3). Neuroendocrine carcinoma (NEC) is a rare histological type, accounting for approximately 1% of newly diagnosed prostate cancer (4). Neuroendocrine prostate cancer (NEPC) possesses highly malignant characteristics such as poorly differentiated and high-grade (3, 5). In recent years, the incidence of NEPC has been rising and arouse wide concern (6, 7). Long-tern androgendeprivation therapy (ADT) for prostate adenocarcinoma could contribute to castration resistant prostate cancer (CRPC), which may eventually develop to NEPC due to heterogeneity and evolution of prostate adenocarcinoma during therapy (8-11). Therefore, the extended application of ADT could partly explain the cause of the rising incidence of NEPC. Notably, the molecular mechanism by which NEPC transforms from prostate adenocarcinoma remains to be elucidated. Besides, as an increasingly recognized histologic subtype of prostate cancer, early diagnosis and effective treatment targeting specific biological characteristics for NEPC has not been developed.

Due to its rarity and a lack of associated published researches, NEPC is prone to be under-recognition and even neglected (12).However, given the upward incidence rates of NEPC in recent years as well as its refractory to medication, NEPC is attracting more attention worldwide increasingly. Currently, studies about NEPC were mainly case reports or retrospective researches based on small sample data. Therefore, our study compared NEPC with prostate adenocarcinoma comprehensively based on large population, aiming to overcome the remarkable challenges in the clinical treatment of patients with the rare subtype of prostate cancer. We utilized the national Surveillance, Epidemiology, and End Results (SEER) database (2004-2018) to compare the clinicopathological characteristics and survival outcomes between NEPC and prostate adenocarcinoma, the most common histological type of prostate cancer. Furthermore, we investigated the prognostic value of NEPC for patients with prostate cancer.

# MATERIALS AND METHODS

## Patients

This retrospective cohort study was conducted *via* the SEER database of the National Cancer Institute (http://seer.cancer.gov/). A total of 530440 patients of prostate cancer, including NEC and adenocarcinoma from 2004 to 2018 were obtained from the latest version of the SEER 18 database, as released in November 2020, using the SEER\*Stat software (version 8.3.9). We identified prostate cancer according to the International Classification of Diseases for Oncology (Third Edition, ICD-O-3). NEPC, a generalized NEC of

prostate, are classified by the American Joint Committee on Cancer (AJCC) as four histological subtypes, mainly including large cell neuroendocrine carcinoma (LCNE, ICD-0-3 codes 8013/3), small cell carcinoma (SCC, ICD-0-3 codes 8041/3), neuroendocrine carcinoma not otherwise specified (NEC NOS, ICD-0-3 codes 8246/3), and neuroendocrine differentiation (NED, ICD-0-3 codes 8574/3). And adenocarcinoma (ICD-0-3 code 8140/3) were included for comparison. All patients included were diagnosed by positive histology. Meanwhile, the exclusion criteria of patients were: (1) the information of age, race, marital status, survival time, surgery, radiotherapy, chemotherapy is unknown; (2) not the first tumor; (3) survival time < 1 month; (4) age at diagnosis < 18 years old; (5) with multiple primary tumor sites; (6) autopsy or death certificate only.

## **Clinical Variables**

Variables covered demographic information (e.g., race, age at diagnosis, marital status and year of diagnosis), tumor characteristics [e.g., grade, tumor-node-metastasis (TNM) stage, lymph nodes and prostate-specific antigen (PSA)], treatment (e.g., surgery, radiation and chemotherapy), and survival information (survival months and vital status). In the SEER database, age is code as 18-59 years old, 60-74 years old and  $\geq$ 75 years old. Race is coded as white, black, or other (e.g., American Indian/Alaskan native or Asian/Pacific Islander). Marital status is coded as married and not married. Between 2004 and 2018, patients were categorized according to 6<sup>th</sup> editions of the TNM classification. PSA was divided into four levels including 0-4.0 ng/ml, 4.1-10.0 ng/ml, 10.1-20 ng/ml, >20 ng/ml and unknown. We also enrolled treatment modality including surgery, chemotherapy, and radiation therapy information, which were divided with "Yes" and "No". The main outcome in this study were overall survival (OS) and cancer specific survival (CSS) according to data in the SEER database. OS was defined as the time interval from diagnosis to death for any cause or last follow-up. CSS refer to death from NEPC or prostate adenocarcinoma based on the recorded cause of death.

# **Statistical Analysis**

Baseline demographic and clinicopathologic characteristics were performed to assess whether the distribution of the study population had significant differences between NEPC and prostate adenocarcinoma. Pearson's chi-square tests were adopted to calculate the differences in the distribution. We used Kaplan-Meier method and log-rank test to compare OS and CSS among patients with the two histological subtypes of prostate cancer. In order to overcome the effect of patient confounding bias, propensity score matching (PSM) method was adopted to remove the potential impact. Covariates of the two histological subtypes groups were matched with a ratio of 1:1 (R package "MatchIt"). The multivariable Cox proportional hazard model was performed to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) according to histological types. We established two adjusted models in Cox regression analysis, in which covariates including age at diagnosis, marital status, lymph nodes examined, lymph nodes positive, PSA and

TNM stage were adjusted. We stratified the two histological subtypes groups based on the covariates into subgroups and applied stratified analyses to determine the subgroups that contribute to survival disadvantage of NEC. Interaction between the subgroups was calculated by R studio. The forest plot was applied to compare the impact of NEC and adenocarcinoma to survival outcomes of prostate cancer patients. Multivariate regression analysis was used to conduct subgroup analyses. Statistical analyses were performed using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided P values < 0.05 were considered as the threshold to define statistical significance.

## RESULT

### **Patient Characteristics**

This study enrolled 530440 eligible prostate cancer patients including 556 patients with NEPC and 529884 patients with prostate adenocarcinoma from SEER database between 2004 and 2018 (Figure 1). Table 1 summarize the baseline demographic and clinicopathologic characteristics of these patients. The age at diagnosis of NEC patients were inclined to be older compared with adenocarcinoma patients, median age at diagnosis 69(61-77) vs. 65(59-72), age≥75 years (29.5% vs. 16.3%). The incidence of NEC in patients newly diagnosed were increasing roughly during our study period whereas the incidence of adenocarcinoma remained stable. Significantly, the NEC patients formed a higher proportion with a more advanced stage than the adenocarcinoma patients (59.6% vs. 12.2%, P<0.001), as displayed by a higher proportion of muscle invasive disease (30.9% vs. 9.2%, P<0.001), lymph node metastasis (32.2% vs. 2.2%, P<0.001), and distal metastasis (45.7% vs. 3.6%, P < 0.001). Lymph nodes were more likely to be examined in adenocarcinoma patients (11.2% vs. 24.7%, P<0.001) whereas positive lymph nodes were more common in the NEC patients (9.2% vs. 1.6%, P <0.001). Additionally, NEC patients with PSA levels higher than 4.0 ng/mL accounted for 47.3%, compared with 72.9% of adenocarcinoma patients. Furthermore, NEC patients had a lower rate of receiving surgery treatment compared with adenocarcinoma patients (28.8% vs. 43.9%, P<0.001). However, NEC patients were prone to receiving chemotherapy treatment, which accounted for 57.9% compared with 1.0% of adenocarcinoma patients. There was no significant difference of radiation between NEC and adenocarcinoma patients.

NEPC are defined by AJCC as different histological subtypes, including LCNE, SCC, NEC NOS, and NED. The first three are *de novo* NEPC while NED originated from the transdifferentiation of adenocarcinoma during the process of resistance to ATD or androgen receptor pathway inhibitors (ARPIs) treatment. The results of comparison among the four histological subtypes of NEPC and prostate adenocarcinoma are summarized in **Table 2**. The four histological subtypes patients all had higher proportions of muscle invasive disease (LCNE 50.0% vs. SCC 30.7% vs. NEC NOS 31.0% vs. NED 30.4%), lymph node metastasis (LCNE 50.0% vs. SCC 31.4% vs. NEC NOS 34.1% vs. NED 31.2%), and distal metastasis (LCNE 66.7% vs. SCC 46.6% vs. NEC NOS 45.7% vs. NED 42.4%), as compared to prostate adenocarcinoma patients (9.2%, 2.2%, 3.6%) respectively. Three histological subtypes of NEPC patients had low rates to receiving surgery treatment (SCC 25.0% vs. NEC NOS 31.0% vs. NED 32.8%) than that of adenocarcinoma (43.9%) except for LCNE (83.3%). However, the proportions of receiving radiation treatment of SCC (38.5%), NEC NOS (36.4%), and NED 33.6%) had no significant difference as compared to adenocarcinoma (35.2%) except for LCNE (66.7%). Additionally, the proportions of receiving chemotherapy treatment of LCNE (50.0%), SCC (67.9%) and NEC NOS (55.0%) patients were obviously higher than that of adenocarcinoma patients (1.0%) while NED patients (37.6%) were between de novo NEPC and prostate adenocarcinoma patients. Notably, NED patients with PSA levels higher than 4.0 ng/mL accounted for 72.0%, which was significantly higher than that of the other three histological subtypes of NEPC patients (LCNE 50.0%, SCC 36.9%, NEC NOS 47.3%). We speculated that it may attributed to the mixed adenocarcinoma and NEC components of NED.

### **Survival Analyses**

We performed Kaplan-Meier curves to compare the OS and CSS between the four histological subtypes of NEC and adenocarcinoma patients (Figure 2). The LCNE patients had the worst OS and CSS among all histological subtypes, followed by SCC, NEC NOS, NED, and adenocarcinoma patients. Intriguingly, these results suggested that the OS and CSS of NED patients were better than that of de novo NEC patients but worse than that of adenocarcinoma patients. Furthermore, we performed the survival analysis of 1-, 2-, 3-, 4- and 5-year OS and CSS rates of patents with the four histological subtypes of NEPC and prostate adenocarcinoma (Table 3). The LCNE patients had the worst 5-year OS rate among all histological subtypes, followed by SCC, NEC NOS, NED, and adenocarcinoma patients. Compared with the four histological subtypes of NEPC, the 1-, 3- and 5-year OS rate of adenocarcinoma (97.7%, 92.7%, 88.0%) roughly remained stable. The 1-, 2-, 3-, 4- and 5-year CSS revealed the similar outcomes.

Due to the imbalanced basic demographic and clinicopathologic characteristics, we conducted PSM via R software to minimize confounding factors. All the covariates in the present study were matched between the two groups. The baseline after PSM was shown in Table 4. We matched 401 NEPC patients with 401 prostate adenocarcinoma patients with a ratio of 1:1. After eliminating the selection bias, all variables were matched as defined by the P value >0.05. We performed multivariable Cox proportional hazard regression based on a non-adjusted model and three adjusted models (Table 5). Adjusted I model adjusts for age, marital status, lymph nodes examined and lymph nodes positive and adjusted II model adjusted for age, marital status, lymph nodes examined and lymph nodes positive, T stage, N stage, M stage, PSA level. NEPC patients faced a remarkably worse OS (HR = 2.78, 95% CI = 2.34-3.31, P < 0.001) and CSS (HR = 3.07, 95% CI = 2.55-3.71,



P < 0.001) compared with prostate adenocarcinoma patients. These findings emphasized the worse survival outcomes for the histological subtype of NEC.

## Subgroup Analyses

After discovering the shortened survival of NEPC patients, we next aimed to evaluate the prognostic consistency and difference in diverse subgroups of prostate cancer patients between NEC and adenocarcinoma patients (Figure 3). According to the baseline demographic and clinicopathologic characteristics, NEC and adenocarcinoma patients were divided into subgroups, respectively. The results demonstrated that NEC patients obtained significantly poorer prognosis than adenocarcinoma patients across all subgroups except for G2 (HR = 3.25, 95%CI=0.68-15.4, P=0.1371), stage II (HR = 2.56, 95%CI=0.64-10.2, P=0.1831) and lymph nodes negative (HR = 3.57, 95%CI=0.94-13.4, P=0.0602) subgroups. We suspected that the insufficient sample size may contribute to no statistic difference of the three subgroups above. Nonetheless, the general tendency for the worse survival outcomes were existing in NEPC patients. Similar results were shown in subgroup analysis for CSS (Figure 4).

Furthermore, we performed subgroup analysis to test the interaction after adjusting for the potential covariates (**Figure 5**).

No significant difference was found for age at diagnosis, race, marital status, grade, T stage, N stage, lymph nodes examined, lymph nodes positive, radiation in both OS and CSS. The results uncovered that NEPC patients had a poorer survival outcome out of all subgroups. These results indicated that among patients with prostate cancer, the histological subtype of NEC had poorer prognosis than adenocarcinoma, which was not affected by other potential variates. Especially, it was reasonable to speculate that the histological subtype of NEC was an independent prognostic factor for patients with prostate cancer.

# DISCUSSION

Our study is the most representative and comprehensive of the latest primary survival information of NEC compared with the most common histological type of prostate cancer. Given that NEPC is a rare and highly aggressive malignancy, majority of investigations are based on case reports or retrospective studies limited by small sample sizes (13–17). Consequently, the present study performed an investigation of a prostate cancer patient cohort based on large population from SEER registries between 2004 and 2018. We aimed to compare the survival outcomes of NEC with adenocarcinoma among prostate cancer patients

TABLE 1 | Baseline demographic and clinicopathologic characteristics of patients with prostate adenocarcinoma compare to NEPC.

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approximative approxi	Year of diagnosis n (%)	110(02.2)	1000+0(20.0)	<0.001
2009.0132008/02.5]1798/02.932014-013236/42.5]4083367.7Crade, n (%)102.2]219729(40.3)C21202.2]219729(40.3)C32004.013219729(40.3)C4210729(10.3)C420014107.4]8700.2]C42002.113300920(10.3)C52004.713300928(10.3)C52007.113300928(10.3)C61122.422.1]300928(10.3)C732483.2]20277.65.6]C732483.2]20277.65.6]C732483.2]20277.65.6]C732483.2]20277.65.6]C732483.2]20277.65.6]C732483.2]20277.65.6]C73030940(63.4)C7506.0415667.6]C730304624.9]C7506.0415667.6]C730304624.9]C7506.041567.6]C730304624.9]C7506.011647.2.2]C73030467.4.2]C73030467.4.2]C711647.2.2]C7100122445.7]C73030467.4.2]C73030467.4.2]C71002.2.1C71002.2.1C71002.2.1C71002.2.1C71002.2.2.1C71002.2.2.1C71002.2.1 <td>2004-2008</td> <td>117(21.0)</td> <td>181794(34-3)</td> <td>&lt;0.001</td>	2004-2008	117(21.0)	181794(34-3)	<0.001
2014.018238(42.5)10204000Grade, n(%)10.2)23037.7).0.001G110.2)213722(0.3).0.001G224040.3.2)228212(42.7).0.001G324040.3.2)228212(42.7).0.001G441(7.4)870(0.2).0.001Stage, n(%).0.0011478(0.5).0.001II00.01478(0.5).0.001II4458.1)34049(43.3).0.001III.0.01122464(3.1).0.001Unknown108(26.4)122424(3.3).0.001Tatage, n(%).0.02(4.5)20840(0.6).0.001Tatage, n(%).0.0011612(100.0.4).0.001Tatage, n(%).0.0011161412(1.9).0.001Tatage, n(%).0.0011161412(1.9).0.001Tatage, n(%).0.0011161412(1.9).0.001No122(1.9)38040674.5).0.001Nind179(32.2)1161412(1.9).0.001Nind179(32.2)1161412(1.9).0.001Nind122(1.9)3804074.2).0.001No22(40.5)1161412(2.0).0.001Nind122(1.9)3949907.6).0.001Nind122(1.9)3949907.6,1.0.001No122(1.9)3949907.6,1.0.001No122(1.9)3949907.6,1.0.001No122(1.9)3949907.6,1.0.001No122(1.9)3949907.6,1.0.001No122(1.9) <td>2009-2013</td> <td>203(36.5)</td> <td>178887(33.8)</td> <td></td>	2009-2013	203(36.5)	178887(33.8)	
Grade, n(%)         Constant	2014-2018	236(42.5)	169203(31.9)	
G1         10.2)         403837.7)           G2         122.2)         21372200.3)           G3         240(48.2)         228126.7)           G4         41(7.4)         8780.2)           Unknown         26247.1)         481410.1)         0.0.01           Stage, r(%)         0.0.01         147810.3)         0.0.01           II         498.1)         3408494.3         0.0.01           III         498.1)         3408494.3         0.0.01           V         32468.3)         297746.6)         0.0.01           Unknown         10262.4)         12245462.3.1)         0.0.01           T4         529.04         1612100.04         0.0.01           T5129         72841.41         0.0.01           T4         122821.9)         72841.41         0.0.01           T4         122821.9         72841.41         0.0.01           No         15287.3         39369674.5         0.0.01           No         15287.3         3936974.5         0.0.01           No         15287.3         3936974.5         0.0.01           No         122846.57         128412.0         0.0.01           No         12821.9         39	Grade, n (%)			< 0.001
G21/22.91/27.40.3G324044.2.92262124.0.7.1G441(7.4)8760.0.1Uhronov262(47.1)4814(9.1)Stage, n (%)	G1	1(0.2)	40933(7.7)	
G3240(43.2)240(42.7)G4117(4)38760.2)Unkowon262(47.1)48141(9.1)Stage, n (%)00.0)14780.3)I00.0)14780.3)II458.1)36236.6)III7(1.3)352366.6)V324(58.3)297746.6)Unkowon10803.4)12245423.1)T529.4)16121030.4)T529.4)16121030.4)T3292454.23.1)415627.63T42921.6.5)2084038.4)T3509.004156827.8)T41222.1.9)7284(1.4)Unkowon152[27.3]3936967.4.3]Natage, n (%)116472.2)Natage, n (%)1221.9)394567.4.5]Natage, n (%)1221.9)394567.4.5]Unkowon122[1.9]394567.4.5]Unkowon122[1.9]394567.4.5]Unkowon122[1.9]394567.4.5]Unkowon122[1.9]394567.4.5]Unkowon122[1.9]394567.4.5]Unkowon1341.20Unkowon234.1121392.3.0]Unkowon394.13072024.7]Unkowon39457.93923927.9]Unkowon39457.93923927.9]Unkowon39471.2]392392.7.4]Unkowon1642.9]392392.7.4]Unkowo3947.9]392392.7.4]Unkowo1642.9]392392.7.4]Unkowo1642.9]392392.7.4]Unkowo1642.9]3942941.0.2] </td <td>G2</td> <td>12(2.2)</td> <td>213722(40.3)</td> <td></td>	G2	12(2.2)	213722(40.3)	
G441(7.4)878(0.2)Unknown252(47.1)48141[9.1)Stage, n (%)-0.001I0.00110.01145(8.1)340943(8.3)1017(1.3)35238(6.6)V324(86.3)29774(6.6)Unknown25(9.4)121030.4)T stage, n (%)	G3	240(43.2)	226212(42.7)	
Unknown262(7)45141(8,1)Stage, n'(%)0(0.0)1.478(0.3)I0(0.0)1.478(0.3)III0(0.0)1.478(0.3)III7(1.3)352356.6)IV0.20324(58.3)2.9274(5.6)Unknown1.8052.4)1.22454(23.1)T stage, n'(%)2.20340(03.4)T29.2(16.5)2.00340(03.4)T30.90(1.6)4.1560(7.6)T40.2014(1.2)1.1614(2.1)T41.222(1.9)7.284(1.4)Unknown1.222(1.9)7.284(1.4)Unknown1.222(1.9)7.284(1.4)Unknown1.222(1.9)1.1614(2.9)No1.262(2.3)1.1614(2.9)No1.262(2.3)1.1614(2.9)Unknown2.52(7.3)9.8969(7.4.5)No1.222(1.9)3.94657(7.4.5)No1.222(1.9)3.94657(7.4.5)No1.222(1.9)3.94657(7.4.5)No1.222(1.9)3.93040(7.4.2)More than one6.2(1.2)3.02047.7)Unknown1.222(1.9)3.03040(7.4.2)None6.2(1.2)3.03040(7.4.2)None6.2(1.2)3.02047.7)Unknown4.98(7.8)3.93040(7.4.2)None6.2(1.2)3.02047.7)Unknown4.98(7.8)3.93040(7.4.2)None6.2(1.2)3.03040(7.4.2)None6.2(1.2)3.03040(7.4.2)None6.2(1.2)3.03040(7.4.2)Unknown4.98(7.8)3.93040(7.4.2)Unknown <td>G4</td> <td>41(7.4)</td> <td>876(0.2)</td> <td></td>	G4	41(7.4)	876(0.2)	
Stage, n(%)	Unknown	262(47.1)	48141(9.1)	
I         00.0         1478(0.3)           III         45(8.1)         34043(94.3)           III         7(1.3)         35235(6.6)           V         324(58.3)         29774(5.6)           Unknown         180(32.4)         122454(23.1)           T stage, n (%)         200440(38.4)           T2         92(16.5)         20040(38.4)           T3         5009.0)         41560(7.8)           T4         122(1.9)         7284(1.4)           Unknown         207(43.2)         116184(21.9)           N stage, n (%)	Stage, n (%)			< 0.001
iii     466.1)     34094364.3)       iii     7(1.3)     352366.8)       IV     32456.8)     297746.8)       IV     32456.3)     297746.8)       IV     32656.3)     297746.8)       Tatage, n(%)	I	O(O.O)	1478(0.3)	
III         `(1.3)         352356.6)           IV         32456.3)         297745.8)           Unknown         10032.4)         122454(23.1)           T stage, n (%)         *0.001           T1         \$29,9.4)         161210(30.4)           T2         92(16.5)         203840(38.4)           T4         122(21.9)         7254(1.4)           Unknown         207(43.2)         116184(21.9)           N stage, n (%)         \$2527.3)         393696(74.3)           N         179(32.2)         116147(2.2)           Unknown         252(7.3)         393696(74.3)           N         179(32.2)         11647(2.2)           Unknown         252(45.7)         18815.8)           Unknown         1202(21.9)         394657(74.5)           More than one         1202(21.9)         393040(74.2)           Unknown         180(32.4)         116412(22.0)           Unknown         1203(22.47)         18815.8)           Unknown         120424.7)         18815.8)           Unknown         234(4.1)         112412.0)           Unknown         234(4.1)         112412.0)           Unknown         234(4.1)         121213823.0)	II	45(8.1)	340943(64.3)	
IV         32496.3)         29774.6.6)           Unknown         18082.4)         12245423.1)           T stage, n (%)         520.40         16121080.4           T         509.0)         416667.8)           T4         20216.5)         203840(38.4)           T3         509.0)         416667.8)           T4         122[19]         7284(1.4)           Unknown         2021(3.2)         1161421.9)           Ntage, n (%)         11618421.9)         <0.001		7(1.3)	35235(6.6)	
Unknown         1982.4)         122434(23.1)           T stage, n(%)	IV	324(58.3)	29774(5.6)	
I stage, n (%)	Unknown	180(32.4)	122454(23.1)	
11     05(8).4)     1612(10,00.4)       T2     50(9,0)     41566(7,8)       T3     50(9,0)     41566(7,8)       T4     122(21,9)     7284(1,4)       Uhrown     207(3,2)     116184(21,9)       No     152(27,3)     393666(7,4)       N1     179(32,2)     11647(2,2)       Uhrown     225(40,5)     12641(2,3)       Ntage, n%)	T stage, n (%)			<0.001
12         92(16.5)         203640(36.4)           T3         50(90.0)         41566(7.8)           T4         122(21.9)         7284(1.4)           Unknown         207(43.2)         116184(21.9)           N stage, n(%)          <0.001		52(9.4)	161210(30.4)	
13         30(9.0)         41,300(1.3)           T4         12(21.9)         724(1.4)           Unknown         207(43.2)         116184(21.9)           N stage, n (%)         52(27.3)         393696(74.3)           N1         179(32.2)         11647(2.2)           Unknown         225(40.5)         124541(23.5)           M stage, n (%)         225(40.5)         124541(23.5)           M stage, n (%)         254(45.7)         18815(3.6)           Unknown         180(32.4)         116412(2.0)           M1         254(45.7)         18815(3.6)           Unknown         180(32.4)         116412(2.0)           None         471(8.47)         393040(74.2)           None         421(1.2)         300720(24.7)           Unknown         23(4.1)         6124(1.2)           Unknown         23(4.1)         6124(1.2)           Unknown         463(97.9)         39929(75.4)           None         51(2.2)         8448(1.5)           Unknown         429(8.2)         57511(10.9)           Vol         22(2.8)         57511(10.9)           Vol         22(2.8)         55511(10.9)           Vol         22(2.8)         55511(10.9) <td>12</td> <td>92(16.5)</td> <td>203640(38.4)</td> <td></td>	12	92(16.5)	203640(38.4)	
Interpret         Interpret         Interpret           Unknown         207(43.2)         116144(21.9)            N stage, n (%)         52(27.3)         393696(74.3)            N0         152(27.3)         11647(2.2)         11647(2.2)           Unknown         22(40.5)         124541(23.5)            M stage, n (%)         22(21.9)         394657(74.5)            M1         254(45.7)         18815(3.6)            Unknown         180(32.4)         1161412(22.0)            Unknown         180(32.4)         1161412(22.0)            Unknown         23(4.1)         6124(1.2)             Unknown         23(4.1)         6124(1.2)              Unknown         23(4.1)         6124(1.2)	15 T4	122(21.0)	41300(7.0) 7284(1.4)	
One Norm         201 (NO.2)         11010 (21.3)           Notage, n (%)             N0         152(27.3)         333696(74.3)           N1         179(32.2)         11647(2.2)           Unknown         225(40.5)         124541(23.5)           M stage, n (%)             M0         122(21.9)         394657(74.5)           M1         254(45.7)         18815(3.6)           Unknown         180(32.4)         116412(22.0)           Verph nodes examined, n (%)             None         471(84.7)         333040(74.2)           More than one         62(11.2)         130720(24.7)           Unknown         23(4.1)         6124(1.2)           Vone         62(12.2)         130720(24.7)           Unknown         23(4.1)         6124(1.2)           Unknown         23(4.1)         6124(1.2)           Verph nodes positive, n (%)             Verph node         16(2.9)         122138(23.0)           Unknown         139(87.9)         399298(7.6.4)           Unknown         127(22.8)         57511(10.9)           10.1-20.0         42(7.6)         66929(12.6)		207(43.2)	116184/21 0)	
No         152(27.3)         393696(74.3)           N1         179(32.2)         11647(2.2)           Unknown         225(40.5)         124541(23.5)           M stage, n(%)	N stage n (%)	207(40.2)	110104(21.3)	<0.001
N1         12(12)         00000(10.0)           N1         179(32.2)         11647(2.2)           Unknown         225(40.5)         124541(23.5)           M stage, n (%)             M0         122(21.9)         394657(74.5)           M1         254(45.7)         18815(3.6)           Unknown         262(40.5)         116412(22.0)           Lymph nodes examined, n (%)             None         471(84.7)         393040(74.2)           More than one         62(11.2)         130720(24.7)           Unknown         23(4.1)         6124(1.2)           Lymph nodes positive, n (%)             None         16(2.9)         122138(23.0)           Nore than one         16(2.9)         393929675.4)           Unknown         499(87.9)         399298(75.4)           Unknown         499(87.9)         399298(75.4)           Ota-0         127(22.8)         57511(10.9)           4.1-10.0         92(16.5)         265323(50.1)           10.1-20.0         42(7.6)         66929(12.6)           >20.0         129(23.2)         53942(10.2)           Unknown         166(2.9)         36179(1	NO	152(27.3)	393696(74.3)	(0.001
Unknown         225(40.5)         124541(23.5)           M stage, n (%)	N1	179(32.2)	11647(2.2)	
M stage, n (%)	Unknown	225(40.5)	124541(23.5)	
M0         122(21.9)         394657(74.5)           M1         254(45.7)         18815(3.6)           Unknown         180(32.4)         116412(22.0)           Lymph nodes examined, n (%)         -         <0.001	M stage, n (%)			< 0.001
M1     254(45.7)     18815(3.6)       Unknown     180(32.4)     116412(2.0)       Lymph nodes examined, n (%)     393040(74.2)        None     471(84.7)     393040(74.2)       More than one     62(11.2)     130720(24.7)       Unknown     23(4.1)     6124(1.2)       Lymph nodes positive, n (%)     62(11.2)     6124(1.2)       None     16(2.9)     122138(23.0)       More than one     16(2.9)     8448(1.6)       Unknown     45(9.2)     8523(50.1)       0.4.0     127(22.8)     57511(10.9)       4.1-10.0     92(16.5)     265323(50.1)       10.1-20.0     42(7.6)     66929(12.6)       >20.0     12923.2)     53942(10.2)       Unknown     166(29.9)     86179(16.3)       Stringt     96(7.12)     86179(16.3)       Stringt     96(7.2)     929267(56.1)       No     390.5)     1202(0.2)       No     390.5)     1202(0.2)       TURP     10(20.9)     25297(4.8)       Patilal prostatectomy     30(7.0)	MO	122(21.9)	394657(74.5)	
Unknown       180(32.4)       116412(22.0)         Lymp nodes examined, n(%)           None       471(84.7)       393040(74.2)         More than one       62(11.2)       130720(24.7)         Unknown       23(4.1)       6124(1.2)         Lymp nodes positive, n (%)           None       16(2.9)       122138(23.0)         More than one       15(9.2)       8448(1.6)         Unknown       489(67.9)       399298(75.4)         O.4.0       127(22.8)       57511(10.9)         4.1-10.0       92(16.5)       265323(50.1)         0.4.0       129(23.2)       53942(10.2)         10.1-20.0       42(7.6)       66929(12.6)         >20.0       129(23.2)       53942(10.2)         Unknown       129(23.2)       53942(10.2)         Unknown       396(71.2)       297267(56.1)         Surgery        <	M1	254(45.7)	18815(3.6)	
Lymph nodes examined, n (%) <t< td=""><td>Unknown</td><td>180(32.4)</td><td>116412(22.0)</td><td></td></t<>	Unknown	180(32.4)	116412(22.0)	
None         471(84.7)         393040(74.2)           More than one         62(11.2)         130720(24.7)           Unknown         23(4.1)         6124(1.2)           Lymph nodes positive, n (%)             None         16(2.9)         122138(23.0)           More than one         51(9.2)         8448(1.6)           Unknown         498(87.9)         3993298(75.4)           PSA, ng/mL, n (%)         127(22.8)         57511(10.9)           4.1-10.0         127(22.8)         57511(10.9)           4.1-10.0         92(16.5)         265323(50.1)           10.1-20.0         42(7.6)         66929(12.6)           >20.0         129(23.2)         39342(10.2)           Unknown         396(71.2)         297267(56.1)           Surgery             No         396(71.2)         297267(56.1)           Ciyoprostatectomy         0(0)         4875(0.9)           Lase rablation         3(0.5)         1202(0.2)           TURP         116(20.9)         25297(4.8)           Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	Lymph nodes examined, n (%)			< 0.001
More than one         62(11.2)         130720(24.7)           Unknown         23(4.1)         6124(1.2)           Lymph nodes positive, n (%)          <           None         16(2.9)         12138(23.0)           More than one         51(9.2)         8448(1.6)           Unknown         489(87.9)         399298(75.4)           PSA, ng/mL, n (%)         399298(75.4)            0.4.0         127(22.8)         57511(10.9)           4.1-10.0         92(16.5)         265323(50.1)           0.1-20.0         42(7.6)         66929(12.6)           >20.0         129(23.2)         53942(10.2)           Unknown         166(29.9)         86179(16.3)           Surgery             No         396(71.2)         297267(56.1)           Cryoprostatectomy         0(0)         4875(0.9)           Laser ablation         3(0.5)         1202(0.2)           TURP         116(20.9)         25297(4.8)           Partial prostatectomy         39(7.0)         200120(37.8)	None	471(84.7)	393040(74.2)	
Unknown         23(4.1)         6124(1.2)           Lymph nodes positive, n (%)             None         16(2.9)         122138(23.0)           More than one         51(9.2)         8448(1.6)           Uhknown         489(87.9)         399298(75.4)           PSA, ng/mL, n (%)             0-4.0         127(22.8)         57511(10.9)           4.1-10.0         92(16.5)         265323(50.1)           10.1-20.0         42(7.6)         66929(12.6)           >20.0         129(23.2)         53942(10.2)           Uhknown         166(29.9)         86179(16.3)           Surgery             No         396(71.2)         297267(56.1)           Cryoprostatectomy         0(0)         4875(0.9)           Laser ablation         3(0.5)         1202(0.2)           TURP         116(20.9)         25297(4.8)           Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	More than one	62(11.2)	130720(24.7)	
Lymph nodes positive, n (%) </td <td>Unknown</td> <td>23(4.1)</td> <td>6124(1.2)</td> <td></td>	Unknown	23(4.1)	6124(1.2)	
None         16(2.9)         122138(23.0)           More than one         51(9.2)         8448(1.6)           Unknown         489(87.9)         399298(75.4)           PSA, ng/mL, n (%)          <           0-4.0         127(22.8)         57511(10.9)           4.1-10.0         92(16.5)         265323(50.1)           10.1-20.0         42(7.6)         66929(12.6)           >20.0         129(23.2)         53942(10.2)           Unknown         166(29.9)         86179(16.3)           Surgery             No         396(71.2)         297267(56.1)           Cryoprostatectomy         0(0)         4875(0.9)           Laser ablation         3(0.5)         1202(0.2)           TURP         116(20.9)         25297(4.8)           Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	Lymph nodes positive, n (%)			<0.001
More than one         51(9.2)         8448(1.6)           Unknown         489(87.9)         399298(75.4)           PSA, ng/mL, n (%)             0-4.0         127(22.8)         57511(10.9)           4.1-10.0         92(16.5)         265323(50.1)           10.1-20.0         42(7.6)         66929(12.6)           >20.0         129(23.2)         53942(10.2)           Unknown         166(29.9)         6179(16.3)           Surgery             No         396(71.2)         297267(56.1)           Cryoprostatectomy         0(0)         4875(0.9)           Laser ablation         3(0.5)         1202(0.2)           TURP         116(20.9)         25297(4.8)           Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	None	16(2.9)	122138(23.0)	
Unknown         489(87.9)         399298(75.4)           PSA, ng/mL, n (%)  <	More than one	51(9.2)	8448(1.6)	
PSA, ng/mL, n (%)        0-4.0     127(22.8)       4.1-10.0     92(16.5)       10.1-20.0     42(7.6)       20.0     129(23.2)       20.0     129(23.2)       20.0     166(29.9)       86179(16.3)       Surgery       No     396(71.2)       Cryoprostatectomy     0(0)       Laser ablation     3(0.5)       TURP     116(20.9)       25297(4.8)       Partial prostatectomy     2(0.4)       1123(0.2)       Radical prostatectomy     39(7.0)	Unknown	489(87.9)	399298(75.4)	0.001
0-4.0     127(22.8)     57511(10.9)       4.1-10.0     92(16.5)     265323(50.1)       10.1-20.0     42(7.6)     66929(12.6)       >20.0     129(23.2)     53942(10.2)       Unknown     166(29.9)     86179(16.3)       Surgery         No     396(71.2)     297267(56.1)       Cryoprostatectomy     0(0)     4875(0.9)       Laser ablation     3(0.5)     1202(0.2)       TURP     116(20.9)     25297(4.8)       Partial prostatectomy     2(0.4)     1123(0.2)       Radical prostatectomy     39(7.0)     200120(37.8)	PSA, ng/mL, n (%)	107(00.0)		<0.001
4.1-0.0     92(16.5)     205323(50.1)       10.1-20.0     42(7.6)     66929(12.6)       >20.0     129(23.2)     53942(10.2)       Unknown     166(29.9)     86179(16.3)       Surgery         No     396(71.2)     297267(56.1)       Cryoprostatectomy     0(0)     4875(0.9)       Laser ablation     3(0.5)     1202(0.2)       TURP     116(20.9)     25297(4.8)       Partial prostatectomy     2(0.4)     1123(0.2)       Radical prostatectomy     39(7.0)     200120(37.8)	0-4.0	127(22.8)	57511(10.9)	
No.         42(1.0)         00929(12.0)           >20.0         129(23.2)         53942(10.2)           Unknown         166(29.9)         86179(16.3)           Surgery          <0.001           No         396(71.2)         297267(56.1)           Cryoprostatectomy         0(0)         4875(0.9)           Laser ablation         3(0.5)         1202(0.2)           TURP         116(20.9)         25297(4.8)           Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	4.1-10.0	92(10.3) 10(7 A)	200020(00.1) 66020(10.6)	
No         396(71.2)         30942(10.2)           Unknown         396(71.2)         207267(56.1)           Cryoprostatectomy         0(0)         4875(0.9)           Laser ablation         3(0.5)         1202(0.2)           TURP         116(20.9)         25297(4.8)           Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	>20.0	42(7.0)	52042(12.0)	
Surgery <th<< td=""><td>Jakaowa</td><td>166(29.9)</td><td>86170(16.3)</td><td></td></th<<>	Jakaowa	166(29.9)	86170(16.3)	
No         396(71.2)         297267(56.1)           Cryoprostatectomy         0(0)         4875(0.9)           Laser ablation         3(0.5)         1202(0.2)           TURP         116(20.9)         25297(4.8)           Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	Surgery	100(20.0)	00110(10.0)	~0.001
Cryoprostatectomy         O(0)         4875(0.9)           Laser ablation         3(0.5)         1202(0.2)           TURP         116(20.9)         25297(4.8)           Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	No	396(71.2)	297267(56.1)	<0.001
Laser ablation         3(0.5)         1202(0.2)           TURP         116(20.9)         25297(4.8)           Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	Cryoprostatectomy	0(0)	4875(0.9)	
TURP         116(20.9)         25297(4.8)           Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	Laser ablation	3(0.5)	1202(0.2)	
Partial prostatectomy         2(0.4)         1123(0.2)           Radical prostatectomy         39(7.0)         200120(37.8)	TURP	116(20.9)	25297(4.8)	
Radical prostatectomy 39(7.0) 200120(37.8)	Partial prostatectomy	2(0.4)	1123(0.2)	
	Radical prostatectomy	39(7.0)	200120(37.8)	

(Continued)

#### TABLE 1 | Continued

Characteristics	NEPC (n = 556)	Prostate Adenocarcinoma (n = 529884)	P value
Radiation			<0.001
No	349(62.8)	343593(64.8)	
Beam radiation	199(35.8)	128148(24.2)	
Radioactive implants	3(0.5)	34974(6.6)	
Combination of beam with implants or isotopes	1(0.2)	20895(3.9)	
Radioisotopes	O(O)	871(0.2)	
Radiation method unknown	4(0.7)	1404(0.3)	
Chemotherapy			< 0.001
No	234(42.1)	524571(99.0)	
Yes	322(57.9)	5313(1.0)	
Overall mortality			< 0.001
Alive	113(20.3)	431549(81.4)	
Dead	443(79.7)	98335(18.6)	
Cause special mortality			< 0.001
Alive	150(27.0)	495892(93.6)	
Dead	406(73.0)	33992(6.4)	

PSA, prostate-specific antigen; NEPC, neuroendocrine prostate cancer; IQR, interquartile range; TURP, Transurethral resection of prostate.

TABLE 2 | Baseline demographic and clinicopathologic characteristics of patients with prostate adenocarcinoma compare to four histological subtypes of NEPC.

Characteristics	Prostate adenocarcinoma (n = 529884)		NEPC	(n = 556)		P value
		LCNE (n = 6)	SCC (n = 296)	NEC NOS (n = 129)	NED (n = 125)	
Age at diagnosis, y, n (%)						<0.001
18-59	138473(26.1)	3(50.0)	56(18.9)	32(24.8)	24(19.2)	
60-74	304879(57.5)	1(16.7)	151(51.0)	58(45.0)	71(56.8)	
≥75	86532(16.3)	2(33.3)	89(30.1)	39(30.2)	30(24.0)	
Race, n (%)						0.020
White	414093(78.1)	5(83.3)	244(82.4)	107(82.9)	108(86.4)	
Black	86273(16.3)	O(O)	32(10.8)	13(10.1)	12(9.6)	
Other	29518(5.6)	1916.7)	20(6.8)	9(7.0)	5(4.0)	
Marital status, n (%)						0.002
Married	395936(74.7)	3(50.0)	208(70.3)	86(66.7)	80(64.0)	
Not married	133948(25.3)	3(50.0)	88(29.7)	43(33.3)	45(36.0)	
Year of diagnosis, n (%)						< 0.001
2004-2008	181794(34.3)	1(16.7)	57(19.3)	37(28.7)	22(17.6)	
2009-2013	178887(33.8)	3(50.0)	109(36.8)	48(37.2)	43(34.4)	
2014-2018	169203(31.9)	2(33.3)	130(43.9)	44(34.1)	60(48.0)	
Grade, n (%)						< 0.001
G1	40933(7.7)	O(O)	O(O)	O(O)	1(0.8)	
G2	213722(40.3)	O(O)	6(2.0)	2(1.6)	4(3.2)	
G3	226212(42.7)	1(16.7)	79(26.7)	72(55.8)	88(70.4)	
G4	876(0.2)	1(16.7)	27(9.1)	11(8.5)	2(1.6)	
Unknown	48141(9.1)	4(66.7)	184(62.2)	44(34.1)	30(24.0)	
Stage, n (%)						< 0.001
1	1478(0.3)	O(O)	O(O)	O(O)	O(O)	
11	340943(64.3)	O(O)	22(7.4)	13(10.1)	10(8.0)	
111	35235(6.6)	O(O)	1(0.3)	2(1.6)	4(3.2)	
IV	29774(5.6)	5(83.3)	176(59.5)	74(57.4)	69(55.2)	
Unknown	122454(23.1)	1(16.7)	97(32.8)	40(31.0)	42(33.6)	
T stage, n (%)						< 0.001
T1	161210(30.4)	O(O)	27(9.1)	13(10.1)	12(9.6)	
T2	203640(38.4)	1(16.7)	55(18.6)	19(14.7)	17(13.6)	
ТЗ	41566(7.8)	O(O)	27(9.1)	9(7.0)	14(11.2)	
T4	7284(1.4)	3(50.0)	64(21.6)	31(24.0)	24(19.2)	
Unknown	116184(21.9)	2(33.3)	123(41.6)	57(44.2)	58(46.4)	
N stage, n (%)						<0.001
NO	393696(74.3)	O(O)	84(28.4)	34(26.4)	34(27.2)	
N1	11647(2.2)	3(50.0)	93(31.4)	44(34.1)	39(31.2)	
Unknown	124541(23.5)	3(50.0)	119(40.2)	51(39.5)	52(41.6)	

(Continued)

#### TABLE 2 | Continued

LCNE (n = 6)         SCC (n = 290)         NED (n = 129)         NED (n = 129)           M stage, n (%)	Characteristics	Prostate adenocarcinoma (n = 529884)		NEPC (n = 556)									
M stage, n (%)			LCNE (n = 6)	SCC (n = 296)	NEC NOS (n = 129)	NED (n = 125)							
M0         99465774.5)         11(6.7)         6820.3)         32(24.8)         2922.2)           M1         18815(3.6)         4(66.7)         138(46.6)         58(45.7)         53(42.4)           Lymph nodes examined, n (%)	M stage, n (%)						<0.001						
M1         188153.6, 11841222.0, 118471222.0, 118471222.0, 118471222.0, 118471222.0, 118471222.0, 118471222.0, 118471222.0, 118471222.0, 118471222.0, 118471222.0, 118471222.0, 118471222.0, 11847122, 11847122, 11847122, 11847122, 11847122, 11847122, 11847122, 11847122, 11847122, 11847122, 118471, 1184712, 118471,	MO	394657(74.5)	1(16.7)	60(20.3)	32(24.8)	29(23.2)							
Uknown         116412(22.0)         11(16.7)         98(33.1)         38(29.5)         43(34.4)           Lymph nodes examined, n (%)	M1	18815(3.6)	4(66.7)	138(46.6)	59(45.7)	53(42.4)							
Lymph nodes examined, n (%)         Construction         Construction <t< td=""><td>Unknown</td><td>116412(22.0)</td><td>1(16.7)</td><td>98(33.1)</td><td>38(29.5)</td><td>43(34.4)</td><td></td></t<>	Unknown	116412(22.0)	1(16.7)	98(33.1)	38(29.5)	43(34.4)							
Nome         393040(74.2)         6(100.0)         258(87.2)         102(79.1)         105(84.0)           More than one         130720(24.7)         0(0)         25(8.4)         19(14.7)         18(14.4)           Lymph nodes positive, n (%)   <	Lymph nodes examined, n (%)	- ( -/	( - )	()		- ()	< 0.001						
Mare than one         130720(24.7)         0(0)         25(8.4)         19(14.7)         18(14.4)           Unknown         6124(1.2)         0(0)         13(4.4)         8(8.2)         2(1.6)           None         122138(23.0)         0(0)         7(2.4)         3(2.3)         6(4.8)           More than one         8448(1.6)         0(0)         21(7.1)         16(12.4)         14(11.2)           Unknown         399298(75.4)         6(100.0)         26890.5)         11065.3         10564.0)           PSA. ng/mL, n (%)	None	393040(74.2)	6(100.0)	258(87.2)	102(79.1)	105(84.0)							
Unknown         6124(1.2)         00         13(4.4)         8(6.2)         2(1.6)           Lymph nodes positive, n (%)	More than one	130720(24.7)	0(0)	25(8.4)	19(14.7)	18(14.4)							
Chardinal Structure         Control         Contro         Control <thcontrol< th=""></thcontrol<>	Unknown	6124(1.2)	0(0)	1.3(4.4)	8(6.2)	2(1.6)							
Since         Since         Since           None         122138(23.0)         0(0)         7(2.4)         3(2.3)         6(4.8)           More than one         8448(1.6)         0(0)         21(7.1)         16(12.4)         14(11.2)           Unknown         399298(75.4)         6(100.0)         268(90.5)         110(85.3)         105(64.0)           PSA, ng/mL, n (%)             <0.001	I ymph nodes positive n (%)	0121(1.2)	0(0)	10(11)	0(0.2)	2(1.0)	<0.001						
Natic         Tat 108 (20.5)         O(0)         T(2-1)         O(1,0)         O(1,0)           More than one         6448(1.6)         O(0)         28(90.5)         110(85.3)         105(84.0)           PSA, ng/mL, n (%) <td>None</td> <td>122138/23 ())</td> <td>0(0)</td> <td>7(2.4)</td> <td>3(2,3)</td> <td>6(4.8)</td> <td>10.001</td>	None	122138/23 ())	0(0)	7(2.4)	3(2,3)	6(4.8)	10.001						
Minice function         Operation	More than one	8448(1.6)	0(0)	21(7, 1)	16(12.4)	1/(11.2)							
Ontomin         Oscilation         Oscilation         Oscilation         Oscilation         Oscilation           0-4.0         57511(10.9)         1(16.7)         81(27.4)         32(24.8)         13(10.4)           4.1-10.0         265323(50.1)         1(16.7)         47(15.9)         17(13.2)         27(21.6)           10.1-20.0         66929(12.6)         0(0)         18(61.1)         13(10.1)         11(8.8)           >20.0         53942(10.2)         2(33.3)         44(14.9)         31(24.0)         52(41.6)           Unknown         86179(16.3)         2(33.3)         106(35.8)         36(67.2)         6.001           Surgery          200.0         0(0         0(0)         0(0)         0(0)         0(0)           Laser ablation         1202(0.2)         0(0)         10.3         0(0)         2(16.5)           TURP         25297(4.8)         5(83.3)         58(19.6)         29(22.5)         24(19.2)           Partial prostatectomy         2012(37.8)         0(0)         13(4.4)         11(8.5)         15(12.0)           Radical prostatectomy         2012(37.8)         0(0)         3(10.0)         0(0)         0(0)           No         343592(64.8)         2(33.3)		300208(75.4)	6(100.0)	268(00.5)	110(12.4)	105(84.0)							
O-4.0         57511(10.9)         1(16.7)         81(27.4)         32(24.8)         13(10.4)           4.1-10.0         265323(50.1)         1(16.7)         47(15.9)         17(13.2)         27(21.6)           10.1-20.0         66929(12.6)         0(0)         18(6.1)         13(10.1)         11(8.8)           >20.0         53942(10.2)         2(33.3)         44(1.4)         31(24.0)         52(41.6)           Unknown         86179(16.3)         2(33.3)         106(35.8)         36(27.9)         22(17.6)           Surgery	BSA ng/ml n (%)	033230(73.4)	0(100.0)	200(30.3)	110(00.0)	100(04.0)	~0.001						
One-D         Of S1 (10.9)         (10.7)         Of (27.8)         S2(24.3)         IO(10-4)           1.1-1.0.0         265323(50.1)         11(16.7)         47(15.9)         17(13.2)         27(21.6)           10.1-20.0         66929(12.6)         0(0)         18(6.1)         13(10.1)         11(8.8)           >20.0         53942(10.2)         2(33.3)         44(14.9)         31(24.0)         52(41.6)           Unknown         86179(16.3)         2(33.3)         44(14.9)         31(24.0)         52(41.6)           Okynomic         297267(56.1)         11(16.7)         47(17.2)         27(7.6)         84(67.2)           Cyoporstatectomy         4975(0.9)         0(0)         0(0)         0(0)         2(1.6)           Partial prostatectomy         1202(0.2)         0(0)         1(0.3)         0(0)         2(1.6)           Partial prostatectomy         25297(4.8)         5(83.3)         58(19.6)         29(2.5)         24(19.2)           Partial prostatectomy         200120(37.8)         0(0)         2(0.7)         0(0)         0(0)           Radical prostatectomy         200120(37.8)         0(0)         3(1.6)         82(63.6)         83(64.1)           No         343592(64.6)         0(0)	0.4.0	57511(10.0)	1(16.7)	91/07 A)	20(24.8)	12(10.4)	<0.001						
A. 1600         26032(0.1)         1(10.1)         4(1(1.3)         1(10.2)         2(121.0)           10.1-20.0         66329(12.6)         0(0)         18(6.1)         13(10.1)         11(8.2)         22(1.3)           20.0         53942(10.2)         2(3.3)         44(14.9)         31(24.0)         52(41.6)           Unknown         86179(16.3)         2(3.3)         106(35.8)         36(27.9)         22(0.0)           Surgery         -         -         -         -         -         -           No         297267(56.1)         11(16.7)         22(27.0)         89(69.0)         84(67.2)           Cryoprostatectomy         4875(0.9)         0(0)         0(0)         0(0)         2(1.6)           Laser ablation         1202(0.2)         0(0)         14(.4)         11(8.5)         15(1.0)           Partial prostatectomy         1123(0.2)         0(0)         2(0.7)         0(0)         0(0)           Radiation         122148(24.2)         4(66.7)         109(36.8)         48(35.7)         40(32.0)           Radiaction method unknown         129148(24.2)         4(66.7)         109(36.8)         48(35.7)         40(32.0)           Radiation method unknown         129148(24.2)         0(0)<	4.1.10.0	265222(50.1)	1(16.7)	47(15.0)	17(12.2)	27(21.6)							
Intersection         0000 (000 (000)         10(0.1) <td>10.1.20.0</td> <td>66020(12.6)</td> <td>0(0)</td> <td>19(6.1)</td> <td>12(10.1)</td> <td>11/9.9)</td> <td></td>	10.1.20.0	66020(12.6)	0(0)	19(6.1)	12(10.1)	11/9.9)							
>20.0       30342(10.2)       2(33.3)       44(14.9)       3(24.10)       52(41.0)         Unknown       86179(16.3)       2(33.3)       106(35.8)       36(27.9)       22(17.6)         Surgery       297267(56.1)       1(16.7)       222(75.0)       89(69.0)       84(67.2)         Cryoprostatectomy       4875(0.9)       0(0)       0(0)       0(0)       2(93.3)       58(19.6)       29(2.5)       24(19.2)         Laser ablation       1202(0.2)       0(0)       1(16.3)       29(22.5)       24(19.2)         Partial prostatectomy       1202(0.2)       0(0)       13(4.4)       11(8.5)       15(12.0)         Radiation       1202(0.2)       0(0)       13(4.4)       11(8.5)       15(12.0)         Radiator prostatectomy       200120(37.8)       0(0)       13(4.4)       11(8.5)       15(12.0)         Radiator metatom       128148(24.2)       4(66.7)       109(36.8)       46(35.7)       40(32.0)         Radiactor inplants       343592(64.8)       2(93.3)       182(61.5)       82(63.6)       83(66.4)         Beam radiation       128148(24.2)       4(66.7)       109(36.8)       46(35.7)       40(32.0)         Radioactorie inplants       20895(3.9)       0(0)       0(0)	> 20.0	52042(10.0)	0(0)	10(0.1)	31(34.0)	F0(41.6)							
Olikitowin         Bit P(16.3)         2 (3.3.)         100(35.3)         3 (3(27.9)         22 (77.6)           Surgery	>20.0	003942(10.2)	2(33.3)	106(25.0)	31(24.0)	02(41.0)							
Augery         Constraint         Constraint         Constraint           No         297267(66.1)         1(16.7)         222(75.0)         89(69.0)         84(67.2)           Cryoprostatectomy         4875(0.9)         0(0)         0(0)         0(0)         2(1.6)           TURP         25297(4.8)         5(83.3)         58(19.6)         29(2.5)         24(19.2)           Partial prostatectomy         200120(37.8)         0(0)         13(4.4)         11(8.5)         15(12.0)           Radiation         200120(37.8)         0(0)         13(4.4)         11(8.5)         46(6.7)           No         34359(64.8)         2(33.3)         182(61.5)         82(63.6)         83(66.4)           Beam radiation         128148(24.2)         4(66.7)         109(36.8)         46(35.7)         40(32.0)           Radioactive implants         34974(6.6)         0(0)         3(1.0)         0(0)         0(0)           Radioactive implants         34974(6.6)         0(0)         0(0)         0(0)         0(0)           Radioactive implants         34974(6.6)         0(0)         0(0)         0(0)         0(0)         0(0)           Radioactive implants         34974(6.6)         0(0)         0(0)         0(0)	Surger	00179(10.3)	2(33.3)	100(35.6)	30(27.9)	22(17.0)	-0.001						
No         29726 (36.1)         (110.7)         222(15.0)         89(69.0)         64(67.2)           Cryoprostatectomy         4875(0.9)         0(0)         0(0)         0(0)         0(0)         0(0)           Laser ablation         1202(0.2)         0(0)         1(0.3)         0(0)         2(1.6)           TURP         25297(4.8)         5(83.3)         58(19.6)         29(22.5)         24(19.2)           Partial prostatectomy         1123(0.2)         0(0)         13(4.4)         116.5)         15(12.0)           Radiation         200120(37.8)         0(0)         20(0.2)         0(0)         0(0)         0(0)           Radiactive implants         343592(64.8)         2(33.3)         182(61.5)         82(63.6)         83(66.4)           Beam radiation         128148(24.2)         4(66.7)         109(36.8)         46(35.7)         40(32.0)           Radioactive implants         34974(6.6)         0(0)         3(1.0)         0(0)         0(0)           Combination of beam with implants or isotopes         20895(3.9)         0(0)         0(0)         0(0)         200.7           Radiactor method unknown         1404(0.3)         0(0)         2(0.7)         1(0.8)         1(0.8)         2(0.01	Surgery	007007/FC 1	1(107)	000/75 0)	00/00 0)	04/07 0)	<0.001						
Cryoprostatectomy4875(0.9)0(0)0(0)0(0)0(0)0(0)Laser ablation1202(0.2)0(0)1(0.3)0(0)2(1.6)TURP25297(4.8)5(83.3)58(19.6)29(2.5)24(19.2)Partial prostatectomy1123(0.2)0(0)13(4.4)11(8.5)15(12.0)Radical prostatectomy200120(37.8)0(0)13(4.4)11(8.5)82(63.6)83(66.4)No343592(64.8)2(33.3)182(61.5)82(63.6)83(66.4)Beam radiation128148(24.2)4(66.7)109(36.8)46(35.7)40(32.0)Radioactive implants34974(6.6)0(0)3(1.0)0(0)0(0)Combination of beam with implants or isotopes20895(3.9)0(0)0(0)0(0)1(0.8)Radiostopes871(0.2)0(0)0(0)0(0)1(0.8)0(0)Radiostopes871(0.2)0(0)0(0)1(0.8)0(0)0(0)Radiostopes524571(99.0)3(50.0)95(32.1)58(45.0)78(62.4)No524571(99.0)3(50.0)95(32.1)58(45.0)78(62.4)Yes5313(1.0)3(50.0)201(67.9)71(55.0)47(37.6)Alive431549(81.4)1(16.7)48(16.2)21(16.3)43(34.4)Dead2035(18.6)58(3.3)248(8.8)108(8.7)82(65.6)Alive49589(293.6)1(16.7)65(2.0)31(24.0)53(42.4)Dead33992(6.4)58(3.3)231(78.0)98(76.0) <td></td> <td>297267(56.1)</td> <td>1(16.7)</td> <td>222(75.0)</td> <td>89(69.0)</td> <td>84(67.2)</td> <td></td>		297267(56.1)	1(16.7)	222(75.0)	89(69.0)	84(67.2)							
Laser ablation       1202(0.2)       0(0)       1(0.3)       0(0)       2(1.5)         TURP       25297(4.8)       5(8.3)       58(19.6)       29(2.5)       24(19.2)         Partial prostatectomy       200120(37.8)       0(0)       13(4.4)       11(8.5)       15(12.0)         Radical prostatectomy       200120(37.8)       0(0)       13(4.4)       11(8.5)       15(12.0)         Radiation       343592(64.8)       2(33.3)       182(61.5)       82(63.6)       83(66.4)         Beam radiation       128148(24.2)       4(66.7)       109(36.8)       46(35.7)       40(32.0)         Radiostorpes       20895(3.9)       0(0)       0(0)       0(0)       0(0)         Combination of beam with implants or isotopes       20895(3.9)       0(0)       0(0)       0(0)         Radiostorpes       871(0.2)       0(0)       0(0)       0(0)       10.8)         Radiostorpes       871(0.2)       0(0)       0(0)       0(0)       10.8)         Vers       5313(1.0)       3(50.0)       95(32.1)       58(45.0)       78(62.4)         Vers       5313(1.0)       3(50.0)       201(67.9)       71(55.0)       47(37.6)         Vers       5313(1.6)       3(50.0)		4875(0.9)	0(0)	0(0)	0(0)	0(0)							
TOHP         2529/(4.8)         5(83.3)         58(19.6)         29(22.5)         24(19.2)           Partial prostatectomy         1123(0.2)         0(0)         2(0.7)         0(0)         0(0)           Radical prostatectomy         200120(37.8)         0(0)         13(4.4)         11(8.5)         15(12.0)           Radiation         343592(64.8)         2(33.3)         182(61.5)         82(63.6)         83(66.4)           Beam radiation         128148(24.2)         4(66.7)         109(36.8)         46(35.7)         40(32.0)           Radioactive implants         34974(6.6)         0(0)         3(1.0)         0(0)         0(0)         0(0)           Combination of beam with implants or isotopes         20895(3.9)         0(0)         0(0)         0(0)         0(0)         Radioactive implants         10.8)         4(6.7)         10.8)         10.8)         4(6.8)         2(1.0)         3(10.8)         2(1.0)         3(10.8)         2(1.0)         3(10.8)         2(1.0)         3(10.8)         2(1.0)         3(1.0)         2(1.0)         3(1.0)         2(1.0)         3(3.2)         4(1.8)         4(1.8)         4(1.8)         4(1.8)         2(1.6)         4(3.2.4)         4(1.8)         2(1.6)         4(3.2.4)         2(0.0)         2(1.6) <td>Laser adiation</td> <td>1202(0.2)</td> <td>0(0)</td> <td>1(0.3)</td> <td>0(0)</td> <td>2(1.6)</td> <td></td>	Laser adiation	1202(0.2)	0(0)	1(0.3)	0(0)	2(1.6)							
Partial prostatectomy       1123(0.2)       0(0)       2(0.7)       0(0)       0(0)         Radical prostatectomy       200120(37.8)       0(0)       13(4.4)       11(8.5)       15(12.0)         Radical prostatectomy       343592(64.8)       2(33.3)       182(61.5)       82(63.6)       83(66.4)         Beam radiation       128148(24.2)       4(66.7)       109(36.8)       46(35.7)       40(32.0)         Radioactive implants       34974(6.6)       0(0)       3(1.0)       0(0)       0(0)         Combination of beam with implants or isotopes       2085(3.9)       0(0)       0(0)       0(0)       0(0)         Radioisotopes       871(0.2)       0(0)       0(0)       0(0)       0(0)       0(0)         Radiation method unknown       1404(0.3)       0(0)       0(0)       0(0)       0(0)       0(0)         Radizion method unknown       524571(99.0)       3(50.0)       95(32.1)       58(45.0)       78(62.4)         Yes       5313(1.0)       3(50.0)       95(32.1)       58(45.0)       78(62.4)         Yes       5313(1.0)       3(50.0)       201(67.9)       71(55.0)       47(37.6)         Quead       9335(18.6)       5(83.3)       248(83.8)       108(8.7)       48(3		25297(4.8)	5(83.3)	58(19.6)	29(22.5)	24(19.2)							
Radical prostatectomy       200120(37.8)       0(0)       13(4.4)       11(8.5)       15(12.0)         Radiation   11(8.5)       15(12.0)	Partial prostatectomy	1123(0.2)	0(0)	2(0.7)	0(0)	0(0)							
Radiation <t< td=""><td>Radical prostatectomy</td><td>200120(37.8)</td><td>0(0)</td><td>13(4.4)</td><td>11(8.5)</td><td>15(12.0)</td><td></td></t<>	Radical prostatectomy	200120(37.8)	0(0)	13(4.4)	11(8.5)	15(12.0)							
No         343592(64.8)         2(33.3)         182(61.5)         82(63.6)         83(66.4)           Beam radiation         128148(24.2)         4(66.7)         109(36.8)         46(35.7)         40(32.0)           Radioactive implants         34974(6.6)         0(0)         3(1.0)         0(0)         0(0)           Combination of beam with implants or isotopes         20895(3.9)         0(0)         0(0)         0(0)         1(0.8)           Radioisotopes         871(0.2)         0(0)         0(0)         0(0)         0(0)         0(0)           Radiation method unknown         1404(0.3)         0(0)         2(0.7)         1(0.8)         0(0.8)           Chemotherapy         524571(99.0)         3(50.0)         95(32.1)         58(45.0)         78(62.4)           Yes         5313(1.0)         3(50.0)         201(67.9)         71(55.0)         47(37.6)           Overall mortality            Alive         431549(81.4)         1(16.7)         48(16.2)         21(16.3)         43(34.4)           Dead         98335(18.6)         5(83.3)         248(83.8)         108(83.7)         82(65.6)           Cause special mortality            5(83.3)         231(78.0)	Radiation		- ()				<0.001						
Beam radiation       128148(24.2)       4(66.7)       109(36.8)       46(35.7)       40(32.0)         Radioactive implants       34974(6.6)       0(0)       3(1.0)       0(0)       0(0)         Combination of beam with implants or isotopes       20895(3.9)       0(0)       0(0)       0(0)       1(0.8)         Radioisotopes       871(0.2)       0(0)       0(0)       0(0)       0(0)       0(0)         Radiation method unknown       1404(0.3)       0(0)       2(0.7)       1(0.8)       1(0.8)         Chemotherapy       524571(99.0)       3(50.0)       95(32.1)       58(45.0)       78(62.4)         No       524571(99.0)       3(50.0)       201(67.9)       71(55.0)       47(37.6)         Overall mortality	No	343592(64.8)	2(33.3)	182(61.5)	82(63.6)	83(66.4)							
Radioactive implants       34974(6.6)       0(0)       3(1.0)       0(0)       0(0)         Combination of beam with implants or isotopes       20895(3.9)       0(0)       0(0)       0(0)       1(0.8)         Radioisotopes       871(0.2)       0(0)       0(0)       0(0)       0(0)       0(0)         Radiation method unknown       1404(0.3)       0(0)       2(0.7)       1(0.8)       1(0.8)         Chemotherapy          No       524571(99.0)       3(50.0)       95(32.1)       58(45.0)       78(62.4)         Yes       5313(1.0)       3(50.0)       201(67.9)       71(55.0)       43(34.4)         Overall mortality          Alive       98335(18.6)       5(83.3)       248(83.8)       108(83.7)       82(65.6)         Cause special mortality          Alive       495892(93.6)       1(16.7)       65(22.0)       31(24.0)       53(42.4)         Dead       33992(6.4)       5(83.3)       231(78.0)       98(76.0)       72(57.6)	Beam radiation	128148(24.2)	4(66.7)	109(36.8)	46(35.7)	40(32.0)							
Combination of beam with implants or isotopes         20895(3.9)         0(0)	Radioactive implants	34974(6.6)	O(O)	3(1.0)	O(O)	O(O)							
Radioisotopes     871(0.2)     0(0)     0(0)     0(0)     0(0)       Radiation method unknown     1404(0.3)     0(0)     2(0.7)     1(0.8)     1(0.8)       Chemotherapy        No     524571(99.0)     3(50.0)     95(32.1)     58(45.0)     78(62.4)       Yes     5313(1.0)     3(50.0)     201(67.9)     71(55.0)     47(37.6)       Overall mortality        Alive     431549(81.4)     1(16.7)     48(16.2)     21(16.3)     43(34.4)       Dead     98335(18.6)     5(83.3)     248(83.8)     108(83.7)     82(65.6)       Cause special mortality        Alive     495892(93.6)     1(16.7)     65(22.0)     31(24.0)     53(42.4)       Dead     33992(6.4)     5(83.3)     231(78.0)     98(76.0)     72(57.6)	Combination of beam with implants or isotopes	20895(3.9)	O(O)	O(O)	O(O)	1(0.8)							
Radiation method unknown       1404(0.3)       0(0)       2(0.7)       1(0.8)       1(0.8)         Chemotherapy	Radioisotopes	871(0.2)	O(O)	O(O)	O(O)	O(O)							
Chemotherapy	Radiation method unknown	1404(0.3)	0(0)	2(0.7)	1(0.8)	1(0.8)							
No         524571(99.0)         3(50.0)         95(32.1)         58(45.0)         78(62.4)           Yes         5313(1.0)         3(50.0)         201(67.9)         71(55.0)         47(37.6)           Overall mortality            Alive         431549(81.4)         1(16.7)         48(16.2)         21(16.3)         43(34.4)           Dead         98335(18.6)         5(83.3)         248(83.8)         108(83.7)         82(65.6)           Cause special mortality            Alive         495892(93.6)         1(16.7)         65(22.0)         31(24.0)         53(42.4)           Dead         33992(6.4)         5(83.3)         231(78.0)         98(76.0)         72(57.6)	Chemotherapy						<0.001						
Yes         5313(1.0)         3(50.0)         201(67.9)         71(55.0)         47(37.6)           Overall mortality            Alive         431549(81.4)         1(16.7)         48(16.2)         21(16.3)         43(34.4)           Dead         98335(18.6)         5(83.3)         248(83.8)         108(83.7)         82(65.6)           Cause special mortality            Alive         495892(93.6)         1(16.7)         65(22.0)         31(24.0)         53(42.4)           Dead         33992(6.4)         5(83.3)         231(78.0)         98(76.0)         72(57.6)	No	524571(99.0)	3(50.0)	95(32.1)	58(45.0)	78(62.4)							
Overall mortality                                  < <th>             &lt;<th>&lt;<th>&lt;<th>&lt;<th>&lt;<th>&lt;<t< td=""><td>Yes</td><td>5313(1.0)</td><td>3(50.0)</td><td>201(67.9)</td><td>71(55.0)</td><td>47(37.6)</td><td></td></t<></th></th></th></th></th></th>	< <th>&lt;<th>&lt;<th>&lt;<th>&lt;<th>&lt;<t< td=""><td>Yes</td><td>5313(1.0)</td><td>3(50.0)</td><td>201(67.9)</td><td>71(55.0)</td><td>47(37.6)</td><td></td></t<></th></th></th></th></th>	< <th>&lt;<th>&lt;<th>&lt;<th>&lt;<t< td=""><td>Yes</td><td>5313(1.0)</td><td>3(50.0)</td><td>201(67.9)</td><td>71(55.0)</td><td>47(37.6)</td><td></td></t<></th></th></th></th>	< <th>&lt;<th>&lt;<th>&lt;<t< td=""><td>Yes</td><td>5313(1.0)</td><td>3(50.0)</td><td>201(67.9)</td><td>71(55.0)</td><td>47(37.6)</td><td></td></t<></th></th></th>	< <th>&lt;<th>&lt;<t< td=""><td>Yes</td><td>5313(1.0)</td><td>3(50.0)</td><td>201(67.9)</td><td>71(55.0)</td><td>47(37.6)</td><td></td></t<></th></th>	< <th>&lt;<t< td=""><td>Yes</td><td>5313(1.0)</td><td>3(50.0)</td><td>201(67.9)</td><td>71(55.0)</td><td>47(37.6)</td><td></td></t<></th>	< <t< td=""><td>Yes</td><td>5313(1.0)</td><td>3(50.0)</td><td>201(67.9)</td><td>71(55.0)</td><td>47(37.6)</td><td></td></t<>	Yes	5313(1.0)	3(50.0)	201(67.9)	71(55.0)	47(37.6)	
Alive         431549(81.4)         1(16.7)         48(16.2)         21(16.3)         43(34.4)           Dead         98335(18.6)         5(83.3)         248(83.8)         108(83.7)         82(65.6)           Cause special mortality            Alive         495892(93.6)         1(16.7)         65(22.0)         31(24.0)         53(42.4)           Dead         33992(6.4)         5(83.3)         231(78.0)         98(76.0)         72(57.6)	Overall mortality						< 0.001						
Dead         98335(18.6)         5(83.3)         248(83.8)         108(83.7)         82(65.6)           Cause special mortality            Alive         495892(93.6)         1(16.7)         65(22.0)         31(24.0)         53(42.4)           Dead         33992(6.4)         5(83.3)         231(78.0)         98(76.0)         72(57.6)	Alive	431549(81.4)	1(16.7)	48(16.2)	21(16.3)	43(34.4)							
Cause special mortality </td <td>Dead</td> <td>98335(18.6)</td> <td>5(83.3)</td> <td>248(83.8)</td> <td>108(83.7)</td> <td>82(65.6)</td> <td></td>	Dead	98335(18.6)	5(83.3)	248(83.8)	108(83.7)	82(65.6)							
Alive495892(93.6)1(16.7)65(22.0)31(24.0)53(42.4)Dead33992(6.4)5(83.3)231(78.0)98(76.0)72(57.6)	Cause special mortality						< 0.001						
Dead 33992(6.4) 5(83.3) 231(78.0) 98(76.0) 72(57.6)	Alive	495892(93.6)	1(16.7)	65(22.0)	31(24.0)	53(42.4)							
	Dead	33992(6.4)	5(83.3)	231(78.0)	98(76.0)	72(57.6)							

PSA, prostate-specific antigen; NEPC, neuroendocrine prostate cancer; TURP, Transurethral resection of prostate; LCNE, large cell neuroendocrine carcinoma; SCC, small cell carcinoma; NEC NOS, neuroendocrine carcinoma not otherwise specified; NED, neuroendocrine differentiation.

according to clinicopathologic characteristics and explore the prognostic values in NEPC. Several meaningful conclusions could be obtained from our study. Among patients with prostate cancer, NEC had a worse prognosis than adenocarcinoma, even after adjustment for potential covariates. Moreover, subgroup analysis suggested that NEC patients obtained significantly poorer survival outcomes than adenocarcinoma patients across almost all subgroups. Last but not the least, there was no interaction among age at diagnosis, race, marital status, year of diagnosis, grade, T stage, N stage, lymph nodes examined, lymph nodes positive, radiation and the histological subtype of NEC was an independent prognostic factor for prostate cancer.

Although NEPC is a rare entity, the incidence rates of it maintained an upward trend in recent years (18). It had risen by

approaching 6.8% per year, which could be mainly attributed to advanced medical technology and improved diagnostic methods (10, 18). Specially, the incident rates of small cell carcinoma (SCC) had a similar increasing trend of nearly 7.0% per year (18). Previous studies revealed that it was quite possible that the rise in incidence of NEPC was driven by SCC (19–21). On the other hand, several studies hold the view that the utilization of ADT was related to the incidence of NEPC (22–24). ADT was a primary therapy for prostate cancer targeting the androgen axis, which was first put forward by Huggins and Hodges in 1941 (11). Recently, the incidence rates of NEPC rose accompanied by the utilization of highly potent ADT, such as abiraterone and enzalutamide before or after chemotherapy for CRPC (25, 26). Long-term androgen deprivation could promote



adenocarcinoma cells lose androgen receptor (AR) expression and eventually developed to NEC cells, which was called treatment-related NEPC (t-NEPC) (10, 27). However, it was reported that the utilization of ADT obviously decreased in 2004 and 2005 while the incident rates of NEPC, by contrast, displayed an increasing trend (19). Hence, such hypothesis is still not exactly elucidated. The upward incident trend of NEPC were supposed to be highlighted and the issue of long-term exposure to ADT in the clinic was warranted to be resolved in the coming years.

In the present study, NEC patients with PSA levels higher than 4.0 ng/mL accounted for 43.7%, compared with 72.9% of adenocarcinoma patients. This result suggested that except for loss of AR, NEPC patients are typically manifested by the downregulation of PSA (28). Our investigation was consistent with previous studies, which demonstrated that the PSA marker was usually expressed in adenocarcinoma while SCC, large cell carcinoma, or mixed adenocarcinoma neuroendocrine histology were scarcely expressed PSA (29). Hence, the low or non-rising serum PSA levels in tumor cells may indicate a relatively poorer prognosis (30). It also implied that serum PSA screening may not be effective for detection of NEPC in the clinic (7). The US Preventive Services Task Force (USPSTF) has recommended against PSA screening first in 2008 for men aged 75 years and older and then in 2012 for all men. However, since USPSTF's 2012 recommendation, the incidence of advanced-stage prostate cancer has continued to rise though rates of localized disease have declined (6). Currently, the diagnosis of NEPC is mainly according to metastatic tumor biopsy confirming tumor morphology. Although there were no standard criteria for the best opportunity to conduct tumor biopsy, the NCCN guidelines recommended performing metastatic biopsy in suspected patients with particularly atypical spread, aggressive characteristics, and/or development with low serum PSA levels (30). Serum NE markers like CgA and NSE levels as well as synaptophysin (SYP), chromogranin and CD56 were classic biomarkers of NE cell, which were frequently upregulated in NEPC by immunohistochemistry (IHC), but neither of them was

		0	verall survival			Cancer specific survival				
Year	Prostate		I	NEPC		Prostate		I	NEPC	
	Adenocarcinoma	LCNE	SCC	NEC NOS	NED	Adenocarcinoma	LCNE	SCC	NEC NOS	NED
1	97.7	0	38.1	54.0	70.4	98.8	0	39.9	57.6	73.5
	(97.7-97.8)		(32.8-44.3)	(46.0-63.5)	(62.6-79.2)	(98.8-98.9)		(34.4-46.2)	(49.6-67.0)	(65.8-82.0)
2	95.2	0	19.1	32.3	57.4	97.5	0	20.5	37.7	59.9
	(95.1-95.2)		(14.9-24.5)	(24.9-41.9)	(48.9-67.3)	(97.5-97.6)		(16.0-26.2)	(29.8-47.9)	(51.4-69.8)
3	92.7	0	11.7	22.0	38.9	96.4	0	13.8	25.7	43.2
	(92.7-92.8)		(8.3-16.5)	(15.4-31.4)	(30.4-49.7)	(96.4-96.5)		(10.0-19.1)	(18.3-36.1)	(34.2-54.5)
4	90.3	0	10.8	15.1	28.8	95.5	0	12.7	17.7	35.6
	(90.2-90.4)		(7.5-15.5)	(9.5-24.1)	(20.9-39.8)	(95.4-95.6)		(9.0-17.9)	(11.2-27.8)	(26.7-47.4)
5	88.0	0	9.7	11.6	25.6	94.7	0	11.5	13.6	31.6
	(87.9-88.1)		(6.6-14.4)	(6.7-20.2)	(17.8-36.8)	(94.6-94.8)		(7.9-16.6)	(7.9-23.4)	(22.7-44.0)

TABLE 3 | Overall survival and cancer specific survival of patients with NEPC and prostate adenocarcinoma.

NEPC, neuroendocrine prostate cancer; LCNE, large cell neuroendocrine carcinoma; SCC, small cell carcinoma; NEC NOS, neuroendocrine carcinoma not otherwise specified; NED, neuroendocrine differentiation.

 TABLE 4 | Propensity score matching for baseline factors.

App at disposis, y, n(%)0.77215.90(2010)(2010)60-74(2010)(2010)60-75(2010)(2010)75(14) (205)(2010)Race, n(%)(2010)(2010)Race, n(%)(2010)(2010)Race, n(%)(2010)(2010)Race, n(%)(2010)(2010)Race, n(%)(2010)(2010)Race, n(%)(2010)(2010)Race, n(%)(2010)(2010)Race, n(%)(2010)(2010)Corollogical (2010)(2010)(2010)Corollogical (2010)	Characteristics	Prostate Adenocarcinoma (n = 484)	NEPC (n = 484)	P value
15.5020 [16.0]10 [10.9]275143 (23.5]138 (27.9)275143 (23.5]138 (27.9)27628 (7.9, 1)386 (1.1.8)178028 (7.9, 1)386 (1.1.8)178028 (7.9, 1)387 (7.9, 1)178028 (7.9, 1)710 (94.0)210 (95.0)178010 (94.0)210 (95.0)100 (95.0)178010 (94.0)210 (95.0)100 (95.0)178010 (94.0)10 (95.0)100 (95.0)1780177 (95.2)97 (70.0)100 (95.0)2014-2018210 (4.0)110 (2.3)100 (7.2)2014-2018210 (4.0)110 (2.3)100 (7.2)2014-2018210 (4.1)110 (2.3)100 (7.2)2014-2019210 (4.1)110 (2.3)100 (7.2)2014-2018210 (4.1)110 (2.3)100 (7.2)2014-2018210 (4.1)110 (2.3)100 (7.2)2014-2019210 (4.2)210 (4.2)100 (7.2)2014-2019210 (4.2)210 (4.2)100 (7.2)2014-2019210 (4.2)210 (4.2)100 (7.2)2014-2019210 (4.2)210 (4.2)100 (7.2)2014-2019210 (4.2)210 (4.2)100 (7.2)2014-2019210 (4.2)210 (4.2)100 (7.2)2014-2019210 (4.2)210 (4.2)100 (7.2)2014-2019210 (4.2)210 (4.2)100 (7.2)2014-2019210 (4.2)210 (4.2)210 (4.2)2014-2019210 (4.2)210 (4.2)210 (	Age at diagnosis, y, n (%)			0.722
60.74446 (61.4)426 (52.73)75160.0369 (74.8)369 (74.8)180.0124 (15.3)369 (17.8)322180.0124 (15.3)361 (17.8)360180.0121 (18.3)361 (18.1)360180.0121 (18.0.3)360 (17.8)360180.0121 (18.0.3)360 (17.8)360180.0121 (18.0.3)360 (17.8)360180.0121 (18.0.3)360 (17.8)3602017-2019127 (18.2.3)360 (17.8)3602010-2012202 (14.5)360 (18.8)3602010-2012202 (14.5)360 (18.8)3602010-2012204 (18.3)360 (18.8)3602010-2012204 (18.3)360 (18.8)3602010-2012204 (18.3)360 (18.8)3602010-2012204 (19.3)360 (18.8)3602010-2012204 (19.3)360 (18.8)3602010-2012204 (19.3)360 (19.8)3602010-2012204 (19.3)360 (19.8)3602010-2012204 (19.8)360 (19.8)3602010-2012204 (19.8)360 (19.8)3602010-2012204 (19.8)360 (19.8)3602010-2012204 (19.8)360 (19.8)3602010-2012204 (19.8)360 (19.8)3602010-2012204 (19.8)360 (19.8)3602010-2012204 (19.8)360 (19.8)3602010-2012204 (19.8)360 (19.8)360<	18-59	92 (19.0)	101 (20.9)	
275145 (20.5)156 (13.6)22.2Winke382 (7.9.3)396 (13.0)29.0.5020.0.000Black74 (15.3)396 (10.0)20.0.00020.0.000Marikel stans, n(%)	60-74	249 (51.4)	248 (51.2)	
Race, r(s)	≥75	143 (29.5)	135 (27.9)	
WhiteSide (18,8)Side (18,1)Black28 (5.8)28 (5.8)28 (5.8)Other28 (5.8)28 (5.8)28 (5.8)Marliel staus, n(%)	Race, n (%)		× ,	0.222
Black Other'4' (15.3' 28 (5.8)'9 (11)Other28 (5.8)22 (6.9)000000000000000000000000000000000	White	382 (78.9)	396 (81.8)	
Online26 (5.6)27 (16.3)0.500Marrid tours, n(%)310 (64.0)321 (160.3)0.500Narrad174 (16.0, 0)153 (13.3.7)0.0062007 4200157 (128.3)100 (07.2)0.0062007 4200157 (128.3)100 (07.2)0.0062007 4200157 (128.3)207 (12.0)0.004Cade10 (2.0)207 (12.0)0.004Cade20 (45.0)220 (45.0)227 (12.0)Cade20 (45.0)22.0)207 (12.0)0.004Cade21 (12.3)33 (18.0)0.004Cade11 (2.3)33 (18.0)0.004Cade11 (2.3)33 (18.0)0.001Uhrkown214 (14.2)201 (11.3)4.6 (19.0)Stage, n(%)0.0010.00,00.00,0Ill0.002,010 (10.3)4.6 (19.0)Ill0.004,117.1 (1.4)7.1 (1.4)Virkown210 (12.3)4.2 (17.7)Virkown210 (12.3)4.2 (17.7)Tade5.0 (12.3)4.0 (10.0)Uhrkow	Black	74 (15 3)	56 (11 6)	
NamedDefDefDefDefDefNer manned174 (86.0)133 (83.7)10200.60002004 2006177 (82.6.0)100 (07.2.0)0.0002004 2006177 (92.8.1)100 (07.2.0)0.0002010 2012220 (45.0)207 (42.0)0.0002010 2012220 (45.0)207 (42.0)0.0002010 2012220 (45.0)201 (42.0)0.0012013 2012220 (46.0)220 (40.0)0.0012014 2012220 (40.0)220 (40.0)20 (41.0)2014 2012220 (40.0)220 (40.0)20 (41.0)2014 201417 (40.0)0.0010.0002014 201417 (40.0)20 (41.1)77 (40.0)2014 2014270 (45.0)20 (41.0)20 (41.0)10.0010.0010.0010.00110.0100.00120 (41.0)20 (41.0)10.0100.00120 (41.0)20 (41.0)10.0100.00120 (41.0)20 (41.0)10.01177 (40.0)20 (41.0)20 (41.0)110.0020.00120 (40.0)20 (40.0)110.00342 (8.7)20 (40.0)20 (40.0)110.00310.00220 (40.0)20 (40.0)110.00310.00220 (40.0)20 (40.0)110.00310.00220 (40.0)20 (40.0)110.00310.00220 (40.0)20 (40.0)110.00310.00210.003	Other	28 (5.8)	32 (6 6)	
Number (19)         (19) (94.0)         (196.3)         (196.3)           Net manned (19)         (19) (33) (33)         (10) (30)           2007 2009         (19) (78.3)         (10) (77.2)           2010 2012         (20) (10) (10)         (10) (20)           Carda, (16)         (10) (20)         (10) (20)           Universent         (20) (11) (20)         (20) (20)           Universent         (20) (20)         (20) (20)           Universent         (20) (20)         (20)           Universent         (20) (20)         (20)           Carda, (16)         (10) (20)         (20)           Carda, (16)         (10) (20)         (20)	Marital status n (%)	20 (0.0)	02 (0.0)	0.500
Net parside174 (86.0)168 (87.)2004 coords177 (83.0)160 (97.)2004 coords177 (28.0)160 (97.)2010 coords202 (45.0)207 (42.0)2010 coords20 (40.0)10.0.2)2010 coords20 (40.0)10.0.2)Grads, n (%)20 (40.0)10.0.2)Gall20 (40.0)10.0.2)Gall20 (40.0)10.0.2)Gall20 (40.0)30 (66.0)Gall20 (40.0)30 (66.0)Gall11 (2.0)30 (66.0)Gall11 (2.0)30 (66.0)Gall11 (2.0)30 (66.0)Gall11 (2.0)30 (66.0)Gall11 (2.0)30 (66.0)Gall11 (2.0)46 (96.0)Gall11 (2.0)46 (96.0)Gall11 (2.0)46 (96.0)Gall20 (40.1)71 (4.0)Gall20 (40.1)71 (4.0)Gall20 (40.1)71 (4.0)Juli20 (40.1)70 (4.0)Juli20 (40.1)70 (4.0)Juli20 (40.1)70 (4.0)Juli20 (40.1)70 (4.0)Juli20 (40.1)70 (4.0)Juli20 (4.0)10 (4.0) <td>Married</td> <td>310 (64 0)</td> <td>321 (66 3)</td> <td>0.000</td>	Married	310 (64 0)	321 (66 3)	0.000
Num of disposis, n (%)         P(200, 000         P(200, 000           2004-2005         127 (6.2)         180 (67.2)           2016-2012         220 (96.3)         180 (67.2)           2016-2012         220 (96.3)         127 (26.2)           2016-2012         220 (96.3)         127 (26.2)           2016-2012         220 (96.3)         127 (26.2)           2016-2012         23 (48.3)         127 (25.2)           3006         234 (48.3)         237 (40.0)           3006         234 (48.3)         237 (40.0)           Sige, n(%)         (14.4.2)         30 (69.3)           Infracom         210 (46.4)         27 (56.8)           Infracom         210 (46.4)         27 (56.8)           Infracom         201 (45.1)         76 (15.7)           Tatage, n(%)         (201,1)         76 (15.7)           Tatage, n(%)         (201,2)         (201,1)           Tatage, n(%)         (201,2)         (201,1)           Tatage, n(%)         (201,2)         (201,1)           Tatage, n(%)         (201,2)         (201,2)           Unhnown         201 (40,3)         (201,2)           Unhnown         (201,2)         (201,4)           Matatata, not <td>Not married</td> <td>174 (36 0)</td> <td>163 (33 7)</td> <td></td>	Not married	174 (36 0)	163 (33 7)	
Teal or bagin (%)         C.0.00           2004-2006         127 (26.2)         97 (20.0)           2007-2009         137 (28.3)         106 (97.2)           2010-2012         220 (4.5.3)         207 (40.0)           Gal         2 (2.4, 4.6)         1 (2.2, 6.7)           Gal         2 (2.4, 4.6)         1 (2.2, 6.7)           Gal         2 (2.4, 4.6)         2 (2.4, 4.6)           Gal         11 (2.3)         3 (3.6, 8.6)           Unknown         2 (1.4, 4.1)         7 (1.4, 1.6)           V         2 (0.4, 1.1)         7 (1.4, 1.6)           V         2 (0.4, 1.1)         12 (2.6, 1.6)           Unknown         2 (2.4, 6.1)         7 (2.6, 1.6)           T tage, n(%)         7 (1.4, 1.6)         48 (9.9)           T tage, n(%)         7 (1.4, 1.6)         7 (2.6, 1.6)           T tage, n(%)         7 (2.6, 1.6)         49 (2.6, 1.6)           T tage, n(%)         7 (1.4, 1.6)         7 (1.6, 1.6)           T tag	Yoar of diagnosis n (%)	174 (88.8)	100 (00.7)	0.006
Add         12 (22.)         18 (27.2)           207-20.03         13 (26.3)         18 (07.2)           2010-20.12         20 (46.5)         20 (7 (42.8)           Cade, n (%)         0.004         10 (2.3)           Gal         2.04 (40.3)         2.37 (40.0)           Gal         2.04 (40.3)         2.37 (40.0)           Gal         2.04 (40.3)         2.37 (40.0)           Gal         0.00.0         0.00.0           Dispon (%)         0.00.0         0.00.0           I         0.00.0         4.6 (9.3)           III         0.00.0         4.6 (9.3)           III         2.04 (4.1)         7.14,4           Dispon (%)         7.14,4         2.00.01           Takep, n (%)         7.14,1         7.14,1           Unknown<		107 (06 0)	07 (20 0)	0.000
ADV-2008150 (26.3)207 (42.8)0.004Grade, n(%)220 (45.6)27.042.8)0.004G12.00.4111.02.3)2.52.00.001G22.32 (4.8)2.57.043.00.000.00G22.32 (4.8.3)2.57.043.00.000.00G411.02.3)3.3.06.300.00Unknown2.14 (44.2)2.01 (41.5)0.00Stage, n(%)0.00.00.00.00.00.0III0.00.00.00.00.00.0IIII0.00.00.00.00.00.0IIII0.00.17.01.40.00.0Victore Victore Vic	2004-2000	127 (20.2)	97 (20.0)	
Alth2al2Zor (H2.8)Zor (H2.8)Zor (H2.8)G12 (0.4)1 (0.2)0.00G22 (0.4)1 (0.2)33 (0.8)G323 (0.4)33 (0.8)0.00G323 (0.4)201 (0.1)0.00G411 (1.2)33 (0.8)0.00Unixown201 (0.1)0.000.00Stape, n (%)50 (10.3)45 (0.3)0.00Unixown200 (0.1)7 (1.4)7 (1.4)Stape, n (%)200 (0.1)7 (0.5)0.01Tatage, n (%)60 (1.6)48 (0.9)0.01Tatage, n (%)70 (0.5)9 (0.0)0.00Unixown237 (0.0)219 (0.5)0.01Tatage, n (%)70 (0.5)9 (0.0)0.00Unixown237 (0.0)219 (0.5)0.001Tatage, n (%)72 (25.5)127 (25.2)0.001Unixown224 (0.3)208 (0.4)0.001Unixown224 (0.3)208 (0.5)224 (0.3)Unixown232 (0.6)224 (0.3)0.011Unixown232	2007-2009	137 (20.3)	180 (37.2)	
Grade, r(%)UU04G12 (0.4)1 (0.2)G223 (4.8)27 (48.0)G323 (48.3)27 (48.0)G41 (2.3)33 (6.8)Unknown21 (4 (4.2)21 (14.5)Stepe, r(%)rNaN10 (0.0)0.00120 (4.1)7 (1.4)1V20 (4.2.1)7 (1.4)1V20 (4.2.1)7 (1.4)1V20 (4.2.1)7 (1.6)1166 (11.6)48 (9.9)1263 (17.1)76 (15.7)1360 (10.3)42 (8.7)1360 (10.3)42 (8.7)1468 (11.6)99 (20.5)Unknown207 (49.0)219 (45.2)15127 (26.2)40016137 (28.5)149 (30.6)1713106 (21.9)1016 (23.7)106 (21.9)1016 (28.7)20.9010177 (28.5)16 (21.9)1016 (28.7)20.901016 (28.7)20.901016 (28.7)20.901016 (29.8)20.901016 (29.8)20.901016 (29.8)20.901016 (29.8)20.901016 (29.8)20.901016 (29.8)20.901016 (29.8)20.901116 (29.8)20.901216 (29.8)20.901316 (29.8)20.901416 (29.8)20.90 <td< td=""><td>2010-2012</td><td>220 (45.5)</td><td>207 (42.8)</td><td>0.004</td></td<>	2010-2012	220 (45.5)	207 (42.8)	0.004
G12 (0.4)1 (0.2)G22 (4.8)12 (2.3)G3234 (48.3)237 (49.0)G311 (2.3)33 (6.8)Unknown214 (4.2)201 (41.5)Sage, f (%)NameI0 (0.0)0 (0.0)Name50 (10.3)45 (9.3)Ulknown204 (4.1)7 (1.4)V210 (43.4)270 (55.8)Unknown204 (42.1)162 (35.5)Unknown204 (42.1)76 (15.7)Tatage, f (%)65 (11.6)44 (9.0)Tatage, f (%)237 (48.0)24 (42.7)Tatage, f (%)237 (48.0)24 (42.7)Tatage, f (%)237 (48.0)24 (43.7)Unknown237 (48.0)24 (43.7)Unknown237 (48.0)219 (45.2)Tatage, f (%)237 (48.0)219 (45.2)Unknown237 (48.0)219 (45.2)Unknown237 (48.0)219 (45.2)Unknown237 (48.0)219 (45.2)Unknown237 (48.0)219 (45.2)Unknown237 (48.0)219 (45.2)Unknown242 (43.3)208 (49.1)Unknown242 (43.3)208 (49.1)Unknown237 (48.0)214 (42.2)Unknown237 (48.7)243 (44.2)Unknown237 (48.7)244 (42.2)Unknown237 (48.7)244 (42.2)Unknown237 (48.7)244 (42.2)Unknown237 (48.9)277 (15.3)Unknown237 (48.7)244 (42.2)Unkno	Grade, n (%)			0.004
G223 (48)12 (2.5)G323 (48.3)23 (49.0)G411 (2.3)33 (6.3)Stage, n(%)0.0.00.0.0III0.0.00.0.0III0.0.00.0.0III0.0.045 (9.3)V210 (43.4)270 (65.8)Uhrown204 (42.1)162 (33.5)T stage, n(%)7.1.4T56 (11.6)48 (9.9)T1253 (17.1)76 (15.7)T350 (10.3)42 (8.7)T350 (10.3)42 (8.7)T458 (12.0)98 (20.5)Uhrown27 (42.3)27 (42.2)Name, n(%)77 (25.5)127 (82.2)Name, n(%)127 (82.3)100 (21.9)Uhrown137 (82.3)100 (21.9)Mandee seamined, n (%)137 (82.3)100 (21.9)Uhrown137 (82.3)100 (21.9)Uhrown137 (82.3)100 (21.9)More than one137 (82.3)100 (21.9)Uhrown28 (63.5)428 (83.7)Uhrown28 (63.5)16 (33.9)Uhrown28 (63.7)16 (33.9)Uhrown13 (64.7)45 (83.5)Uhrown13 (64.7)46 (85.7)Uhrown13 (64.7)45 (83.7)Uhrown13 (64.7)46 (85.7)Uhrown13 (64.7)46 (85.7)Uhrown13 (64.7)46 (85.7)Uhrown13 (64.7)46 (85.7)Uhrown13 (64.7)46 (85.7)Uhrown13 (64.7)4	G1	2 (0.4)	1 (0.2)	
GG244 (43.)237 (40.0)G411 (2.3)33 (6.8)Unknown214 (4.4.2)201 (41.5)I0 (0.0)0 (0.0)N0 (0.0)0 (0.0)I0 (0.0)0 (0.0)III0 (0.0)0 (0.0)N20 (4.1)7 (1.4)V20 (42.1)12 (3.3)Unknown20 (42.1)12 (3.3)T stage, n (%)48 (0.9)0.011T 16 (1.6)48 (0.9)T233 (17.1)76 (15.7)T350 (10.3)42 (8.7)T458 (12.0)99 (20.5)Unknown27 (40.3)12 (4.5.2)Viknown27 (40.3)12 (4.5.2)N0137 (28.3)106 (21.9)N188 (18.2)149 (30.8)Unknown137 (28.3)106 (21.9)Mon137 (28.3)0.06 (21.9)Mon137 (28.3)0.66 (21.9)Unknown26 (63.5)0.026Non405 (83.5)405 (83.5)Non405 (83.5)0.026Non31 (6.4)42 (8.7)Unknown19 (3.9)16 (3.3)Unknown26 (63.9)0.011Unknown26 (63.9)0.011Non19 (3.9)16 (3.3)Unknown19 (3.9)16 (3.3)Unknown19 (3.9)16 (3.3)Unknown19 (3.9)16 (3.3)Unknown19 (3.9)16 (3.3)Unknown19 (3.9)16 (3.3)Unknown19 (3.9)	G2	23 (4.8)	12 (2.5)	
G411 [2,3]33 (6.8)Unknown14 [4.42)20 (14.1.5)Stage, n (%)0 (0.0)NaNII0 (0.0)0 (0.0)II0 (0.0)45 (6.3)III20 (4.1)7 (1.4)V20 (4.2)162 (3.5)Unknown20 (4.2)162 (3.5)T stage, n (%)0 (1.6)48 (6.9)T 156 (11.6)48 (6.9)T 283 (7.1)76 (15.7)T350 (10.3)42 (6.7)T450 (10.3)42 (6.7)T450 (10.3)42 (6.7)T450 (10.3)42 (6.7)T450 (10.3)42 (6.3)Unknown237 (40.0)219 (45.2)Unknown237 (40.0)219 (45.2)T481 (15.2)140 (0.08)Unknown24 (4.39)206 (4.9)T576 (5.7)70 (2.9)N0172 (5.5)127 (26.2)N188 (15.2)140 (0.08)Unknown224 (4.39)206 (4.9)M0172 (5.5)100 (2.9)M1168 (4.7)214 (42.2)Unknown24 (6.12)0.00M0163 (3.7)0.02M019 (3.9)16 (3.3)Unknown32 (6.6)22 (6.7)M019 (3.9)16 (3.3)M043 (89.7)422 (87.2)N063 (3.1)125 (25.8)Unknown19 (2.9)33 (7.0)M010 (2.9)103 (7.1)M010 (2.9)33 (7.0)<	G3	234 (48.3)	237 (49.0)	
Unknown2/4 (4.2)2/1 (4.5)NaNI0 (0.0)0 (0.0)NaNI0 (0.0)0 (0.0)NaNIII0 (0.0)45 (0.3)NanIIII2/0 (61.2)2/0 (65.8)NanV2/0 (42.1)102 (33.5)NanT stage, n (%)76 (11.6)48 (0.9)NanT283 (17.1)76 (15.7)NanT305 (10.3)42 (6.7)NanT456 (12.0)99 (20.5)NanValue Non27 (40.0)219 (45.2)NanNo72 (5.5)127 (26.2)NanNan86 (18.2)146 (30.8)NanNand137 (26.3)106 (21.9)NanNand137 (26.3)106 (21.9)NanNan137 (26.3)106 (21.9)Nan </td <td>G4</td> <td>11 (2.3)</td> <td>33 (6.8)</td> <td></td>	G4	11 (2.3)	33 (6.8)	
Stage, n(%)0(0,0)0,0,0)0,0,0)II0(0,0)0(0,0)0(0,0)II50(10,3)45(0,3)0V210 (43,4)270 (53,8)0Unknown20 (42,1)120 (53,8)0Tatage, n(%)8(1,0)48(0,9)0T250(10,3)42 (8,7)0T350(10,3)42 (8,7)0T450(10,3)42 (8,7)0T450(10,3)42 (8,7)0T450(10,3)42 (8,7)0T450(10,3)42 (8,7)0T450(10,3)42 (8,7)0T450(10,3)42 (8,7)0T450(10,3)42 (8,7)0T450(10,3)127 (26,2)0Unknown237 (40,0)127 (26,2)0No137 (28,3)106 (21,9)0Unknown24 (43,2)126 (44,2)0Unknown24 (43,2)126 (44,2)0Unknown168 (34,7)214 (44,2)0Unknown169 (23,7)124 (44,2)0Unknown24 (63,7)214 (44,2)0Unknown24 (63,7)124 (44,2)0Unknown34 (63,7)124 (44,2)0Unknown34 (63,7)124 (44,2)0Unknown34 (63,7)124 (44,2)0Unknown34 (63,7)124 (44,2)0Unknown34 (63,7)124 (44,2)0Unknown34 (63,7)124 (4	Unknown	214 (44.2)	201 (41.5)	
I0 (0.0)0 (0.0)II0 (0.1)45 (0.3)III20 (4.1)7 (1.4)V210 (43.4)270 (65.8)Unknown204 (42.1)162 (33.5)T stage, n(%)76 (15.7)58 (17.0)7283 (17.1)76 (15.7)7358 (12.0)99 (20.5)7458 (12.0)99 (20.5)7458 (12.0)99 (20.5)7577 (25.5)177 (26.2)7471 (19.6)72 (35.5)7472 (35.5)177 (26.2)7574 (19.0)72 (35.5)7674 (19.0)72 (35.3)7673 (28.3)106 (21.9)76137 (28.3)106 (21.9)7774 (19.7)74 (14.2)7879 (27.0)164 (33.9)7979 (7.0)70 (14.8)7970 (14.8)70 (14.8)7071 (18.9)70 (18.9)7071 (18.9)70 (18.9)7071 (18.9)70 (18.9)7071 (18.9)70 (18.9)7070 (18.9)70 (18.9)7070 (18.9)70 (19.9)7170 (18.9)70 (19.9)7270 (18.9)70 (19.9)7370 (19.9)70 (19.9)7470 (19.9)70 (19.9)7470 (19.9)70 (19.9)7570 (19.9)70 (19.9)7671 (19.9)70 (19.9)7470 (19.9)70 (19.9)7470 (19.9)70 (19.9)	Stage, n (%)			NaN
IISO (10.3)45 (9.3)III20 (4.1)7 (1.4)V210 (43.4)270 (55.8)Unknown204 (42.1)152 (35.5)Tstage, n (%)56 (11.6)48 (9.9)T156 (11.6)48 (9.9)T263 (12.0)99 (20.5)T350 (10.3)42 (8.7)T463 (12.0)99 (20.5)Unknown237 (49.0)219 (45.2)T575 (49.2)128 (43.2)No77 (35.5)127 (80.8)Name24 (43.2)208 (43.1)Unknown179 (25.3)106 (21.9)Name137 (28.3)106 (21.9)Name137 (28.3)106 (21.9)Name137 (28.3)106 (21.9)Mon137 (28.3)405 (83.5)Unknown137 (28.3)405 (83.5)Unknown23 (6.6)24 (4.2)Unknown24 (63.7)57 (11.8)Unknown23 (6.6)24 (4.5)Unknown24 (63.7)57 (11.8)Unknown24 (63.7)65 (13.4)More than one13 (6.4)46 (9.5)Unknown24 (63.7)65 (13.4)One13 (6.4)46 (13.7)Unknown12 (24.5)10.12Unknown13 (26.9)37 (7.6)Unknown14 (20.7)57 (11.8)Unknown13 (6.4)48 (17.1)Unknown14 (26.2)16 (23.7)Unknown14 (26.2)16 (25.7)Unknown12 (26.2)16 (25.7)Unknown	1	0 (0.0)	0 (0.0)	
III20 (4.1)7 (1.4)IV210 (43.4)270 (55.8)Unknown204 (42.1)162 (35.5)T stage, 1(%)76 (15.7)76 (15.7)T283 (17.1)76 (15.7)T456 (12.0)99 (20.5)Unknown250 (49.2)219 (45.2)T458 (12.0)99 (20.5)Unknown172 (35.5)127 (26.2)N88 (18.2)149 (20.8)Unknown172 (35.5)149 (20.8)Unknown179 (37.0)168 (37.7)Stage, 1(%)179 (37.0)168 (37.7)Unknown179 (37.0)168 (39.7)Unknown179 (37.0)168 (39.7)Unknown199 (39.9)168 (39.7)Unknown199 (39.9)168 (39.7)Unknown199 (39.9)168 (39.7)Unknown129 (29.7)168 (29.7)Unknown129 (29.7)168 (29.7)Unknown129 (29.7)168 (29.7)Unknown129 (29.7)168 (29.7)Unknown129 (29.7)169 (29.7)Unknown126 (29.7)168 (29.7) </td <td>11</td> <td>50 (10.3)</td> <td>45 (9.3)</td> <td></td>	11	50 (10.3)	45 (9.3)	
N         210 (43.4)         270 (65.6)           Unknown         204 (42.1)         162 (83.5)           T stage, (%)         0.011           T1         56 (1.6)         48 (9.9)           T2         63 (17.1)         76 (15.7)           T3         50 (10.3)         42 (8.7)           T4         58 (12.0)         99 (20.5)           Unknown         237 (49.0)         219 (45.2)           No         727 (25.5)         127 (26.2)           N1         88 (18.2)         149 (60.8)           Unknown         127 (26.3)         08 (49.1)           Unknown         137 (28.3)         060 (21.9)           M1         68 (34.7)         214 (44.2)           Unknown         137 (28.3)         060 (21.9)           M2         137 (28.3)         045 (83.5)           M1         168 (34.7)         214 (44.2)           Unknown         137 (28.3)         045 (83.5)           Unknown         137 (28.3)         045 (83.5)           Unknown         24 (43.9)         214 (44.2)           Unknown         137 (28.3)         045 (83.5)           Unknown         137 (28.3)         045 (83.5)           Unknown		20 (4.1)	7 (1.4)	
Unknown     204 (42.1)     16 2 (33.5)       T stage, n (%)     0.011       T1     66 (11.6)     48 (9.9)       T2     83 (17.1)     76 (15.7)       T4     56 (12.0)     99 (20.5)       Unknown     237 (40.0)     219 (45.2)       Value     74     58 (12.0)     99 (20.5)       Unknown     237 (40.0)     219 (45.2)     0.001       Natage, n (%)     72 (25.5)     127 (26.2)     0.001       Natage, n (%)     224 (43.9)     208 (49.1)     0.001       Unknown     224 (43.9)     208 (49.1)     0.001       M1     168 (34.7)     214 (44.2)     0.001       Mono     172 (25.5)     166 (21.9)     0.001       M1     168 (34.7)     214 (44.2)     0.001       M1     168 (34.7)     214 (44.2)     0.001       Mono     129 (30.1)     166 (21.9)     0.001       M1     168 (35.7)     428 (49.7)     0.012       None     405 (83.5)     405 (83.5)     0.012       None     199 (3.9)     168 (3.3)     0.012       None     199 (3.9)     168 (3.3)     0.012       None     199 (3.9)     168 (3.3)     0.012       None     199 (3.9)     168 (3.9) <td< td=""><td>IV</td><td>210 (43.4)</td><td>270 (55.8)</td><td></td></td<>	IV	210 (43.4)	270 (55.8)	
Tatage, n (%)       0.011         T1       56 (11.6)       48 (9.9)         T2       38 (17.1)       76 (15.7)         T3       50 (10.3)       42 (8.7)         T4       58 (12.0)       99 (20.5)         Unknown       237 (49.0)       219 (45.2)         N 100       172 (25.5)       177 (26.2)         N1       88 (18.2)       149 (30.8)         Unknown       224 (43.9)       206 (40.1)         M 10       157 (25.3)       177 (26.2)         N1       88 (18.2)       149 (30.8)         Unknown       224 (43.9)       206 (40.1)         M 11       168 (34.7)       214 (42.2)         Unknown       179 (37.0)       164 (33.9)         M1       168 (34.7)       214 (42.2)         Unknown       179 (37.0)       164 (33.9)         Unknown       179 (37.0)       164 (33.9)         Unknown       22 (6.6)       22 (4.5)         Unknown       23 (6.6)       22 (4.5)         Unknown       43 (89.7)       42 (87.2)         Unknown       43 (89.7)       42 (87.2)         Unknown       16 (3.3)       10.12         Unknown       43 (89.7) <t< td=""><td>Unknown</td><td>204 (42 1)</td><td>162 (33.5)</td><td></td></t<>	Unknown	204 (42 1)	162 (33.5)	
Top         Constraint of the second sec	T stage n (%)	201 (1211)	102 (0010)	0.011
11       36 (17.)       76 (15.7)         72       36 (17.1)       76 (15.7)         73       50 (10.3)       42 (8.7)         74       56 (12.0)       99 (20.5)         Unknown       237 (49.0)       219 (45.2)         N       58 (12.2)       149 (30.8)         Unknown       227 (26.5)       127 (26.5)         N1       88 (18.2)       149 (30.8)         Unknown       208 (49.1)       0.001         M5 dage, n(%)       106 (21.9)       0.005         M1       168 (34.7)       214 (44.2)         Unknown       179 (37.0)       164 (33.9)       0.005         M1       168 (34.7)       214 (44.2)       0.005         M1       168 (34.7)       214 (44.2)       0.005         None       137 (28.3)       106 (21.9)       0.005         M1       168 (34.7)       214 (45.2)       0.05         Unknown       179 (37.0)       164 (33.9)       0.016         Unknown       22 (6.5)       22 (4.5)       0.018         None       19 (3.9)       16 (3.3)       0.018         None fun one       13 (6.4)       46 (9.5)       0.012         Unknown       23 (	T1	56 (11 6)	(18 (0 0)	0.011
Ta         Sol (Th.)         To (SA)           T3         Sol (Th.)         To (SA)           T4         S6 (12.0)         99 (20.5)           Unknown         237 (49.0)         219 (45.2)           N stage, n (%)	T2	83 (17.1)	76 (15 7)	
13       30 (10.3)       12 (27)         74       58 (12.0)       99 (20.5)         Unknown       237 (49.0)       219 (45.2)         N stage, n (%)       172 (35.5)       127 (26.2)         N1       88 (18.2)       149 (30.8)         Unknown       224 (43.9)       208 (49.1)         M stage, n (%)       172 (35.5)       106 (21.9)         M stage, n (%)       106 (21.9)       0.006         M0       137 (28.3)       106 (21.9)         M1       168 (34.7)       214 (44.2)         Unknown       179 (37.0)       164 (33.9)         More than one       47 (9.7)       57 (11.8)         Unknown       32 (6.6)       22 (4.5)         Unknown       32 (8.6)       33 (1.1)         Unknown       434 (89.7)       422 (87.2)         Unknown       434 (89.7)       422 (87.2)         0.4.0       65 (13.4)       63 (17.1)         0.4.0       43 (8.9)       37 (7.6)         0.4.0       43 (8.9)       37 (7.6)	T2	50 (17.1)	40 (8 7)	
14     36 (12.0)     99 (0.03)       Unknown     237 (49.0)     219 (45.2)       N stage, n (%)     72 (35.5)     127 (26.2)       N1     88 (18.2)     149 (30.8)       Unknown     224 (43.9)     208 (49.1)       M stage, n (%)     62 (1.9)     0.006       M stage, n (%)     168 (34.7)     214 (42.2)       Unknown     168 (34.7)     214 (42.2)       Unknown     179 (37.0)     164 (33.9)       Lymph nodes examined, n (%)     0.005 (83.5)     005 (83.5)       More than one     47 (9.7)     57 (11.8)       Unknown     32 (6.6)     22 (4.5)       Unknown     46 (9.5)     0.012       Unknown     43 (89.7)     42 (67.2)       Unknown     46 (9.5)     0.012       Unknown     43 (8.9)     37 (7.6)       20.0     160 (33.1)     15	13	50 (10.3)	42 (6.7)	
Dirklowin         23 ( 19.0)         219 (45.2)           Natage, n (%)		58 (12.0) 007 (40.0)	99 (20.5)	
No         172 (35.5)         127 (26.2)           N1         88 (18.2)         149 (30.8)           Unknown         224 (43.9)         208 (49.1)           Motage, n (%)         000 (49.1)         000           Motage, n (%)         137 (28.3)         106 (21.9)           M1         168 (34.7)         214 (44.2)           Unknown         179 (37.0)         164 (33.9)           Lymph nodes examined, n (%)         405 (83.5)         000           None         405 (83.5)         22 (4.5)           None         32 (6.6)         22 (4.5)           Unknown         32 (6.6)         22 (4.5)           None         434 (89.7)         457 (11.8)           Unknown         32 (6.6)         22 (4.5)           Unknown         32 (6.6)         22 (4.5)           Unknown         32 (6.6)         20 (8.2)           None         31 (6.4)         46 (9.5)           Unknown         32 (6.6)         20 (8.2)           Unknown         39 (16.3)         012           0.40         63 (13.4)         45 (9.5)           Unknown         39 (16.3)         012           0.43 (89.7)         77 (6.5)         0012	Unknown	237 (49.0)	219 (45.2)	
N0         1/2 (35.5)         127 (26.2)           N1         88 (18.2)         149 (30.8)           Unknown         224 (43.9)         208 (49.1)           M stage, n (%)         224 (43.9)         208 (49.1)           M stage, n (%)         166 (21.9)         M1           M 100         137 (28.3)         106 (21.9)           M1         168 (34.7)         214 (44.2)           Unknown         179 (37.0)         164 (33.9)           Symph nodes examined, n (%)         0         65 (83.5)           None         405 (83.5)         405 (83.5)           More than one         47 (9.7)         57 (11.8)           Unknown         22 (4.5)         1.88           None         19 (3.9)         16 (3.3)           More than one         19 (3.9)         16 (3.3)           Unknown         31 (6.4)         46 (9.5)           Unknown         43 (89.7)         422 (87.2)           Out, n (%)         0 (18.6)         76 (15.7)           10.1-20.0         43 (8.9.7)         33 (7.0.1)           2.20.0         160(33.1)         125 (25.8)           Unknown         126 (26.0)         163 (37.7)           2.20.0         160(23.7)	N stage, n (%)			<0.001
N1     88 (18.2)     149 (30.8)       Unknown     224 (43.9)     208 (49.1)       Mstage, n(%)     0.006       M0     137 (28.3)     106 (21.9)       M1     168 (34.7)     214 (44.2)       Unknown     179 (37.0)     164 (33.9) <b>Lymph nodes examined, n (%)</b> 405 (83.5)     405 (83.5)       More than one     405 (83.5)     405 (83.5)       Unknown     32 (6.6)     22 (4.5)       Unknown     32 (6.6)     22 (4.5)       Unknown     31 (6.4)     46 (9.5)       More than one     13 (6.4)     46 (9.5)       Unknown     434 (89.7)     422 (87.2)       Unknown     166 (33.4)     83 (17.1)       4.1-10.0     90 (18.6)     76 (15.7)       10.1-22.0     43 (89.9)     37 (7.6)       >20.0     160 (33.1)     125 (25.8)       Unknown     126 (26.0)     163 (33.7)       Cryporostatectomy     2 (0.4)     0 (0)       Laser ablation     0 (0)	NO	172 (35.5)	127 (26.2)	
Unknown     224 (43.9)     208 (49.1)       M stage, n (%)     0.006       M stage, n (%)     137 (28.3)     106 (21.9)       M1     168 (34.7)     214 (44.2)       Unknown     168 (34.7)     214 (44.2)       Unknown     168 (35.7)     405 (83.5)       Kone     405 (83.5)     405 (83.5)       More than one     47 (9.7)     57 (11.8)       Unknown     32 (6.6)     22 (4.5)       Lymph nodes positive, n (%)     7 (9.7)     6.18       None     19 (3.9)     16 (3.3)       More than one     19 (3.9)     16 (3.3)       Unknown     434 (89.7)     422 (87.2)       Unknown     10 (10.1)     10 (10.2)       Sa (grid     33 (17.1)     10.1       Unknown     126 (26.0)     163 (33.7)       Unknown     126 (26.0)     163 (33.7)       Unknown     126 (26.3)	N1	88 (18.2)	149 (30.8)	
Mstage, n (%)         0.00 (137 (28.3)         1.06 (21.9)           M1         1.68 (34.7)         2.14 (44.2)           Unknown         1.79 (37.0)         1.64 (33.9)           Lymp nodes examined, n (%)         0.05 (83.5)         0.00           None         4.05 (83.5)         0.05 (83.5)           More than one         4.7 (9.7)         5.7 (11.8)           Unknown         32 (6.6)         22 (4.5)           Lymp nodes positive, n (%)         32 (6.6)         22 (4.5)           None         1.9 (3.9)         1.6 (3.3)           More than one         1.9 (3.9)         1.6 (3.3)           More than one         31 (6.4)         46 (9.5)           Unknown         33 (6.4)         46 (9.5)           Unknown         4.6 (9.5)         0.01           O4.0         65 (13.4)         46 (9.5)           Unknown         4.0 (0)         0.01           4.1-10.0         90 (18.6)         76 (15.7)           10.1-20.0         43 (8.9)         37 (7.6)           >20.0         160 (33.1)         125 (25.8)           Unknown         126 (26.0)         163 (3.7)           Strapp	Unknown	224 (43.9)	208 (49.1)	
M0     137 (28.3)     106 (21.9)       M1     188 (34.7)     214 (44.2)       Unknown     179 (37.0)     164 (33.9)       Lymph nodes examined, n (%)     0.245       None     405 (83.5)     405 (83.5)       More than one     47 (9.7)     57 (11.8)       Unknown     32 (6.6)     22 (4.5)       Lymph nodes positive, n (%)     0.188     0.188       None     19 (3.9)     16 (3.3)       More than one     19 (3.9)     16 (3.3)       More than one     13 (4.3)     422 (87.2)       Unknown     13 (4.3)     422 (87.2)       None     65 (13.4)     83 (17.1)       0.4.0     65 (13.4)     83 (17.1)       4.1-10.0     90 (18.6)     76 (15.7)       10.1-20.0     43 (8.9.7)     76 (15.7)       >20.0     160(33.1)     125 (25.8)       Unknown     126 (26.0)     103 (33.7)       >20.0     160(33.1)     125 (25.8)       Unknown     126 (26.0)     100       Surgery     0.00     0.01       Cyoprostatectomy     2 (0.4)     0 (0)       Laser ablation     0(0)     2(0.4)       TURP     61(13.2)     106(21.9)       Partial prostatectomy     2(0.4)     10(2) <td>M stage, n (%)</td> <td></td> <td></td> <td>0.006</td>	M stage, n (%)			0.006
M1     168 (64.7)     214 (44.2)       Unknown     198 (63.7)     164 (63.9)       Lymph nodes examined, n (%)     0.5 (83.5)     405 (83.5)       None     405 (83.5)     405 (83.5)       More than one     47 (9.7)     57 (11.8)       Unknown     22 (6.6)     22 (4.5)       Lymph nodes positive, n (%)     70 (11.8)     108 (3.9)       None     19 (3.9)     16 (3.3)       More than one     31 (6.4)     46 (9.5)       Unknown     43 (8.9)     46 (9.5)       Unknown     43 (8.9)     63 (17.1)       O4.0     65 (13.4)     83 (17.1)       4.1-10.0     90 (18.6)     76 (15.7)       10.1-20.0     43 (8.9)     37 (7.6)       >20.0     160(33.1)     126 (25.8)       Unknown     126 (26.0)     163 (3.7)       0.12     126 (26.0)     163 (3.7)       0.12     126 (26.0)     163 (3.7)       0.12     126 (26.0)     163 (3.7)       0.14     126 (26.0)     163 (3.7)       0.15     339 (70.0)     77.6)       20.0     160 (23.1)     126 (25.8)       Unknown     126 (26.0)     160 (3.3.7)       0.15     339 (70.0)     77.6)       20.0     20.4)     0.0)<	MO	137 (28.3)	106 (21.9)	
Unknown     179 (37.0)     164 (33.9)       Lymp hodes examined, n (%)     0.245       None     405 (83.5)     405 (83.5)       More than one     47 (9.7)     57 (11.8)       Unknown     32 (6.6)     22 (4.5)       Lymp hodes positive, n (%)     22 (4.5)     108       None     19 (3.9)     16 (3.3)       More than one     31 (6.4)     46 (9.5)       Unknown     434 (89.7)     422 (87.2)       D4.0     65 (13.4)     83 (17.1)       0.4.0     65 (13.4)     83 (17.1)       0.1.20.0     43 (8.9)     76 (15.7)       10.1-20.0     43 (8.9)     37 (7.6)       >20.0     160 (33.1)     125 (25.8)       Unknown     126 (26.0)     160       Sargery     0.00     0.01       Surgery     0.00     20.4)       Chyporostatectomy     2 (0.4)     0 (0)       Lase rablation     00()     20.4)       TURP     64 (13.2)     106 (21.9)       Partial prostatectomy     2(0.4)     10.2       Radical prostatectomy     40 (0.1)     36(7.4)	M1	168 (34.7)	214 (44.2)	
Lymph nodes examined, n (%)         0.245           None         405 (83.5)         405 (83.5)           More than one         47 (9.7)         57 (11.8)           Lymph nodes positive, n (%)         22 (4.5)         188           None         19 (3.9)         16 (3.3)           More than one         19 (3.9)         16 (3.3)           More than one         31 (6.4)         46 (9.5)           Unknown         43 (8.7)         42 (3.2)           PSA, ng/mL, n(%)         65 (13.4)         83 (17.1)           0.4.0         65 (13.4)         83 (17.1)           1.1.20.0         43 (8.9)         37 (7.6)           >20.0         160 (33.1)         125 (25.8)           Vinknown         126 (26.0)         163 (3.7)           Surgery         0.00         20.4)           No         367 (75.8)         339 (70.0)           Surgers         0.00         20.4)           No         367 (75.8)         339 (70.0)           Lase rablation         0(0)         20.4)           TURP         64 (13.2)         0(0)           Partial prostatectomy         20.4)         1062(1.9)           Partial prostatectomy         20.4)         10.2)	Unknown	179 (37.0)	164 (33.9)	
None         405 (83.5)         405 (83.5)           More than one         47 (9.7)         57 (11.8)           Unknown         32 (6.6)         32 (4.5)           Lymph nodes positive, n (%)          0.18           None         19 (3.9)         16 (3.3)           More than one         31 (6.4)         46 (9.5)           Unknown         434 (89.7)         422 (87.2)           PSA. gr/mL, n (%)          0.012           O4.0         65 (13.4)         83 (17.1)           1.1-0.0         90 (18.6)         76 (15.7)           10.1-20.0         43 (8.9)         37 (7.6)           >20.0         160(33.1)         125 (25.8)           Unknown         126 (27.8)         309 (70.0)           Surgery	Lymph nodes examined, n (%)			0.245
More than one         47 (9.7)         57 (11.8)           Unknown         32 (6.6)         22 (4.5)           Lymph nodes positive, n (%)         0.188           None         19 (3.9)         16 (3.3)           More than one         31 (6.4)         46 (9.5)           Unknown         434 (89.7)         422 (87.2)           PSA, ng/mL, n (%)         0         0.012           0-4.0         65 (13.4)         83 (17.1)           4.1-10.0         90 (18.6)         76 (15.7)           10.1-20.0         43 (8.9)         37 (7.6)           >20.0         160(33.1)         125 (25.8)           Unknown         126 (26.0)         163 (33.7)           No         367 (75.8)         339 (70.0)           20.0         0(0)         2(0.4)         0 (0)           Laser ablation         0(0)         2(0.4)         0(0)           Laser ablation         0(0)         2(0.4)         106(21.9)           Partial prostatectomy         2(0.4)         10(2)           Radical prostatectomy         49(10.1)         36(7.4)	None	405 (83.5)	405 (83.5)	
Uknown       32 (6.6)       22 (4.5)         Lymph nodes positive, n (%)       0.188         None       19 (3.9)       16 (3.3)         More than one       31 (6.4)       46 (9.5)         Uhknown       434 (89.7)       426 (87.2)         PSA, ng/mL, n (%)       0       0.012         O-4.0       65 (13.4)       83 (17.1)         4.1-10.0       90 (18.6)       76 (15.7)         10.1-20.0       43 (8.9)       37 (7.6)         >20.0       160(33.1)       125 (25.8)         Uhknown       126 (26.0)       163 (33.7)         Surgery	More than one	47 (9.7)	57 (11.8)	
Lymph nodes positive, n (%)         0.188           None         19 (3.9)         16 (3.3)           More than one         31 (6.4)         46 (9.5)           Unknown         434 (89.7)         422 (87.2)           PSA, ng/mL, n (%)         0.012           0-4.0         65 (13.4)         83 (17.1)           0.1.20.0         90 (18.6)         76 (15.7)           0.1.20.0         43 (8.9)         37 (7.6)           >20.0         160(33.1)         125 (25.8)           Unknown         126 (26.0)         163 (33.7)           Surgery         0.003           No         367 (75.8)         339 (70.0)           Cryoprostatectomy         2 (0.4)         0 (0)           Laser ablation         0(0)         2(0.4)           TURP         64(13.2)         106(21.9)           Partial prostatectomy         2 (0.4)         10.2)           Radical prostatectomy         49(10.1)         36(7.4)	Unknown	32 (6.6)	22 (4.5)	
None         19 (3.9)         16 (3.3)           More than one         31 (6.4)         46 (9.5)           Unknown         434 (89.7)         422 (87.2)           PSA, ng/mL, n (%)         0.012           0-4.0         65 (13.4)         83 (17.1)           4.1-10.0         90 (18.6)         76 (15.7)           10.1-20.0         43 (8.9)         37 (7.6)           >20.0         160 (33.1)         125 (25.8)           Unknown         126 (26.0)         163 (33.7)           Surgery         0.003         00           No         367 (75.8)         339 (70.0)           Cryoprostatectomy         2 (0.4)         0 (0)           Laser ablation         0(0)         2(0.4)           TURP         64 (13.2)         106 (21.9)           Partial prostatectomy         2 (0.4)         1(0.2)           Radical prostatectomy         49 (10.1)         36(7.4)	Lymph nodes positive, n (%)			0.188
More than one         31 (6.4)         46 (9.5)           Unknown         434 (89.7)         422 (87.2)           PSA, ng/mL, n (%)         0.012           0-4.0         65 (13.4)         83 (17.1)           4.1-10.0         90 (18.6)         76 (15.7)           10.1-20.0         43 (8.9)         37 (7.6)           >20.0         160(33.1)         125 (25.8)           Unknown         126 (26.0)         163 (33.7)           Surgery         0.003         010           No         367 (75.8)         339 (70.0)           Cryoprostatectomy         2 (0.4)         0 (0)           Laser ablation         0(0)         2(0.4)           TURP         64(13.2)         106(21.9)           Partial prostatectomy         2 (0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	None	19 (3.9)	16 (3.3)	
Hole of all o	More than one	31 (6 4)	46 (9 5)	
PSA, ng/mL, n (%)       0.012         0-4.0       65 (13.4)       83 (17.1)         4.1-10.0       90 (18.6)       76 (15.7)         10.1-20.0       43 (8.9)       37 (7.6)         >20.0       160(33.1)       125 (25.8)         Unknown       126 (26.0)       163 (33.7)         Surgery       0.003         No       367 (75.8)       339 (70.0)         Cryoprostatectomy       2 (0.4)       0 (0)         Laser ablation       0(0)       2(0.4)         TURP       64(13.2)       106(21.9)         Partial prostatectomy       2 (0.4)       1(0.2)         Radical prostatectomy       49(10.1)       36(7.4)	Unknown	434 (89 7)	422 (87 2)	
O-4.0         65 (13.4)         83 (17.1)           4.1-10.0         90 (18.6)         76 (15.7)           10.1-20.0         43 (8.9)         37 (7.6)           >20.0         160(33.1)         125 (25.8)           Unknown         126 (26.0)         163 (33.7)           Surgery         0.003           No         367 (75.8)         339 (70.0)           Cryoprostatectomy         2 (0.4)         0 (0)           Laser ablation         0(0)         2(0.4)           TURP         64(13.2)         106(21.9)           Partial prostatectomy         2 (0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	PSA ng/ml n (%)	10 (0011)	.22 (01.12)	0.012
4.1-10.0     90 (18.6)     76 (15.7)       10.1-20.0     43 (8.9)     37 (7.6)       >20.0     160(33.1)     125 (25.8)       Unknown     126 (26.0)     163 (33.7)       Surgery     0.003       No     367 (75.8)     339 (70.0)       Cryoprostatectomy     2 (0.4)     0 (0)       Laser ablation     0(0)     2(0.4)       TURP     64(13.2)     106(21.9)       Partial prostatectomy     2 (0.4)     1(0.2)       Radical prostatectomy     49(10.1)     36(7.4)	0-4.0	65 (13 4)	83 (17 1)	0.012
4. 1-0.0     30 (10.0)     10 (13.7)       10.1-20.0     43 (8.9)     37 (7.6)       >20.0     160(33.1)     125 (25.8)       Unknown     126 (26.0)     163 (33.7)       Surgery     0.003       No     367 (75.8)     339 (70.0)       Cryoprostatectomy     2 (0.4)     0 (0)       Laser ablation     0(0)     2(0.4)       TURP     64(13.2)     106(21.9)       Partial prostatectomy     2 (0.4)     1(0.2)       Radical prostatectomy     49(10.1)     36(7.4)	4 1 10 0	00 (18.6)	76 (15 7)	
10.7200         40 (0.9)         57 (7.0)           >20.0         160(33.1)         125 (25.8)           Unknown         160 (26.0)         163 (33.7)           Surgery         0.003           No         367 (75.8)         339 (70.0)           Cryoprostatectomy         2 (0.4)         0 (0)           Laser ablation         0(0)         2(0.4)           TURP         64(13.2)         106(21.9)           Partial prostatectomy         2 (0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	10.1.20.0	3U (10.0) 30 (10.0)	27 (7 6)	
>20.0         100(33.1)         125 (25.8)           Unknown         126 (26.0)         163 (33.7)           Surgery         0.003           No         367 (75.8)         339 (70.0)           Cryoprostatectomy         2 (0.4)         0 (0)           Laser ablation         0(0)         2(0.4)           TURP         64(13.2)         106(21.9)           Partial prostatectomy         2 (0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	10.1-20.0 > 00.0	43 (0.9)	ST (T.D)	
Onknown         126 (26.0)         163 (33.7)           Surgery         0.003           No         367 (75.8)         339 (70.0)           Cryoprostatectomy         2 (0.4)         0 (0)           Laser ablation         0(0)         2(0.4)           TURP         64(13.2)         106(21.9)           Partial prostatectomy         2 (0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	>20.0	160(33.1)	125 (25.8)	
Surgery         0.003           No         367 (75.8)         339 (70.0)           Cryoprostatectomy         2 (0.4)         0 (0)           Laser ablation         0(0)         2(0.4)           TURP         64(13.2)         106(21.9)           Partial prostatectomy         2(0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	Unknowh	126 (26.0)	163 (33.7)	0.00-
No         367 (75.8)         339 (70.0)           Cryoprostatectomy         2 (0.4)         0 (0)           Laser ablation         0(0)         2(0.4)           TURP         64(13.2)         106(21.9)           Partial prostatectomy         2(0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	Surgery			0.003
Cryoprostatectomy         2 (0.4)         0 (0)           Laser ablation         0(0)         2(0.4)           TURP         64(13.2)         106(21.9)           Partial prostatectomy         2(0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	No	367 (75.8)	339 (70.0)	
Laser ablation         0(0)         2(0.4)           TURP         64(13.2)         106(21.9)           Partial prostatectomy         2(0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	Cryoprostatectomy	2 (0.4)	O (O)	
TURP         64(13.2)         106(21.9)           Partial prostatectomy         2(0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	Laser ablation	O(0)	2(0.4)	
Partial prostatectomy         2(0.4)         1(0.2)           Radical prostatectomy         49(10.1)         36(7.4)	TURP	64(13.2)	106(21.9)	
Radical prostatectomy 49(10.1) 36(7.4)	Partial prostatectomy	2(0.4)	1(0.2)	
	Radical prostatectomy	49(10.1)	36(7.4)	

(Continued)

#### TABLE 4 | Continued

Characteristics	Prostate Adenocarcinoma (n = 484)	NEPC (n = 484)	P value
Radiation			0.046
No	327 (67.6)	310 (64.0)	
Beam radiation	139 (28.7)	166 (34.3)	
Radioactive implants	8(1.7)	3(0.6)	
Combination of beam with implants or isotopes	7(1.4)	1(0.2)	
Radioisotopes	1(0.2)	O(O)	
Radiation method unknown	2(0.4)	4(0.8)	
Chemotherapy			0.479
No	246 (50.8)	234 (48.3)	
Yes	238 (49.2)	250 (51.7)	
Overall mortality			< 0.001
Alive	241 (49.8)	105 (21.7)	
Dead	243 (50.2)	379 (78.3)	
Cause special mortality			< 0.001
Alive	294 (60.7)	141 (29.1)	
Dead	190 (39.3)	343 (70.9)	

PSA, prostate-specific antigen; TURP, Transurethral resection of prostate; NEPC, neuroendocrine prostate cancer.

necessary for the diagnosis of NEPC in the clinic (31, 32). In order to achieve early diagnosis and effective treatment, it will be crucial to confirm feasible biomarkers that can detect the emergence of NEPC transformation during sequential therapies. A further investigation of biological characteristics of NEPC is indispensable to overcome the obstacle of this highly malignant prostate cancer.

The prevalent therapeutic modalities for prostate adenocarcinoma patients mainly include surgical removal of the prostate (radical prostatectomy), or radiation therapy with or without ADT. For early-stage or localized tumors, radical prostatectomy or radiation therapy is potentially effective and safe treatment option (33). ADTs is still first-line treatment for metastatic prostate cancer. However, after initial response to ADT, the tumor develops an androgen-insensitive form known as CRPC (34). ARPIs including abiraterone, enzalutamide, apalutamide and darolutamide have been developed for CRPC treatment. Nevertheless, partial ARPI- resistant CRPC may eventually develop NEPC due to AR- independent mechanisms in prostate cancer.

Our study suggested that the median OS of NEPC patients was only 12 months compared with 42 months of prostate adenocarcinoma patients. The severe invasiveness and the

TABLE 5   Multivariable Cox proportional hazard model.						
Outcomes	NEPC HR (95% CI)	P-value				
Overall survival						
Non-adjusted	23.20 (21.02-25.60)	< 0.001				
Adjust I	19.24 (17.43-21.23)	< 0.001				
Adjust II	6.35 (5.75-7.02)	< 0.001				
PSM	2.78 (2.34-3.31)	< 0.001				
Cancer specific survival						
Non-adjusted	48.08 (43.38-52.29)	< 0.001				
Adjust I	34.65 (31.24-38.43)	< 0.001				
Adjust II	7.70 (6.94-8.56)	< 0.001				
PSM	3.07 (2.55-3.71)	<0.001				

PSM, propensity score matching; NEPC, neuroendocrine prostate cancer. HR, hazard ratios.

delayed diagnosis contributed to the final poor survival outcomes of NEPC. For example, we found that NEPC patients had an extremely high rate of metastasis, accounted for 45.4% of the group. In addition, the proportion of receiving surgery treatment for NEPC patients was significantly lower than prostate adenocarcinoma patients due to patients in advanced stage missing optimal opportunity for surgery. Until now, radical resection and palliative resection are the primary treatment for early NEPC without distal metastasis (35). Currently, the firstline treatment for NEPC is platinum- based chemotherapy, such as a combination of cisplatin and etoposide (36, 37). Cisplatin-or etoposide-based systemic chemotherapies, combined with surgery or radiation is the main therapy for NEPC with metastasis currently (38). The initial response of NEPC to chemotherapy is considerable. Unfortunately, its limitations are obvious: high and short response duration owing to acquired drug resistance (36). However, the effect of systemic treatment is not so satisfactory. Accurate assessment, early diagnosis and timely treatment of NEPC is critical for enhancing the clinical effect and thereby improving the prognosis.

Considering that the poor prognosis of NEPC is overwhelming, the novel effective therapeutic methods aiming at specific targets is warranted to be explored. Currently, emerging molecular targets with in the landscape of NEC differentiation put insight into individual therapy for NEPC. Rearrangement of TMPRSS2-ERG in NEPC was a crucial finding to prove that NEPC is evolved from conventional prostate adenocarcinoma (39). In the progression of evolution, several underlying molecular mechanism function, including loss of AR and tumor suppressors (TP53, PTEN, RB1) and induction of neural programs (39, 40). Especially, activation of mitotic programs such as Aurora kinase A (AURKA) upregulation and MYCN amplification are involved. AURKA, associated with MYCN amplification could regulates the assembly of mitotic spindle apparatus and eventually influences chromosome separation (41, 42). In addition, epigenetics regulation changes play an important role as well. Transcription factor RE1-silencing transcription factor (REST), suppressing neuronal differentiation, was found to be downregulated in 50% NEPC (43). Furthermore,

IEPC Prostate		
Adenocarcinon	HR(95%CI)	Pvalue
20 77	0 40/4 07 0 07	-0.004
89 77	2.48(1.67,3.67)	< 0.001
201 203	2.92(2.28,3.76)	<0.001
111 121	3.12(2.15,5.03)	<0.001
204 044	0.07/0.00.0.40	-0.004
524 311 52 62	2.87(2.36,3.48)	<0.001
52 63	2.27(1.42,3.62)	<0.001
25 27	4.35(2.25,8.43)	<0.001
274 260	267(24522)	-0.001
274 200	2.07(2.10,0.0)	<0.001
127 141	3.20(2.43,4.38)	<0.001
90 94	2 01/1 47 2 75)	~0.001
09 04 132 122	2.01(1.47,2.73)	<0.001
170 197	2.32(2.22,3.03)	<0.001
179 104	3.70(2.7,5.09)	<0.001
13 5	3 25(0 68 15 4)	0 1371
170 101	2 49(2 60 4 51)	~0.001
1/0 101	3.40(2.09,4.31)	<0.001
21 20	2.00(1.05,5.79)	0.0333
195	2.02(2.03,3.37)	<0.001
37 20	3 76(1 0 7 44)	~0.001
57 20	3.70(1.9,7.41)	<0.001 0.1021
0 9 217 200	2.00(0.04, 10.2)	0.1031
217 209 141 155	2.34(1.9,2.07)	<0.001
141 100	0.11(0.04,0.00)	SU.001
41 20	2 00/1 77 5 07)	~0.001
41 50 65 60	2.99(1.11, 3.01)	<0.001
21 24	2.24(1.0,0.04)	<0.001
70 60	3.19(1.0,3.03)	<0.001
19 00 185 001	2.49(1.70,3.52)	<0.001
201	5.40(2.0,4.39)	~0.00T
110 100	274/204 200	~0.004
10 120	2.14(2.04,3.69)	<0.001
107 84 176 407	2.19(1.0,2.99)	<0.001
197	3.33(2.05,4.74)	<0.001
20 70	4 07/0 47 7 47	-0.004
09 12 171 477	4.0/(3.1/,/.4/)	<0.001
1/1 1//	Z.17(1.73,Z.71)	<0.001
141 152	4.72(3.18,0.98)	<0.001
225 225	0.00/0.00.0.40	-0.004
330 335	2.00(2.30,3.48)	<0.001
40 4/	3.9(2.08,7.31)	<0.001
18 19	2.39(1.17,4.88)	0.0166
47 45	0.57/0.04.40.5	0.0000
17 15	3.57(0.94,13.4)	0.0602
31 32	4.37(2.14,8.92)	<0.001
353 354	2.85(2.37,3.41)	<0.001
		0.00
64 62	4.85(3.07,7.66)	< 0.001
63 43	4.21(2.51,7.06)	< 0.001
41 48	4.40(,2.59,7.48	<0.001
90 147	1.43(1.06,1.92)	0.0163
143 101	3.76(2.63,5.38)	<0.001
		_
292 308	2.58(2.12,3.14)	<0.001
109 93	4.04(2.76,5.91)	<0.001
263 271	2.94(2.38,3.64)	< 0.001
138 130	2.59(1.93,3.48)	<0.001
173 171	3.82(2.91,5.01)	<0.001
228 230	2.25(1.8,2.82)	<0.001
2	in OS. NEPC, neuroendocrine pro	in OS. NEPC, neuroendocrine prostate cancer; OS, c

microenvironment changes including endogenous IL-6 expression (44), MMP-9 production and other pro-inflammation cytokines upregulation fulfil complicated and comprehensive function in the process of adenocarcinoma transdifferentiating into NEC (45). Correspondingly, AURKA inhibitor PHA-739358 (danusertib)

was confirmed to be effective on the growth of NE tumor cells and mouse xenograft models (46). This kinase inhibitor is being evaluated in phase II clinical trials and is expected to be applied for individual therapy prospectively in the clinic (46). Besides, other promising therapeutic targets for NEPC are also currently

ge at diagnosis	Total	NEPC	Adenocarcinoma	HR(95%CI)	Pval
	166	89	77	2 44(1 62 3 67)	<0.0
)-74	404	201	203	3 1(2 37 4 04)	<0.0
·5 –	- 232	111	121	4 54(3 22 6 4)	<0.0
ace	- 202		121	1.01(0.22,0.1)	.0.0
hite H	635	324	311	3 16(2 56 3 9)	<0.0
	115	52	63	2 2(1 36 3 58)	0.00
	→ 52	25	27	6 88(3 08 15 3)	<0.00
arital status	- 02	20	21	0.00(0.00,10.0)	.0.0
	534	274	260	2 99(2 37 3 76)	<0.0
t married	- 268	127	141	3 49(2 53 4 82)	<0.0
ar of diagnosis	200	121	141	0.40(2.00,4.02)	-0.0
	173	89	84	2 21(1 57 3 11)	<00
09-2013	- 266	133	133	3 34(2 48 4 5)	<0.0
	- 363	170	184	3 01(2 78 5 5)	<0.0
ade	- 000	115	104	0.01(2.10,0.0)	-0.0
ade	18	13	5		0.08
	H 350	179	181	3 76(2 85 4 07)	~0.00
	41	21	20	204(104307)	0.03
	201	120	20	2.04(1.04,3.97)	20.00
	304	109	190	2.32(2.22,3.00)	<u>∽0.</u> (
age		37	28	13 6(1 13 15 2)	~0.0
	- 05	51	20	5 08(0 02 27 7)	~0.0
	- 10	217	300	3.00(0.93,21.1)	20.00
	420	211	209	2.41(1.94,3)	~0.0
	- 296	141	100	0.85(4.35,10.7)	<0.0
stage		44	20	2 4 4 (4 0 4 6 0 0)	-0.0
	19	41	30	3.44(1.94,0.00)	<0.0
	125	00	60	2.62(1.68,4.09)	<0.0
		31	34	3.42(1.87,0.20)	<0.0
	147	79	68	2.52(1.75,3.62)	<0.0
known	- 386	185	201	3.91(2.86,5.33)	<0.0
stage		440	100	0.44/0.00.4.00	
	- 238	118	120	3.11(2.26,4.29)	<0.0
	191	107	84	2.28(1.64,3.17)	<0.0
known —	3/3	1/6	197	4(2.91,5.49)	<0.0
stage		00	70	7 45(4 05 40 7)	
		89	12	7.45(4.35,12.7)	<0.0
	348	1/1	1//	2.27(1.79,2.86)	<0.0
Known	293	141	152	5.67(3.65,8.8)	<0.0
mph hodes examined	070	005	005	0 40/0 50 0 00	~ ~
ne H	670	335	335	3.18(2.59,3.89)	<0.0
re than one	95	48	47	4.09(2.08,8.01)	<0.0
known	3/	18	19	2.74(1.24,6.05)	0.01
mpn nodes positive		47	45	E 40/4 4 04 5	0.00
ne	32	1/	15	5.19(1.1,24.5)	0.03
	- 63	31	32	4.23(1.99,8.97)	<0.0
known	/0/	353	354	3.15(2.59,3.83)	<0.0
A, ng/mL	-		00	4 00/0 00 0 000	
4.0	126	64	62	4.96(3.06,8.03)	<0.0
-10.0	106	63	43	5.25(2.90,9.51)	<0.0
1-20.0		41	48	5.06(2.87,8.91)	<0.0
0.0	237	90	147	1.42(1.03,1.95)	0.02
known –	244	143	101	4.95(3.28,7.46	<0.0
rgery					_
P#4	600	292	308	2.85(2.31,3.51)	<0.0
s.,	202	109	93	4.7(3.04,7.27)	<0.0
diation					_
	- 534	263	271	3.41(2.7,4.31)	<0.0
s • <b></b> -	268	138	130	2.63(1.92,3.59)	<0.0
nemotherapy					
	344	173	171	4.85(3.53,6.65)	<0.0
S Hereita	458	228	230	2.36(1.87,2.98)	<0.0

Overall survival				Cancer specific	survival		
		HR	P for interaction			HR	P for interaction
Age at diagnosis			0.239	Age at diagnosis	· · · · · ·		0.0568
18-59		2.48(1.67,3.67)		18-59		2.44(1.62,3.67)	
0-74	H	2.92(2.28,3.76)		60-74	H <b>B</b> -1	3.10(2.37,4.04)	
75	- <b>-</b>	3.72(2.75.5.03)		≥75		4.54(3.22.6.40)	
ace			0.2857	Race			0.0511
Vhite	181	2 87(2 36 3 49)	012001	White	H.	3 16(2 56 3 90)	010011
lack		2 27(1 42 3 63)		Black		2 20(1 36 3 58)	
thor		1 25(2 25 9 42)		Other		- 6 99/2 09 15 26)	
	· - ·	4.55(2.25,0.45)	0.0740	Other	-	0.00(3.00, 15.30)	0 4000
iarital status			0.2/16	Marital status			0.4399
arried	-	2.67(2.15,3.31)		Married	H <b>H</b> H	2.99(2.37,3.76)	
ot married	- <b></b>	3.26(2.43,4.38)		Not married	-	3.49(2.53,4.82)	
rade			0.2669	Year of diagnosis			0.0545
2		→ 3.25(0.68,15.41)		2004-2008		2.21(1.57,3.11)	
3	<b>⊢∎</b> →	3.48(2.69.4.51)		2009-2013	<b>⊢≣</b> →	3 34(2 48 4 50)	
4	- <b></b>	2.00(1.05.3.80)		2014-2018		3 91(2 78 5 50)	
nknown	-	2 62(2 03 3 38)		Grade	_	0.01(2.10,0.00)	0.0719
stano	_	2.02(2.00,0.00)	0.4056	62	±	1 00(1 00 1 00)	0.0715
stage		2 00/1 77 5 07)	0.4050	02	T	2 76/2 956 4 07	
		2.99(1.11, 0.01)		03		3.70(2.030,4.97)	
2		2.24(1.50, 5.34)		G4		2.04(1.047,3.97)	
3		3.19(1.80,5.63)		Unknown		2.92(2.229,3.86)	
4		2.49(1.76,3.52)		T stage			0.3822
nknown		3.46(2.60,4.59)		T1	- <b>-</b>	3.44(1.94,6.08)	
stage			0.0817	T2	- <b>-</b>	2.62(1.68,4.09)	
0	H	2.74(2.04,3.69)		T3	<b>-</b>	3.42(1.87,6.26)	
1		2.19(1.61,3.00)		T4		2.52(1.75,3.62)	
nknown		3.55(2.65,4.74)		Unknown		3 91(2 863 5 33)	
vmph nodes examined			0.5556	N stage		0.01(2.000,0.00)	0.0533
one	1 <b>8</b> -1	2 88(2 39 3 48)	0.0000	NO		3 11/2 262 4 201	0.0000
ore than one		3 00(2 09 7 32)		NO NI		2 29(1 64 2 17)	
pknown		2 20(1 17 4 99)				2.20(1.04,3.17)	
	-	2.39(1.17,4.00)	0 4007	Unknown		4.00(2.91,5.49)	
ymph hodes positive	_		0.4827	Lymph nodes examined			0./141
one		3.57(0.94,13.48)		None	HEH	3.18(2.59,3.89)	
ore than one		4.37(2.14,8.93)		More than one		4.09(2.08,8.01)	
nknown	H <b>B</b> 4	2.85(2.37,3.42)		Unknown	-	2.74(1.24,6.05)	
adiation			0.487	Lymph nodes positive			0.616
0	H <b>B</b> -1	2.94(2.38,3.65)		None		→ 5.19(1.10,24,50)	
es	H	2.59(1.93.3.48)		More than one	-	4 23(1 99 8 97)	
	2 4 6 8	10		Linknown		3 15(2 59 3 83)	
0	2 4 0 0	10		Badiation	_	0.10(2.00,0.00)	0 1001
				No	-	2 44/2 70 4 24)	0.1001
				Vee		3.41(2.70,4.31)	
				162		2.034(1.92,3.59)	
				0	2 4 6 8	10	
<b>URE 5</b>   Subgroup analy	sis for interaction b	etween NEPC a	nd potential covari	ates in both OS and CSS. N	IEPC, neuroendoc	rine prostate cand	er; OS, overall
web CSS apport appoint							

undergoing investigation in clinical trials, such as rocalpituzumab tesirine (DLL3 inhibitor) (47), GSK126 (EZH2 inhibitor) (48), and avelumab (immune-checkpoint PDL1 inhibitor) (49). Therefore, the remarkable progress in the molecular mechanism of NEPC established the foundation for the new effective treatment.

Peptide receptor radionuclide therapy (PRRT) is considered a curative and safe treatment option for NEPC (50). NEC cells have a higher expression of somatostatin receptors (SSTRs) than normal cells, which renders SSTR2 a potential target for NEPC treatment. The radiolabelled (Lutetium-177 or Yttrium-90) somatostatin analogues (SSAs) can target SSTR subtypes on the tumor cell surface and cause DNA damage in the cell nucleus which subsequently leads to cell death (51). Currently, 177Lu-DOTATATE or 177Lu-oxodotreotide is registered for the treatment of progressive and advanced grade 1-2 NEPC (50). On the other hand, 177Lu-PSMA-617 targets prostate-specific membrane antigen (PSMA), a cell-surface protein enriched in prostate cancer, which is used to treat metastatic prostate cancer (52). Besides, Radium-223 (223Ra) is another radiopharmaceutical treatment for patients with metastatic castration resistant prostate cancer patients (mCRPC) with symptomatic bone metastases and no known visceral metastatic disease (53). However, no research has showed that 223Ra could be performed in the treatment of NEPC.

De novo NEPC is a rare clinical entity, accounting for approximately 1% of all prostate cancers. Correspondingly,

t-NEPC occurs in 10-17% of patients with CRPC by developing resistance to ADT and/or APRI treatment (54). The managements for the two types of NEPC are not identical and the difference in the details should attract enough attention (55). For locally advanced de novo NEPC, radiation therapy and radical resection are usually recommended. Given that majority of de novo NEPC patients present with distal metastatic disease at diagnosis, platinum-based chemotherapy should be adopted rather than ADT or APRI treatment (56). Previous researched suggested that t-NEPC occur in approximately 30% of metastatic CRPC, which suggests a strong possibility of distal metastasis at diagnosis. Thus, radiation therapy or radical resection is not recommended generally for t-NEPC. Considering prostate adenocarcinoma admixed with extensive neuroendocrine differentiation in t-NEPC, a trial of ADT in combination with cytotoxic chemotherapy is recommended. The chemotherapy regimens for de novo NEPC are usually platinum plus etoposide combinations. However, t-NEPC is frequently treated with docetaxel or a combination of carboplatin plus docetaxel rather than etoposide. Because docetaxel is an effective chemotherapeutic agent both for neuroendocrine and the adenocarcinoma components (56).

Due to the rarity of NEPC, our study conducted a retrospective study enrolling 482 patients with NEPC from the SEER. Thus, based on a large population, we had sufficient cases to make more credible and valuable analyses. Moreover, we provided the latest and comprehensive clinicopathological information of NEPC according to the recent released database. Nevertheless, our study had several limitations. Firstly, the detailed information such as chemotherapy regimens and operational styles were not available from the SEER, which was a severe obstacle for us to estimate the effect of treatment and assess the survival outcomes. Secondly, the retrospective nature of the study caused unavoidable selection biases, although PSM was performed. Thirdly, the ADT exposure history can't be provided by the SEER. This factor is a critical variable for investigating the issue about adenocarcinoma transdifferentiates into NEC.

# CONCLUSION

The results of our study suggested that the prognosis of NEC was worse than that of adenocarcinoma among prostate cancer patients, even after adjustment for demographic and clinicopathological characteristics by PSM. Subgroup analysis further demonstrated that NEPC patients obtained significantly poorer prognosis than prostate adenocarcinoma patients across nearly all subgroups. Besides, the histological subtype of NEC was an independent prognostic factor for prostate cancer.

# DATA AVAILABILITY STATEMENT

The dataset from SEER database generated and/or analyzed during the current study are available in the SEER dataset repository (https://seer.cancer.gov/).

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# **ETHICS STATEMENT**

The data from SEER are publicly available and de-identified.

# **AUTHOR CONTRIBUTIONS**

JPY: designed this research, completed the data analysis statistics work, and wrote the manuscript. YL: conception and design, collection and assembly of data, and data analysis and interpretation. XL, JS, YZ, and JY: worked in data collection and analysis. MZ: guided all research work, reviewed the manuscript, and provided financial support. All authors contributed to the article and approved the submitted version.

# FUNDING

This work was supported by grants from National Natural Science Foundation of China (U20A20348, 81871646) and Key R & D Projects of Zhejiang Province (2021C03039).

# ACKNOWLEDGMENTS

We acknowledged the efforts of the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of SEER database. Thanks to Liubo Chen, Tingting Xiao and Xujun Zhang for their disinterested support and help.

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