

Clinicopathological characteristics and survival outcomes in neuroendocrine prostate cancer

A population-based study

Jiamin Zhu, MD, MMed^a , Xiao Liang, MD, MMed^a, Dan Wu, MD, MMed^a, Shusen Chen, MD, MMed^b, Baixia Yang, MD, MMed^b, Weidong Mao, MD, MMed^a, Dong Shen, MD, PhD^{a,*}

Abstract

Objective: This study aimed to investigate the clinicopathological features and the survival outcomes of neuroendocrine prostate cancer (NEPC).

Methods: Within the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, we identified a total of 510 patients with NEPC between 2006 and 2015. Age-adjusted incidence rates were evaluated in the study by the SEER*Stat Software version 8.3.6. Kaplan–Meier analysed assessed overall survival (OS) after stratification according to marital status, age, histologic subtype, metastatic status, and treatment. The significant differences were assessed in a log-rank test. Univariate and multivariate cox hazard regression analysis were performed to determine independent predictors of OS.

Results: From a total of 560,124 patients with prostate cancer diagnosed between 2006 and 2015, we identified 510 cases of de novo NEPC. Regarding histology, among all the NEPC, 329 (64.5%) patients were diagnosed as small cell carcinoma, 181 (39.8%) were non-small cell carcinoma. The overall age-adjusted incidence of NEPC statistically significantly increased from 0.321/1,000,000 person-years in 2006 to 0.587/1,000,000 person-years in 2015. The median OS in our study cohort was 9months (95% CI, 8–10months). Multivariate cox regression analysis showed that age, histologic subtype, and stage were independent prognostic factors for NEPC patients. The majority of NEPC (78.2%) were metastatic at diagnosis. In terms of treatment, for metastatic tumor patients, chemotherapy was the most effective therapy. Chemotherapy increased the OS of patients with regional (distant) metastases from 8months (5months) to 13.5 months (9months).

Conclusion: NEPC is extremely rare but the incidence of NEPC has been increasing in the past years. The prognosis of NEPC is poor because most cases are diagnosed at metastatic stage. The patients with metastases are typically treated with chemotherapy and chemotherapy shows survival benefits in both regional and distant metastatic tumor patients.

Abbreviations: AAI = age-adjusted incidence, ADT = androgen deprivation therapy, AURKA = aurora kinase A, HR = hazard ratio, NE = neuroendocrine, NEPC = neuroendocrine prostate cancer, NSCC = non-small cell carcinoma, OS = overall survival, PCa = prostate cancer, RP = radical prostatectomy, RT = radiation therapy, SCC = small cell carcinoma, SEER = surveillance, epidemiology, and end results.

Keywords: incidence, neuroendocrine, prostate cancer, small-cell carcinoma, treatment

1. Introduction

As is reported, prostate cancer (PCa) is the second most common cancer and the sixth leading cause of cancer-related death in males worldwide.^[1,2] Androgen deprivation therapy (ADT) is the

primary treatment for metastatic prostate cancer, which was proposed by Huggins and Hodges^[3] in 1941 based on the androgenic dependence of prostate cancer. Although the early treatment effect has been widely recognized, almost all patients

Editor: Jian-Guo Zhou.

JZ, XL, and WD contributed equally to this work.

This study was sponsored by grants from the General Project of Jiangyin Municipal Health Commission (No. S201803).

The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

^a Department of Oncology, the Affiliated Jiangyin Hospital of Southeast University Medical College, Jiangyin, ^b Department of Radiation Oncology, Nantong Tumor Hospital, Affiliated Tumor Hospital of Nantong University, Nantong, China.

* Correspondence: Dong Shen, Department of Oncology, the Affiliated Jiangyin Hospital of Southeast University Medical College, 163 Shoushan Road, Jiangyin 214400, P.R. China (e-mail: sdshendong@126.com).

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Zhu J, Liang X, Wu D, Chen S, Yang B, Mao W, Shen D. Clinicopathological characteristics and survival outcomes in neuroendocrine prostate cancer: A population-based study. *Medicine* 2021;100:15(e25237).

Received: 27 July 2020 / Received in final form: 2 December 2020 / Accepted: 25 February 2021

<http://dx.doi.org/10.1097/MD.00000000000025237>

receiving ADT will eventually develop castration resistance and further express neuroendocrine markers and progress to neuroendocrine prostate cancer (NEPC).^[4] NEPC is a highly aggressive subtype of castration-resistant prostate cancer, which often results from neuroendocrine (NE) differentiation of prostate cancer cells. Studies have shown that NEPC is mostly caused by ADT.^[5,6] NEPC is a rare entity (<1%) with an incidence of 35 per 10,000 people each year.^[7] It is investigated that 0.5% to 2% of newly diagnosed PCa are classified as NEPC, which is insensitive to all forms of hormone therapy.^[8]

Recent studies have highlighted the rising incidence of NEPC in as many as 15% to 20% of patients with advanced prostate cancer, partly because of the development of resistance to AR pathway inhibitors and the increasing application of ADT therapy. The histopathological characteristics of NEPC are similar to those of other neuroendocrine tumors. According to literature reports, NEPC can be divided into the following types: small cell carcinoma, large cell NEPC, adenocarcinoma with Paneth cells, carcinoid tumors, and adenocarcinoma admixed with neuroendocrine differentiation.^[9] The clinical features of NEPC are as follows: no response to hormone therapy, osteolytic lesions, rapid progress of disease, visceral metastasis, and obvious enlargement of prostate, which plays a disproportionate role in the treatment of metastatic diseases.^[10] NEPC is identified as the most lethal prostate cancer and there is no definitive treatment for this tumor.^[11] Data from recent study showed the median prostate adenocarcinoma survival was 125 months, while the median NEPC survival was only 7 months.^[12]

Because of the lack of a uniform consensus definition based on histology or biomarker expression, NEPC is often missed. Furthermore, as the patients with advanced and metastatic prostate cancer tend not to receive a histological diagnosis, the incidence of NEPC is likely to be underestimated.^[13] Therefore, the incidence of prostate cancer has always been rare. Owing to the rarity of NEPC, the investigations on the molecular mechanism of NEPC and large population-based studies on its clinical features are still limited. Most reports on NEPC are small sample size series or case reports.^[14–17] Inadequate research has limited our ability to make definitive conclusions on clinical course, prognosis, and the most effective treatment. Thus, further studies are needed to increase our understanding of this important disease that may

eventually help find novel therapies. In this case, we attempted to investigate the clinicopathological characteristics of NEPC and morbidity and mortality over time using a national database well suited to this rare disease. In addition, this study was designed to update the survival rate of NEPC and clarify the factors that influence the prognosis of NEPC. Finally, the value of different processing methods in NEPC is illustrated.

2. Material and methods

2.1. Data source and study population

We used the Surveillance, Epidemiology, and End Results (SEER) database that consisted of 18 population-based tumor registries released in November 2018 for this analysis. SEER is registered as approximately 26% of the population of the United States. It is considered to represent the demographic composition of the United States, as well as the cancer incidence and mortality.

Using PCa-specific diagnostic code (International Classification of Disease for Oncology, site code C61.9) combined with specific histology codes for NEPC, we identified histologically confirmed de-novo NEPC cases in the SEER registry from 2006 to 2015. NEPC was identified according to the ICD-0-3/WHO 2008 with the code: 8012, 8013, 8020, 8021, 8041, 8042, 8240, 8246, and 9473. Due to the low incidence and small sample size, we focused on the most common histological subtype of NEPC and small cell carcinoma (SCC). Prostate SCC was identified according to the ICD-0-3/WHO 2008 with the code: 8041/3 Small cell carcinoma, NOS. All histological types in the study group were stratified according to SCC and nonsmall cell carcinoma (NSCC).

2.2. Variable definition

Patient characteristics such as age at diagnosis, race, and marital status were obtained. Tumor characteristics including tumor grade, SEER summary stage, tumor characteristics (histologic type, clinical T stage, nodal status, M stage), etc, were illustrated from the database. We also collected treatment modality such as surgery, chemotherapy, and radiation therapy information.

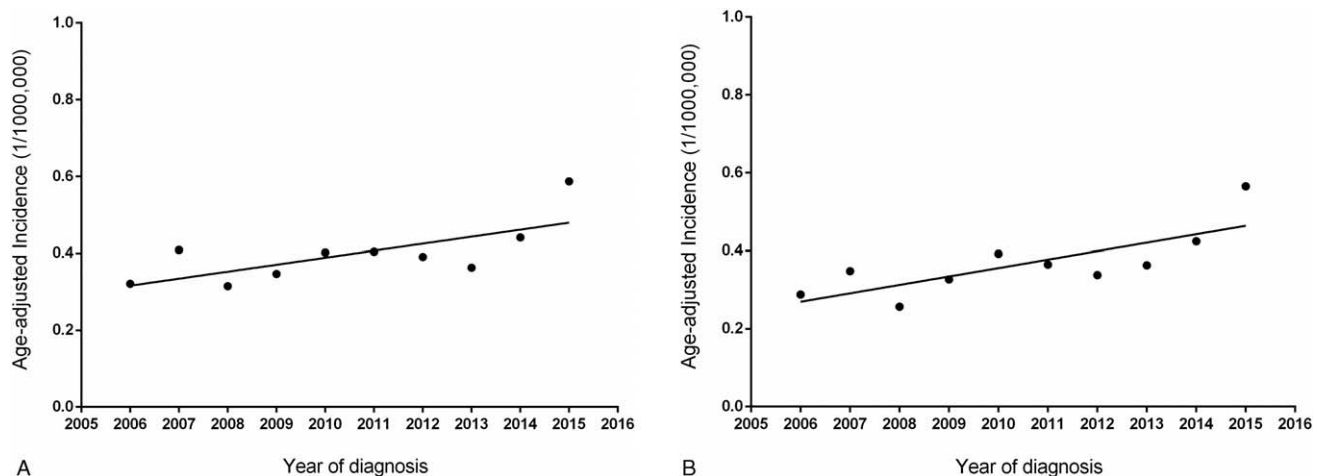


Figure 1. The incidence of NEPC (neuroendocrine prostate cancer) (A) and SCC (small cell carcinoma) prostate patients (B) during 2006 to 2015. NEPC = neuroendocrine prostate cancer.

Table 1**Patient clinical and tumor characteristics.**

Variable	NEPC N = 510 (100%)	SCC N = 329 (64.5%)	NSCC N = 181 (35.5%)	P value
Age				.704
≤70	245 (48%)	156 (30.6%)	89 (17.5%)	
>70	265 (52%)	173 (33.9%)	92 (18.0%)	
Race				.514
Caucasian	421 (82.5%)	271 (53.1%)	150 (29.4%)	
African American	56 (11.0%)	34 (6.7%)	22 (4.3%)	
Other/unknown	33 (6.5%)	24 (4.7%)	9 (1.8%)	
Marital status				861
Single/other	143 (28.0%)	91 (17.8%)	52 (10.2%)	
Married	332 (65.1%)	214 (42.0%)	118 (23.1%)	
Unknown	35 (6.9%)	24 (4.7%)	11 (2.2%)	
Grade				<.01
I	1 (0.2%)	0 (0.0%)	1 (0.2%)	
II	11 (2.2%)	7 (1.4%)	4 (0.8%)	
III	170 (33.3%)	89 (17.5%)	81 (15.9%)	
IV	63 (12.4%)	37 (7.3%)	26 (5.1%)	
Unknown	265 (52.0%)	196 (38.4%)	69 (13.5%)	
AJCC T stage				.377
T0	3 (0.6%)	2 (0.4%)	1 (0.2%)	
T1	66 (12.9%)	44 (8.6%)	22 (4.3)	
T2	119 (23.3%)	79 (15.5%)	40 (7.8%)	
T3	45 (8.8%)	34 (6.6%)	11 (2.2%)	
T4	152 (29.8%)	98 (19.2%)	54 (10.6%)	
Unknown	125 (24.5%)	72 (14.1%)	53 (10.4%)	
Lymph node metastases				.441
N0	210 (41.2%)	142 (27.8%)	68 (13.4%)	
N1	187 (36.7%)	118 (23.1%)	69 (13.6%)	
Unknown	113 (22.2%)	69 (13.5%)	44 (8.5%)	
Distant metastase				.850
M0	170 (33.3)	110 (21.6%)	60 (11.7%)	
M1	293 (57.5%)	187 (36.7%)	106 (20.8)	
Unknown	47 (9.2%)	32 (6.3%)	15 (2.9%)	
Radiation therapy				.325
Yes	160 (31.4%)	106 (20.8%)	54 (10.6%)	
No	350 (68.6%)	223 (43.7%)	127 (24.9%)	
Chemotherapy				<.01
Yes	267 (52.4%)	188 (36.9%)	79 (15.5%)	
No	243 (47.6%)	141 (27.6%)	102 (20.0%)	
Surgery				<.932
Yes	161 (31.6%)	102 (20.9%)	59 (11.7%)	
No	346 (67.8%)	225 (44.1%)	121 (23.7%)	
Unknown	3 (0.6%)	2 (0.4%)	1 (0.2%)	

NEPC = neuroendocrine prostate cancer, NSCC = non-small cell carcinoma, SCC = small-cell carcinoma.

2.3. Statistical analyses

Incidence rates per 100,000 age-adjusted to the population evaluated in the study by the SEER*Stat Software version 8.3.6. Kaplan–Meier analyses assessed overall survival (OS) after stratification according to marital status, age, histologic subtype, metastatic status, and treatment. The significant differences were assessed in a log-rank test. Univariate and multivariate cox hazard regression analysis were performed to determine independent predictors of OS. Only the significant variables from univariate analysis were enrolled in the multivariate analysis. All statistical tests were 2-sided with a level of significance set at $P < .05$. Statistical analysis was performed with SPSS Statistical Package version 20.0.

2.4. Ethical approval

Our study was approved by the Ethics Committee of the Affiliated Jiangyin Hospital of Medical School of Southeast University. The data released by the SEER database do not require informed patient consent because cancer is a reportable disease in every state in the United States.

3. Results

3.1. Patient characteristics

The overall age-adjusted incidence (AAI) of NEPC statistically significantly increased during the study period from 0.321/

Table 2**Univariate and multivariate analyses for OS of patients.**

	Univariable		Multivariable	
	HR (95% CI)	P value	HR(95% CI)	P value
Marital status				
Single/other	Ref.		Ref.	
Married	1.259 (1.023–1.551)	.030	1.271 (1.024–1.577)	.029
Unknown	0.823 (0.562–1.206)	.318	0.936 (0.627–1.396)	.745
Age				
≤70	Ref.		Ref.	
>70	1.512 (1.253–1.823)	<.001	1.652 (1.355–2.015)	<.001
Histologic subtype				
NSCC	Ref.		Ref.	
SCC	0.819 (0.673–0.996)	.045	0.733 (0.600–0.897)	.003
AJCC T stage				
T0	Ref.		Ref.	
T1	0.810 (0.198–3.321)	.770	0.887 (0.213–3.692)	.869
T2	0.743 (0.183–3.017)	.678	0.870 (0.212–3.579)	.848
T3	0.627 (0.151–2.606)	.627	0.739 (0.173–3.158)	.683
T4	0.955 (0.236–3.861)	.955	1.067 (0.259–4.403)	.928
Unknown	0.910 (0.225–3.685)	.910	0.788 (0.192–3.245)	.742
Nodal stage				
N0	Ref.		Ref.	
N1	1.466 (1.183–1.815)	<.001	1.345 (1.053–1.717)	.017
Unknown	1.391 (1.088–1.777)	.008	1.320 (0.969–1.799)	.079
Distant metastase				
M0	Ref.		Ref.	
M1	1.678 (1.361–2.068)	<.001	1.727 (1.346–2.216)	<.001
Unknown	1.155 (0.812–1.644)	.422	0.918 (0.595–1.416)	<.001
Radiation therapy				
Yes	Ref.		Ref.	
No	1.288 (1.053–1.575)	.014	1.072 (0.861–1.335)	.534
Chemotherapy				
Yes	Ref.		Ref.	
No	1.235 (1.024–1.490)	.027	1.525 (1.222–1.903)	<.001

AJCC=American Joint Committee on Cancer, HR=hazard ratio, OS=overall survival.

1,000,000 person-years in 2006 to 0.587/1,000,000 person-years in 2015 (Fig. 1A). As shown in Figure 1B, the AAI of prostate SCC has increased from 0.288/1,000,000 person-years in 2006 to 0.565/1,000,000 person-years in 2015.

Our research provides an overview of the clinical characteristics of NEPC and prostate SCC. From a total of 560,124 patients with PCa diagnosed between 2006 and 2015, we identified 510 cases of de novo NEPC. The mean age was 70 years (median, 71 years; range, 34–96 years). A total of 421 (82.5%) were Caucasian, 56 (11%) were African American, and 33 (6.5%) were others. The majority of patients were married (65.1%). Regarding histology, among all the NEPC, 329 (64.5%) patients were diagnosed as SCC versus 118 (39.8%) were NSCC. All histologic type stratifications of the study cohort were performed according to SCC versus NSCC groupings in Table 1.

In our study, 3 patients (0.6%), 66 patients (12.9%), 119 patients (23.3%), 45 patients (8.8%), and 152 patients (29.8%) had clinical stages of T0, T1, T2, T3, and T4 respectively, while 125 patients (24.5%) did not report clinical stage of T stage. Furthermore, 210 (41.2%) and 187 (36.7%) were clinically staged as N0 and N1, respectively. In 113 (14.2%) patients, the N stage was unknown. Regional invasion or distant metastases were common, with 293(57.5%) distant metastases. In general, these results indicated that NEPC had a

high degree of malignancy, with frequent and extensive metastasis.

3.2. Prognosis factor of NEPC

Univariate and multivariate cox regression results were shown in Table 2. Univariate cox regression analysis suggested that older age (hazard ratio [HR]: 1.652; 95% CI: 1.355–2.015; $P < .05$), SCC (HR: 0.733; 95% CI: 0.600–0.897; $P < .05$), lymph node metastasis (HR: 1.345; 95% CI: 1.053–1.717; $P < .05$), distant metastasis (HR: 1.727; 95% CI: 1.346–2.216; $P < .05$), no chemotherapy (HR: 1.525; 95% CI: 1.222–1.903; $P < .05$) were risk factors for poor prognosis.

3.3. Treatment and prognosis

As for the treatment modalities used, a total of 250 (49%) patients underwent local treatment, either in the form of radiation therapy or radical prostatectomy. For SCC patients, chemotherapy was the primary (57.1%) therapy. Thirty-one percent of patients were treated by surgery, and 32.2% of patients were treated with radiotherapy. Among patients with NSCC, chemotherapy was also the primary (43.6%) therapy. 32.6% of patients were treated by surgery, and 29.8% of patients were treated with radiotherapy.

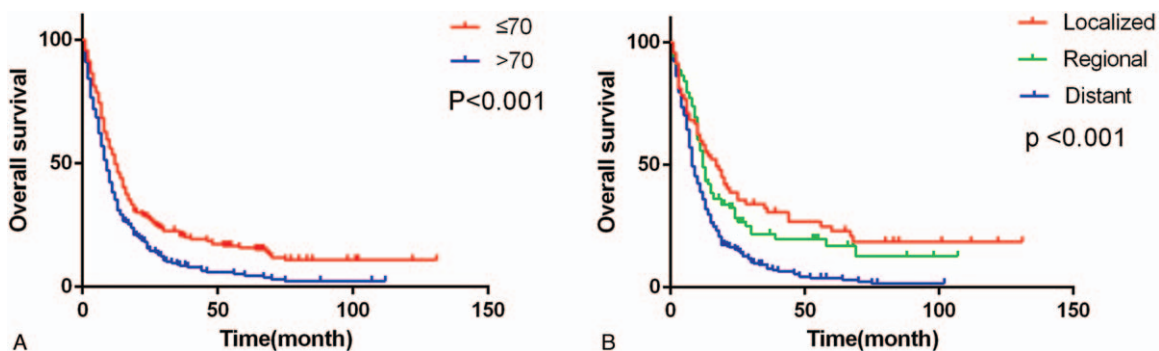


Figure 2. Kaplan–Meier estimated survival curve of patients with NEPC patients. (A) Based on age at the time of diagnosis; (B) based on the summary stage (localized, regional, and distant). NEPC = neuroendocrine prostate cancer.

As shown in Figure 2A, the median OS in our study cohort was 9 months (95% CI, 8–10 months). The median survival of young patients was 12 months, which was better than that of old patients with median survival time of 8 months ($P < .001$). Furthermore, Figure 2B showed the survival was related to summary stage, with median survival of 13 months in localized tumor patients, 12 months in regional tumor patients, and 8 months in distant metastasis patients ($P < .001$). We further analyzed the effect of treatment at different cancer stages (Fig. 3). Different treatment methods had different effects on different summary stage of NEPC patients. For localized tumor patients, radiation therapy was more effective, which could increase the median survival of patients from 10.5 to 25 months.

For regional tumor patients, chemotherapy is the most effective treatment. Chemotherapy could increase the median survival of regional invasion patients from 8 to 13.5 months. Similarly, chemotherapy is the most effective treatment in patients with distant metastases patients, increased the median survival from 5 to 9 months. Unfortunately, surgery showed no significant effect for NEPC when stratified by the summary stage.

3.4. Subgroup analysis

We further analyzed the overall survival of different treatment methods at different stages in the 2 pathological types, SCC and NSCC. Across the entire cohort, our data showed that the SCC

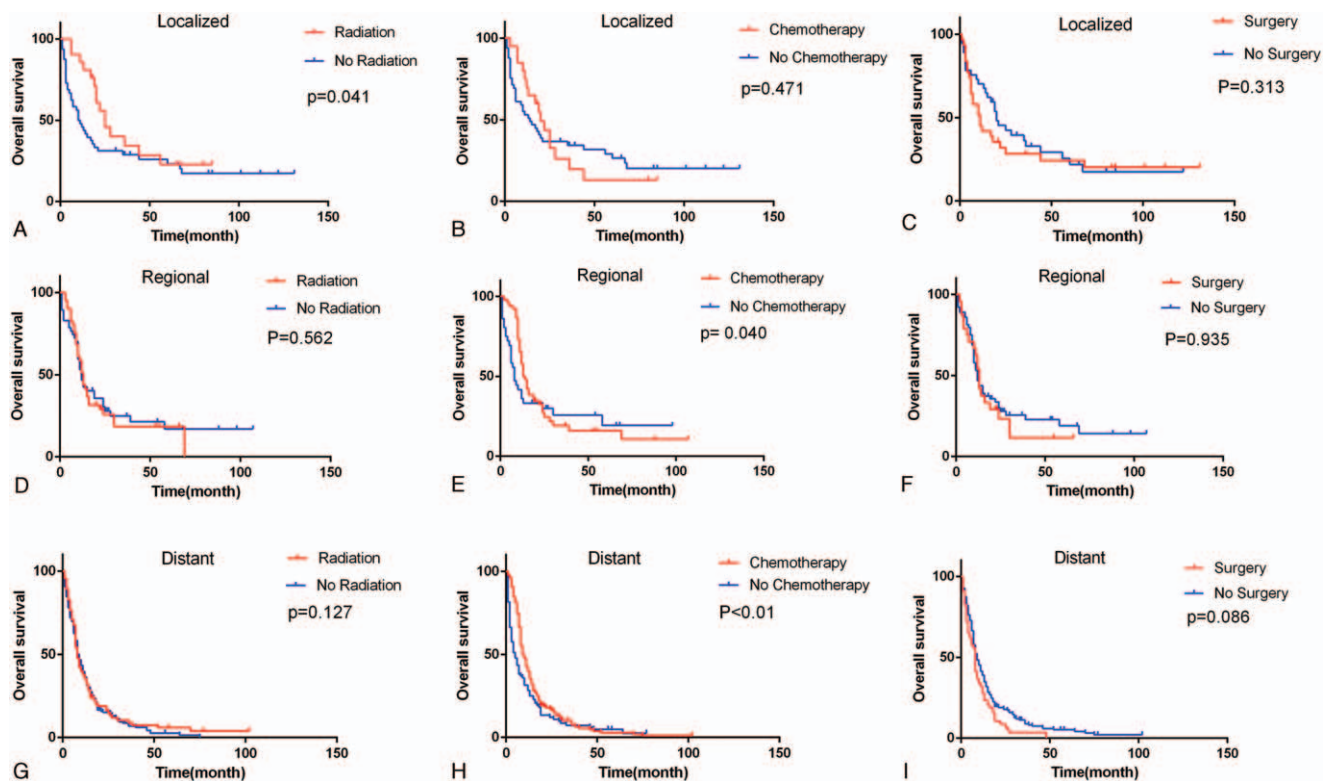


Figure 3. Kaplan–Meier estimated survival curve of patients with NEPC patients based on the summary stage (localized, regional, and distant). A to C, Based on localized NEPC patients: (A) radiotherapy; (B) chemotherapy; (C) surgery. D to F, Based on Regional NEPC patients: (D) radiotherapy; (E) chemotherapy; (F) surgery. G to I, Based on distant NEPC patients: (G) radiotherapy; (H) chemotherapy; (I) surgery. NEPC = neuroendocrine prostate cancer.

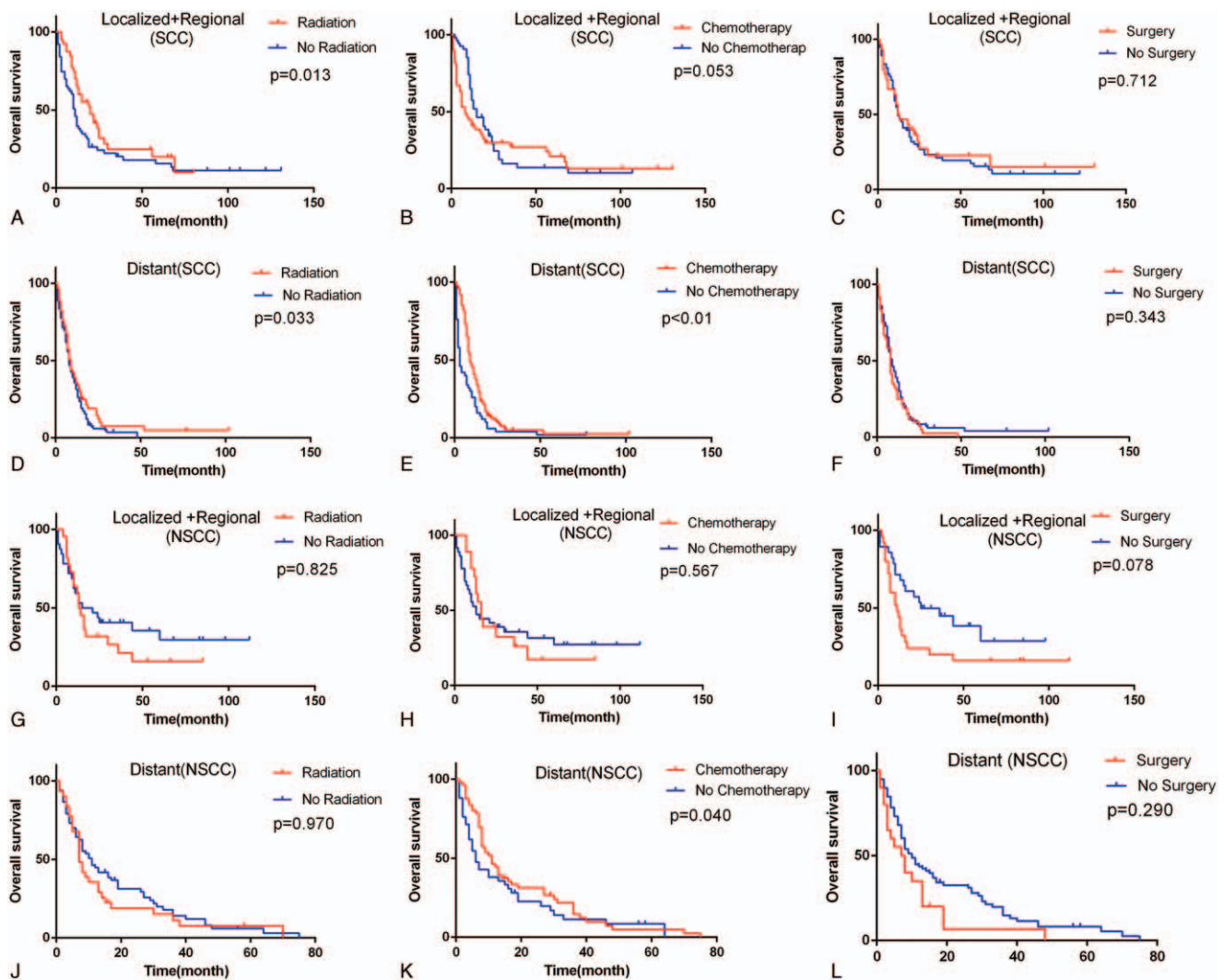


Figure 4. Kaplan–Meier estimated survival curve of patients with SCC patients (A–F) and NSCC prostate patients (G–L). A to C, Based on localized + regional stage: (A) radiotherapy, (B) chemotherapy, (C) surgery. D to F, Based on distant stage: (D) radiotherapy, (E) chemotherapy, (F) surgery. G, H, Based on localized + regional stage: (G) radiotherapy, (H) chemotherapy, (I) surgery. J to L, Based on distant stage: (J) radiotherapy, (K) chemotherapy, (L) surgery. NSCC = nonsmall cell carcinoma.

subtype represented 64.5% of all cases of NEPC. In all patients with NEPC, 59.4% patients were found in distant metastasis stage. In Figure 4 we could conclude that in SCC subtype without distant metastasis, radiation therapy was the most effective, increased the median survival from 8 to 15 months. In SCC subtype with distant metastasis, chemotherapy and radiation therapy showed more effective than surgery. Chemotherapy could increase the median survival from 3 to 9 months and radiation therapy could increase the median survival from 8 to 9 months. Furthermore, in NSCC subtype without distant metastasis, no treatment has been shown to improve survival. In the distant metastasis stage, chemotherapy showed the most effective, which could increase the median survival of patients from 6 to 11 months.

4. Discussion

NEPC is an invasive tumor with aggressive malignancy with poor prognosis.^[18] Current research shows that NEPC is a rare clinical entity, and most investigations in the literature are limited by

extremely small sample sizes. In normal cells, the neuroendocrine phenotype may play a role in regulating the growth and differentiation of epithelial.^[19] However, the neuroendocrine phenotype presented itself in cancer as more aggressive pathological feature, indicating poor clinical outcomes relative to primary neuroendocrine cancers from other organ systems. Our results showed the AAI of NEPC had been increasing in the United States in the past years. Currently, available evidence shows: under specific conditions, such as receiving new highly potent androgen receptor-targeted therapies (like abiraterone and enzalutamide), adenocarcinoma cells could acquire NEC markers and lose AR expression thereby transdifferentiating into NEPC cells.^[20] However, the mechanism by which adenocarcinoma cells acquire the NEPC phenotype is still not fully elucidated. More studies are needed to improve our understanding of this trend.

In terms of treatment type, early radical resection is still the most effective method, even if there is local infiltration, should be radical resection or palliative resection.^[21] As the disease is easy

to metastasize, the vast majority of NEPC are already in advanced stage when they are diagnosed, so they need systemic treatment (mainly chemotherapy) which combined with radiotherapy (or surgery). Cisplatin-based combination chemotherapy is usually used to treat NEPC patients, and the effective rate of chemotherapy is about 50%.^[22] However, the overall treatment effect was still not satisfactory.^[23]

Our report is the most representative of the latest de novo NEPC rate and survival rate data. The data showed that the metastasis rate from the SEER database was 78.2%. Because of the invasiveness of NEPC and the delay in late diagnosis, the median OS in our study was 9 months. In non-metastatic NEPC, the most commonly used treatment was surgery (47.1%), chemotherapy (41.9%) and radiotherapy (36%). Furthermore, chemotherapy was offered to 61.7% of patients with metastatic NEPC, while surgery and radiation accounted for less, 23.8% and 30.7%, respectively. According to our study, in the treatment of NEPC, especially metastatic NEPC, chemotherapy has shown certain efficacy. Our study also shows that patient survival is related to the summary stage. Although radiotherapy and surgery can prolong the overall survival of NEPC patients, the treatment effect is still unsatisfactory, which is related to the fact that most patients have been found to be in the metastatic stage. Accurate identification and early diagnosis of NEPC is very important for clinical treatment and further improve the therapeutic effect. At present, the molecular mechanism of NEPC is still limited, but more and more attention has been paid recently. In terms of targeted drug therapy, the most recognized molecular markers are TMPRSS2-ERG gene fusion, and aurora kinase A (AURKA) gene amplification.^[24] With the in-depth study on the origin and mechanism of neuroendocrine cells, more and more targeted herapeutic drugs such as AURKA inhibitors, mTOR inhibitors and anti epidermal growth factor receptor pathway drugs are used in clinical practice.

We realize that our research has several limitations. Firstly our study was a retrospective analyses, selection bias could not be excluded. Secondly, the number of cases of prostate neuroendocrine cancer is still limited, and more data are expected to be included. Moreover, since SEER database does not provide detailed chemotherapy drugs and radiotherapy plans, we cannot comment on the ideal treatment plans. Additionally, we have no information about ADT exposure. This variable indicates an integral part of analysis where NE differentiation is examined. All of these are worthy of further study. More studies are warranted to increase our understanding of this important disease that may eventually help find novel therapies to this rare disease.

5. Conclusion

Our study of the SEER database is an attempt to understand the clinicopathological characteristics and survival outcome of NEPC. NEPC is extremely rare but the incidence of NEPC has been increasing in the past years. The prognosis of NEPC is poor because most cases are diagnosed at metastatic stage. The patients with metastases are typically treated with chemotherapy, and chemotherapy shows survival benefit in both regional and distant metastatic tumor patients.

Acknowledgment

The authors appreciated the SEER database of the National Cancer Institute for providing the high-quality data.

Author contributions

Conceptualization: Dong Shen.

Data curation: Baixia Yang, Dong Shen.

Formal analysis: Baixia Yang.

Investigation: Jiamin Zhu, Xiao Liang.

Methodology: Xiao Liang.

Project administration: Xiao Liang, Dan Wu, Weidong Mao.

Resources: Dan Wu, Weidong Mao.

Software: Shusen Chen.

Supervision: Shusen Chen, Dong Shen.

Validation: Dan Wu.

Visualization: Dan Wu, Dong Shen.

Writing – original draft: Jiamin Zhu.

Writing – review & editing: Jiamin Zhu.

References

- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68: 394–424.
- Teoh JYC, Hirai HW, Ho JMW, et al. Global incidence of prostate cancer in developing and developed countries with changing age structures. *PLoS One* 2019;14:e0221775.
- Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. *J Urol* 2002;167(2 pt 2):948–51.
- Wang HT, Yao YH, Li BG, et al. Neuroendocrine Prostate Cancer (NEPC) progressing from conventional prostatic adenocarcinoma: factors associated with time to development of NEPC and survival from NEPC diagnosis—a systematic review and pooled analysis. *J Clin Oncol* 2014;32:3383–90.
- Thoreson GR, Gayed BA, Chung PH, et al. Emerging therapies in castration resistant prostate cancer. *Can J Urol* 2014;21(2 suppl 1): 98–105.
- Quicios-Dorado C, Bolufer-Moragues E, Carmen Gomis-Goti C, et al. [Aggressive variants of castration resistant prostate cancer (CRPC): neuroendocrine prostate cancer.]. *Arch Esp Urol* 2018;71: 721–34.
- Aggarwal R, Zhang T, Small EJ, et al. Neuroendocrine prostate cancer: subtypes, biology, and clinical outcomes. *J Natl Compr Canc Netw* 2014;12:719–26.
- Komiya A, Yasuda K, Watanabe A, et al. The prognostic significance of loss of the androgen receptor and neuroendocrine differentiation in prostate biopsy specimens among castration-resistant prostate cancer patients. *Mol Clin Oncol* 2013;1:257–62.
- Hirano D, Okada Y, Minei S, et al. Neuroendocrine differentiation in hormone refractory prostate cancer following androgen deprivation therapy. *Eur Urol* 2004;45:586–92.
- Marcus DM, Goodman M, Jani AB, et al. A comprehensive review of incidence and survival in patients with rare histological variants of prostate cancer in the United States from 1973 to 2008. *Prostate Cancer Prostatic Dis* 2012;15:283–8.
- Kranitz N, Szepesváry Z, Kocsis K, et al. Neuroendocrine cancer of the prostate. *Pathol Oncol Res* 2020;26:1447–50.
- Sargos P, Ferretti L, Gross-Goupil M, et al. Characterization of prostate neuroendocrine cancers and therapeutic management: a literature review. *Prostate Cancer Prostatic Dis* 2014;17:220–6.
- Alanee S, Moore A, Nutt M, et al. Contemporary incidence and mortality rates of neuroendocrine prostate cancer. *Anticancer Res* 2015;35: 4145–50.
- Aljarba SI, Murad M, Bafaquh M, et al. Brain metastasis from large cell neuroendocrine carcinoma of the prostate: a case report and literature review. *Int J Surg Case Rep* 2020;67:245–9.
- Mather RL, Andrews H, Pandha H, et al. The Open University's first one-day symposium on treatment-emergent neuroendocrine prostate cancer. *Future Oncol* 2020;16:147–9.
- Erratum: primary large cell neuroendocrine carcinoma of the prostate in a hormone naive patient: a case report from Taiwan. *J Cancer Res Ther* 2019;15:1425.

- [17] Priftakis D, Kritikos N, Stavrinides S, et al. Neuroendocrine differentiation in castration-resistant prostate cancer: a case report. *Mol Clin Oncol* 2015;3:1392–4.
- [18] Aggarwal R, Huang J, Alumkal JJ, et al. Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study. *J Clin Oncol* 2018;36:2492–503.
- [19] Epstein JI, Amin MB, Beltran H, et al. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. *Am J Surg Pathol* 2014;38:756–67.
- [20] Wang ZA, Toivanen R, Bergren SK, et al. Luminal cells are favored as the cell of origin for prostate cancer. *Cell Rep* 2014;8:1339–46.
- [21] Apostolidis L, Nientiedt C, Winkler EC, et al. Clinical characteristics, treatment outcomes and potential novel therapeutic options for patients with neuroendocrine carcinoma of the prostate. *Oncotarget* 2019;10:17–29.
- [22] Vlachostergios PJ, Papandreou CN. Targeting neuroendocrine prostate cancer: molecular and clinical perspectives. *Front Oncol* 2015;5:6.
- [23] Papandreou CN, Daliani DD, Thall PF, et al. Results of a phase II study with doxorubicin, etoposide, and cisplatin in patients with fully characterized small-cell carcinoma of the prostate. *J Clin Oncol* 2002;20:3072–80.
- [24] Park K, Chen Z, MacDonald TY, et al. Prostate cancer with Paneth cell-like neuroendocrine differentiation has recognizable histomorphology and harbors AURKA gene amplification. *Hum Pathol* 2014;45:2136–43.