Contemporary Incidence and Mortality Rates of Neuroendocrine Prostate Cancer

SHAHEEN ALANEE, AARON MOORE, MAX NUTT, BRADLEY HOLLAND, DANUTA DYNDA, AHMED EL-ZAWAHRY and KEVIN T. McVARY

Division of Urology, Southern Illinois University School of Medicine, Springfield, IL, U.S.A.

Abstract. *Aim: The purpose of the study was to provide an update ever the incidence and mortality for neuroendocrine prostate cancer (NEPC) in the United States. Patients and Methods: Using a large national database, we examined changes in age-adjusted incidence (AAIR), mortality rates (MR) and 5-year cancer-specific survival (CSS) for 378 patients diagnosed with NEPC between 1992 and 2011. Analysis was performed for all NEPC and for its two major sub-groups [small cell carcinoma (SCC) and neuroendocrine carcinoma (NEC)]. Results: AAIR of NEPC continues to rise in recent years (2004-2011:+6.8%/year, p>0.05). AAIR of SCC has been increasing significantly by 6.94%/year since 2001 (from 0.470 to 0.582/1,000,000 person years, p<0.05). Overall incidence-based mortality rates for NEPC did not change significantly since 1992 and similar trends were observed for SCC and NEC. Conclusion: The AAIR of SCC is increasing with no change in the MR of NEPC over the past 20 years.*

The interest in neuroendocrine prostate cancer (NEPC) was rekindled in recent years coinciding with the increased utilization of androgen deprivation therapy (ADT), the introduction of more potent ADT agents and the possible association between ADT and NEPC. This association is supported given that (i) multiple reports have shown that the majority of NEPC have evolved from typical prostatic adenocarcinoma treated with ADT (1), (ii) prostate cancer-specific genetic changes are seen with increasing frequency in NEPC similar to that of prostate adenocarcinoma (1, 2), and (iii) androgen withdrawal is a strong stimulus of neuroendocrine differentiation (2, 3). The low incidence of NEPC, together with its under-recognition due to the general lack of biopsies in advanced prostate cancer, limited reporting on NEPC to small case series only. Under this setting, we sought to examine the incidence and mortality rates of NEPC over time using a national database that is well suited for such rare disease.

Correspondence to: Shaheen Alanee, MD, MPH, Division of Urology, Southern Illinois University School of Medicine, 301 N. Eighth St., St. John's Pavilion, P.O. Box 19665, Springfield, IL 62794, U.S.A. Tel: +1 2175458860, Fax: +1 2175457305, e-mail: salanee@siumed.edu

Key Words: Prostate, prostate cancer, neuroendocrine prostate cancer, androgen deprivation therapy, incidence, 5-year survival, mortality.

Patients and Methods

Data source. Population-based data on cancer incidence were abstracted from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program. The identification of individuals with NEPC diagnosed between 1992 and 2011 were based on 13 cancer registries in the SEER Program and account for approximately 14% of the US population (4). Patients with histologically confirmed cases of neuroendocrine tumors of the prostate (International Classification of Diseases Oncology (ICD-O-3) codes 8012, 8013, 8020, 8021, 8041, 8042, 8240, 8246, 9473, site code C61.9) were abstracted. Analyses were restricted to patients aged ≥18 years old to avoid including pediatric varieties of neuroendocrine tumors of the prostate.

Statistical analyses. Overall incidence, mortality and the 5-year cancer-specific survival (CSS) rates were computed for the entire cohort of patients with NEPC and for major histologic subtypes (ICD-O-3 8041: small cell carcinoma (SCC) and ICD-O-3 8246: neuroendocrine carcinoma (NEC)). Incidence rates and incidence-based mortality rates were adjusted to the 2000 United States standard population and calculated per 1,000,000 person-years. Temporal trends of age-adjusted rates were assessed using joinpoint regression, which involves fitting a series of joined straight lines on a logarithmic scale to the trends in the annual age adjusted rates, and quantified using the annual percent change (APC). Both long-term (1992-2011) and short-term trends were examined. The time frame interval for short-term trends assessment in mortality rates were limited to diagnoses between 1992 and 2006 to allow for at least 5 years of follow-up. All statistical tests were two-sided with a significance level set at 0.05. SEER*Stat 8.1.5, Joinpoint 4.1.1.1 (https://surveillance.cancer.gov/joinpoint/download) and SAS 9.3 were used for the analysis (Cary, NC).

Results

Patients' characteristics. Patients' age, race, disease stage, cause-specific death and treatment (surgery/radiation) are provided in Table I, stratified by disease histology

Table I. *Patients' characteristics by histology, in patients diagnosed with NEPC between 1992 and 2011.*

	LCNE	UC	AC	SCC	OCC	MCT	NEC	PNEc
Frequency	2	31	10	213	2	1	109	1
Age								
18-49	0	0	0	7 (3%)	0	0	7 (6%)	1 (100%)
50-60	2 (100%)	2 (7%)	2 (20%)	26 (12%)	0	0	13 (12%)	0
60-70	0	6 (19%)	3 (30%)	52 (24%)	2 (100%)	0	29 (26%)	0
>70	0	23 (74%)	5 (50%)	128 (61%)	0	1(100%)	60 (56%)	0
Stage								
Localized/regional	0	9 (29%)	2 (20%)	68 (32%)	0	0	40(37%)	1 (100%)
Distant	1 (50%)	8 (26%)	2 (20%)	110 (52%)	2 (100%)	1 (100%)	53 (48%)	0
Blank/Unstaged	1 (50%)	14 (45%)	6 (60%)	35 (16%)	0	0	16 (15%)	0
Race								
White	2 (100%)	19 (61%)	6 (60%)	174 (82%)	1 (50%)	1 (100%)	93 (85%)	1 (100%)
Black	0	8 (26%)	1 (10%)	21 (9%)	1 (50%)	0	10 (9%)	0
American Indian/Alaska								
Native	0	0	0	4 (2%)	0	0	0	0
Asian or Pacific Islander	0	4 (13%)	3 (30%)	12 (6%)	0	0	5 (5%)	0
Unknown	0	0	0	2 (1%)	0	0	1(1%)	0
Cause of Death								
Alive or dead of other cause	1 (50%)	16 (52%)	3 (30%)	90 (42%)	2 (100%)	1 (100%)	35 (32%)	1 (100%)
Attributable to this cancer	1 (50%)	15 (48%)	7 (70%)	126 (58%)	0	0	74 (68%)	0
Surgery								
Performed	1 (100%)	12 (39%)	5 (50%)	63 (29%)	1 (50%)	0	41 (38%)	1 (100%)
Not performed	0	19 (61%)	5 (50%)	150 (71%)	1 (50%)	1 (100%)	68 (62%)	0
Radiation								
Beam Radiation	50%	10 (32%)	3 (30%)	63 (29%)	1 (50%)	0	49 (45%)	0
Radioactive implants	0	0	0	5 (3%)	0	0	1(1%)	0
Radiation, not specified method	0	0	0	2 (1%)	0	0	0	0
Not done/unknown	50%	21 (68%)	7 (70%)	150 (77%)	1 (50%)	1 (100%)	60 (54%)	1 (100%)

LCNE, large cell neuroendocrine; UC, undifferentiated carcinoma; AC, anaplastic carcinoma; SCC, small cell carcinoma; OCC, oat cell carcinoma; MCT, malignant carcinoid tumor; NEC, neuroendocrine carcinoma; PNEc, primitive neuroectoderm.

Incidence. Overall, age-adjusted incidence rates of NEPC decreased significantly by -5.06% /year between 1992 and 2004 (from 0.554 to 0.295/1,000,000 person years, $p<0.05$) but started rising in recent years, although not significantly (2004-2011: +6.75%/year, $p>0.05$) (Figure 1). The incidence rates of SCC showed non-significant fluctuation between 1992 and 2001 (1992-1996 APC=+20.44%/year, $p>0.05$, 1996-2001 APC=–14.63%/year, $p>0.05$) but has been rising significantly by 6.94%/year between 2001 and 2011 (from 0.470 to 0.582/1,000,000 person years, $p<0.05$) (Figures 2a and 2b), while no significant change was observed in the incidence rates of NEC for the total period of study (1992-2011 APC=0.11%/year from 0.095 to 0.143/1,000,000 person year, $p>0.05$) (Figures 3a and 3b). A combined analysis of incidence rates of SCC and NEC showed no significant increase in the incidence rates between 1992 and 2011 indicating that the increase in NEPC rates after 2001 was probably driven by the increase in the incidence of SCC (1992-2011 APC=0.58%/year, $p>0.05$).

5-year CSS. There was no change in the 5-year CSS rate for NEPC diagnosed between 1992 and 2006 (from 19.05% (95% confidence interval (CI)=0.03-45.56%) for diagnosis year 1992 to 17.95% (95% CI=6.00-35.05%) for diagnosis year 2006, $p>0.05$). The 5-year CSS rates for SCC did not significantly improve as well: from 16.67% (95% CI=0.77-51.68%) in 1992 to 24.69% (95% CI=7.82-46.41%) in 2006 ($p>0.05$) and the same findings apply to NEC (1992: 33.33% (95% CI=0.9-77.41%) - 2006: 30% (95% CI=4.42-62.82%), $p>0.05$).

Mortality. Overall, NEPC mortality rates did not change significantly between 1992 and 2006 (from 0.17 for diagnosis year 1992 to 0.15 for diagnosis year 2006/1,000,000 person years, APC=–2.45%/year, $p>0.05$). SCC mortality rates followed the same pattern (from 0.006 for diagnosis year 1992 to 0.007 for diagnosis year 2006/1,000,000 person years, APC=–2.06%/year, $p>0.05$) and so did NEC (from 0.004 for diagnosis year 1992 to 0.006 for diagnosis year 2006/1,000,000 person years, APC=2.85%/year, $p>0.05$).

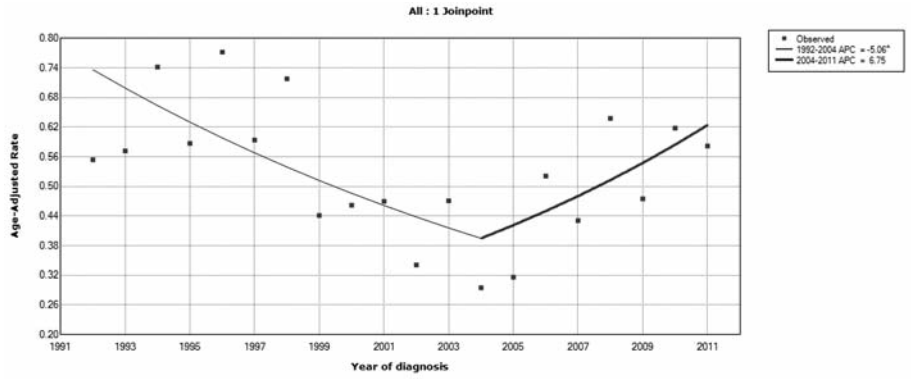

Figure 1. *Annual percentage change in age-adjusted incidence rates of neuroendocrine prostate cancer, 1992-2011.*

Discussion

There exist many reports in recent years connecting NEPC with ADT (1, 2). This is important because ADT's role in treating prostate cancer is increasing with the advent of new and more potent agents functioning on the androgen axis before and after chemotherapy for castration-resistant prostate cancer (5-8). Therefore, one may wonder whether such increase in the utilization of ADT is equally associated with a rise in the incidence of NEPC. To test this hypothesis is problematic considering that NEPC is a rare disease and repeat biopsy is not common in the context of advanced prostate cancer. In addition, many cases of aggressive NEPC are mislabeled as castration-resistant prostate cancer due to challenges in differentiating the two on pathologic examination (9). Under such circumstances, we sought to provide an update on the variations in NEPC incidence and mortality in long- and short-term trends. First and foremost, our results suggest that the incidence rates of NEPC maintain an upward trend in recent years (2004-2011) rising by nearly 6.8% per year. Such a rise in incidence was probably largely driven by SCC, where rates increased in a significant fashion by almost 7% per year, while rates of NEC did not change significantly in the same period of time. It has been previously reported that ADT utilization was increasing in the 1990s and early 2000s and then significantly decreased in 2004 and 2005 compared to 2003 (10), a period during which incidence rates of SCC (and by proxy NEPC) have seen an upward trend in the current analyses. If we accept the hypothesis that NEPC appears late in the course of advanced prostate cancer and that the increase in NEPC incidence can be solely attributed to the increased use of ADT in prostate cancer, then the incidence rates of these tumors should, theoretically, decrease over time as ADT use is decreasing since 2004. Therefore, the exploration and testing of such hypotheses will be crucial in upcoming years.

Other contributing factors are possible. The rise in the incidence of SCC may be due to improved diagnostic methods and increased interest in this disease entity in recent years (detection bias). This hypothesis could as well be tested in coming years. Specifically, if the rise in SCC incidence is due to better detection, then it should, theoretically, plateau with time. An example of such phenomenon is that of prostate cancer itself (adenocarcinoma) whose incidence rates increased steadily by 16.5% per year between 1988 and 1992 with the diffusion of prostatic specific antigen testing (11) but then significantly decreased in recent years: -11.2%/year between 1992 and 1995 and -2.1%/year between 2000 and 2009 (12).

A second important finding of our study is the low 5 year-CSS and the absence of improvement in mortality rates of NEPC in contemporary years. Our 17% 5-year cancer CSS corroborates previous reports suggesting prognosis of NEPC is poor (13). There is no prospective study to guide therapy for NEPC and platinum-based chemotherapy is used based on studies done on pulmonary SCC (14). However, there is little evidence that such therapy is effective in NEPC and, in fact, there exist studies suggesting a lower response rate in NEPC to chemotherapy compared to pulmonary SCC for unclear reasons (15). From a clinical standpoint, our results have important implications. As the incidence of SCC continues to rise and mortality fails to improve, it becomes essential for physicians to better-select candidates who will benefit from therapies associated with NEPC and spare those for which treatment would be unnecessary or perhaps harmful. Indeed, multiple retrospective studies failed to show benefit from ADT for localized prostate cancer (16-19). In the future, improved selection of patients with non-metastatic prostate cancer who would benefit from early aggressive treatment will depend on the identification of biomarkers that can help predict tumors with high potential for metastasis.

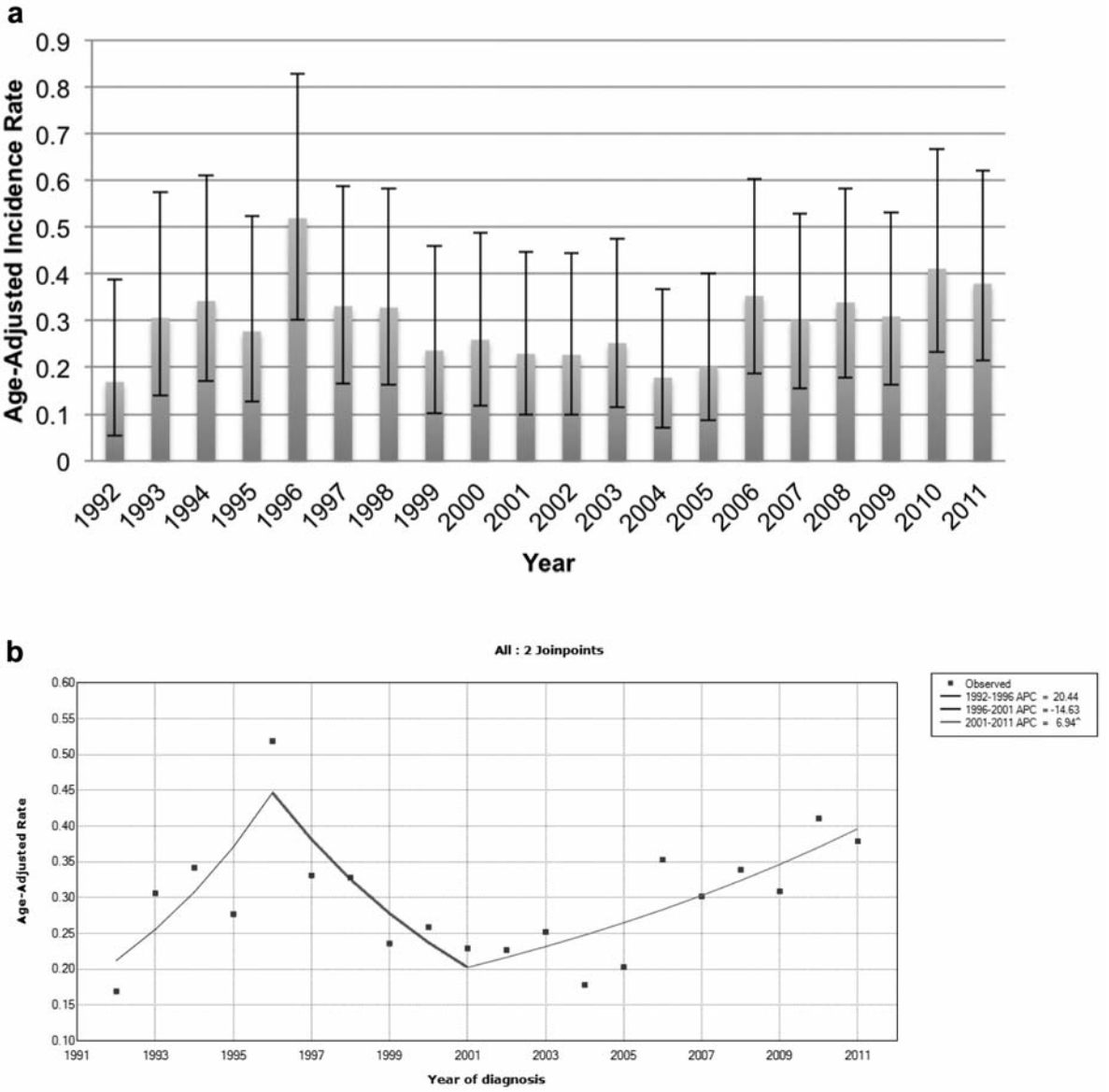

Figure 2. *a) Age-adjusted incidence rate of SCC by year. Error bars indicate 95% confidence interval using the Tiwari model. b) Results of joinpoint analysis for the change in age-adjusted incidence rate of SCC by year. Rates are per 1,000,00 and age-adjusted to 2000 US standard population.*

Studies focusing specifically on NEPC are rare and suffer from small sample sizes. To the best of our knowledge, this is the first study utilizing SEER database to examine the trends of NEPC incidence and mortality. The most significant aspect of our study is that it may increases the awareness of the mounting risk of NEPC among treating physicians. Additional prospective studies are necessary to identify molecular features of the disease and treatment methods that may be associated with improved survival. Such studies will require for international collaborations similar to what has been instituted for testicular cancer (20) to overcome the issue of the small sample sizes that plagues individual medical centers' experience with NEPC.

Our study makes use of a large population database that offers a broad representation of patients across the nation. However, our results have the typical limitations associated with population-based studies, most importantly the lack of central pathology in research based on the SEER database. In addition, we were unable to analyze if regional differences exist due to the small sample size, which may be an interesting issue to investigate in the future using multinational cooperative registries for NEPC. We focused

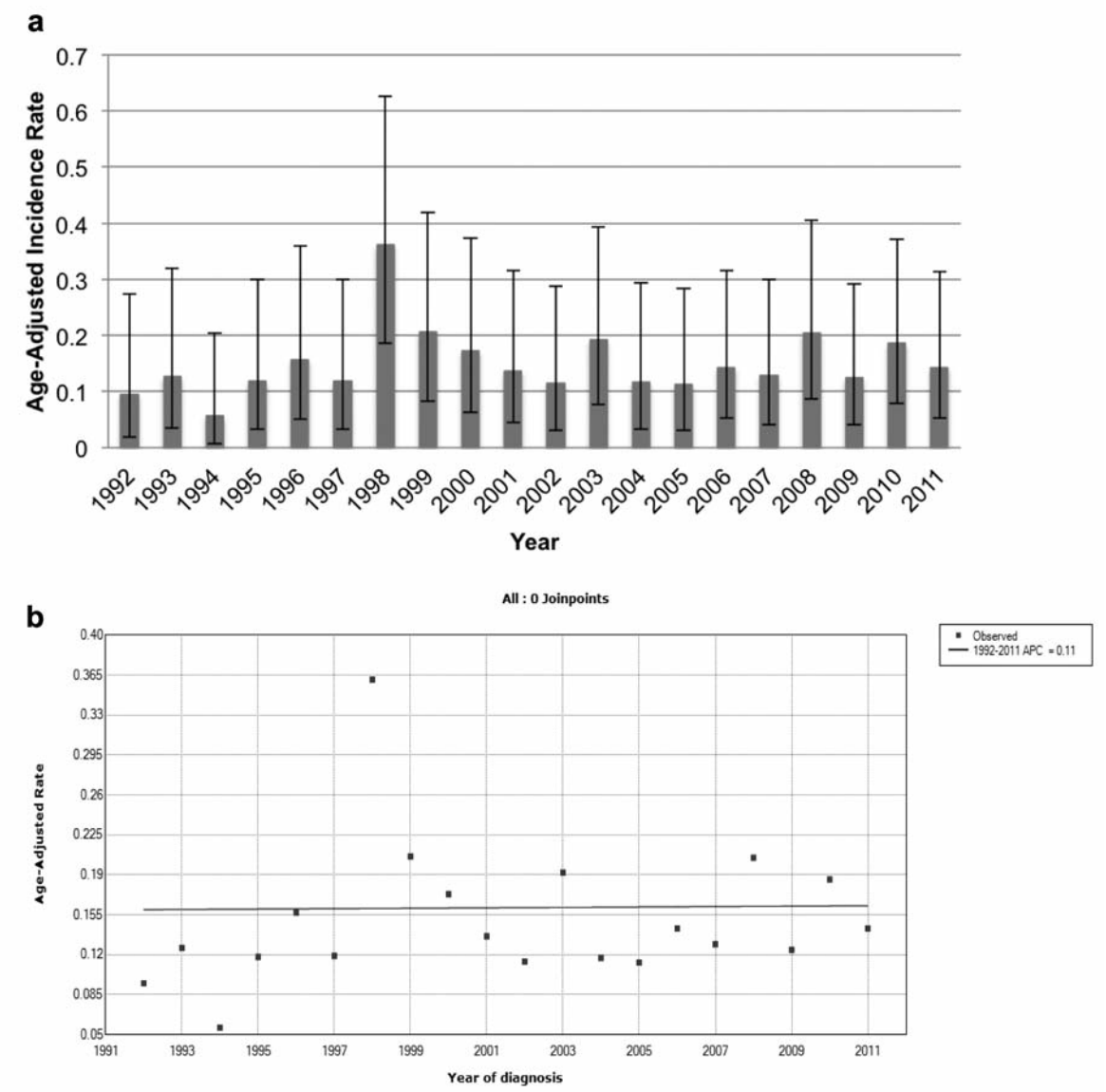

Figure 3. *a) Age-adjusted incidence rate of NEC by year. Error bars indicate 95% confidence interval using Tiwari model. B) Results of joinpoint analysis for the change in age adjusted incidence rate of NEC by year. Rates are per 1,000,00 and age-adjusted to 2000 US standard population.*

in our discussion on the association between ADT and NEPC because ADT is the commonly cited cause for NEPC; however, we acknowledge that a more complete study would include analysis of data on ADT utilization within the study cohort. Finally, the representation of African Americans in SEER is low and our conclusions about the change in NEPC incidence and mortality could have been different if another database, that has a higher percentage of African Americans, was utilized. With those limitations in mind, SEER is a large database that is well fit to examine rare diseases like NEPC and its results could be generalized to the population of the United States.

Conclusion

Our analysis of the SEER database is an attempt to understand the long-term changes in the incidence and mortality of NEPC. The incidence of SCC is significantly rising in recent years and no improvement has been achieved in survival rates of NEPC over the past 20 years. Considering

the low incidence of NEPC, such finding can only be validated and disease survival can only be improved through multi-national collaborations similar to those established for testicular cancer and pediatric malignancies.

Conflicts of Interest

The Authors have no conflict of interest to declare.

References

1 Beltran H, Tagawa ST, Park K, MacDonald T, Milowsky MI, Mosquera JM, Rubin MA and Nanus DM: Challenges in recognizing treatment-related neuroendocrine prostate cancer. J Clin Oncol *30*: e386-389, 2012.

2 Terry S and Beltran H: The many faces of neuroendocrine differentiation in prostate cancer progression. Front Oncol *4*: 60, 2014.

3 Shen R, Dorai T, Szaboles M, Katz AE, Olsson CA and Buttyan R: Transdifferentiation of cultured human prostate cancer cells to a neuroendocrine cell phenotype in a hormone-depleted medium. Urol Oncol *3*: 67-75, 1997.

4 National Cancer Institute. Surveillance Epidemiology and End Results (SEER) Program (http://seer.cancer.gov/).

5 Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS and Investigators A: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med *367*: 1187-1197, 2012.

6 Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, Staffurth JN, North S, Vogelzang NJ, Saad F, Mainwaring P, Harland S, Goodman OB, Sternberg CN, Li JH, Kheoh T, Haqq CM, de Bono JS and Investigators C-A-: Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol *13*: 983-992, 2012.

7 de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI and Investigators C-A-: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med *364*: 1995-2005, 2011.

8 Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID, de Bono JS, Evans CP, Fizazi K, Joshua AM, Kim CS, Kimura G, Mainwaring P, Mansbach H, Miller K, Noonberg SB, Perabo F, Phung D, Saad F, Scher HI, Taplin ME, Venner PM, Tombal B and Investigators P: Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med *371*: 424-433, 2014.

9 Epstein JI, Amin MB, Beltran H, Lotan TL, Mosquera JM, Reuter VE, Robinson BD, Troncoso P and Rubin MA: Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. Am J Surg Pathol *38*: 756-767, 2014.

10 Elliott SP, Jarosek SL, Wilt TJ and Virnig BA: Reduction in physician reimbursement and use of hormone therapy in prostate cancer. J Natl Cancer Inst *102*: 1826-1834, 2010.

11 Jemal A, Thun MJ, Ries LA, Howe HL, Weir HK, Center MM, Ward E, Wu XC, Eheman C, Anderson R, Ajani UA, Kohler B and Edwards BK: Annual report to the nation on the status of cancer, 1975-2005, featuring trends in lung cancer, tobacco use, and tobacco control. J Natl Cancer Inst *100*: 1672-1694, 2008.

12 Jemal A, Simard EP, Dorell C, Noone AM, Markowitz LE, Kohler B, Eheman C, Saraiya M, Bandi P, Saslow D, Cronin KA, Watson M, Schiffman M, Henley SJ, Schymura MJ, Anderson RN, Yankey D and Edwards BK: Annual Report to the Nation on the Status of Cancer, 1975-2009, featuring the burden and trends in human papillomavirus(HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst *105*: 175-201, 2013.

13 Wang HT, Yao YH, Li BG, Tang Y, Chang JW and Zhang J: 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 *32*: 3383-3390, 2014.

14 Galanis E, Frytak S and Lloyd RV: Extrapulmonary small cell carcinoma. Cancer *79*: 1729-1736, 1997.

15 Papandreou CN, Daliani DD, Thall PF, Tu SM, Wang X, Reyes A, Troncoso P and Logothetis CJ: 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 *20*: 3072-3080, 2002.

16 Cooperberg MR, Grossfeld GD, Lubeck DP and Carroll PR: National practice patterns and time trends in androgen ablation for localized prostate cancer. J Natl Cancer Inst *95*: 981-989, 2003.

17 Potosky AL, Haque R, Cassidy-Bushrow AE, Ulcickas Yood M, Jiang M, Tsai HT, Luta G, Keating NL, Smith MR and Van Den Eeden SK: Effectiveness of primary androgen-deprivation therapy for clinically localized prostate cancer. J Clin Oncol *32*: 1324-1330, 2014.

18 Kawakami J, Cowan JE, Elkin EP, Latini DM, DuChane J, Carroll PR and Investigators C: Androgen-deprivation therapy as primary treatment for localized prostate cancer: data from Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE). Cancer *106*: 1708-1714, 2006.

19 Keating NL, O'Malley AJ, McNaughton-Collins M, Oh WK and Smith MR: Use of androgen deprivation therapy for metastatic prostate cancer in older men. BJU Int *101*: 1077-1083, 2008.

20 Bono A and Zurlo A: The EORTC Genito-Urinary Tract Cancer Group: 25 years of achievements and future strategies. Eur J Cancer *38(Suppl 4)*: S71-74, 2002.

Received April 27, 2015
Revised May 8, 2015
Accepted May 11, 2015