



# Treatment-induced neuroendocrine prostate cancer and *de novo* neuroendocrine prostate cancer: Identification, prognosis and survival, genetic and epigenetic factors

Mohamed Wishahi

**Specialty type:** Oncology

**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B, Grade C

**Novelty:** Grade B, Grade B

**Creativity or Innovation:** Grade B, Grade B

**Scientific Significance:** Grade B, Grade B

**P-Reviewer:** Ji Y, China; Zhang Z, China

**Received:** December 18, 2023

**Revised:** February 10, 2024

**Accepted:** April 7, 2024

**Published online:** May 6, 2024



**Mohamed Wishahi**, Department of Urology, Theodor Bilharz Research Institute, Cairo 12411, Egypt

**Corresponding author:** Mohamed Wishahi, MD, PhD, Professor, Surgical Oncologist. Department of Urology, Theodor Bilharz Research Institute, Giza, Cairo 12411, Egypt. [moh.weshahy@gmail.com](mailto:moh.weshahy@gmail.com)

## Abstract

Neuroendocrine prostate cancer (NEPC) shows an aggressive behavior compared to prostate cancer (PCa), also known as prostate adenocarcinoma. Scanty foci in PCa can harbor genetic alternation that can arise in a heterogeneity of prostate cancer. NEPC may arise *de novo* or develop following androgen deprivation therapy (ADT). NEPC that arise following ADT has the nomenclature "treatment-emerging/induced NEPC (t-NEPC)". t-NEPC would be anticipated in castration resistant prostate cancer (CRPC) and metastatic PCa. t-NEPC is characterized by low or absent androgen receptor (AR) expression, independence of AR signaling, and gain of neuroendocrine phenotype. t-NEPC is an aggressive metastatic tumor, develops from PCa in response to drug induced ADT, and shows very short response to conventional therapy. t-NEPC occurs in 10%-17% of patients with CRPC. *De novo* NEPC is rare and is accounting for less than 2% of all PCa. The molecular mechanisms underlying the trans-differentiation from CRPC to t-NEPC are not fully elucidated. Sphingosine kinase 1 plays a significant role in t-NEPC development. Although neuroendocrine markers: Synaptophysin, chromogranin A, and insulinoma associated protein 1 (*INSM1*) are expressed in t-NEPC, they are non-specific for diagnosis, prognosis, and follow-up of therapy. t-NEPC shows enriched genomic alteration in tumor protein P53 (*TP53*) and retinoblastoma 1 (*RB1*). There are evidences suggest that t-NEPC might develop through epigenetic evolution. There are genomic, epigenetic, and transcriptional alterations that are reported to be involved in development of t-NEPC. Knock-outs of *TP53* and *RB1* were found to contribute in development of t-NEPC. PCa is resistant to immunotherapy, and at present there are running trials to approach immunotherapy for PCa, CRPC, and t-NEPC.

**Key Words:** Prostate cancer; Neuroendocrine carcinoma; Treatment induced neuroendocrine prostate cancer; Androgen deprivation therapy; Genetic and epigenetic factors;

**Core Tip:** Neuroendocrine prostate cancer (NEPC) are aggressive metastatic tumors, and there are two distinct types. *De novo* NEPC, which is less than 2% of all prostate cancer, is categorized as an entity of the endocrine tumors. The other type is the treatment induced NEPC (t-NEPC) that develops in castration resistant prostate cancer (CRPC) following androgen deprivation therapy, and it is an aggressive metastatic tumor occurs in 10%-17% of patients with CRPC and metastatic cancer, with median survival of 7 months after diagnosis. Genomic, epigenetic, and transcriptional alternation has been reported to be involved in its development. Future expectations for treatment would be tumor-directed immunotherapy.

**Citation:** Wishahi M. Treatment-induced neuroendocrine prostate cancer and *de novo* neuroendocrine prostate cancer: Identification, prognosis and survival, genetic and epigenetic factors. *World J Clin Cases* 2024; 12(13): 2143-2146

**URL:** <https://www.wjgnet.com/2307-8960/full/v12/i13/2143.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v12.i13.2143>

## INTRODUCTION

Neuroendocrine prostate cancer (NEPC) shows an aggressive biological behavior compared to prostate cancer (PCa), also known as prostate adenocarcinoma (PRAD). Recently, there has been extensive research on NEPC to elucidate its aggressive lethal characteristics. Prostatic adenocarcinoma foci can harbor genomic alterations that can arise in heterogeneity of prostate cancer.

Prostate cancer is not always adenocarcinoma with an elevated prostate specific antigen (PSA), and considerations of rare aggressive variants of NEPC should be born in mind. NEPC may arise *de novo* or develop after castration-resistant prostate cancer (CRPC) following androgen deprivation therapy (ADT). This type of tumor is more common than the *de novo* type and has the nomenclature “treatment-emergent NEPC” (t-NEPC). t-NEPC represents a challenge in early diagnosis by the urologist and pathologist and would be anticipated in CRPC and in metastatic PCa.

Recently, Weng *et al*[1] published an article on an aggressive variant PCa. They described a case of NEPC that was diagnosed as PRAD that received ADT, and 4 months later the patients had metastases and poor prognosis, finally the case was considered NEPC. In this work recognition of the variant of NEPC would be of significance.

The WHO fifth edition has joined together neuroendocrine tumors from different sites in each system into a separate chapter. This new classification is applied to the genitourinary system with specific consideration of *de novo* NEPC. t-NEPC has its own section in the PCa chapter with detailed description. Moreover, t-NEPC has its distinctive clinical and biological behavior differ from *de novo* NEPC[2,3]. t-NEPC develops in 10%-17% in patients with PRAD who received ADT and are CRPC[4,5]. *De novo* NEPC accounts for less than 2% of all PCa[6,7].

The second highest incidence of carcinomas in men worldwide is PCa[1]. While 90%-95% of PCa are adenocarcinoma which is characterized by strong androgen receptor (AR) and PSA expression. The tumor depends on the AR mediated signalling for maintenance and growth. Standard treatment of localized PCa is surgery or radiotherapy. For advanced PCa, ADT is the first-line treatment. In rare cases the PCa tumor can adapt to ADT leading to CRPC.

A subset CRPC, is the t-NEPC that differs from PRAD by low expression or absent AR and/or signaling, and it acquires neuroendocrine phenotype. Furthermore, t-NEPC is an aggressive metastatic subtype of PCa, it develops from prostate adenocarcinoma in response to drug induced ADT. The incidence rate of t-NEPC has increased in the last 2 decades in the United States. Median overall survival of t-NEPC after initial diagnosis of PCa is 53.5 months, and median survival is 7 months after diagnosis of t-NEPC[8,9]. The t-NEPC shows P53 positive immunostaining, while PSA and prostatic acid phosphatase are negative[9].

The molecular mechanisms underlying the trans-differentiation from CRPC to t-NEPC are not fully distinguished. Sphingosine kinase 1 (SphK1) plays a significant role in t-NEPC development. SphK1 is transcriptionally repressed by AR-RE1-silencing transcription factor (REST). SPHK1 produces sphingosine 1phosphate that modulate REST protein turnover. Also, the decreased REST protein levels enhance the expression of neuroendocrine markers in CRPC, leading to the transition to t-NEPC[10]. t-NEPC is disguised by loss of AR activities and the expression of chromatin, chromogranin A, synaptophysin, CD56 and INSM1 which are neuroendocrine markers[11,12]. t-NEPC shows dysregulated cytokine function. Tumor-plasticity is characteristic of t-NEPC that leads to dedifferentiate into different cell lineages. Tumor plasticity and epithelial-to-mesenchymal transition-induced cellular-plasticity and stem-cell signaling pathways lead to the progression of NEPC[13-16]. Genomic, epigenetic, and transcriptional alterations have been reported to be involved in the development of t-NEPC[17].

Combinatorial knock-outs (KO) of *TP53* and *RB1* have induced the growth of an AR-low neuroendocrine-like tumor. A triple KO model with *PTEN* loss has exhibited multiple metastases. Aberrations of these three genes mediated increased lineage plasticity. t-NEPC exhibits genomic aberrations that include the amplification of aurora kinase A (AURKA) and N-MYC (encoded by *MYCN*). N-MYC is highly enriched in t-NEPC tumors (40% *vs* 5% in PRAD). AURKA and N-MYC expression increased by reduced protein degradation mediated by *TP53* mutation and microRNA[9]. Transforming

growth factor-beta is expressed in PCa tumor cells and stromal cells are enriched in stromal cells of CRPC and bone metastases.

Recently there is data on the features of trans-differentiating from adenocarcinoma to neuroendocrine phenotype. t-NEPC shows enriched genomic alterations in *RB1* and *TP53*, in addition to epigenetic changes, these findings suggest that t-NEPC might develop through epigenetic changes evolution[18].

The difficulties in the clinical study of t-NEPC are presence of focal neuroendocrine differentiation detected with immunohistochemistry among the standard acinar adenocarcinoma of the prostate without any clinical evidence or circulating markers. PRAD expresses varying degrees of neuroendocrinal differentiation, consequently the WHO fifth edition and other authors do not recommend routine application of immunohistochemistry to detect synaptophysin and chromogranin. Moreover, these markers are insignificant in diagnosis or prognosis of t-NEPC[19-23].

The prediction of patients who will develop t-NEPC necessitates serial prostate biopsies at different timing from the initiation of ADT to achieve surveillance on development of CRPC and possible development of t-NEPC[13].

The origin of t-NEPC is postulated to arise from basal or neuroendocrine cells which are scanty, small in number and distributed in the normal prostate. Induction of ADT leads to inhibition of AR resulting in development of t-NEPC[10, 18]. Prostate cancers are often resistant to immunotherapies. There are running research trials to approach immunotherapy for PCa, CRPC, and t-NEPC[24].

## CONCLUSION

NEPC shows an aggressive biological behavior compared to PRAD. NEPC represents a challenge in early diagnosis by the urologist and pathologist. NEPC may arise *de novo* or develop after CRPC following treatment with ADT. t-NEPC is reported to arise in 10%-17% of patients with CRPC. *De novo* NEPC is rare, it accounts for less than 2% of PCa. t-NEPC develops from PRAD in response to drug induced ADT to AR signaling inhibition, it would be anticipated in CRPC and in metastatic PCa. Genetic, epigenetic, and transcriptional alternation has been reported to be involved in the development of t-NEPC. The molecular mechanism underlying the trans-differentiation from CRPC to t-NEPC is not fully elucidated. PCa are often resilient to immunotherapy. There are running research trials to approach tumor-immunotherapy for PCa, CRPC, and t-NEPC.

## FOOTNOTES

**Author contributions:** Wishahi M conceived the design; analyzed published data; wrote, reviewed, and edited the manuscript; and revised and approved the final version.

**Conflict-of-interest statement:** The author confirms that he has no conflict of interest of any kind.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

**Country/Territory of origin:** Egypt

**ORCID number:** Mohamed Wishahi 0000-0002-4559-619X.

**S-Editor:** Che XX

**L-Editor:** A

**P-Editor:** Zhao S

## REFERENCES

- 1 Weng XT, Lin WL, Pan QM, Chen TF, Li SY, Gu CM. Aggressive variant prostate cancer: A case report and literature review. *World J Clin Cases* 2023; **11**: 6213-6222 [PMID: 37731555 DOI: 10.12998/wjcc.v11.i26.6213]
- 2 Kench JG, Amin MB, Berney DM, Comp  rat EM, Cree IA, Gill AJ, Hartmann A, Menon S, Moch H, Netto GJ, Raspollini MR, Rubin MA, Tan PH, Tsuzuki T, Turajlic S, van der Kwast TH, Zhou M, Srigley JR. WHO Classification of Tumours fifth edition: evolving issues in the classification, diagnosis, and prognostication of prostate cancer. *Histopathology* 2022; **81**: 447-458 [PMID: 35758185 DOI: 10.1111/his.14711]
- 3 Netto GJ, Amin MB, Berney DM, Comp  rat EM, Gill AJ, Hartmann A, Menon S, Raspollini MR, Rubin MA, Srigley JR, Hoon Tan P, Tickoo SK, Tsuzuki T, Turajlic S, Cree I, Moch H. The 2022 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs-Part B: Prostate and Urinary Tract Tumors. *Eur Urol* 2022; **82**: 469-482 [PMID: 35965208 DOI: 10.1016/j.eururo.2022.07.002]
- 4 Aggarwal R, Huang J, Alumkal JJ, Zhang L, Feng FY, Thomas GV, Weinstein AS, Friedl V, Zhang C, Witte ON, Lloyd P, Gleave M, Evans CP, Youngren J, Beer TM, Rettig M, Wong CK, True L, Foye A, Playdle D, Ryan CJ, Lara P, Chi KN, Uzunangelov V, Sokolov A, Newton Y, Beltran H, Demichelis F, Rubin MA, Stuart JM, Small EJ. Clinical and Genomic Characterization of Treatment-Emergent Small-Cell

- Neuroendocrine Prostate Cancer: A Multi-institutional Prospective Study. *J Clin Oncol* 2018; **36**: 2492-2503 [PMID: [29985747](#) DOI: [10.1200/JCO.2017.77.6880](#)]
- 5 **Bluemn EG**, Coleman IM, Lucas JM, Coleman RT, Hernandez-Lopez S, Tharakan R, Bianchi-Frias D, Dumpit RF, Kaipainen A, Corella AN, Yang YC, Nyquist MD, Mostaghel E, Hsieh AC, Zhang X, Corey E, Brown LG, Nguyen HM, Pienta K, Ittmann M, Schweizer M, True LD, Wise D, Rennie PS, Vessella RL, Morrissey C, Nelson PS. Androgen Receptor Pathway-Independent Prostate Cancer Is Sustained through FGF Signaling. *Cancer Cell* 2017; **32**: 474-489.e6 [PMID: [29017058](#) DOI: [10.1016/j.ccell.2017.09.003](#)]
- 6 **Zaffuto E**, Pompe R, Zanaty M, Bondarenko HD, Leyh-Bannurah SR, Moschini M, Dell'Oglio P, Gandaglia G, Fossati N, Stabile A, Zorn KC, Montorsi F, Briganti A, Karakiewicz PI. Contemporary Incidence and Cancer Control Outcomes of Primary Neuroendocrine Prostate Cancer: A SEER Database Analysis. *Clin Genitourin Cancer* 2017; **15**: e793-e800 [PMID: [28506524](#) DOI: [10.1016/j.clgc.2017.04.006](#)]
- 7 **Vlachostergios PJ**, Puca L, Beltran H. Emerging Variants of Castration-Resistant Prostate Cancer. *Curr Oncol Rep* 2017; **19**: 32 [PMID: [28361223](#) DOI: [10.1007/s11912-017-0593-6](#)]
- 8 **Wang HT**, Yao YH, Li BG, Tang Y, Chang JW, 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* 2014; **32**: 3383-3390 [PMID: [25225419](#) DOI: [10.1200/JCO.2013.54.3553](#)]
- 9 **Merkens L**, Sailer V, Lessel D, Janzen E, Greimeier S, Kirfel J, Perner S, Pantel K, Werner S, von Amsberg G. Aggressive variants of prostate cancer: underlying mechanisms of neuroendocrine transdifferentiation. *J Exp Clin Cancer Res* 2022; **41**: 46 [PMID: [35109899](#) DOI: [10.1186/s13046-022-02255-y](#)]
- 10 **Lee CF**, Chen YA, Hernandez E, Pong RC, Ma S, Hofstad M, Kapur P, Zhau H, Chung LW, Lai CH, Lin H, Lee MS, Raj GV, Hsieh JT. The central role of Sphingosine kinase 1 in the development of neuroendocrine prostate cancer (NEPC): A new targeted therapy of NEPC. *Clin Transl Med* 2022; **12**: e695 [PMID: [35184376](#) DOI: [10.1002/ctm2.695](#)]
- 11 **Epstein JI**, Amin MB, Beltran H, Lotan TL, Mosquera JM, Reuter VE, Robinson BD, Troncoso P, Rubin MA. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. *Am J Surg Pathol* 2014; **38**: 756-767 [PMID: [24705311](#) DOI: [10.1097/PAS.0000000000000208](#)]
- 12 **Quintanal-Villalonga Á**, Chan JM, Yu HA, Pe'er D, Sawyers CL, Sen T, Rudin CM. Lineage plasticity in cancer: a shared pathway of therapeutic resistance. *Nat Rev Clin Oncol* 2020; **17**: 360-371 [PMID: [32152485](#) DOI: [10.1038/s41571-020-0340-z](#)]
- 13 **Wang Y**, Wang Y, Ci X, Choi SYC, Crea F, Lin D. Molecular events in neuroendocrine prostate cancer development. *Nat Rev Urol* 2021; **18**: 581-596 [PMID: [34290447](#) DOI: [10.1038/s41585-021-00490-0](#)]
- 14 **Soundararajan R**, Paranjape AN, Maity S, Aparicio A, Mani SA. EMT, stemness and tumor plasticity in aggressive variant neuroendocrine prostate cancers. *Biochim Biophys Acta Rev Cancer* 2018; **1870**: 229-238 [PMID: [29981816](#) DOI: [10.1016/j.bbcan.2018.06.006](#)]
- 15 **Pérez-González A**, Bévant K, Blanpain C. Cancer cell plasticity during tumor progression, metastasis and response to therapy. *Nat Cancer* 2023; **4**: 1063-1082 [PMID: [37537300](#) DOI: [10.1038/s43018-023-00595-y](#)]
- 16 **Beltran H**, Hruszkewycz A, Scher HI, Hildesheim J, Isaacs J, Yu EY, Kelly K, Lin D, Dicker A, Arnold J, Hecht T, Wicha M, Sears R, Rowley D, White R, Gulley JL, Lee J, Diaz Meco M, Small EJ, Shen M, Knudsen K, Goodrich DW, Lotan T, Zoubeidi A, Sawyers CL, Rudin CM, Loda M, Thompson T, Rubin MA, Tawab-Amiri A, Dahut W, Nelson PS. The Role of Lineage Plasticity in Prostate Cancer Therapy Resistance. *Clin Cancer Res* 2019; **25**: 6916-6924 [PMID: [31363002](#) DOI: [10.1158/1078-0432.CCR-19-1423](#)]
- 17 **Abida W**, Cyrt A, Heller G, Prandi D, Armenia J, Coleman I, Cieslik M, Benelli M, Robinson D, Van Allen EM, Sboner A, Fedrizzi T, Mosquera JM, Robinson BD, De Sarkar N, Kunju LP, Tomlins S, Wu YM, Nava Rodrigues D, Loda M, Gopalan A, Reuter VE, Pritchard CC, Mateo J, Bianchini D, Miranda S, Carreira S, Rescigno P, Filipenko J, Vinson J, Montgomery RB, Beltran H, Heath EI, Scher HI, Kantoff PW, Taplin ME, Schultz N, deBono JS, Demichelis F, Nelson PS, Rubin MA, Chinnaiyan AM, Sawyers CL. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc Natl Acad Sci USA* 2019; **116**: 11428-11436 [PMID: [31061129](#) DOI: [10.1073/pnas.1902651116](#)]
- 18 **Labrecque MP**, Coleman IM, Brown LG, True LD, Kollath L, Lakely B, Nguyen HM, Yang YC, da Costa RMG, Kaipainen A, Coleman R, Higano CS, Yu EY, Cheng HH, Mostaghel EA, Montgomery B, Schweizer MT, Hsieh AC, Lin DW, Corey E, Nelson PS, Morrissey C. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. *J Clin Invest* 2019; **129**: 4492-4505 [PMID: [31361600](#) DOI: [10.1172/JCI128212](#)]
- 19 **Shehabeldin AN**, Ro JY. Neuroendocrine tumors of genitourinary tract: Recent advances. *Ann Diagn Pathol* 2019; **42**: 48-58 [PMID: [31306859](#) DOI: [10.1016/j.anndiagpath.2019.06.009](#)]
- 20 **Priemer DS**, Montironi R, Wang L, Williamson SR, Lopez-Beltran A, Cheng L. Neuroendocrine Tumors of the Prostate: Emerging Insights from Molecular Data and Updates to the 2016 World Health Organization Classification. *Endocr Pathol* 2016; **27**: 123-135 [PMID: [26885643](#) DOI: [10.1007/s12022-016-9421-z](#)]
- 21 **Santoni M**, Conti A, Burattini L, Berardi R, Scarpelli M, Cheng L, Lopez-Beltran A, Cascinu S, Montironi R. Neuroendocrine differentiation in prostate cancer: novel morphological insights and future therapeutic perspectives. *Biochim Biophys Acta* 2014; **1846**: 630-637 [PMID: [25450825](#) DOI: [10.1016/j.bbcan.2014.10.008](#)]
- 22 **Aggarwal R**, Zhang T, Small EJ, Armstrong AJ. Neuroendocrine prostate cancer: subtypes, biology, and clinical outcomes. *J Natl Compr Canc Netw* 2014; **12**: 719-726 [PMID: [24812138](#) DOI: [10.6004/jnccn.2014.0073](#)]
- 23 **Conteduca V**, Oromendia C, Eng KW, Bareja R, Sigouros M, Molina A, Faltas BM, Sboner A, Mosquera JM, Elemento O, Nanus DM, Tagawa ST, Ballman KV, Beltran H. Clinical features of neuroendocrine prostate cancer. *Eur J Cancer* 2019; **121**: 7-18 [PMID: [31525487](#) DOI: [10.1016/j.ejca.2019.08.011](#)]
- 24 **Meng L**, Yang Y, Mortazavi A, Zhang J. Emerging Immunotherapy Approaches for Treating Prostate Cancer. *Int J Mol Sci* 2023; **24**: 14347 [PMID: [37762648](#) DOI: [10.3390/ijms241814347](#)]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [office@baishideng.com](mailto:office@baishideng.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

