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**Treatment-induced neuroendocrine prostate cancer and de novo neuroendocrine prostate cancer: Two variant distinct aggressive tumors, identification, prognosis and survival, genetic and epigenetic factors**

Wishahi M Treatment-induced and de novo NEPC

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## **Abstract**

Neuroendocrine prostate cancer (NEPC) shows an aggressive behavior compared to prostate adenocarcinoma (PCa). Scanty foci in PCa can harbor genetic alternation that can arise in a heterogenous tumors. 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 INSMI are expressed in t-NEPC, they are non-specific for diagnosis, prognosis, and follow-up of therapy. t-NEPC shows enriched genomic alternation in *TP53* and *RB1*. There are evidences suggest that t-NEPC might develop through epigenomic evolution. There are genomic, epigenetic, and transcriptional alternations 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, at present there are running trials to approach immunotherapy for PCa, CRPC, and t-NEPC.

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

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**Core Tip:** Neuroendocrine prostate cancer (NEPC) are aggressive metastatic tumors, they are two distinct types: De novo NEPC which is less than 2% of all prostate cancer, and is categorized as an entity of the endocrinal tumors. The other type is the treatment induced NEPC (t-NEPC) that develops in castration resistant prostate cancer (CRPC) following androgen deprivation therapy, 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.

## **INTRODUCTION**

Neuroendocrine prostate cancer (NEPC) shows an aggressive biological behavior compared to adenocarcinoma of the prostate. 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 a heterogenous tumors.

Prostate cancer (PCa) is not always adenocarcinoma with an elevated prostatic-specific antigen (PSA), considerations of rare aggressive variant of NEPC should be bear in mind. EPC may arise de novo or develop after castration-resistant PCa 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). -NEPC represents a challenge in early diagnosis by the urologist and pathologist and would be anticipated in castration resistant prostate cancer (CRPC) and in metastatic PCa.

Recently published article by Weng *et al*<sup>[1]</sup> (2023) on an aggressive variant PCa. They described a case of NEPC that was diagnosed as prostate adenocarcinoma that

received ADT, 4 months later the patients had metastases and poor prognosis, the case was considered NEPC<sup>[1]</sup>. In this work it would be the 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. Treatment-related neuroendocrine prostatic carcinoma has its own section in the PCa chapter with detailed description. Moreover, t-NEPC has its distinctive clinical and biological behavior that differs from de novo NEPC<sup>[2,3]</sup>. t-NEPC develops in 10%–17% in patients with prostate adenocarcinoma who received ADT and are CRPC<sup>[4,5]</sup>. De novo NEPC accounts for 2% or less of all PCa<sup>[6,7]</sup>.

The second highest incidence of carcinomas in men worldwide is PCa<sup>[1]</sup>. 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. 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 prostate adenocarcinoma 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 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 of 7 months after diagnosis of t-NEPC<sup>[8, 9]</sup>. The t-NEPC shows P53 positive immunostaining, while, prostate-specific antigen (PSA) and prostatic acid phosphatase are negative<sup>[10]</sup>.

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 1-phosphate that modulates

REST protein turnover. Also, the <sup>1</sup> decreased REST protein levels enhance the expression of neuroendocrine markers in CRPC, leading to the transition to t-NEPC<sup>[11]</sup>. t-NEPC is disguised by loss of AR activities and the expression of chromatin, chromogranin A, synaptophysin, CD56 and INSM1 which are neuroendocrine markers<sup>[12,13]</sup>. 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 leads to the progression of NEPC<sup>[14-17]</sup>. Genomic, epigenetic, and transcriptional alterations have been reported to be involved in the development of t-NEPC<sup>[18]</sup>.

Combinatorial knock-outs (KO) of <sup>2</sup> *TP53* and *RB1* has 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 exhibit genomic aberrations that includes <sup>2</sup> 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 prostate adenocarcinoma). <sup>2</sup> *AURKA* and N-MYC expression increased by reduced protein degradation mediated by *TP53* mutation and microRNA<sup>[9]</sup>. TGFβ 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 s epigenome evolution<sup>[19]</sup>.

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. Prostate adenocarcinoma 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<sup>[20-24]</sup>.

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<sup>[25]</sup>.

The origin of t-NEPC is postulated to arise from basal or neuroendocrinal cells which are small in number and distributed in normal prostate. Induction of ADT leads to inhibition of AR resulting in development of t-NEPC<sup>[10,18]</sup>. Prostate cancers are often resistant to immunotherapies. There are running research trials to approach immunotherapy for PCa, CRPC, and t-NEPC<sup>[26]</sup>.

### CONCLUSION

NEPC shows an aggressive biological behavior compared to prostate adenocarcinoma. NEPC represent a challenge in early diagnosis by the urologist and pathologist. NEPC may arise de novo or develop after CRPC following treatment with ADT, the t-NEPC. t-NEPC is reported to arise in 10%-17% of patients with CRPC. De novo NEPC is rare, it accounts for 25 or less of PCa. t-NEPC develops from prostate adenocarcinoma 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 immunotherapy for PCa, CRPC, and t-NEPC.

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Cheng-Fan Lee, Yu-An Chen, Elizabeth Hernandez, Rey-Chen Pong et al. "The central role of Sphingosine kinase 1 in the development of neuroendocrine prostate cancer (NEPC): A new targeted therapy of NEPC", Clinical and Translational Medicine, 2022

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