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Anthony Kodzo-Grey Venyo *

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Research Article

Treatment Related Neuroendocrine Prostatic Carcinoma: Review and Update

Anthony Kodzo-Grey Venyo

Medical Examiner Member (RC Path) London and Retired Urologist United Kingdom

***Corresponding Author:** Anthony Kodzo-Grey Venyo, Medical Examiner Member (RC Path) London and Retired Urologist United Kingdom.

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Abstract

Treatment-related neuroendocrine carcinoma of the prostate gland is stated to be a distinctive category of carcinoma of the prostate gland which tends to ensue intensive suppression of the androgen receptor by next-generation therapeutic inhibition of androgen receptor signalling. The biological processes which set in motion the series of events emanating in transformation of adenocarcinoma to neuroendocrine carcinoma has been iterated to include genomic (loss of tumour suppressors TP53 and RB1, amplification of oncogenes N-MYC and Aurora Kinase A, dysregulation of transcription factors SOX2, achaete-scute-homolog 1, and others) as well as epigenomic (DNA methylation, EZH2 overexpression, and others). Pathology examination diagnosis of specimens of the tumour has been iterated to be the key to effective treatment for this disease, and this is aided by localizing metastatic lesions for biopsy utilising radioligand imaging in the appropriate clinical context. As the understanding of biology of the tumour has evolved, there has been increased morphological examination recognition and characterization of tumour phenotypes which are present within this advanced post-treatment setting. New and promising biomarkers (delta-like ligand 3 and others) have been discovered, which has opened up novel treatment avenues including immunotherapy and antibody-drug conjugates for this lethal disease with currently limited treatment options. It is important for clinicians and patients all over the world to appreciate that treatment related neuroendocrine carcinoma of the prostate gland generally has tended to portend an aggressive clinical and biological behaviour that has tended to be associated with poor prognosis and early death of individuals afflicted by the tumour. There is the need for clinicians and research workers to undertake research work that would identify new treatment options that would help improve the outcome of the tumour by destroying the tumour cells effectively.

Key words: treatment-related prostatic cancer; treatment-related prostate cancer; aggressive tumour; histopathology; immunohistochemistry

Introduction

Prostate cancer (PCa) is stated to be the second most common malignancy among men worldwide. [1] [2] [3] The standard treatment for metastatic PCa is ADT; [4] nevertheless, eventually cancer cells do acquire resistance and castrate resistant prostate cancer (CRPC) develops. It is now widely understood that the majority of CRPCs are still dependent upon the androgen receptor (AR) signalling pathway, [5] [6] and novel AR pathway inhibitors, such as enzalutamide and abiraterone, have demonstrated efficacy against CRPC. [7] [8] [9] 10] treatment-related neuroendocrine prostate cancer (T-NEPC) is a rare AR-independent cancer subtype which develops at the later stage of CRPC treatment. [11] [12] Morphologically, it shows features of small cell carcinoma, and typically has low or absent AR expression. [13] Clinically, it overlaps with “anaplastic prostate carcinoma” or “AVPC,” which are characterized by extensive visceral metastases, short response duration to ADT, sensitivity to platinum-containing chemotherapy and poor prognosis. [14 [15] t-NEPC develops as a consequence of lineage plasticity, a phenomenon in which tumour cells acquire phenotypic characteristics of a cell lineage whose survival is no longer regulated by a certain drug target. [16] The incidence of t-NEPC has been rising rapidly as a result of the increasing use of potent AR pathway inhibitors, and it is now imperative to study the molecular characteristic of this aggressive subtype and identify specific molecular targets. Recent integrative genomic analysis and novel *in vivo* models of t-NEPC have identified several key molecular features of NEPC. In the present review, we discuss various clinical and molecular aspects of t-NEPC.

Aim: To review and update the literature on treatment-related neuroendocrine prostatic carcinoma.

Method

Internet data bases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: treatment related prostate carcer; treatment related carcinoma of prostate; treatment related prostatic carcinoma. Fifty-four (54) references were identified which

were used to write the article which has been divided into two parts: (A) Overview, and (B) Miscellaneous narrations and discussions from some case reports, case series, and studies related to neuroendocrine prostatic carcinoma.

Results

[A] Overview

Definition / general statement

- Treatment-related prostatic carcinomas are stated to represent prostatic carcinomas that show complete or partial neuroendocrine differentiation following intensive suppression of androgen receptors by androgen deprivation therapy (ADT) [17].

Essential features

The essential features of treatment-related prostatic carcinomas had been summated as follows: [17]

- Documented history of antiandrogen therapy is required for the diagnosis of treatment related neuroendocrine prostatic carcinoma (tNEPC).
- There are 3 histologic presentations: small cell neuroendocrine carcinoma (SCNEC), large cell neuroendocrine carcinoma (LCNEC) and tNEPC (SCNEC or LCNEC) combined with acinar adenocarcinoma.
- Neuroendocrine differentiation is the result of a trans-differentiation of a castration resistant prostate cancer following ADT.
- Gleason score is not reportable for areas with neuroendocrine components
- Prognosis of tNEPC is dismal, with a median survival following neuroendocrine trans-differentiation of < 1 year.

Epidemiology

The epidemiology of treatment-related prostatic carcinomas had been summated as follows: [17]

- tNEPC comprises 10% to 15% of castration resistant prostate adenocarcinomas [18]
- Overall, primary SCNEC of the prostate represents 1 - 5% of prostate cancer [19]
- However, focal neuroendocrine differentiation is common in adenocarcinomas with a high Gleason score

Sites

The sites of treatment-related prostatic carcinomas, had been summated to include the following: [17]

- Prostate
- Metastatic sites

Pathophysiology

The pathophysiology of treatment-related prostatic carcinomas had been summated as follows: [17]

- Phenotypic transition from an androgen responsive to an androgen indifferent state is associated with losses of *TP53*, *RB1* and *PTEN*. [20]
- Epigenetic factors including chromatin modification and DNA methylation also play a role in the development of tNEPC. [21]

Aetiology

- It has been iterated that treatment-related prostatic carcinomas entail trans-differentiation of a castration resistant prostate cancer following ADT [1]

Clinical features

The clinical features of treatment-related prostatic carcinomas had been summated as follows: [17]

- Locally, the vast majority present with the same obstructive symptoms seen in conventional prostatic adenocarcinoma; however, tNEPC commonly presents with lymph node and visceral metastasis [22]
- Bone metastases are typically lytic (as opposed to classic osteoblastic bone metastasis on conventional prostatic adenocarcinoma) [22]

Diagnosis

The diagnosis of treatment-related prostatic carcinomas had been summated as follows: [17]

- Histologic examination of tissue demonstrating partial or complete neuroendocrine differentiation (small cell or large cell components) [17]
- Documented prior history of ADT [17]

Laboratory tests

Laboratory tests that tend to be undertaken in cases of treatment-related prostatic carcinomas had been summated as follows: [17]

- Prostate specific antigen (PSA) levels tend to be lower than in conventional adenocarcinoma, reflecting trans-differentiation [17]
- Occasionally, serum levels of chromogranin A may be identified) [23]

Radiology description

- It has been stated that in treatment-related prostatic carcinomas, metastatic foci can be detected by radiology imaging. [17]

Prognostic factors

The prognostic factors associated with treatment-related prostatic carcinomas, had been summated as follows: [17]

- tNEPC develops within 2 years of ADT [24]
- Median survival following neuroendocrine trans-differentiation is < 1 year. [24]
- Tumours with pure SCNEC or LCNEC morphology have worse overall survival than those admixed with a conventional adenocarcinoma component [22], [25]

Treatment

The treatment of treatment-related prostatic carcinomas had been summated as follows: [17]

- Pure SCNEC: adjuvant therapy with platinum-based chemotherapy plus etoposide [26]
- Mixed acinar adenocarcinoma and SCNEC: platinum and taxane [26]

- Lutetium 177 prostate specific membrane antigen (^{177}Lu PSMA) 617 radioligand therapy is under approval for treatment of metastatic disease [27]

Gross description

Macroscopy examination features of treatment-related prostatic carcinomas had been summated as follows: [17]

- Extensive infiltration into surrounding structures.
- Grossly identifiable necrosis may be seen.

Microscopic (histologic) description

Microscopy examination features of treatment-related prostatic carcinomas had been summated as follows: [17]

- SCNEC [26]
    - Diffuse, sheet-like growth pattern
    - Salt and pepper chromatin without prominent nucleoli
    - Nuclear moulding and crushing artifact
    - Frequent tumour necrosis and brisk mitotic activity
- LCNEC [26]
    - Organoid nests and sheets of cells with peripheral palisading
    - Large nuclei with coarse to vesicular chromatin and occasional visible nucleoli
    - Frequent tumour necrosis and brisk mitotic activity
- tNEPC (SCNEC or LCNEC) combined with acinar adenocarcinoma [24] [26]
    - Glandular component is usually high grade: Gleason score 8 or higher
    - Do not consider neuroendocrine component in Gleason score

Positive stains

Positive immunohistochemistry staining of treatment-related prostatic carcinomas had been summated as follows: [17]

- Up to 90% of cases are positive for at least 1 neuroendocrine marker [28]
    - Synaptophysin.
    - Chromogranin.
    - CD56.
    - INSM1
- **TTF1** (positive in 50% of cases of SCNEC)
- **Ki67**: up to 90% in SCNEC and up to 50% in LCNEC
- **p53**: nuclear staining in most SCNEC
- **Pankeratin**: may be positive in a dot-like cytoplasmic pattern

Negative stains

Negative immunohistochemistry staining of treatment-related prostatic carcinomas had been summated as follows: [17]

- **AR**: may be positive in subset of SCNEC
- **PSA** and **PAP** (negative in up to 80% of tNEPC) [28]
- **RB1** loss (lost in up to 56% of tNEPC; however, not specific to tNEPC as it is present in 35% of all advanced prostate cancers) [29]

Molecular / cytogenetics description

Molecular / cytogenetics description in treatment-related prostatic carcinomas had been summated as follows: [17]

- Progression to androgen independent state may be driven by loss of *TP53*, *RB1* and *PTEN* function
- Amplification of *MYCN* and *AURKA* [26]

Differential diagnoses

The differential diagnoses of treatment-related prostatic carcinomas had been summated as follows: [17]

- **Neuroendocrine carcinomas not related to antiandrogen therapy**: [17]
    - Tumors presenting with identical morphology as tNEPC but no documented history of antiandrogen therapy
- **Metastatic SCNEC of other sites**: [17]
    - Challenging differential diagnosis given that morphology and immunoprofile (including **TTF1** expression) is essentially the same
    - History of prostate cancer with ADT and evidence of residual / recurrent local disease in the prostate / pelvic floor / pelvic lymph nodes might be helpful in the differential diagnosis
- **Prostatic adenocarcinoma**,
    - Poorly differentiated (Gleason 5). [17]
    - May show focal neuroendocrine differentiation and loss of glandular architecture.
    - Combination of positive acinar markers (**PSA, NKX3.1 and PSMA**) and weak / focal or negative neuroendocrine markers, whereas tNEPC has predominantly neuroendocrine markers with focal / negative acinar markers.
    - Diffuse membranous **pankeratin** expression is suggestive of adenocarcinoma (whereas in tNEPC, it is cytoplasmic dot-like).
- **Poorly differentiated urothelial carcinoma**
    - Crush artifact in urothelial carcinoma can mimic tNEPC, especially SCNEC.
    - Negative for neuroendocrine markers and diffusely positive for **high molecular weight keratin and p63.**

[B] Miscellaneous Narrations and Discussions from some Case Reports, Case Series, and Studies Related to Treatment Effect Prostatic Carcinoma.

Akamatsu et al. [1] made the ensuing iterations:

- Treatment-related neuroendocrine prostate cancer is a lethal form of prostate cancer that emerges in the later stages of castration-resistant prostate cancer treatment.
- Treatment-related neuroendocrine prostate cancer transdifferentiates from adenocarcinoma as an adaptive response to androgen receptor pathway inhibition.
- The incidence of treatment-related neuroendocrine prostate cancer had been rising due to the increasing use of potent androgen receptor pathway inhibitors.
- Typically, treatment-related neuroendocrine prostate cancer is typified by either low or absent androgen receptor expression, small cell carcinoma morphology and expression of neuroendocrine markers.
- Clinically, it manifests with predominantly visceral or lytic bone metastases, bulky tumour masses, low prostate-specific antigen levels or a short response duration to androgen deprivation therapy.
- In addition, although the tumour initially responds to platinum-based chemotherapy, the duration of the response is short.
- Based upon the poor prognosis, it is imperative to identify novel molecular targets for treatment-related neuroendocrine prostate cancer.
- Recent advances in genomic and molecular research, supported by novel in vivo models, had identified some of the key molecular characteristics of treatment-related neuroendocrine prostate cancer.
- The gain of MYCN and AURKA oncogenes, along with the loss of tumour suppressor genes TP53 and RB1 are key genomic alterations associated with treatment-related neuroendocrine prostate cancer.
- Androgen receptor repressed genes, such as BRN2 and PEG10, are also necessary for treatment-related neuroendocrine prostate cancer.
- These genetic changes converge on pathways upregulating genes, such as SOX2 and EZH2, that facilitate lineage plasticity and neuroendocrine differentiation.
- As a result, on potent androgen receptor pathway inhibition, castration-resistant prostate cancer transdifferentiates to treatment-related neuroendocrine prostate cancer in a clonally divergent manner.
- Further understanding of the disease biology is necessary to develop novel drugs and biomarkers that would help treat this aggressive prostate cancer variant.

Hirano et al. [11] evaluated the relationship between neuroendocrine differentiation (NED) status and hormone refractory prostate cancer (HRPC) following hormone therapy based upon immunohistochemical study. Hirano et al. [11] examined seventy-two prostate cancer specimens obtained at radical prostatectomy and 21 prostate cancer autopsy specimens from patients who died from HRPC after androgen deprivation therapy for NED status using an antibody against chromogranin A. They classified the specimens into 3 arms: 38 radical prostatectomy specimens from patients with no neoadjuvant hormone therapy (Group 1); 34 from patients with neoadjuvant hormone therapy for 3 months to 6 months (Group 2); and 21 autopsy specimens from patients with HRPC after androgen deprivation therapy for more than 1 year (Group 3). Hirano et al. [11] scored the staining of prostatic carcinoma as: 0 = no staining; 1 = staining cells <10%; 2 = staining cells 10-20%; and 3 = staining cells >20%. Hirano et al. [11] compared the differences in scores among the groups using the Kruskal-Wallis rank test. Hirano et al. [11] performed multivariate analysis using a logistic regression model to examine whether NED status was associated with pathological stage (pT), grade and group. Hirano et al. [11] summarised the results as follows:

- Forty-nine (53%) tumours had CgA stained cells. NED status increased with longer duration of hormone therapy ($p<0.0001$).
- The mean staining score (and standard deviation) was 0.4+/-0.7 in Group 1, 0.7+/-0.7 in Group 2, and 1.4+/-1.1 in Group 3, respectively.
- By multivariate analysis Group 3 had a relative risk of 5.46 (95%CI 1.28-23.29) for NED compared to the other groups.
- However, other variables were not related to NED. HRPC following Long-term hormonal therapy was the only independent predictor of NED.

Hirano et al. [11] concluded that the results of this study demonstrated that NED status was significantly increased in patients with HRPC following long-term androgen deprivation therapy, but it could not be discriminate whether the increase of NED is attributable to condition of hormone refractoriness or long-term hormonal therapy. Bishop et al. [16] made the ensuing iterations.

- Treatment-related neuroendocrine prostate cancer is a lethal form of prostate cancer that emerges in the later stages of castration-resistant prostate cancer treatment.
- Treatment-related neuroendocrine prostate cancer transdifferentiates from adenocarcinoma as an adaptive response to androgen receptor pathway inhibition.
- The incidence of treatment-related neuroendocrine prostate cancer had been rising due to the increasing use of potent androgen receptor pathway inhibitors.
- Typically, treatment-related neuroendocrine prostate cancer is typified by either low or absent androgen receptor expression, small cell carcinoma morphology and expression of neuroendocrine markers.
- Clinically, it presents with predominantly visceral or lytic bone metastases, bulky tumour masses, low prostate-specific antigen levels or a short response duration to androgen deprivation therapy.
- In addition, even though the tumour initially responds to platinum-based chemotherapy, the duration of the response is short.
- Based upon the poor prognosis, it is imperative to identify novel molecular targets for treatment-related neuroendocrine prostate cancer.
- Recent advances in genomic and molecular research, supported by novel *in vivo* models, had identified some of the key molecular characteristics of treatment-related neuroendocrine prostate cancer.
- The gain of *MYCN* and *AURKA* oncogenes, together with the loss of tumour suppressor genes *TP53* and *RB1* are key genomic alterations associated with treatment-related neuroendocrine prostate cancer.
- Androgen receptor repressed genes, such as *BRN2* and *PEG10*, are also necessary for treatment-related neuroendocrine prostate cancer.
- These genetic changes converge upon pathways upregulating genes, such as *SOX2* and *EZH2*, which facilitate lineage plasticity and neuroendocrine differentiation.
- As a result, on potent androgen receptor pathway inhibition, castration-resistant prostate cancer transdifferentiates to treatment-related neuroendocrine prostate cancer in a clonally divergent manner.
- Further understanding of the disease biology is necessary in order to develop novel drugs and biomarkers that would help treat this aggressive prostate cancer variant.

Stock et al. [21] stated the following:

- The androgen receptor (AR) signalling pathway is critical for growth and differentiation of prostate cancer cells.

- For that reason, androgen deprivation therapy with medical or surgical castration is the principal treatment for metastatic prostate cancer.
- More recently, new potent AR signalling inhibitors (ARSIs) had been developed.
- These drugs improve survival for men afflicted by metastatic castration-resistant prostate cancer (CRPC), the lethal form of the disease.
- Nevertheless, ARSI resistance is nearly universal.
- One recently appreciated resistance mechanism is lineage plasticity or switch from an AR-driven, luminal differentiation program to an alternate differentiation program.
- Importantly, lineage plasticity appears to be increasing in incidence in the era of new ARSIs, strongly implicating AR suppression in this process.
- Lineage plasticity and shift from AR-driven tumours occur on a continuum, ranging from AR-expressing tumours with low AR activity to AR-null tumours that have activation of alternate differentiation programs versus the canonical luminal program found in AR-driven tumours.
- In many cases, AR loss coincides with the activation of a neuronal program, most commonly exemplified as therapy-induced neuroendocrine prostate cancer (t-NEPC).
- While genetic events clearly contribute to prostate cancer lineage plasticity, it is also clear that epigenetic events-including chromatin modifications and DNA methylation-play a major role.
- Many epigenetic factors are now targetable with drugs, establishing the importance of clarifying critical epigenetic factors that promote lineage plasticity.
- In addition, epigenetic marks are readily measurable, demonstrating the importance of clarifying which measurements will help to identify tumours that have undergone or are at risk of undergoing lineage plasticity.

Conteduca et al. [22] made the ensuing iterations:

- Neuroendocrine prostate cancer (NEPC) is an aggressive variant of prostate cancer which may arise de novo or in patients previously treated with hormonal therapies for prostate adenocarcinoma as a mechanism of resistance.

- Despite being important to recognise, the clinical manifestations of NEPC are poorly defined and could help guide when to perform a biopsy to look for NEPC histological transformation.

Conteduca et al. [22] reviewed baseline, treatment and outcome data of 87 patients with metastatic prostate cancer and tumour biopsy confirming NEPC histology. Forty-seven (54.0%) NEPC cases had presented de novo, and 40 (46.0%) were therapy-related (t-NEPC). Thirty-six (41.4%) were classified as pure small-cell carcinoma, and 51 (58.6%) demonstrated mixed features with both small-cell carcinoma and adenocarcinoma present. Genomic data were available for 47 patients. Conteduca et al. [22] summated the results as follows:

- The median age at time of NEPC was 68.1 years, median prostate-specific antigen (PSA) was 1.20 ng/ml (0.14 ng/mL small-cell carcinoma, 1.55 ng/mL mixed carcinoma) and sites of metastases included bone (72.6%), lymph node (47.0%), and viscera (65.5%).

- The median time from adenocarcinoma to t-NEPC diagnosis was 39.7 months (range, 24.5-93.8) with a median of two lines of prior systemic therapy.

- Platinum chemotherapy was used to treat 57.5% of patients, with a median progression-free survival of 3.9 months.

- Small-cell carcinoma was associated with worse overall survival (OS) than mixed histology (8.9 months from NEPC diagnosis versus 26.1 months, $P < 0.001$).

- The median OS of de novo NEPC was shorter than that of t-NEPC (16.8 months from prostate cancer diagnosis versus 53.5 months, $P = 0.043$).

- An average serum PSA rise per month of ≤0.7 ng/ml before t-NEPC; elevated lactate dehydrogenase levels, RB1 and TP53 loss and liver metastases were poor prognostic features.

Conteduca et al. [22] concluded that they had described the clinical features of a cohort of patients with NEPC. These characteristics may inform future diagnostic strategies.

Tritschler et al. [23] made the ensuing iterations:

- Neuroendocrine prostate cancer (NEPC) mostly occurs as a treatment-emergent adaptive response under the pressure of intensive androgen deprivation treatment (t-NEPC).
- About 30% to 40% of patients with metastatic castration-resistant prostate cancer (mCRPC) also have neuroendocrine involvement. In contrast primary small cell prostate cancer is very rare (<1%).
- A t-NEPC should be clinically suspected in patients who have particularly aggressive mCRPC but a disproportionately low prostate-specific antigen (PSA) level and elevated neuroendocrine tumour markers, such as chromogranin A and neuron-specific enolase.
- The initial Gleason score was shown to be an independent factor correlated to the risk of development of t-NEPC.
- Treatment is oriented to that of small cell lung cancer. In patients with negative PSA levels, chemotherapy with cisplatin and etoposide is the first line treatment, for which response rates in the range of 30% to 60% with a median survival time of usually less than 1 year can be achieved.
- In patients with much higher serum PSA levels, chemotherapy with carboplatin plus docetaxel should be considered.

Tu et al. [25] stated that large cell neuroendocrine carcinoma (LCNEC) of the prostate is an extremely rare entity, and the clinicopathological course, potential effective treatment, and prognosis are yet to be elucidated. Tu et al. [25] undertook a systematic search in Pubmed, Embase, and Ovid from inception to January 2019. Tu et al. [25] reviewed each individual case of prostatic LCNEC and summarized specific features and outcomes for this rare pathologic entity. Tu et al. [25] summarised the results as follows:

- Thirteen studies with a total of 20 patients (mean age: 70.3, range 43-87) were included in our review.
- Seventeen patients had harboured primary LCNEC of the prostate, of which 9 patients were diagnosed with de novo carcinoma, and 8 patients were with a history of prostatic adenocarcinoma treated with hormonal therapy (mean duration: 2.9 years, range 2 years to 5 years).
- The other 3 patients were diagnosed with metastatic LCNEC originating from lung (2 cases) and bladder (1 case).
- All patients met the diagnostic criteria of the typical morphological features as well as immunohistochemical staining results.
- Nearly all primary de novo LCNEC of the prostate were at a late stage at initial diagnosis.
- The pattern of distant metastasis resembled that of prostatic adenocarcinoma with the most common sites as bone spread (8/16, 50%).
- Majority of the patients received systematic chemotherapy after diagnosis; however, the prognosis remained poor and patients deteriorated rapidly but with exception.

- Three reported cases in the context of de novo LCNEC admixed with prostatic adenocarcinoma kept sustained response to androgen deprivation therapy (ADT) and achieved obviously better survival outcomes compared with other patients.

Tu et al. [25] made the ensuing conclusions:

- LCNEC of the prostate is a rare entity which mostly occurs pursuant to long-standing hormonal therapy of prostatic adenocarcinoma.
- The prognosis was universally poor irrespective of the systematic chemotherapy.
- Nevertheless, patients of de novo tumour mixed with prostatic adenocarcinoma may respond to ADT and harbour a better outcome than those of pure de novo or post-ADT LCNEC of the prostate.

George et al. [27] made the ensuing iterations:

- ^{177}Lu is a radioisotope that has become increasingly popular as a therapeutic agent for treating various conditions, including neuroendocrine tumours and metastatic prostate cancer.
- ^{177}Lu-tagged radioligands are molecules precisely designed to target and bind to specific receptors or proteins characteristic of targeted cancer.

Yao et al. [28] made the ensuing iterations:

- Small cell carcinoma of the prostate (SCPC) is morphologically similar to small cell carcinoma of the lung (SCLC) and maybe misinterpreted as Gleason pattern 5b prostate adenocarcinoma (HGPC).
- Recognition of SCPC is important because of its different clinical behaviour.

Yao et al. [28] undertook a study which was aimed to characterize the immunophenotype of histologically classic SCPC using a comprehensive panel of markers, to better understand its histogenesis, aid in its classification, and evaluate potential therapeutic targets. Yao et al. [28] using the World Health Organization morphologic criteria for SCLC, identified 18 SCPC cases and studied for the following tumour marker groups: prostate specific/related, neuroendocrine, sex steroid hormone receptors, and prognostic/treatment target-related. Yao et al. [28] used ten cases of UPC as controls. Yao et al. [28] summarised the results as follows:

- PSA was positive in 17% of SCPC and neuroendocrine markers were expressed in HGPC. PSA, TTF-1 and CD56 were the most helpful markers in differentiating between SCPC and HGPC ($P<0.01$), whereas bombesin/GRP, c-kit, bcl-2, and EGFR expression was more frequent in SCPC.

Yao et al. [28] made the ensuing conclusions:

- SCPC is best diagnosed by following the World Health Organization diagnostic criteria for SCLC.
- Immunohistochemistry markers can help separate SCPC from HGPC and may be useful in histologically borderline cases.
- Potential therapeutic targets are identified immunohistochemically in SCPC (Bombesin/GRP, c-kit, bcl-2, and EGFR).

Nava Rodrigues et al. [29] stated the ensuing:

- Metastatic castration-resistant prostate cancer (mCRPC) is a lethal but clinically heterogeneous disease, with patients having variable benefit from endocrine and cytotoxic treatments.
- Intra-patient genomic heterogeneity could be a contributing factor to this clinical heterogeneity.

Nava Rodrigues et al. [29] used whole-genome sequencing (WGS) to investigate genomic heterogeneity in 21 previously treated CRPC metastases from 10 patients to investigate intrapatient molecular heterogeneity (IPMH). Nava Rodrigues et al. [29] performed WGS on topographically separate metastases from patients with advanced metastatic prostate cancer. IPMH of the *RB1* gene was identified and further evaluated by FISH and IHC assays. Nava Rodrigues et al. [29] summarised the results as follows:

- WGS had identified limited IPMH for putative driver events. Nevertheless, heterogeneous genomic aberrations of *RB1* were detected.
- They had confirmed the presence of these *RB1* somatic copy-number aberrations, initially identified by WGS, with FISH, and identified novel structural variants involving *RB1* in 6 samples from 3 of these 10 patients (30%; 3/10).
- WGS had uncovered a novel deleterious *RB1* structural lesion constituted of an intragenic tandem duplication involving multiple exons and associating with protein loss.
- Using RB1 IHC in a large series of mCRPC biopsies, they had identified heterogeneous expression in approximately 28% of mCRPCs.

Nava Rodrigues et al. [29] made the ensuing conclusions:

- mCRPCs have a high prevalence of *RB1* genomic aberrations, with structural variants, including rearrangements, being common.
- Intra-patient genomic and expression heterogeneity favours *RB1* aberrations as late, sub-clonal events that increase in prevalence due to treatment-selective pressures.

Uehara et al. [30] stated that a new subtype of prostate cancer called treatment-related neuroendocrine prostate carcinoma (t-NEPC) was added to the revised World Health Organization classification of prostate cancer in 2022. t-NEPC cases are increasing, and there is no established standard treatment. Uehara et al. [30] reported a 49-year-old male patient, who was referred to their department for dysuria. He underwent a rectal examination and a prostate biopsy, which revealed stony hardness and prostate adenocarcinoma, respectively. He had radiology imaging studies which confirmed the presence of multiple bone and lymph node metastases. The patient was commenced upon upfront treatment with androgen deprivation therapy and an androgen receptor signalling inhibitor, that resulted in a significant (>90%) decrease in his serum prostate-specific antigen (PSA) levels. The patient experienced postrenal failure 6 months subsequently, which was attributable to local disease progression. Concurrently, there was an elevation in neuron-specific enolase (NSE) levels and an enlargement of pelvic lymph node metastases, without PSA progression. Uehara et al. [30] also reported the ensuing results:

- Biopsy specimen for cancer genome profiling demonstrated deletion of BRCA 2 and PTEN, AR amplification, and the presence of the TMPRSS2-ERG fusion gene.
- Based upon increased NSE and BRCA2 mutations, a diagnosis of t-NEPC with BRCA2 mutation was eventually made.
- The patient received docetaxel chemotherapy and pelvic radiotherapy.
- He was subsequently, treated with olaparib. His NSE levels decreased, and he achieved a complete response (CR). Nevertheless, 18 months following the olaparib administration, brain metastases appeared despite the absence of pelvic tumour relapse, and the patient's serum PSA levels remained low. Consequently, the patient underwent resection of the brain metastases using gamma knife and whole-brain radiotherapy but died about 3 months subsequently.

Uehara et al. [30] made the ensuing conclusions:

- Platinum-based chemotherapy is often administered for the treatment of t-NEPC; however, there are few reports on the effectiveness of olaparib in patients with BRCA2 mutations.
- In a literature review, their reported case had demonstrated the longest duration of effectiveness with olaparib alone without platinum-based chemotherapy.
- Additionally, the occurrence of relatively rare, fatal brain metastases in prostate cancer after a long period of CR indicates the necessity of regular brain imaging examinations.

Wang et al. [24] stated that an often-under-recognized late manifestation of prostate adenocarcinoma (PCa) is the development of treatment-related neuroendocrine prostate cancer (NEPC). Wang et al. [24] undertook a study in order to identify the risk factors related to survival after NEPC diagnosis (NEPCS) and time from initial diagnosis of PCa to development of NEPC (TTNEPC). Wang et al. [24] undertook a literature search on NEPC using databases such as MEDLINE and EMBASE. Wang et al. [24] iterated that the studies were eligible if outcomes data (NEPCS and/or TTNEPC) were reported in patients with a prior history of PCa and histopathologically confirmed NEPC. Wang et al. [24] evaluated NEPCS and TTNEPC using the Cox regression model with the robust sandwich estimates of the covariance matrix. Wang et al. [24] summarised the results as follows:

- There were 54 eligible publications, contributing 123 patients.
- The median TTNEPC was 20 months.
- In multivariable analyses, the Gleason score was found to be significantly associated with shorter TTNEPC (hazard ratio [HR], 1.66; P = .032).
- The median NEPCS was 7 months.
- In multivariable analyses, the number of organs with metastatic disease at NEPC was significantly associated with shorter NEPCS (HR, 3.31; P = .001).
- Type of treatment after NEPC was found to be significantly associated with longer NEPCS, with HRs of 0.66 (radiotherapy v palliative therapy; P = .034), 0.38 (chemotherapy v palliative therapy; P = .018), and 0.29 (chemoradiotherapy v palliative therapy; P = .012), respectively.

Wang et al. [24] made the ensuing conclusions:

- Treatment-related NEPC is an often-under-recognized late manifestation of PCa with poor prognosis.
- Their study found that Gleason score was the only independent factor contributing to TTNEPC.
- Once NEPC is diagnosed, type of treatment and the number of organs with metastatic disease were the most important factors related to survival.

Ikeda et al. [31] made the ensuing iterations:

- PARP is critical in DNA damage repair. Olaparib, its selective inhibitor, exploits synthetic lethality against CRPC with HRD. [32]
- NEPC, a CRPC status after androgen deprivation therapy (ADT), is typified by either low or absent androgen receptor expression, small-cell carcinoma morphology, and expression of neuroendocrine markers. [33]
- It has been documented that in majority of cases with t-NEPC, the efficacy of chemotherapy is limited, and the prognosis is extremely poor. [1]
- Mutations in HRR genes, including breast cancer gene (*BRCA*) mutation, are rare in t-NEPC, [34] and the efficacy of olaparib for t-NEPC remains unclear.
- They had reported a case of t-NEPC with a *BRCA2* mutation that was treated with sustained tumour regression for 1 year.

Ikeda et al. [31] reported that in 2008, a 64-year-old man with a serum PSA level of 6.5 ng/mL and a family history of breast and prostate cancers was diagnosed as having cT3N0M0 prostate cancer. Pathology examination of his prostate biopsy specimen revealed adenocarcinoma with a Gleason score of 4 + 5 = 9. The patient underwent a prostatectomy 3 months after receiving neoadjuvant hormonal treatment. One year pursuant to his prostatectomy surgery, salvage ADT was introduced for biochemical recurrence, and the PSA level was <0.02 ng/mL. In 2015, the patient progressed to non-metastatic CRPC, with elevated PSA levels and local recurrence within his pelvic floor. The disease was controlled with salvage radiotherapy (74 Gy/37 Fr) to the pelvic floor, with decreased serum PSA levels. His NSE and proGRP levels were 12.5 ng/mL (normal: <16.3 ng /mL) and 53.8 ng/mL (normal: <67 pg/mL), respectively, at the end of his salvage radiotherapy. In 2019, his serum PSA levels decreased to 0.001 ng/mL. Nevertheless, his NSE and proGRP levels increased to 31.8 ng/mL and 65.8 pg/mL, respectively, despite his low serum PSA levels. He underwent radiology imaging which demonstrated a resurgence of the pelvic floor tumour and mediastinal and pelvic lymph node metastases. Pathology examination of specimens of his biopsy of the pelvic floor tumour demonstrated small malignant cells with a high nuclear-to-cytoplasmic ratio, and frequent mitotic figures were noted to be arranged in diffuse sheets. Immunohistochemistry staining studies of specimens of the tumour showed that the tumour cells had exhibited positive staining for synaptophysin, CD56, and chromogranin A but negative for PSA. Based upon the appearance of tumour cells and positive findings for neuroendocrine markers, the recurrent tumour was pathologically diagnosed as small-cell NEPC and clinically diagnosed as t-NEPC. Adenocarcinoma components were not identified.

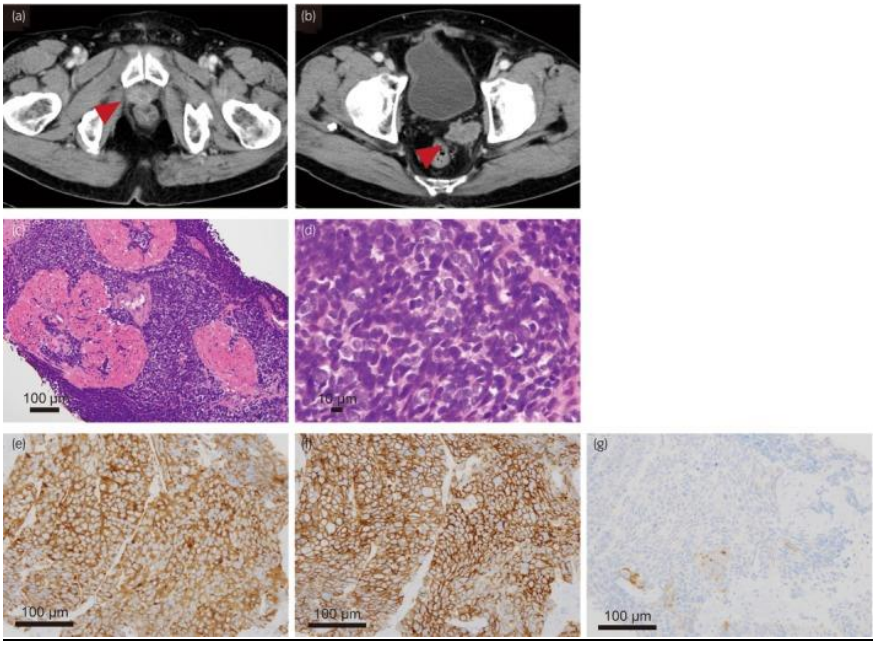

Figure 1: Computed tomography image when the patient was diagnosed with t-NEPC (a, b) and microscopic findings of the tumour (c–g). (c) Small, clustered cells with a high nuclear-to-cytoplasmic ratio and no glandular pattern are observed (hematoxylin and eosin staining: ×20). (d) There are frequent mitotic figures (hematoxylin and eosin staining: ×100). (e) The tumour cells are positive for synaptophysin, (f) CD56, and (g) chromogranin A, partially (×200). Reproduced from [31] under the Creative Commons Attribution License.

The clinical course pursuant to the NEPC diagnosis is shown in Figure 2. Four-month chemotherapy with ETP and CBDCA resulted in a complete response. Nevertheless, in 2021, the pelvic floor tumour recurred again (see figure 3). Ikeda et al. [31] recommenced ETP and CBDCA chemotherapy, but the patient discontinued because he experienced delirium. At that time, the FoundationOne® genomic test on the biopsy specimen of the pelvic floor tumour diagnosed as NEPC revealed a *BRCA2* gene mutation and some variants of uncertain significance. A single-site analysis with peripheral blood was undertaken to confirm the pathogenic variant identified in FoundationOne®; the patient harboured a *BRCA2* germline mutation. Therefore, olaparib was administered as a fifth-line treatment for prostate cancer. The proGRP level decreased, and the tumour diminished in size, suggesting stable disease following the revised Response Evaluation Criteria in Solid Tumours version 1.1. [35] Nevertheless, the proGRP level gradually increased after 1 year of treatment with olaparib and 15 months after commencing olaparib, the pelvic floor tumour demonstrated regrowth, indicating progressive disease. The patient continued olaparib for 40 months after t-NEPC diagnosis because of a slow increase in tumour size and minimal side effects.

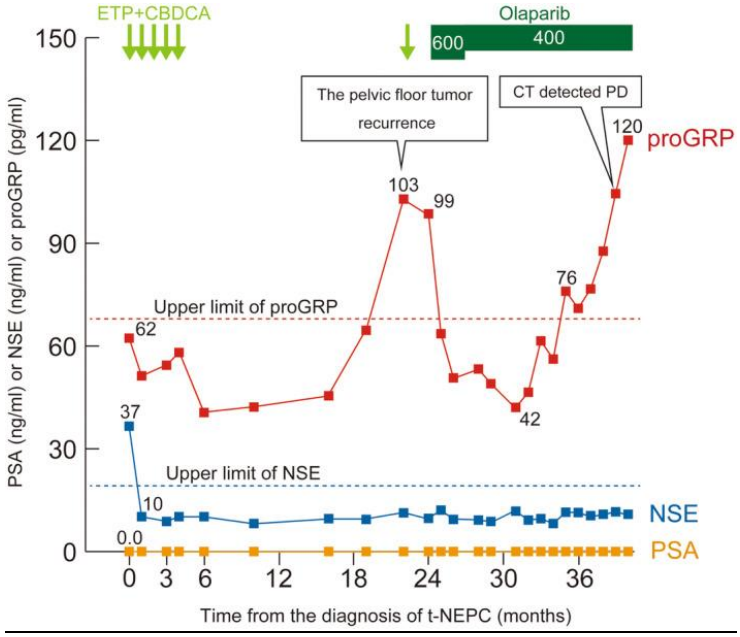

Figure 2: The clinical course after the diagnosis of t-NEPC. Olaparib resulted in decreased proGRP level and tumour reduction. Reproduced from [31] under the Creative Commons Attribution License.

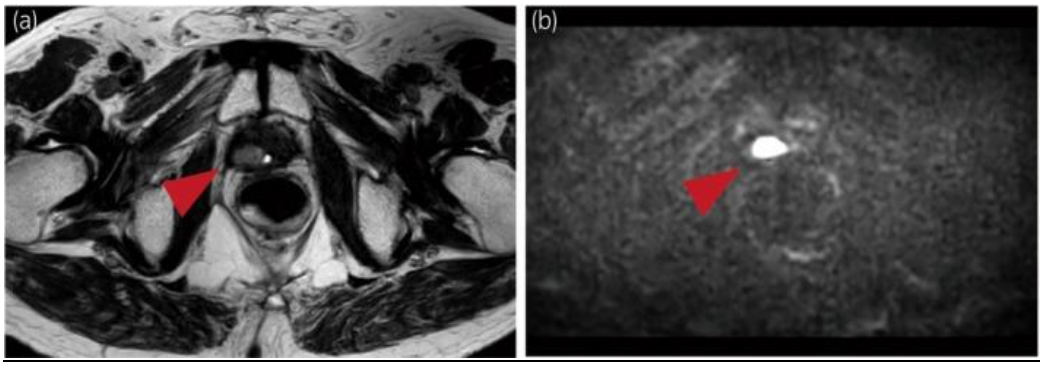

Figure 3: Magnetic resonance imaging of recurrent pelvic floor tumour before olaparib administration. The tumours show faintly high signal intensity on T2-weighted images and are diffusion-weighted image-positive. Reproduced from [31] under the Creative Commons Attribution License.

Ikeda et al. [31] made the ensuing educative discussions

- To their knowledge, their reported case was the eighth t-NEPC case treated with olaparib, and the rarity of their case is due to the relatively long-term disease control with olaparib.
- Low serum PSA levels, positive neuroendocrine markers, and an aggressive clinical course characterize t-NEPC. [1] [36]
- Their patient experienced rapid local progression and distant lymph node metastasis with low PSA levels and was diagnosed with t-NEPC after a 10-year ADT. de novo NEPC at the initial diagnosis of prostate cancer is very rare; [37] nevertheless, the incidence of t-NEPC in CRPC is considered high because of the widely used ADT and androgen receptor axis-targeted agents [38]
- Aggarwal et al. reported that 17% of patients with CRPC had histologic neuroendocrine features in biopsies of metastatic sites. [34]
- In reports of t-NEPC genomic alteration, *MYCN* and *AURKA* amplifications were detected in 65% of patients with primary prostate cancer who developed t-NEPC. [39]
- Loss of function in *TP53* or *RB1* is not found in a few t-NEPC cases. [40]
- These genomic features may be deeply involved in the development of t-NEPC; [1] however, we did not observe these gene mutations in our patient, indicating there might be other genomic or epigenetic alterations that trigger t-NEPC arising from initial adenocarcinoma. [41]
- t-NEPCs often manifest poorer prognosis than common prostate adenocarcinoma. [34]
- Following the National Comprehensive Cancer Network guidelines version 1.2023, the standard treatment for NEPC is chemotherapy with ETP and platinum-based drugs such as CDDP. t-NEPCs are initially sensitive to chemotherapy; tumours soon develop resistance, and median overall survival is approximately 7 months. [1] [24]
- Therefore, more effective treatment options are required. Recently, several cases of t-NEPC treated with olaparib have been reported. [42] [43] [44] [45] [46] [47]
- Three patients had exhibited a partial response to Olaparib.
- However, in majority of the cases, the efficacy of olaparib in treating t-NEPC was observed only for a short duration (<6 months).
- In contrast, in their reported case, olaparib provided >1-year efficacy with stable t-NEPC.
- Regarding ovarian cancer, platinum resistance is stated to be related to olaparib resistance. [48]
- In their patient, platinum-based chemotherapy was still effective, and olaparib was initiated before the tumour acquired platinum resistance. This suggested that olaparib can be successfully used to treat t-NEPC before chemotherapy or as an early-line treatment.

Ikeda et al. [31] made the ensuing conclusions:

- They had reported a case of t-NEPC treated with olaparib that achieved a 1-year stable disease.
- Additional cases are required in order to clarify the ideal treatment strategy for t-NEPC; nevertheless, olaparib may be the treatment of choice for this aggressive disease.

Nguyen et al. [49] stated the following:

- The use of potent treatments inhibiting critical oncogenic pathways active in epithelial cancers has led to multiple resistance mechanisms including the development of highly aggressive, small cell neuroendocrine carcinoma (SCNC).
- SCNC patients have a dismal prognosis due in part to a limited understanding of the molecular mechanisms driving this malignancy and the lack of effective treatments.
- They had demonstrated that a common set of defined oncogenic drivers reproducibly reprograms normal human prostate and lung epithelial cells to small cell prostate cancer (SCPC) and small cell lung cancer (SCLC), respectively.
- They had identified shared active transcription factor binding regions in the reprogrammed prostate and lung SCNCs by integrative analyses of epigenetic and transcriptional landscapes.
- These results indicated that neuroendocrine cancers arising from distinct epithelial tissues may share common vulnerabilities that could be exploited for the development of drugs targeting SCNCs.

Iwamoto et al. [50] stated that neuroendocrine prostate cancer (NEPC) is rare and has a poor prognosis; its clinical course and treatment outcomes are also unclear. Iwamoto et al. [50] undertook a study to investigate the clinical

characteristics, clinical course, and treatment outcomes of patients with NEPC. Iwamoto et al. [50] undertook a retrospective study to investigate 14 patients, who were histologically diagnosed with NEPC at Kanazawa University Hospital between 2000 and 2019. Iwamoto et al. [50] reported that the overall survival (OS) and progression-free survival (PFS) were retrospectively analysed using the Kaplan–Meier method. Iwamoto et al. [50] additionally, used log-rank tests to compare survival distributions. Iwamoto et al. [50] summarised the results as follows:

- They had included 14 patients histologically diagnosed with NEPC among 1,845 patients with prostate cancer.
- Four patients (0.22%) were diagnosed with de novo NEPC, and ten patients were diagnosed with NEPC during treatment.
- First-line platinum-based therapy's objective response rate (ORR) was 66.7%, and disease control rate was 91.7%; median PFS was 7.5 months.
- The median OS from NEPC diagnosis was 20.3 months. The median OS of the liver metastasis (−) group was 31.6 months, and that of the (+) group was 9.4 months (p=0.03, hazard ratio=0.24). The median OS of the somatostatin receptor scintigraphy (SRS)-positive group was 31.6 months, and that of the SRS-negative group was 10.6 months (p=0.04, hazard ratio=0.14).

Iwamoto et al. [50] made the ensuing conclusions:

- Platinum-based chemotherapy is effective to some extent; however, the duration of response is not sufficient; therefore, new treatment options are required.
- Their reported study, was the first study to show that SRS findings and the presence of liver metastases might be prognostic predictors of NEPC.

Beltran and Demichelis [51] made the ensuing iterations:

- Lineage plasticity and histological transformation to small cell neuroendocrine prostate cancer (NEPC) is an increasingly recognized mechanism of treatment resistance in advanced prostate cancer.
- This is associated with aggressive clinical features and poor prognosis.
- Recent work had identified genomic, epigenomic, and transcriptome changes that distinguish NEPC from prostate adenocarcinoma, pointing to new mechanisms and therapeutic targets.
- Treatment-related NEPC arises clonally from prostate adenocarcinoma during the course of disease progression, retaining early genomic events and acquiring new molecular features that lead to tumour proliferation independent of androgen receptor activity, and ultimately demonstrating a lineage switch from a luminal prostate cancer phenotype to a small cell neuroendocrine carcinoma.
- Identifying the subset of prostate tumours most vulnerable to lineage plasticity and developing strategies for earlier detection and intervention for patients with NEPC may ultimately improve prognosis.
- Clinical trials focused upon drug targeting of the lineage plasticity process and/or NEPC would require careful patient selection.

Yamada and Beltran [52] made the ensuing iterations:

- Neuroendocrine prostate cancer (NEPC) is an aggressive histologic subtype of prostate cancer which most commonly arises in later stages of prostate cancer as a mechanism of treatment resistance.
- The poor prognosis of NEPC is attributed in part to late diagnosis and a lack of effective therapeutic agents.
- They had reviewed the clinical and molecular features of NEPC based on recent studies and outline future strategies and directions.

Yamada Y, Beltran [52] summarised recent findings as follows:

- NEPC could arise "de novo" but most commonly emanates as a result of lineage plasticity whereby prostate cancer cells adopt alternative lineage programs as a means to bypass therapy.
- Dependence upon androgen receptor (AR) signalling is lost as tumours progress from a prostate adenocarcinoma to a NEPC histology, typically manifested by the downregulation of AR, PSA, and PSMA expression in tumours.
- Genomic analyses from patient biopsies combined with preclinical modelling have pointed to loss of tumour suppressors *RB1* and *TP53* as key facilitators of lineage plasticity.
- Activation of oncogenic drivers combined with significant epigenetic changes (e.g., EZH2 overexpression, DNA methylation) further drives tumour proliferation and expression of downstream neuronal and neuroendocrine lineage pathways controlled in part by pioneer and lineage determinant transcription factors (for example., SOX2, ASCL1, BRN2).
- These biological insights have provided a framework for the study of this subgroup of advanced prostate cancers and have started to provide rationale for the development of biomarker-driven therapeutic strategies.

Yamada and Beltran [52] made the ensuing summating recommendation:

- Further study of the dynamic process that leads to NEPC is required for the development of effective strategies to identify and treat patients developing lineage plasticity as a mechanism of treatment resistance is required.

Apostolidis et al. [53] stated the following:

- Neuroendocrine carcinomas of the prostate (NEPCs) are rare tumours which are associated with poor prognosis.
- While platinum and etoposide-based chemotherapy regimens (PE) are commonly applied in first-line for advanced disease, evidence for second-line therapy and beyond is very limited.

Apostolidis et al. [53] undertook a retrospective analysis of all patients with NEPCs including mixed differentiation with adenocarcinoma component and well differentiated neuroendocrine tumours (NETs, carcinoids) at two high-volume oncological centres between 12/2000 and 11/2017. Apostolidis et al. [53] summarised the results as follows:

- Of 46 identified patients 39.1 % had a prior diagnosis of prostatic adenocarcinoma only, 43.5 % had a mixed differentiation at NEPC diagnosis, 67.4 % developed visceral metastases, 10.9 % showed paraneoplastic syndromes.
- The overall survival (OS) from NEPC diagnosis was 15.5 months, and significantly shorter in patients with a prior prostatic adenocarcinoma (5.4 vs. 32.7 months, p=0.005).

- 34 patients received palliative first-line systemic treatment with a median progression-free survival (PFS) of 6.6 months, mostly PE.
- The overall response rate (ORR) for PE was 48.1 %. 19 patients received second-line therapy, mostly with poor responses. Active regimens were topotecan (1 PR, 3 PD), enzalutamide (1 SD), abiraterone (1 SD), FOLFIRI (1 SD), and ipilimumab+nivolumab (1 PR).
- One patient with prostatic carcinoid was sequentially treated with octreotide, peptide receptor radionuclide therapy and everolimus, and survived for over 9 years.

Apostolidis et al. [53] made the ensuing conclusions:

- EP in first-line shows notable ORR; nevertheless, limited PFS.
- For second-line treatment, topotecan, FOLFIRI, enzalutamide, abiraterone and immune checkpoint blockade are treatment options.
- Prostatic carcinoids could be treated in analogy to well differentiated gastrointestinal NETs.

Jiborn et al. [54] made the ensuing iterations:

- Neuroendocrine differentiation (NED) is a common feature in adenocarcinoma of the prostate.
- Many studies had suggested that NED may have a major impact on cancer progression as neuroendocrine (NE) secretory products have been shown to possess growth stimulatory effects.
- NED has also been postulated to constitute part of the mechanism by which a prostate cancer cell progresses toward androgen independence as NE tumour cells have been demonstrated to be devoid of androgen receptor immunoreactivity.
- In their retrospective study, they had evaluated NED status in prostate cancer specimens from patients undergoing androgen ablation therapy.

Jiborn et al. [54] investigated the degree of NED in trans-urethral resection of the prostate (TURP) samples from 53 patients with prostate cancer by immunohistochemistry staining studies using polyclonal rabbit immunoglobin G (IgG) against chromogranin A (CgA). Jiborn et al. [54] determined changes in NED with time by a manual semiquantitative cell counting method. Jiborn et al. [54] summarised the results as follows:

- During androgen withdrawal therapy, 21 tumours (40%) had displayed increased NED concomitant with histopathologic tumour progression, whereas 29 carcinomas (55%) had shown no change in NED status.
- Nevertheless, a majority of the histopathologically unchanged tumours had displayed marked NED at the first TURP and an increase in NED was by definition not possible.
- In only 3 cases (5%) was a decrease in NED observed with time.

Jiborn et al. [54] concluded that:

Androgen ablation therapy may be a contributing factor to the increase in NED of prostatic adenocarcinoma with time, and their findings implied that androgen withdrawal therapy enhances the selection and progression of NED, androgen-independent tumour cells.

Yao et al. [38] stated the following:

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

Yao et al. [38] obtained a total of 530440 patients of prostate cancer, including neuroendocrine prostate cancer (NEPC) and adenocarcinoma from 2004 to 2018 from the national Surveillance, Epidemiology, and End Results (SEER) database. Yao et al. [38] performed propensity score matching (PSM), multivariable Cox proportional hazard model, Kaplan-Meier method and subgroup analysis in their study. Yao et al. [38] summarised the results as follows:

- 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.
- Nevertheless, 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 had demonstrated that the 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 adenocarcinoma patients after PSM.
- Subgroup analyses had further suggested that NEPC patients obtained significantly poorer prognosis across nearly all subgroups. Yao et al. [38] made the ensuing conclusions:
- The prognosis of NEPC was worse than that of adenocarcinoma among patients with prostate cancer.
- The histopathology sub-type of NEC is an independent prognostic factor for patients with prostate cancer.

Gopalan et al. [26] made the ensuing iterations:

- Treatment-related neuroendocrine carcinoma of the prostate gland is stated to be a distinctive category of carcinoma of the prostate gland which tends to ensue intensive suppression of the androgen receptor by next-generation therapeutic inhibition of androgen receptor signalling.
- The biological processes which set in motion the series of events emanating in transformation of adenocarcinoma to neuroendocrine carcinoma had been iterated to include genomic (loss of tumour suppressors TP53 and RB1, amplification of oncogenes N-MYC and Aurora Kinase A, dysregulation of transcription factors SOX2, achaete-scute-homolog 1, and others) as well as epigenomic (DNA methylation, EZH2 overexpression, and others).
- Pathology examination diagnosis of specimens of the tumour had been iterated to be the key to effective treatment for this disease, and this is aided by localizing metastatic lesions for biopsy utilising radioligand imaging in the appropriate clinical context.
- As the understanding of biology of the tumour has evolved, there has been increased morphology examination recognition and characterization of tumour phenotypes which are present within this advanced post-treatment setting.
- New and promising biomarkers (delta-like ligand 3 and others) had been discovered, which had opened up novel treatment avenues including immunotherapy and antibody-drug conjugates for this lethal disease with currently limited treatment options.

Conclusions

- Neuroendocrine prostate cancer (NEPC) is a highly aggressive variant of castration-resistant prostate cancer.
- NEPC is typified by low or no expression of the androgen receptor (AR), activation of AR-independent signalling, and increased neuroendocrine phenotype.
- Majority of NEPC is induced by treatment of androgen deprivation therapy and androgen receptor pathway inhibitors (ARPIs).
- Currently, the treatment of NEPC follows the treatment strategy that is used for small-cell lung cancer, lacking effective drugs and specific treatment options.
- NEPCs are aggressive tumours that portend a poor prognosis despite treatment.
- It is important for clinicians and patients all over the world to appreciate that treatment related neuroendocrine carcinoma of the prostate gland generally has tended to portend an aggressive clinical and biological behaviour that has tended to be associated with poor prognosis and early death of individuals afflicted by the tumour.
- There is the need for clinicians and research workers to undertake research work which would identify new treatment options that would help improve the outcome of the tumour by destroying the tumour cells effectively.

Conflict of Interest – Nil

Acknowledgements

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