Uro-Technology Journal 2023; 7(3): XX-XX *XX*
DOI: 10.31491/UTJ.2023.09.XXX

Neuroendocrine prostate tumors: histologic features and therapy

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Abstract

Neuroendocrine (NE) tumors of the prostate are rare tumors, that can arise *de novo* but much more commonly occur after androgen deprivation therapy for prostate adenocarcinoma. NE tumors of the prostate are classified into: adenocarcinoma with NE differentiation, well-differentiated NE tumor/carcinoid, small-cell NE carcinoma, large cell NE carcinoma, adenocarcinoma with Paneth cell NE differentiation and mixed NE carcinoma—acinar adenocarcinoma. IHC plays a vital role and should be approached at two levels. For the issue of confirming NE differentiation, markers for NE differentiation include synaptophysin, chromogranin, and CD56. If there is any uncertainty about the histogenesis, that is, whether a tumor is primary to the prostate, markers for prostatic lineage—PSA, PSAP, PSMA, prostein (p501s), NKX3.1, ERG (by IHC or FISH)—may be used. Actually, platinum-based chemotherapy is commonly administered to patients with pure small cell carcinoma based on small cell lung cancer (SCLC) data and the accumulating data for aggressive variants of castration-resistant prostate cancer (AVPC). This may consist of a combination of carboplatin (or sometimes cisplatin) plus either etoposide (based on SCLC) or a taxane (especially if mixed histology or AVPC features). A combination regimen of cisplatin, etoposide, and doxorubicin has been also investigated but the benefit-risk ratio of the three-drug combination was considered unfavorable. Unfortunately, platinum-based chemotherapy often presents high toxicity and a short overall survival. Results of currently ongoing preclinical and clinical studies are expected to enhance our understanding of these tumors' underlying biology and guide our efforts toward the development of personalized medicine through targeted diagnostic and therapeutic approaches.
Keywords: Prostate cancer, neuroendocrine disease, histologic differentiation, systemic therapies

Introduction

Prostate cancer (PC) is the second most commonly diagnosed cancer in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed [1]. The actual prevalence of PC is at age < 30 years of 5% [95% confidence interval (CI): 3–8%], increasing by an odds ratio (OR) of 1.7 (1.6–1.8) per decade, to a prevalence of 59% (48–71%) by age > 79 years [2]. The incidence of PC diagnosis varies widely between different geographical areas, being highest in Australia/New Zealand and Northern America [age-standardized rates (ASR) per 100,000 of 111.6 and 97.2, respectively], and in Western and Northern Europe (ASRs of 94.9 and 85, respectively), largely due to the use of prostate-specific antigen (PSA) testing and the aging population. The incidence is low in Eastern and South-Central Asia (ASRs of 10.5 and 4.5, respectively), whilst rates in Eastern and Southern Europe, which were low, have shown a steady increase [1]. Based on the histological characteristics, PCs are mostly represented by acinar type adenocarcinoma, composed of tumor cells with luminal differentiation including the expression of prostate-specific antigen (PSA) and androgen receptor (AR) [3, 4]. Differently, neuroendocrine (NE) tumors of the prostate are rare, and they usually occur after androgen deprivation therapy for prostate adenocarcinoma.

NE tumors of the prostate can arise *de novo* but much more commonly occur after androgen deprivation therapy for prostate adenocarcinoma. The influence of androgens on the prostate gland represents an important risk factor for the development of PC in different ethnic/racial groups and androgen deprivation therapy (ADT) combined with other therapies which target androgen receptor (AR) sig-

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Received: 27 June 2023 / Accepted: 28 June 2023
Published: XX September 2023

naling such as abiraterone acetate or enzalutamide is a standard first-line approach for metastatic prostate cancer [5]. Most castration-resistant prostate cancers (CRPC) are still dependent on AR signaling through acquired AR gene mutation, amplification, or other means to reactivate the AR [5, 6]. Approximately 15–20% of CRPC tumors will lose dependence on AR signaling at some point during their disease course but the identification of AR-independent disease in the clinic remains challenging. One apparent clinical manifestation is a histologic transformation from an AR-expressing prostate adenocarcinoma to an AR-negative, poorly differentiated small cell neuroendocrine carcinoma histology [7, 8]. This cancer phenotype is often referred to as neuroendocrine prostate cancer (NEPC) to broadly encompass both pure small cell carcinomas and mixed adenocarcinoma neuroendocrine tumor morphologies. AR expression is typically low but even when AR is expressed, NEPC tumors tend to be less dependent, or "indifferent", to canonical AR signaling.

NE cells of the normal prostate

NE cells of the prostate were originally described by Pretl in 1944 [9]. NE cells with the dual properties of endocrine cells and neurons, *i.e*., acting in secretory and autocrine/paracrine fashions, are widely distributed in normal prostatic acini and ducts. In 1999, Aumuller *et al*. suggested human prostate NE cells to be a cell lineage of their own, being of neurogenic origin and therefore distinct from the urogenital sinus-derived prostate secretory and basal cells [10]. There are two types: the open cells with extensions at their apex that connect with the lumen, and closed cells with dendritic processes that extend between adjacent cells, resting on the basal lamina and in close topographical relationship with nerves [11].

NE cells are usually present in the transition zone and peripheral zone of the prostate than the central zone, suggesting their potential involvement in benign prostatic hyperplasia and PC, respectively [4]. NE cells do not express luminal differentiation markers AR or PSA but they are positive for NE markers including chromogranin A (CgA), synaptophysin (SYN), and neural cell adhesion molecule 1 (CD56) [12].

Actually, we ignore the function of NE cells in the prostate. Nevertheless, these cells express serotonin, histamine, CgA, calcitonin, neuron-specific enolase, which play a role in the regulation of the prostate epithelium and sperm function [13].

Pathologic classification of prostate cancer with NE differentiation

In the last decade, the World Health Organization (WHO) and the Prostate Cancer Foundation (PCF) developed a histo-morphologic classification of prostate cancer with NE differentiation, in order to systematically describe this heterogeneous prostate cancer subtype [13, 14] (Table 1).

Neuroendocrine differentiation (NED) is usually present in prostatic carcinomas than in other urogenital tumors because NED is a common feature of prostatic adenocarcinomas and is usually determined by immunoreactivity for neuroendocrine markers (CgA, NSE, or bioactive eutopic hormones such as somatostatin and 5-HT) [11, 15].

As reported in the literature, NED is present in 30–100% of all prostate adenocarcinomas, even if there are other forms of NED associated with small cell carcinomas of the prostate [11, 15]. According to the new WHO classification system, these are entitled small-cell neuroendocrine carcinoma. The malignant phenotype of NED is also found in certain carcinoid and carcinoid-like tumors. However, the most common histopathological pattern is focal NED in conventional adenocarcinomas of the prostate [11, 15]. It has been suggested that NE tumor cells could be found at all stages of PC but they don't express the androgen receptors (AR) [11, 15].

Usual prostate adenocarcinoma with NE differentiation

A usual prostate adenocarcinoma with NE differentiation is referred to prostate adenocarcinoma with acinar or ductal type, in which focal NE cells are appreciable by immunohistochemistry (IHC) alone (*i.e*., synaptophysin, CD56, and chromogranin). The number of NE cells varies from case to case, but generally comprises no more than 1% of the entire tumor cell population. The detection of NE cells depends on the sensitivity and specification of the antibodies against NE markers such as CgA (the most sensitive and specific used marker) and SYN [4, 16]. Several studies have suggested that the number of NE cells is positively correlated with tumor grade and is particularly high in patients treated with hormonal therapy [4, 17]. However, the clinicopathologic significance of NE cells in prostate adenocarcinoma is still uncertain and the role of NED on prognosis could not be explained.

Table 1. Histo-morphologic classifications of prostate cancer with NE differentiation.

Histomorphologic classifications	2016 WHO Classification	PCF Classification
Adenocarcinoma with NE differentiation	YES	YES
Well-differentiated NE tumor/carcinoid	YES	YES
Small cell NE carcinoma	YES	YES
Large cell NE carcinoma	YES	YES
Adenocarcinoma with Paneth cell NE differentiation	NO	YES
Mixed NE carcinoma—acinar adenocarcinoma	NO	YES

Note: NE, neuroendocrine; PCF, Prostate Cancer Foundation; WHO, World Health Organization.

Well-differentiated NE tumor (carcinoid tumor)

A carcinoid tumor is a classic, well-differentiated NE tumor with a morphology similar to that of carcinoid tumors in other sites, including the lung, gastrointestinal tract, and bladder without arising from the urethra/bladder. Carcinoid tumor arises from NE cells and they are positive for NE markers (SYN, CgA, or CD56), negative for PSA but in some cases, these tumors can be positive for prostate-specific acid phosphatase (PAP) [4, 18]. The diagnosis of carcinoid tumor in the prostate needs to meet the following criteria: 1) the tumor must originate from the prostate parenchyma rather than involvement of the prostate by a tumor arising from other organs; 2) the tumor should be distinct from coexisting adenocarcinoma; 3) the tumor must be positive for NE markers and negative for PSA [13]. True carcinoid tumor of prostate is very rare and some cases with a carcinoid-like appearance but positive PSA staining have been found in the literature and therefore cannot be diagnosed as carcinoid tumor and an alternative diagnosis of adenocarcinoma (with focal NE cells) should be considered [19, 20].

Small cell NE carcinoma

Small cell NE carcinoma (SCNC) is an aggressive, high-grade NE tumor with similar morphologic features to those of the lung and other organs. SCNC is defined by characteristic nuclear features, including lack of prominent nucleoli, nuclear molding, fragility, and crush artifact and necrosis is frequent. Approximately, 40% to 50% of small cell carcinomas have a history of usual prostatic adenocarcinoma, with a median interval of diagnosis between the two histological forms of 25 months [13, 21]. Furthermore, SCNCs are generally negative for AR and PSA. Although most cases of SCNC arise in patients who have been treated with hormonal therapy for prostate adenocarcinoma, some patients can develop SCNC as a primary tumor in the prostate. Nevertheless, primary SCNC is rare and comprises less than 1% of prostate cancers [22].
The diagnosis of small cell carcinoma of the prostate is based on the evaluation of morphologic features which are similar to small cell carcinomas of the lung. However, SCNC presents some morphologic variations, such as intermediate cell type, which have slightly more open chromatin and visible small nucleoli in comparison to small cell carcinoma of the lung [21]. Using IHC techniques, the small cell component is positive for 1 or more NE markers (synaptophysin, chromogranin, CD56) in almost 90% of cases, whereas PSA is positive in about 17% to 25% of cases [13, 21]. In 24% and 35% of cases, positivity is noted for p63 and high-molecular weight cytokeratin markers typically negative in prostatic carcinoma [23].
Considering the rarity of primary small cell carcinoma of the prostate, it is important to exclude the presence of metastasis or local extension from other sites such as the bladder. This differential diagnosis can be performed by applying the fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction of a gene fusion between members of the ETS family of genes, in particular ERG (ETS-related gene) and TMPRSS2, found in approximately one-half of the usual prostatic adenocarcinomas [24].
The median cancer-specific survival of patients with small cell carcinoma of the prostate in 191 men according to the SEER database from 1973 to 2004 was 19 months; 60.5% of men presented with metastatic disease with a decreased survival related to the stage; 2- and 5-year survival rates were 27.5% and 14.3%, respectively [25].
Clinically localized small cell prostate cancer is typically treated with multimodality therapy based on chemotherapy and radiation similar to limited-stage small cell lung cancer. In presence of metastases, small cell carcinoma of the prostate is treated with platinum-based combination chemotherapy with regimens similar to those used to treat small cell lung carcinoma. Some experts treat pure small-cell carcinoma with chemotherapy alone, whereas others add ADT [26, 27].

Large cell NE carcinoma

Large cell NE carcinoma (LCNC) was newly included as a type of NE tumor of the prostate in the 2016 World Health Organization classification of prostate tumors [14]. The tumor cells of LCNC grow as solid sheets, ribbons, or nests with focal microscopic necrosis in the center and areas of peripheral palisading [28]. In contrast to SCNC, the tumor cells of LCNC tend to be large, with a polygonal shape and abundant cytoplasm. Tumor cells of LCNC express one or more NE markers (SYN, CgA, or CD56), with variable expression of PSA, PAP, CK7, and CK20 but they are negative for AR. Ki-67 labeling index often exceeds 50% [29, 30]. Pure LCNC is extremely rare and Evans *et al*. presented the largest series of seven cases in 2006 [28]. One patient had a primary prostate tumor, and the other 6 cases arose after hormonal treatment of adenocarcinoma of the prostate. The histologic features are identical to LCNC diagnosed in other anatomic sites such as the lung. The outcome is poor, with a mean survival of 7 months after platinum-based chemotherapy.

Adenocarcinoma with Paneth cell-like NE differentiation

Adenocarcinoma with Paneth cell-like NE differentiation is defined as typical adenocarcinoma of the prostate containing varying proportions of cells with prominent eosinophilic cytoplasmic granules on routine light microscopy (Paneth cell-like change). Paneth cell-like NE differentiation in prostatic adenocarcinoma can be seen as either patchy isolated cells or diffusely involving glands or nests [13, 31]. These Paneth cell-like cells may be present in well-formed glands of Gleason pattern 3 but also can be present in cords of cells with bland cytology, wherein strictly applying the Gleason grading system one would assign a Gleason pattern 5. Although Paneth cell-like NE differentiation could be found in pattern 5, their bland cytology, typically limited nature and frequent association with lower-grade prostate adenocarcinoma suggest not considering this unique histology as high-grade.
Epstein *et al*. reported 16 radical prostatectomy specimens with Paneth cell-like NE cells lacking glandular differ-

entiation. An organ-confined cancer was found in 62.5% of cases, only 4 cases with seminal vesicle invasion and none with pelvic lymph node metastases. The postoperative course was also favorable with a > 90% actuarial PSA progression-free risk at 5 years and the prognosis was influenced by conventional parameters (*i.e.*, the Gleason score, T stage, and positive surgical margins) and not by independent of NE differentiation. Paneth cell-like NE cells are diffusely positive for NE markers but they may not express prostate markers.

Mixed NE carcinoma—acinar adenocarcinom

Mixed NE carcinoma—acinar adenocarcinoma is a carcinoma with distinct, recognizable, admixed components of NE (small cell or large cell) carcinoma and conventional acinar adenocarcinoma. Usually, these tumors are represented by mixed small cell carcinoma and adenocarcinoma of the prostate and each of both are readily identifiable as distinctive. As with other unusual subtypes of prostate cancer, a Gleason score is only assigned to the conventional adenocarcinoma component but not to the small cell carcinoma. In reported mixed cases, small cell carcinoma predominated (median: 80% of the tumor), and the Gleason score of the adenocarcinoma was ≥ 8 in 85% of these cases [21]. The presence of concomitant high-grade adenocarcinoma as opposed to lower-grade adenocarcinoma represents an independent predictor of worse cancer-specific mortality. Most patients with mixed small cell carcinoma and adenocarcinoma present with metastatic castration-resistant disease and they are often treated with both ADT and chemotherapy (platinum + etoposide or platinum + taxane).

IHC and FISH in the diagnosis and classification of NE differentiation in prostate cancer

IHC plays a vital role and should be approached at two levels. For the issue of confirming NE differentiation, markers for NE differentiation include synaptophysin, chromogranin, and CD56. Actually, CD57 (Leu7) and NSE are not more recommended. If there is any uncertainty about the histogenesis, that is, whether a tumor is primary to the prostate, markers for prostatic lineage—PSA, PSAP, PSMA, prostein (p501s), NKX3.1, ERG (by IHC or FISH)—may be used.

Additional considerations for the role of IHC include diagnosis, prognosis, and predictive purposes. The formal utility of Ki-67/MIB-1 IHC is not established; however, generally observed ranges are outlined in Table 2. The IHC expression of AR across the proposed subtypes of NE carcinoma needs to be systematically evaluated such that its role in the classification of these tumors may be determined. Promising new molecular targets that may be amenable to future IHC-based or FISH-based classification and predictive strategies include Aurora A kinase and N-Myc; however, these markers are not yet validated for clinical use [13, 32, 33].

Aggressive variants of castration-resistant prostate cancer (AVPC)

Primary small cell NE differentiation is rare with an incidence of less than 2%. Most NED develops in castration-resistant patients following androgen deprivation therapy [34]. Clinically, treatment-emergent NE/small cell differentiation has been associated with distinct manifestations, including predominantly visceral or lytic bone metastases and bulky tumor masses, frequently in the setting of low PSA levels with high-volume tumor burden [13]. These tumors are typically not responsive to hormonal therapy, while they are sensitive to cytotoxic chemotherapy [35]. However, responses are short-lived and overall survival is reduced. CRPC characterized by one or more of the following was determined to be AVPC:

- histologic evidence of SCPC (pure or mixed), whose presence determines AVPC regardless of hormonal status;
- the presence of only visceral metastases;
- predominantly lytic bone lesions;
- bulky (5 cm) lymphadenopathy or large (5 cm) high-grade (Gleason 8) tumor mass in prostate/pelvis;
- low PSA at presentation with extensive bone metastatic disease;
- the presence of NE markers at histology (CgA and synaptophysin) or serum (CgA and gastrin-releasing peptide)

Table 2. IHC of NE differentiation in prostate tumors.

	PSA	NE Markers	Ki-67
PC	Positive	Scattered + cells	Not increased in NE cells
PC with Paneth cell NE differentiation	Variably positive	Diffuse positive in Paneth cells	Few cases studied—not increased
Carcinoid-like tumor	Usually positive	Positive	Not studied
Carcinoid tumor	Negative	Diffusely positive	Usually low Rarely increased (typically < 5%–20%)
SCNC	Usually negative or scattered positive cells	Positive in ~90% of cases	> 50%, typically > 80%
LCNC	Usually negative but may be positive	Diffusely positive	Usually > 50%
Mixed NE (SC/LC) usual PC	Same as above for each component	Same as above for each component	Same as above for each component

Note: IHC, immunohistochemistry; NE, neuroendocrine; PC, prostate cancer; PSA, prostate-specific antigen; SCNC, small cell neuroendocrine carcinoma; LCNC, large cell neuroendocrine carcinoma.

combined with either elevated lactate dehydrogenase (LDH), malignant hypercalcemia or elevated serum carcinoembryonic antigen (CEA);
- progression to CRPC in six months or less after initiation of hormonal therapy.

Patients affected by CRPC should undergo biopsy of accessible metastatic lesions in order to identify NED which can influence treatment decisions. Recently, Aggarwal *et al*. suggested that even patients without "atypical"/aggressive-variant clinical presentation may harbor tumors with NED and hence diagnostic biopsy of metastatic lesions may be valuable in all metastatic CRPC (mCRPC) patients regardless of clinical manifestations [22].

Systemic therapy

In CRPC with small-cell histology, cytotoxic chemotherapy has been associated with improved outcomes and is generally considered the preferred treatment option [36]. Similarly, to small-cell lung cancer, platinum-based chemotherapy regimens are mainly being employed, with cisplatin/etoposide, carboplatin/etoposide, and docetaxel/carboplatin being the regimens recommended by the NCCN [37]. In patients with clinical AVPC (putting aside pure small-cell histology), there is no clear consensus on the optimal first-line therapy, with 58% of the Advanced Prostate Cancer Consensus Conference (APCCC) 2017 voting in favor of standard mCRPC treatment and 42% of platinum-based chemotherapy [38]. Table 3 summarizes the actual chemotherapy trials in AVPC.

Since the combination of cisplatin with etoposide proved effective in the treatment of small cell lung cancer, the same regimen was also suggested for poorly differentiated NE tumors. Papandreou *et al*. investigated the efficacy of a combination of cisplatin/etoposide and doxorubicin in a phase II trial of 38 patients with histologically confirmed SCPC (67% pure, 33% mixed) [39]. The benefit-risk ratio of the three-drug combination was considered unfavorable in this study and thus the addition of doxorubicin to cisplatin/etoposide was not recommended for clinical practice.

Loriot *et al*. investigated the combination of carboplatin with etoposide in a phase II trial of patients with mCRPC as a second-line therapy after docetaxel [40]. The combination was fairly well tolerated. The median number of cycles received was three and the median PFS in the overall study population was 2.1 months.

The phase II GETUG P01 examined the combination of carboplatin/etoposide in patients with anaplastic CRPC and visceral metastases or elevated serum CgA and/or NSE [41]. The objective response rate (ORR) was 9% with 3 patients presenting a partial response and one patient with a complete response. Nevertheless, the toxicity was high, with 4 patients (7%) presenting febrile neutropenia and one toxicity-related death. Even in this case, the benefit-risk ratio of this combination was considered to be not favorable. Of note, the dosage and application mode of carboplatin and etoposide differed in both studies, with GETUG P01 employing lower doses of carboplatin (AUC 4 *vs*. 5), but higher doses of etoposide (100 mg/m^2/day *i.v*. for three days *vs*. 80 mg/m^2/day *i.v*. on day 1 and *p.o*. on days 2 and 3)—a drug known for its myelotoxicity. Furthermore, the patients underwent 4 cycles in GETUG P01 in contrast with Loriot *et al*. where they underwent three cycles.

Finally, the GETUG P01-population had an overall lower ECOG performance status in comparison to Loriot's study (ECOG PS 2 at baseline: 22% *vs*. 5%), which can explain the poorer safety profile of this regimen in GETUG P01 and underlines the importance of a good performance status prior to chemotherapy initiation.

Culine *et al*. investigated the combination of cisplatin with docetaxel which represents a standard-of-care option in patients affected by mCRPC [42]. The authors presented a phase 2 study including 41 mCRPC patients with elevated serum NSE and/or CGA. Almost half of the patients experienced a PSA response (*i.e*., PSA decline 50%), and 12 patients (41%) had an objective partial response. The median OS was 12 months. Unfortunately, 91% of the patients experienced Grade 3–4 neutropenia, and one patient died from sepsis.

Another phase 2 trial studied the combination of carboplatin/docetaxel in 120 mCRPC patients with clinical AVPC followed by second-line etoposide/cisplatin as salvage therapy [27]. A median of four cycles of carboplatin/docetaxel was administered. A PSA decline 50% at course 2 was achieved in 47% of the patients, while objective response of measurable disease in 34%. The median PFS on carboplatin/docetaxel was 5.1 months. The median overall survival (OS) was 16 months. Toxicity was fairly manageable overall; most common Grade 3 events were represented by infection (*n*=8) and febrile neutropenia (*n*=3). Grade 4 events included thrombosis (*n*=2) and thrombocytopenia (*n*=1) and toxicity-related death was also registered.

Corn *et al*. conducted a phase 2 randomized trial of cabazitaxel *vs*. cabazitaxel plus carboplatin in patients with mCRPC stratified for the presence of AVPC (*ca*. 55% per arm) [43]. The platinum-based combination demonstrated improved efficacy, especially in the AVPC subgroup. More specifically, median PFS was improved in the combination arm *vs*. cabazitaxel alone (7.3 *vs*. 4.5 months), with prespecified subgroup analysis demonstrating that the platinum-combination favored only those with clinical AVPC (HR 0.58; 95% CI: 0.37–0.89). Median OS was similar between the two arms (HR 0.89, 95% CI: 0.63–1.25, P = 0.50) but the combination regimen was tolerated fairly well with a median of six cycles received.

Conclusions

NE prostate cancer is an increasingly recognized histologic subtype of PC that most commonly arises in the later stages of the disease as a mechanism of treatment resistance. These tumors are typically refractory to hormonal therapies and, although they usually respond well to platinum-based chemotherapy regimens, the OS of the pa-

Table 3. Chemotherapy trials in AVPC.

Study	Papandreou *et al*. [39]	Loriot *et al*. [40]	GETUG P01 [41]	Culine *et al*. [42]	Aparicio *et al*. [27]	Corn *et al*. [43]
Study design	Phase 2, single-arm	Phase 2, single-arm	Phase 2, single-arm	Phase 2, single-arm	Phase 2, single-arm	Phase 2, randomized
Drug combination	Cisplatin/etoposide + doxorubicin	Cisplatin/etoposide	Cisplatin/etoposide	Cisplatin/docetaxel	Carboplatin/docetaxel (then second-line cisplatin/etoposide)	Carboplatin/cabacitaxel *vs*. cabacitaxel
Patient population	Histologically confirmed SCPC (pure or mixed)	CRPC after docetaxel with or without elevated NSE/CgA	mCRPC with visceral metastasis or elevated NSE/CgA	mCRPC with elevated NSE/CgA	AVPC (per clinical criteria)	mCRPC stratified by presence of AVPC (per clinical criteria)
n	38	40	60	41	121	160
Efficacy	36% PSA response 61% OR of measurable disease 84% pain improvement median PFS 5.8 mo median OS 10.5 mo	23% PSA response 2 out of 5 OR of measurable disease 54% pain improvement median PFS 2.1 mo median OS 19 mo Note*: No association of outcome with NSE/CGA levels	8% PSA response 9% OR of measurable disease no pain evaluation median PFS 2.9 mo median OS 9.6 mo	48% PSA response 41% OR of measurable disease 45% pain improvement median OS 12 mo	47% PSA response (at course 2) 34% OR of measurable disease median PFS 5.1 mo median OS 16 mo	62% *vs*. 41% PSA response 57% *vs*. 21% OR 7.3 mo *vs*. 4.5 mo median PFS 18.5 mo *vs*. 17.3 mo median OS Note*: PFS and OS improvement with combination greater in AVPC subgroup (clinical and/or molecular)
Safety—Grade 3–4 AEs > 15%	100% neutropenia 68% infection 66% thrombocytopenia 34% nausea 26% anemia 21% vomiting	38% neutropenia (2% neutropenic fever) 25% anemia	66% neutropenia (7% neutropenic fever) 33% thrombocytopenia 27% anemia	91% neutropenia (17% neutropenic fever) 34% anemia 17% thrombocytopenia 15% fatigue	None	23% anemia 20% fatigue
Safety—Toxicity-related deaths	3 (sepsis)	None	1 (febrile neutropenia)	1 (sepsis)	1 (sepsis during second-line etoposide/cisplatin)	1 (thromboembolic event in cabazitaxel arm)

Note: AVPC, aggressive variant prostate cancer; CgA, chromogranin A; mCRPC, metastatic castration resistant prostate cancer; NSE, neuron-specific enolase; OR, objective response; OS, overall survival; PSA, prostate specific antigen; PFS, progression-free survival; SCPC, small cell prostate cancer. *Results refer to the overall study population (including patients with and without AVPC).

tients is generally short, with a dismal prognosis overall. Immune checkpoint inhibition with monoclonal antibodies against cancer immune evasion (PD-L1/2, PD-1, CTLA-4) is currently being studied in combinations or alone in several phase 1/2 interventional trials for NE prostate cancer. Results of currently ongoing preclinical and clinical studies are expected to enhance our understanding of these tumors' underlying biology and guide our efforts towards the development of personalized medicine through targeted diagnostic and therapeutic approaches.

Declarations

Availability of data and materials: Not applicable.

Financial support and sponsorship: None.

Conflicts of interest: Francesco Greco is a member of the editorial board of *Uro-Technology Journal*. The authors declare that they have no conflicts and were not involved in the journal's review or decision regarding this manuscript.

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Cite this article as: Greco F, Lembo F, Gozo M & Domanico L. Neuroendocrine prostate tumors: histologic features and therapy. *Uro-Technology Journal*, 2023, 7(3): XX-XX. doi: 10.31491/UTJ.2023.09.XXX