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REVIEW

PET radiotracers for whole-body in vivo molecular imaging of prostatic neuroendocrine malignancies

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Abstract

Prostatic neuroendocrine malignancies represent a spectrum of diseases. Treatment-induced neuroendocrine differentiation (tiNED) in hormonally treated adenocarcinoma has been the subject of a large amount of recent research. However, the identification of neuroendocrine features in treatment-naïve prostatic tumor raises a differential diagnosis between prostatic adenocarcinoma with de novo neuroendocrine differentiation (dNED) versus one of the primary prostatic neuroendocrine tumors (P-NETs) and carcinomas (P-NECs). While [^{18}F]FDG is being used as the main PET radiotracer in oncologic imaging and reflects cellular glucose metabolism, other molecules labeled with positron-emitting isotopes, mainly somatostatin-analogues labeled with ^{68}Ga and prostate-specific membrane antigen (PSMA)-ligands labeled with either ^{18}F or ^{68}Ga, are now routinely used in departments of nuclear medicine and molecular imaging, and may be advantageous in imaging prostatic neuroendocrine malignancies. Still, the selection of the preferred PET radiotracer in such cases might be challenging. In the current review, we summarize and discuss published data on these different entities from clinical, biological, and molecular imaging standpoints. Specifically, we review the roles that [^{18}F]FDG, radiolabeled somatostatin-analogues, and radiolabeled PSMA-ligands play in these entities in order to provide the reader with practical recommendations regarding the preferred PET radiotracers for imaging each entity. In cases of tiNED, we conclude that PSMA expression may be low and that [^{18}F]FDG or radiolabeled somatostatin-analogues should be preferred for imaging. In cases of prostatic adenocarcinoma with dNED, we present data that support the superiority of radiolabeled PSMA-ligands. In cases of primary neuroendocrine malignancies, the use of [^{18}F]FDG for imaging high-grade P-NECs and radiolabeled somatostatin-analogues for imaging well-differentiated P-NETs is recommended.

Key Points

- *The preferred PET radiotracer for imaging prostatic neuroendocrine malignancies depends on the specific clinical scenario and pathologic data.*
- *When neuroendocrine features result from hormonal therapy for prostate cancer, PET-CT should be performed with [^{18}F]FDG or radiolabeled somatostatin-analogue rather than with radiolabeled PSMA-ligand.*
- *When neuroendocrine features are evident in newly diagnosed prostate cancer, differentiating adenocarcinoma from primary neuroendocrine malignancy is challenging but crucial for selection of PET radiotracer and for clinical management.*

Keywords PET-CT · 18F-FDG · PSMA antigen · Somatostatin · Prostate cancer

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Abbreviations

[^{18}F]FDG	^{18}F-Fluorodeoxyglucose
ADT	Androgen-deprivation therapy
CRPC	Castration-resistant prostate cancer
dNED	De novo neuroendocrine differentiation
DOTATATE	Dodecane tetraacetic acid-octreotate
H&E	Hematoxylin and eosin
MIP	Maximal intensity projection

PET-CT	Positron emission tomography–computed tomography
P-NEC	Primary prostatic neuroendocrine carcinoma
P-NET	Primary prostatic neuroendocrine tumor
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
SSTR	Somatostatin-receptor
tiNED	Treatment-induced neuroendocrine differentiation
TURBT	Transurethral resection of bladder tumor
TURP	Transurethral resection of prostate

Introduction

Prostate cancer is the second most common cancer diagnosed in men [1]. Of the various types of prostate cancer, prostatic adenocarcinoma is by far the most common type, diagnosed in up to 99% of prostate cancer cases [2, 3]. Prostatic adenocarcinoma arises from secretory epithelial cells of the prostatic glands and acini, and this entity by itself can be further subdivided into more specific categories [3]. Upon diagnosis and after risk assessment and relevant whole-body staging of patients diagnosed with prostatic adenocarcinoma, clinical guidelines recommend stage-matched therapeutic strategies for patients with localized, locally advanced, and metastatic disease. Hormonal therapy constitutes the main component of the therapeutic strategies recommended when patients are diagnosed with metastatic adenocarcinoma, either at presentation or later during the course of the disease [4].

While hormonal therapy delays disease progression and improves survival [4], the phenomenon of treatment-induced neuroendocrine differentiation (tiNED) of prostatic adenocarcinoma cells can occur over time, and has been studied and reviewed in depth lately as a mechanism of disease progression during hormonal therapy [5–7]. However, when prostatic malignancy is newly diagnosed and the tumor cells exhibit de novo neuroendocrine features on pathology, the clinical setting might be less straightforward and further workup may be deemed necessary for better tumor characterization. Identification of neuroendocrine features in treatment-naïve prostatic tumor usually raises a differential diagnosis between one of the prostatic adenocarcinoma subcategories that have de novo neuroendocrine differentiation (dNED) versus one of the primary prostatic neuroendocrine tumors (P-NETs) and carcinomas (P-NECs). Although these entities are rare, differentiating P-NETs and P-NECs from prostatic adenocarcinoma with dNED is crucial, as these malignancies greatly differ in terms of biology, natural history and prognosis, and require different therapeutic approaches [8–10].

The positron emission tomography–computed tomography (PET-CT) technology combines the acquisition of anatomical imaging provided by the CT scan with functional molecular imaging obtained by the PET scan. After intravenous injection of a radiotracer, a specific molecule-of-interest labeled with positron-emitting isotope (usually, ^{18}F or ^{68}Ga), the three dimensional image obtained and reconstructed by the PET scanner represents the whole-body distribution of the injected molecule. [^{18}F]Fluorodeoxyglucose ([^{18}F]FDG), a radiolabeled glucose analogue, is the most commonly used PET radiotracer in oncologic imaging for assessing the whole-body extent of various malignancies [11, 12]. However, some malignancies, particularly prostatic adenocarcinomas and primary neuroendocrine malignancies arising in various organs, have been shown to have low [^{18}F]FDG-avidity [13–16]. Radiolabeled somatostatin-analogues (e.g., ^{68}Ga-dodecane tetraacetic acid-octreotate, also known as ^{68}Ga-DOTATATE) [17] and radiolabeled prostate-specific membrane antigen (PSMA) ligands, (e.g., ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007) [18, 19] are two novel groups of PET radiotracers that enable the whole-body localization of cells that overexpress somatostatin-receptors and the PSMA glycoprotein, respectively. These PET radiotracers have been extensively studied during the last decade for their utility in oncologic imaging, and are now routinely used in departments of nuclear medicine and molecular imaging around the world.

Since prostatic neuroendocrine malignancies represent a spectrum of pathologies characterized by different clinical presentation, course, and prognosis, as well as different biologic origins, pathologic features, and metabolic and molecular profiles, they are also characterized by different avidity profile on PET imaging with [^{18}F]FDG, radiolabeled somatostatin-analogues, and radiolabeled PSMA-ligands. Still, the selection of the preferred PET radiotracer in each case might be challenging and current literature lacks relevant standardization. Hence, in the current review, we summarize the current data on PET imaging of different prostatic malignancies located on the neuroendocrine spectrum from clinical, biological, and molecular imaging standpoints, aiming to provide practical recommendations regarding the preferred PET radiotracer for imaging specific entities. The review is unique being directed to basic scientists, clinicians, pathologists, radiologists, and nuclear medicine physicians, representing the multidisciplinary nature of oncologic research nowadays.

Treatment-induced neuroendocrine differentiation of prostatic adenocarcinoma

The primary therapeutic modality for metastatic adenocarcinoma of the prostate is either surgical or biochemical androgen deprivation therapy (ADT) [4, 20, 21]. Upon initiation of hormonal therapy, prostatic adenocarcinoma cells are considered castration-sensitive, as minimizing androgen levels and/or blocking androgen function effectively control cancer growth [22]. The process of treatment-induced neuroendocrine differentiation (tiNED) refers to a phenotypic differentiation of some of the adenocarcinoma malignant cells, from an epithelial-like phenotype to a neuroendocrine-like phenotype, probably as a consequence of the selective cellular pressure induced by the dramatic fall in androgen levels or by the block of its synthesis or action caused by the treatment [23, 24]. This tiNED phenomenon has been suggested as one of the mechanisms leading to castration-resistant prostate cancer (CRPC), namely, disease progression in spite of androgen deprivation, and it is estimated that tiNED constitutes the resistance mechanism in at least 25% of CRPC cases [25]. The formation of CRPC (via tiNED mechanism or other mechanisms) is usually suspected in cases of either clinical or radiographic disease progression [26, 27]. A rise in serum prostate-specific antigen (PSA) levels can be a sign of CRPC, but in cases of tiNED-mediated castration-resistance, blood levels of PSA (a peptidase secreted by prostatic epithelial cells) may be stable or only moderately elevated, while levels of chromogranin A (a neuroendocrine secretory protein) may be rising [28–30]. As the mentioned cellular phenotypic change alters metabolic and regulatory pathways of the malignant cells, the appearance of a more aggressive disease is the frequent clinical consequence, with possible appearance of visceral metastases, lytic skeletal metastases, and an overall clinical deterioration that harbors a dismal prognosis [31, 32]. Therapeutic options for metastatic CRPC patients include novel androgen-receptor axis-targeted agents (androgen synthesis inhibitors and androgen-receptor inhibitors), chemotherapies (docetaxel or cabazitaxel), denosumab (an inhibitor of RANKL), and radionuclide therapies with ^{223}Ra or with ^{177}Lu-PSMA-ligand [4, 33] for selected patients. Although molecular PET imaging is frequently recommended for patient selection before radionuclide therapies [33], neither routine pathologic evaluation of castration-resistant tumor lesions nor defining resistance mechanism (tiNED versus others) are recommended before therapy initiation [4].

From a molecular standpoint, the tiNED-mediated change in cellular phenotype may be evident on metabolic and molecular imaging with different radiotracers on PET-CT. While most prostatic adenocarcinomas usually show high PSMA expression [34–38] and much lower avidity to [^{18}F]FDG and radiolabeled somatostatin-analogues [13, 14, 39–41], this uptake profile could change given the process of tiNED. In the relevant clinical context, a reduced uptake of radiolabeled PSMA-ligand over time should raise the possibility of tiNED [42, 43]. In fact, a study that evaluated the transcript abundance for FOLH1 (the PSMA gene) and for SSTR-2 (one of the somatostatin-receptors gene) concluded that tumors with tiNED show a signature of suppression in FOLH1 and elevation in SSTR-2 gene expression [42]. The authors of this paper caution on the reliability of using PSMA as a target for molecular imaging of patients with tiNED, and raise the possible superiority of PET imaging targeting SSTR in such cases. Indeed, Parida et al reported a case of a patient with pathologically proven tiNED, whose extensive pelvic, nodal, and skeletal disease showed no radiotracer uptake of ^{68}Ga-PSMA-ligand and an intense avidity to both ^{68}Ga-DOTANOC and [^{18}F]FDG [43]. This case demonstrated that lesions involved with tiNED did not overexpress the PSMA glycoprotein, did overexpress somatostatin-receptors, and were also characterized by glucose hypermetabolism.

Indeed, data from several additional scientific publications support the possible high [^{18}F]FDG-avidity in cases of tiNED, particularly in soft tissue tumor lesions [44–48]. In a study that included twenty-three CRPC patients with "clinical NED" (defined as elevated blood levels of chromogranin A), 22% of 510 bone metastases and 95% of 82 soft tissue metastases were [^{18}F]FDG-avid on PET [45]. Liu et al reported a case of a CRPC patient with pathologically proven tiNED whose [^{18}F]FDG PET-CT showed intense radiotracer uptake in the primary prostatic tumor and in multiple nodal, hepatic, and pulmonary metastases [46].

There are also supporting evidences that SSTR-targeted PET imaging is effectual in cases of tiNED [49–52]. Savelli et al used ^{68}Ga-DOTANOC in six CRPC patients, two of whom had metastases that showed variable SSTR expression [49]. In a subsequent study by Gofrit et al, twelve patients with CRPC underwent ^{68}Ga-DOTATATE PET-CT and all of them had at least one blastic metastasis with radiotracer uptake, six of them showed widespread uptake and four of them demonstrated uptake in lytic bone lesions or lymph node metastases [50]. Among relevant case reports, one patient had ^{68}Ga-DOTANOC-avid lung and skeletal metastases [51], and another CRPC patient had multiple ^{68}Ga-DOTANOC-avid hepatic and lymph node metastases, none of which were detected on PET-CT with ^{68}Ga-PSMA-ligand [52].

To summarize, in cases of prostatic adenocarcinoma with tiNED, the cellular phenotypic change may cause a change in radiotracers uptake profile and a shift to a more aggressive disease with possible parenchymal progression. As evident in a representative case (Fig. 1), lower PSMA-avidity may be demonstrated in lesions involved in tiNED. The reviewed papers above also support possible SSTR overexpression and glucose hypermetabolism in these lesions, making [^{18}F]FDG and radiolabeled somatostatin-analogues the preferred PET radiotracers for molecular imaging of patients with tiNED.

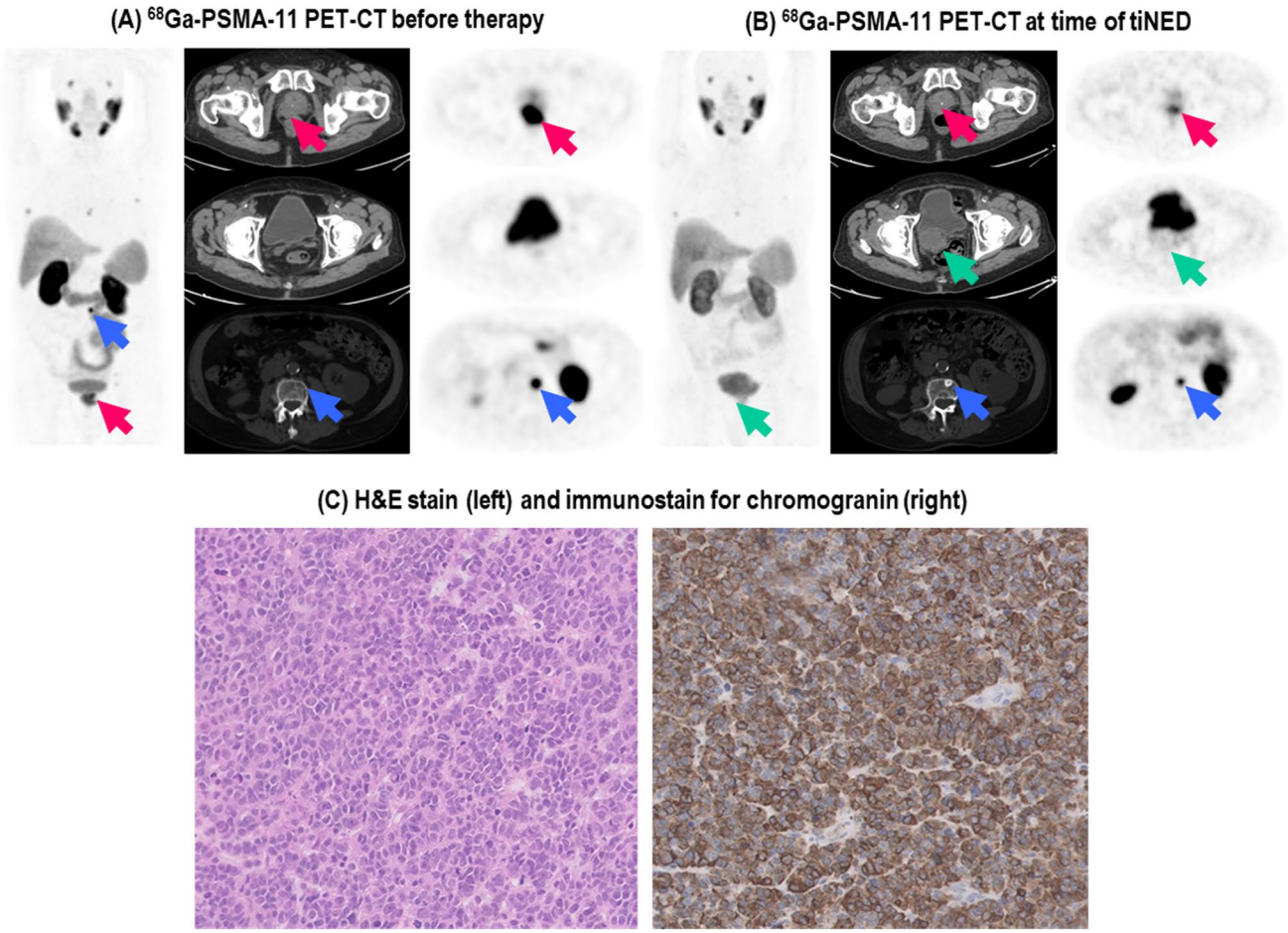

Fig. 1 Treatment-induced neuroendocrine differentiation (tiNED) of prostatic adenocarcinoma. An 85-year-old patient who has been under surveillance for a known low-risk pathologically proven prostatic adenocarcinoma for 8 years was referred to PET-CT scan with ^{68}Ga-PSMA-11 due to a marked elevation of PSA levels from 5.5 to 32.8 ng/mL in 9 months (**A**). High radiotracer uptake was noted in a prostatic mass (pink arrows), and intramedullary skeletal metastases were evident (blue arrows). Categorized as having metastatic adenocarcinoma of prostatic origin, the patient started hormonal therapy consisting of androgen deprivation therapy and abiraterone acetate, an androgen synthesis inhibitor. As a result, PSA levels gradually decreased to 0.29 ng/mL, indicating that the malignancy was castration-sensitive and responded to the hormonal therapy. However, a clinical deterioration was noted a year later, together with a mild increase in PSA levels to 0.74 ng/mL. These findings were suspicious for shifting of the malignancy into the castration-resistant phase, and the patient was referred to PSMA PET-CT (**B**). At that time, radiotracer uptake in the prostate decreased (pink arrows), and a new non-avid mass that involved the prostate and the right seminal vesicle was identified (green arrows). The skeletal metastases demonstrated lower PSMA uptake and sclerotic changes (blue arrows). Weeks later, the patient underwent a palliative channel-transurethral resection of prostate, and on pathology, the diagnosis of tiNED was supported by the tumor's small cell appearance as well as by its positive immunostaining for neuroendocrine markers including chromogranin (**C**). In light of the patient's clinical course, the pathologic data, the reduction in prostatic PSMA expression and the appearance of a new non-PSMA-avid mass, the diagnosis of castration-resistant prostatic cancer due to tiNED has been made

Prostatic adenocarcinomas with de novo neuroendocrine differentiation

While PET imaging of prostatic adenocarcinoma with neuroendocrine differentiation has been reported and studied mostly in the context of the effect of hormonal therapies (tiNED, as discussed in the previous section), de novo neuroendocrine differentiation (dNED) of treatment-naïve prostatic adenocarcinoma is less understood from a biological and functional imaging standpoints.

On pathology, dNED may be evident when newly diagnosed prostatic adenocarcinoma is categorized as one of two entities [53]. The first is *usual prostate adenocarcinoma with neuroendocrine differentiation*, a term that refers to cases where focal neuroendocrine cells, whose abnormal morphological features are hardly identified on hematoxylin and eosin (H&E)–stained sections, are appreciable by immunohistochemical staining with neuroendocrine markers for chromogranin A or synaptophysin. The second is *adenocarcinoma with Paneth cell-like neuroendocrine*

differentiation, defined as typical adenocarcinoma that contains varying proportions of Paneth-like cells, cells whose prominent eosinophilic cytoplasmic granules are evident on routine light microscopy, express neuroendocrine markers on immunostains, and may be scattered among the adenocarcinoma cells or grow as cords or nests.

Up to 100% of prostatic adenocarcinomas probably exhibit some degree of dNED [54], with rates reported by different groups ranging between 5 and 100% [53–57]. These variable rates, however, depend on the extent of the pathologic evaluation, the density of the cells involved with dNED, and the immunohistochemical neuroendocrine markers applied, as their diagnostic accuracies vary [53]. Although higher dNED rates were reported in cases of high-grade adenocarcinomas and high-stage disease [54–57], most studies have not demonstrated that dNED independently affects patient prognosis [58–63], and therefore, immunostains for neuroendocrine markers are not indicated on clinical routine unless neuroendocrine features are prominent on H&E staining [13, 60]. Thus, true rates of dNED among adenocarcinoma cases are practically unknown [28, 54]. With that being said, whenever neuroendocrine features are evident, a thorough evaluation is indicated to confidently differentiate dNED from primary prostatic neuroendocrine malignancies, a differentiation that might sometime be challenging [53]. Once definitively diagnosed, prostatic adenocarcinoma with dNED should be treated like other prostatic adenocarcinomas, depending mainly on the stage and extent of the disease [4, 64].

Given the background data above, one may assume that studies that investigated the use of PET radiotracers in imaging prostatic adenocarcinoma did include cases of dNED. Still, there are no published studies that investigated PET avidity profile for [^{18}F]FDG, somatostatin-analogues, or PSMA-ligands in the specific population of prostatic adenocarcinoma with dNED. An illustrative case of a patient whose newly diagnosed treatment-naïve tumor was hard to be definitively categorized per pathology is presented in Fig. 2 and represents a unique example of the use of PET imaging for providing complementary data to pathology. In this case, imaging finding on PET-CT scans helped making the diagnosis of prostatic adenocarcinoma with dNED, and clinical response to hormonal therapy further supported this diagnosis. To the best of our knowledge, this is the first reported case of a pathologically proven adenocarcinoma with dNED that underwent both PSMA-, FDG-, and DOTATATE-PET scans. With the extensive data that support the use of PSMA-targeted PET in staging prostatic adenocarcinoma [18, 33, 35], and given the assumed high (underreported) rates of dNED among prostatic adenocarcinomas, we believe that in cases when dNED is reported on pathology, radiolabeled PSMA-ligand could be the PET radiotracer of choice for whole-body staging, and the presented case supports its superiority over [^{18}F]FDG and radiolabeled somatostatin-analogues. However, additional studies in this specific patient population are warranted in order to prove this hypothesis. We hence recommend radiolabeled PSMA-ligand as the radiotracer of choice for PET imaging in cases of dNED, but each patient's individual factors should be considered in a case-by-case fashion by a multidisciplinary team before imaging. In addition, in case when discordant lesions between PSMA PET molecular data and CT anatomical data are identified on imaging, additional PET imaging, with [^{18}F]FDG and/or radiolabeled somatostatin-analogues, should be performed as well.

Primary prostatic neuroendocrine malignancies

Primary prostatic neuroendocrine malignancies represent a group of entities with debated cellular origins, which have characteristic pathological features that differ from those of typical prostatic adenocarcinomas [8, 53]. These entities can be schematically divided into two groups: high-grade primary prostatic neuroendocrine carcinomas (P-NECs) and low-grade primary prostatic neuroendocrine tumors (P-NETs). Although cases of tiNED of prostatic adenocarcinoma may share similar features on pathology, we hereby use the terms P-NEC and P-NET (and their subtypes) to refer only to prostatic malignancies which were defined as such on the pathologic evaluation of newly diagnosed treatment-naïve tumors.

Primary prostatic small cell carcinoma, a high-grade neoplasm, constitutes the majority of P-NECs, and still is very rare [65–67]. The incidence rate of prostatic small cell carcinoma is about 0.35 cases per million per year, occurring usually in men aged 70 and above [8, 66, 67]. The diagnosis of prostatic small cell carcinoma is based on a classic morphology on pathology, similar to that observed in small cell lung carcinoma (SCLC). Small cell carcinoma does not form glandular structures, but grows as solid sheets, cords, and single cells. Tumor cells are small with scant cytoplasm, and their nuclei show characteristic features. Approximately 90% of prostatic small cell carcinomas will exhibit immunohistochemical positivity for at least one neuroendocrine marker, negativity for PSA, with Ki-67 labeling usually greater than 50%. TTF1 is often positive. Around 60% of patients diagnosed with prostatic small cell carcinoma are found to be metastatic at the time of diagnosis, and the reported 2- and 5-year survival rates are 27.5% and 14.3%, respectively [65]. Some challenges arise before making this diagnosis, among which is ruling out the possibility of lymphoma involvement or secondary spread of SCLC [9, 53, 68–70].

Due to its rarity, prostatic small cell carcinoma has not been studied specifically in the field of PET imaging. Still, [^{18}F]FDG has been well studied for its utility in imaging SCLC [71] and high-grade neuroendocrine carcinomas

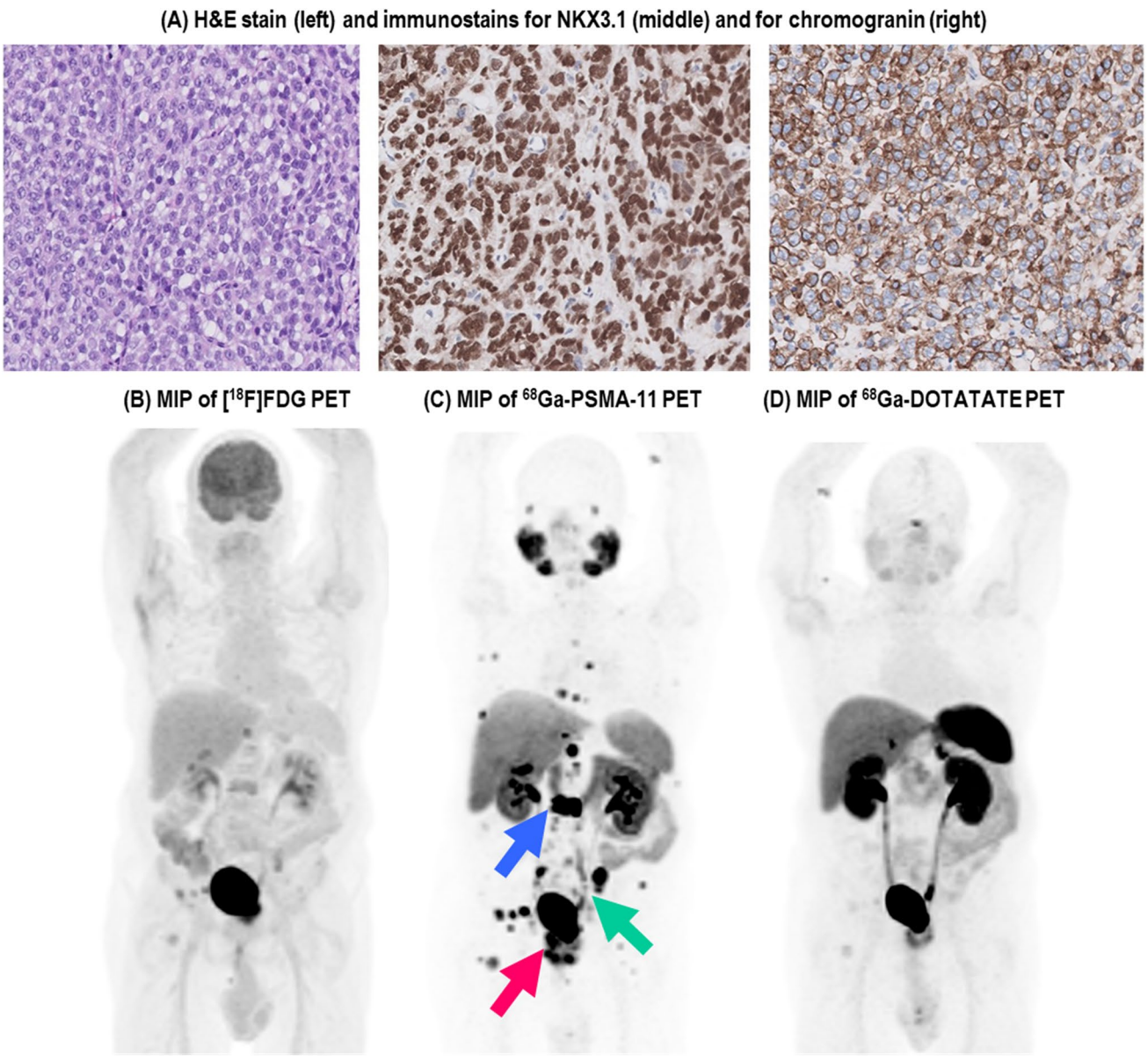

Fig. 2 Prostatic adenocarcinoma with de novo neuroendocrine differentiation (dNED). After suffering urinary symptoms, a 78-year-old patient was found to have high creatinine levels and bilateral hydronephrosis. Serum PSA level was 11.8 ng/mL. A non-contrast CT scan identified thickened urinary bladder wall, retroperitoneal and pelvic lymphadenopathy, and a sclerotic lesion in the body of L2 vertebra. On cystoscopy, the bladder neck seemed nodular, with obstruction of ureteral orifices. With a working diagnosis of bladder versus prostatic tumor, TURBT and TURP were completed soon after. On pathology, fragments from the bladder were involved by a tumor with neuroendocrine features (**A**) that extensively invaded the lamina propria and muscularis propria. On immunostains, tumor cells were diffusely positive for the prostatic marker NKX3.1 but also markedly positive for the neuroendocrine marker chromogranin (**A**). The pathologic features have raised a differential diagnosis of prostatic adenocarcinoma with extensive dNED versus P-NEC. The patient underwent [^{18}F]FDG PET-CT (**B**), ^{68}Ga-PSMA-11 PET-CT (**C**), and ^{68}Ga-DOTATATE PET-CT (**D**) in three different days within a week. The ^{68}Ga-PSMA-11 PET scan identified an extensive high PSMA expression in the prostate, mainly in the right lobe (pink arrow), with cranial extension to the bladder wall. PET data also identified a high-volume PSMA-positive advanced disease, with pathologic uptake in pelvic and retroperitoneal lymph nodes (green arrow) and in numerous skeletal metastases (blue arrow). Only the minority of these lesions expressed low [^{18}F]FDG uptake and/or low somatostatin-receptor expression. The malignancy's avidity profile on PET, similar to the profile that most prostatic adenocarcinomas demonstrate, supported the diagnosis of primary prostatic adenocarcinoma with dNED over P-NEC. Weeks after starting ADT, the patient's PSA levels dropped to 0.48 ng/mL with testosterone levels in castration range

arising in various organs [16, 17, 72]. These data have the potential to support the use of [^{18}F]FDG as the PET radiotracer of choice for staging and follow-up of prostatic small cell carcinoma as well. In line with that, all malignant lesions that were evident on PET-CT scans of a patient with progressing prostatic small cell carcinoma in a representative case presented on Fig. 3 showed high [^{18}F]FDG-avidity.

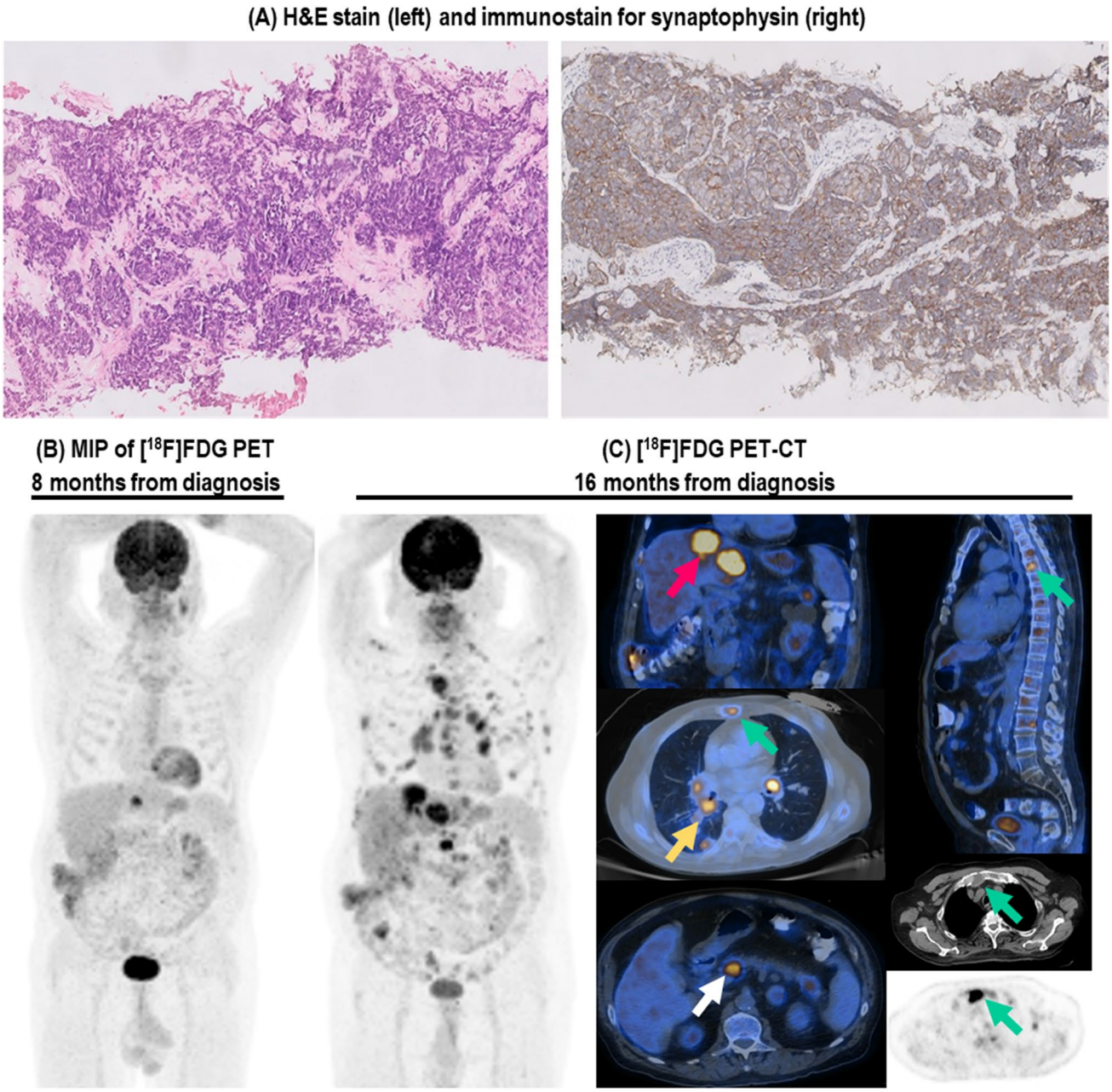

Fig. 3 Primary prostatic neuroendocrine carcinoma. A 69-year-old man presented with a newly diagnosed large prostatic tumor. In the pathologic evaluation of his prostatic biopsies, all 8 cores of prostatic tissue and 4 cores from the seminal vesicles were involved by malignant small cells with hyperchromatic nuclei and scanty cytoplasm (**A**). On immunostains, tumor cells were positive for neuroendocrine markers such as synaptophysin, and negative for PSA and PSAP. Ki-67 was positive in 95% of tumor cells. These findings were compatible with the diagnosis of primary prostatic small cell carcinoma. The patient received chemotherapy, combined with pelvic radiotherapy. An [^{18}F]FDG PET-CT scan performed 8 months from diagnosis (**B**) identified pathologic [^{18}F]FDG uptake in a new hepatic metastasis as a site of disease progression. Immunotherapy was initiated, and a follow-up [^{18}F]FDG PET-CT scan performed 8 months later identified another extensive metastatic progression (**C**). The patient was referred at that point to palliative care and died soon after. On both time-points, the metastatic lesions, including hepatic, skeletal, pulmonary, and pancreatic (pink, green, yellow, and white arrows, respectively), were all [^{18}F]FDG-avid

Reported even more rarely, with anecdotal cases only, there are two other diagnoses that should be mentioned in the context of primary prostatic neuroendocrine malignancies. The first is *primary prostatic large cell carcinoma*, a high-grade P-NEC where, in contrast to small cell carcinoma, tumor cells tend to be large, with a polygonal shape and abundant cytoplasm. This diagnosis has been associated with rapid progression and widespread metastasis to lymph nodes, bone, liver, lung, brain, and meninges. Documented survival is limited, often less than 13 months from diagnosis [8, 54, 73–76]. The second is *well-differentiated prostatic NET* ("*carcinoid*" *tumor*), an entity that was reported mainly in young men (30 years or less), some of whom with a diagnosis of multiple endocrine neoplasia syndrome [8, 54, 77, 78]. This entity is extremely rare, and several features must be verified on pathology before making this diagnosis. The tumor must originate from the prostate parenchyma rather than arising from nearby organs, tumor must be positive on immunostains for neuroendocrine markers, and it must be negative for PSA. Some studies that used radiolabeled somatostatin-analogues for PET imaging of patients with NETs have reported the inclusion of cases of prostatic NETs [79–82]. As with "carcinoid" tumors arising in other locations, mitotic rates and Ki-67 staining index are usually low, making radiolabeled somatostatin-analogues appropriate and the preferred PET radiotracer for functional imaging in such case [17]. It is worth mentioning that beyond staging purposes, assessment of SSTR expression with somatostatin-analogues-based PET imaging is beneficial for determining the suitability of patients with "carcinoid" to SSTR-directed therapies, including to "cold" somatostatin-analogues and to peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE [83].

Conclusions

The identification of neuroendocrine features of tumor cells in the pathologic evaluation of prostatic malignancy may reflect various pathological entities differing in their clinical course and prognosis. The current review focused on the different origins and molecular features of neuroendocrine malignancies located in the prostate. Although the vast majority of prostate cancer cases are of prostatic adenocarcinoma, these malignant cells are prone to phenotypic change from an epithelial-like phenotype to a neuroendocrine-like phenotype as a consequence of hormonal therapy, a phenomenon known as treatment-induced neuroendocrine differentiation. On the other hand, newly diagnosed treatment-naïve prostatic malignancies that show neuroendocrine features include specific subtypes of prostatic adenocarcinoma (referred to as those with de novo neuroendocrine differentiation), as well as high-grade primary prostatic neuroendocrine carcinomas (small cell carcinoma and large cell carcinoma) and well-differentiated primary prostatic neuroendocrine tumors ("carcinoid" tumor).

From a practical standpoint, the current review may guide clinicians and nuclear medicine physicians in their choice of preferred radiotracer for PET-CT assessment of patients presenting with prostatic neuroendocrine malignancies. In cases of tiNED of prostatic adenocarcinoma, published data support that PSMA expression may be low and that [^{18}F]FDG and radiolabeled somatostatin-analogues should be preferred for PET imaging over radiolabeled PSMA-ligands, mainly for detecting soft-tissue malignant lesions. In cases of treatment-naïve prostatic adenocarcinoma reported on pathology to have dNED, published data on the preferred radiotracer are limited, but the case we present, together with the practice to approach these patients similarly to the way other patients with prostatic adenocarcinoma are approached, make it likely that radiolabeled PSMA-ligand could be the PET radiotracer of choice (still, this recommendation awaits further validation, and should be considered on a case-by-case fashion). In cases of primary neuroendocrine malignancies of the prostate, as commonly practiced in primary neuroendocrine malignancies arising in other organs, the choice of PET radiotracer should be guided by tumor differentiation. Patients with aggressive P-NECs (e.g., small cell carcinoma and large cell carcinoma) should undergo PET-CT with [^{18}F]FDG, and radiolabeled somatostatin-analogues should be preferred for PET-CT imaging of those with well-differentiated prostatic NET ("carcinoid" tumor).

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Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Data presented in the figures included in this paper were available as part of retrospective study protocols approved by the local institutional ethics committee, which waived written informed consent (Reference ID 0487/1102–20-TLV).

Methodology
• Narrative review

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