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# Evolving concepts in prostatic neuroendocrine manifestations: from focal divergent differentiation to amphicrine carcinoma☆

**Shubha Bellur MD[a,b], Theodorus Van der Kwast MD[a,b], Ozgur Mete MD[a,b,c,*]**

[a]*Department of Pathology, University Health Network, Toronto, ON M5G 2C4, Canada*
[b]*Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON M5S 1A1, Canada*
[c]*Endocrine Oncology, The Princess Margaret Cancer Centre, Toronto, ON M5G 2M9, Canada*

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**Summary** Prostatic neuroendocrine manifestations encompass a heterogeneous spectrum of morphologic entities. In the era of evidence-based and precision-led treatment, distinction of biologically relevant clinical manifestations expanded the evolving clinical role of pathologists. Recent observations on the occurrence of hormone therapy–induced aggressive prostatic cancers with neuroendocrine features have triggered the need to refine the spectrum and nomenclature of prostatic neuroendocrine manifestations. Although the morphologic assessment still remains the basis of the diagnostic workup of prostatic neoplasms, the application of ancillary biomarkers is crucial in the accurate classification of such presentations. This review provides a diagnostic roadmap for the practicing pathologist by reviewing the characteristic morphologic, immunohistochemical, and molecular correlates of various faces of prostatic neuroendocrine manifestations.


## 1. Introduction

Most prostate cancers are conventional acinar adenocarcinomas and largely composed of exocrine cells that typically express androgen receptor (AR), prostate-specific antigen (PSA), and prostatic acid phosphatase (PSAP) [1]. Although isolated neuroendocrine (NE) cells can be found in the nontumorous prostate, focal divergent NE differentiation is also not an uncommon finding in a prostatic adenocarcinoma [2]. The terminology applied to NE proliferations has been refined in several organ systems. For instance, the preferred nomenclature for small cell or large cell NE carcinomas is poorly differentiated NE carcinomas. Mixed NE and non-NE neoplasms (MiNENs) composed of adenoneuroendocrine carcinoma that is a co-occurrence of prostatic acinar adenocarcinoma and NE neoplasm (often poorly differentiated NE carcinoma) have also been described in the prostate [3-5]. Other well-defined prostatic NE manifestations include the very rare well-differentiated NE tumors (also known as carcinoid tumors) and prostatic adenocarcinomas with Paneth cell–like differentiation [6].

Interestingly, the incidence of NE manifestations of the prostate has been on the rise, especially in patients with advanced prostate cancer undergoing androgen deprivation therapy and with the advent of newer more intensified hormone therapy modalities [7]. Their relationship with castration-

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* Corresponding author at: Department of Pathology, University Health Network, 200 Elizabeth St, 11th Floor, Toronto, ON, Canada M5G 2C4.
*E-mail address:* ozgur.mete2@uhn.ca (O. Mete).

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resistant metastatic prostatic acinar adenocarcinoma is a developing field of investigation [8,9]. Among the less well-established NE manifestations, castration-resistant prostate cancers (CRPCs) with an aberrant NE phenotype have been reported [10]. Recently, a distinct subset of aggressive prostate cancers with NE features has been proposed to represent amphicrine carcinoma of the prostate (prostatic carcinoma with amphicrine features) [11]. Although the morphologic assessment remains the basis of the diagnostic workup, the application of ancillary immunohistochemical biomarkers including proliferative index by Ki-67 (MIB-1) staining is crucial in the classification of such NE neoplasms. Recently, the International Agency for Research on Cancer and World Health Organization (WHO) published an expert consensus proposal regarding a common classification framework for NE neoplasms to unify the diagnostic terminologies applied in various organs [12]. Unlike gastroenteropancreatic NE neoplasms, the classification criteria and clinical practice guidelines dealing with similar tumors of the genitourinary tract remain nebulous [13-16].

This review aimed to describe the characteristics of various prostatic NE manifestations by providing a practical diagnostic roadmap that defines a framework for their classification within the NE gamut. In addition, the authors aimed to adopt unified diagnostic terminologies, which are in place in NE manifestations of other organs.

## 2. NE cells in the prostate

NE cells of the prostate are derived of neural crest cells and belong to the diffuse NE system. These cells migrate into the developing prostate gland of the fetus after the age of 12 weeks' gestation [17] with a capacity to self-maintain as a separate population. The normal prostate gland consists predominantly of cells of the luminal (exocrine) and the basal compartment with a small minority of NE cells (Fig. 1A), which are scattered between the luminal and the basal cell compartment [14,18-20]. NE cells in the benign prostate gland are best visualized by immunohistochemical biomarkers like chromogranin A (Fig. 1B), as well as synaptophysin and CD56. In addition to above conventional biomarkers, insulinoma-associated protein 1 (INSM1), a zinc-finger transcriptional factor, has been shown to stain normal NE cells in various organs including the prostate as well as various neoplastic NE manifestations of the prostate [21]. NE cells constitute approximately 1% of the benign prostatic epithelial cells becoming slightly more prominent in high-grade prostatic intraepithelial neoplasia with their numbers intermediate between that seen in benign prostate gland and carcinoma [22]. At the ultrastructural level, they are characterized by neurosecretory granules containing peptide hormones such as serotonin, calcitonin, calcitonin gene-related peptide, bombesin, katacalcin, somatostatin, cholecystokinin, vasoactive intestinal peptide, neuropeptide-YY, aderenomedullin, thyroid-stimulating hormone–like peptide, and β-human chorionic gonadotropin–like peptide [2]. They are typically negative for AR and PSA [1,23]. In contrast, the exocrine cells have secretory vacuoles that contain PSA, and they lack neurosecretory granules [24].

Androgen deprivation induces regressive changes and apoptosis in the AR-positive luminal cells, whereas the AR-negative basal cells and NE cells are typically insensitive to this condition. NE cells do not show any proliferative activity in benign prostate tissues. Therefore, they are considered as post-mitotic terminally differentiated cells [25,26]. A double-labeling study reported the presence of sporadic epithelial cells sharing exocrine (PSA) and NE markers in benign prostate tissues, raising the possibility of naive amphicrine cells [27].

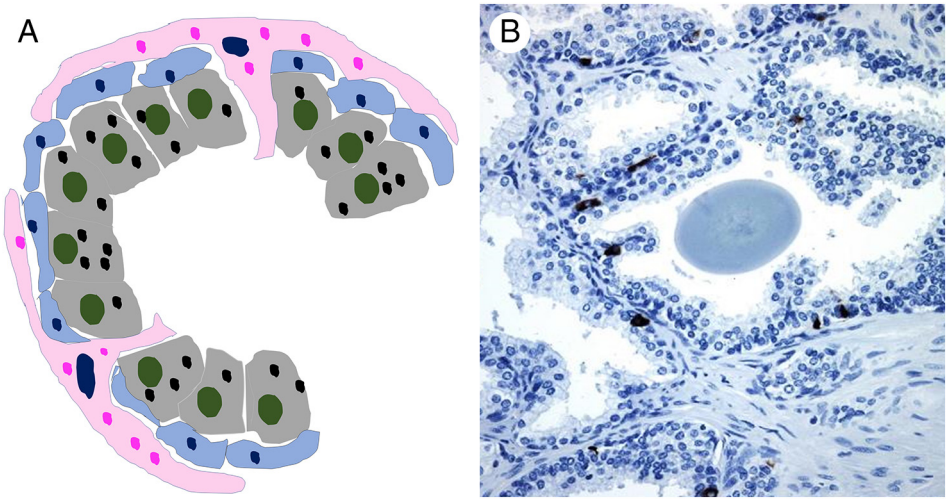


**Fig. 1** NE cells in the normal prostate. A, The normal prostate glands consist predominantly of cells of the luminal (exocrine) and the basal compartment with a small minority of NE cells, which are scattered between the luminal and the basal cells (cells with pink cytoplasm represent NE cells, and those with blue and gray cytoplasm represent basal and luminal cells, respectively). B, NE cells in the benign prostate gland are best visualized by immunohistochemical stains like chromogranin A.

## 3. Categorization of prostatic NE manifestations

The NE manifestations of the prostate and the origin of NE cells in prostatic cancer have gained interest over the past decade. The NE cells in prostate cancers are thought to differentiate from progenitor cells located in the AR-negative basal cell compartment of the prostate or from a transit cell in the AR-positive luminal (exocrine) cell compartment; the latter process has been referred to as a transdifferentiation phenomenon [14-16] (Fig. 2). The growing evidence suggests that genomic alterations coupled with microenvironmental factors can affect lineage plasticity to enable transdifferentiation and cellular proliferation that determine various prostatic NE manifestations [28,29].

The various categories of NE manifestations in prostatic neoplasms are listed in the Table. An attempt was made to include recent observations on this topic and to keep the categorization as practical and simple as possible, using unified terminologies.

### 3.1. Conventional acinar adenocarcinomas with divergent NE differentiation

Most if not all conventional acinar-type prostatic adenocarcinomas contain variable numbers of tumor cells with NE differentiation, which are scattered amid the adenocarcinoma cells (Fig. 3). Although the NE cells in conventional prostatic adenocarcinomas with focal Paneth cell–like cell features (see below) can be recognized based on their characteristic cytomorphology, the remaining NE cells in prostatic carcinomas lack specific morphologic features. Therefore, they can only be visualized by using immunohistochemical biomarkers including chromogranin A, synaptophysin, CD56, and INSM1 (nuclear). Similar to the NE cells of benign prostate glands, they lack AR expression [1]. However, they can express AMACR, in contrast to their nontumorous counterpart [23]. Because scattered NE cells are also found in metastatic prostatic carcinomas, they ought to be part of the neoplastic process and do not merely represent entrapped benign NE cells [30,31]. Identical allelotype of microdissected acinar and NE cells are also evidence of the common clonality of exocrine and tumor cells with NE differentiation in those conventional acinar adenocarcinomas [32]. A recent study using INSM1 nuclear transcription factor expression identified an overall rate of 4% for focal divergent NE differentiation in prostatic adenocarcinoma [21]. However, the numbers of NE cells in prostatic adenocarcinomas may increase during androgen deprivation.

The PC310 human xenograft cell line is the prototype model, which represents postmitotic terminally differentiated NE cells derived from exocrine prostate carcinoma cells by a

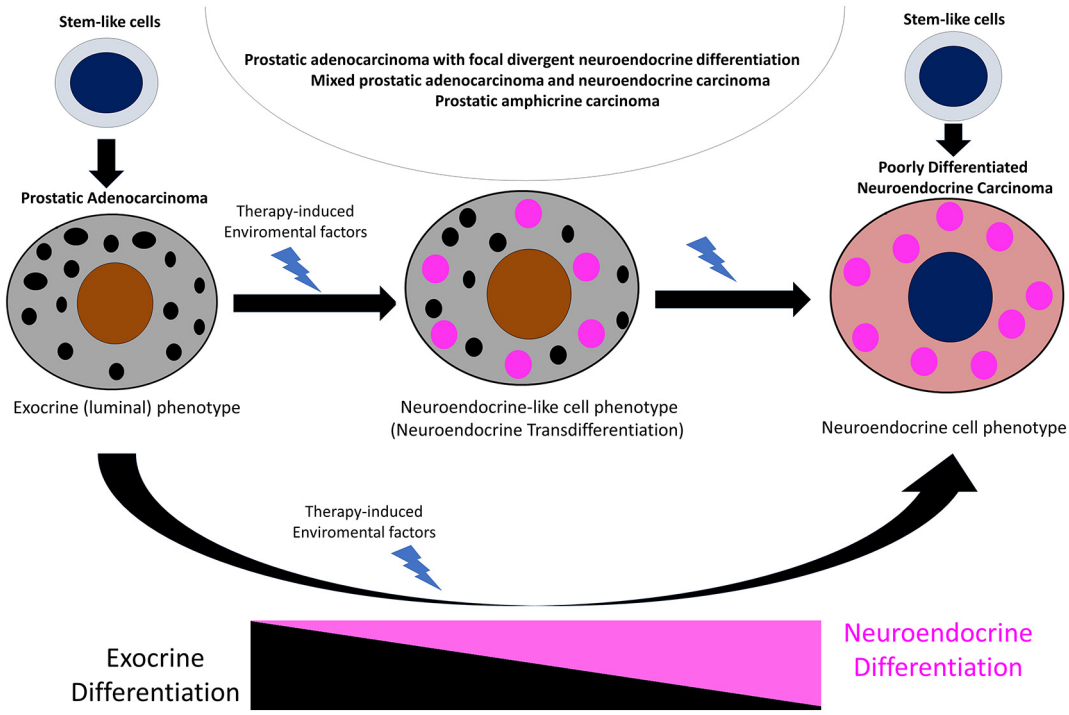


**Fig. 2** Simplified schematic overview of prostatic NE manifestations with respect to the link of NE phenotype during progression of prostatic adenocarcinoma. This algorithmic scheme excludes the rare well-differentiated NE tumors, which are thought to arise from NE cells of the prostate. The poorly differentiated NE carcinoma can originate either from cancer stem–like cells or from a prostatic adenocarcinoma via NE transdifferentiation. Evidence suggests that androgen-deprivation therapy and/or environmental factors can result in NE-like cell phenotype. The extent of NE differentiation and the degree of loss of exocrine differentiation within the tumor determine the spectrum of NE manifestations including prostatic adenocarcinoma with focal divergent NE differentiation, mixed prostatic adenocarcinoma and NE carcinoma, amphicrine carcinoma, and finally poorly differentiated NE carcinoma. Pink granules represent NE phenotype characterized by neurosecretory granules, whereas exocrine differentiation is represented with black granules.

**Table** Clinicopathological and immunohistochemical features of prostatic NE manifestations

| Category | Clinicopathological features | Immunohistochemical correlates [a] |
|---|---|---|
| Prostatic adenocarcinoma with divergent NE differentiation | Adenocarcinoma, conventional, hormone-naive or after hormone treatment. Considered to have no clinical significance<br>Prostatic adenocarcinoma with Paneth cell–like NE differentiation | Focal expression for Chr+ and Syn+ |
| Well-differentiated NE tumor (typical or atypical carcinoid tumors) | Monotonous bland tumor, may be associated with MEN1syndrome, favorable prognosis | Chr+, Syn+, AR−, PSA−, low Ki-67 labeling index, absence of p53 overexpression, intact Rb, menin+/− |
| Poorly differentiated NE carcinoma | Small or large cell NE carcinoma. Aggressive, more frequent in castration-resistant prostate cancer, but also in hormone-naive de novo tumors | Chr+, Syn+, AR−/+ [b], PSA−, high Ki-67 labeling index (>55%), p53 overexpression, loss of Rb expression, TTF-1+/− |
| Mixed NE and non-NE neoplasm (MiNEN) | Most often manifest as MANEC (mixed adenocarcinoma and NE carcinoma), in combination of poorly differentiated NEC and conventional prostatic adenocarcinoma. Aggressive tumors, more frequent in castration-resistant prostate cancer, but also in hormone-naive men | NE component is often poorly differentiated NE carcinoma: Chr+, Syn+, AR−/+, PSA−, high Ki-67 (>55%), p53 overexpression, TTF-1+/−<br>Non-NE carcinoma: Chr−, Syn−, AR+, PSA+, TTF-1− |
| Amphicrine carcinoma | Often present with metastatic disease, mitotically highly active acinar adenocarcinoma, hormone-naive or castration-resistant prostate cancer | Diffuse expression for Chr+, Syn+, AR+, PSA+, PSAP+ |

Abbreviations: Chr, chromogranin A; Syn, synaptophysin; Rb, retinoblastoma.

[a] Common immunohistochemical phenotype.

[b] De novo (hormone-naive) small cell prostatic NE carcinomas typically lack AR reactivity and are not associated with elevated PSA levels; however, AR can be identified in androgen ablation therapy–induced small cell NE carcinoma [9].

process of transdifferentiation when exposed to an androgen-deprived environment [33]. Androgen deprivation rapidly induced NE differentiation in an otherwise AR-positive acinar type adenocarcinoma xenograft paralleled by an immediate drop in the proliferative activity and disappearance of AR expression. These AR-negative NE cells persisted for at least 156 days after androgen deprivation [34] and could therefore be considered terminally differentiated. Similarly, in vitro deprivation of androgens induces a neuronal phenotype in the AR-positive lymph node carcinoma of prostate cell line associated with downregulation of proliferative activity and AR expression [35].

The clinical significance of these postmitotic NE cells in hormone-naive prostate cancers is controversial. Some studies failed to show a prognostic impact [36], whereas others showed an unfavorable prognosis after prostatectomy or radiotherapy [37,38] or in response to subsequent hormone therapy [39].

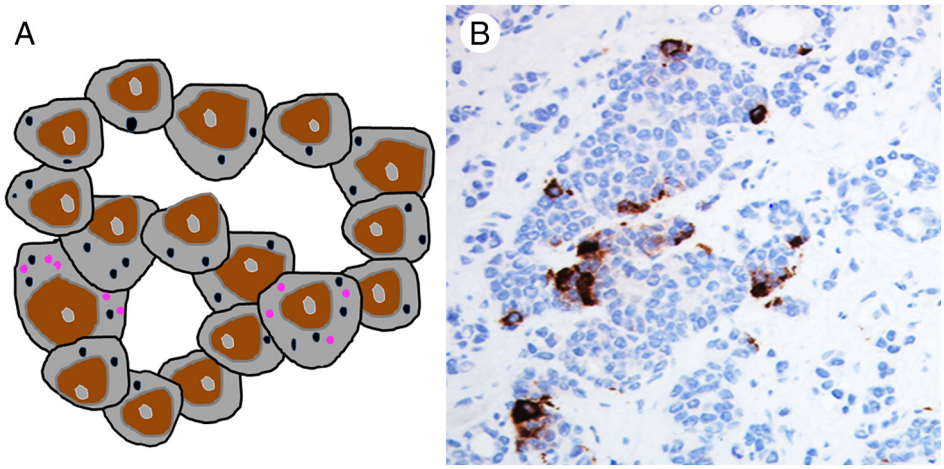


**Fig. 3** Prostatic adenocarcinoma with divergent NE differentiation. A, The schematic illustration highlights the presence of focal divergent NE differentiation in scattered tumor cells with neurosecretory granules (pink granules). B, This finding can be highlighted with NE differentiation markers (chromogranin A). The extent of focal divergent NE differentiation is estimated to account for less than 30% of the tumor volume.

### 3.2. Prostatic adenocarcinomas with Paneth cell–like NE differentiation

Scattered cells with the typical morphology of Paneth cells can infrequently be seen in the lining of benign prostate glands, a phenomenon considered as Paneth cell metaplasia. These cells contain diastase-resistant Periodic acid-Schiff (PAS)-positive granules just like the Paneth cells of the small intestine but are positive for serotonin just like enterochromaffin cells. Furthermore, they are positive for chromogranin A and AMACR [40,41]. Variable proportions of tumor cells showing typical Paneth cell–like morphology may also be encountered in conventional prostate carcinomas (Fig. 4). They have amphophilic cytoplasm and often contain eosinophilic granules, but they are also positive for chromogranin A, synaptophysin, and serotonin, and negative for lysozyme and AR [41]. At the ultrastructural level, these cells contain neurosecretory granules and lack lysosomal granules of true Paneth cells of the gastrointestinal cells [42-45]. The suggested terminology for these terminally differentiated cells in prostate cancers is "Paneth cell–like cells" by some [41] and "neuroendocrine cells with large eosinophilic granules" by others [44]. So et al [46] described a variant of Paneth cell–like carcinoma cells with sparse or complete lack of cytoplasmic granules when examined by routine histology, but otherwise showed the typical dense amphophilic cytoplasm and bland nuclear features of typical Paneth cell–like carcinoma cells including the expression of NE markers. It is important to recognize this morphologic variant of PCa. Paneth cell–like carcinoma cells can be seen admixed with conventional acinar adenocarcinoma cells as isolated single cells or cords of cells, recapitulating a Gleason grade 5 pattern. The latter should not be interpreted as an evidence for Gleason pattern 5. These Paneth-like tumor cells have low proliferative activity and are generally associated with Gleason score 6 prostate cancer, and their biology is thought to be indolent. Therefore, while assigning a Gleason score of these tumors, only areas displaying conventional prostate adenocarcinoma morphology should be taken into consideration [47].

A recent publication noted that 45% of localized prostate carcinomas with Paneth cell–like component showed *AURKA* (aurora kinase A) amplification [48]. The authors also noted that when they compared with histologically similar cases with and without *AURKA* amplification, in the presence of the gene alteration, a larger number of tumor cells displayed Paneth cell–like morphology, as they were more likely to involve the entire tumor nodule rather than a few scattered Paneth cell–like cells. At this time, the clinical significance of this observation remains unclear.

### 3.3. Well-differentiated prostatic NE tumors (carcinoid tumors)

Well-differentiated NE tumors are extremely rare in the prostate with a few anecdotal case reports in the literature [49-51]. The diagnosis of this pure NE tumor originating from

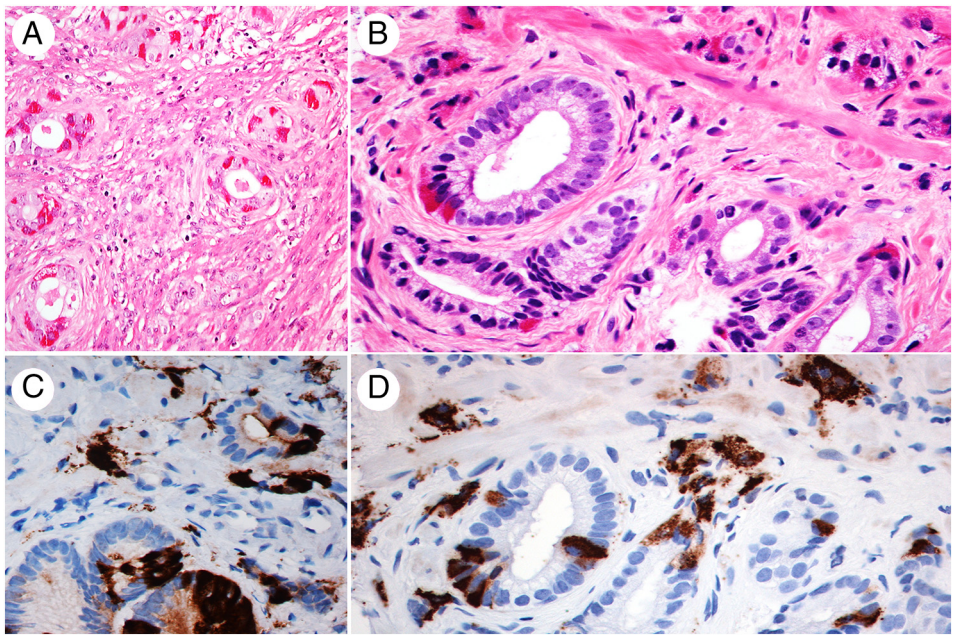


**Fig. 4** Prostatic adenocarcinoma with Paneth cell–like NE differentiation. A and B, This morphologic entity is characterized by a prostatic adenocarcinoma with focal or confluent Paneth cell–like tumor cells containing abundant cytoplasmic granules. Paneth cell–like cells are typically negative for Periodic acid-Schiff (PAS) and PAS diastase (PASD) (not illustrated herein). These are positive with NE markers including chromogranin A, synaptophysin (C), and serotonin (D). One may consider this finding as a variant of focal divergent NE differentiation within a conventional prostatic adenocarcinoma.

the prostate gland is typically based on morphology and immunohistochemical features. These tumors display cords and nests of cells exhibiting NE morphology as well as diffuse expression of NE biomarkers, including chromogranin A and synaptophysin (Fig. 5). They typically lack PSA and AR. The mitotic activity is often low. Those with low-grade proliferative features have a mitotic rate less than 2 per 2 $mm^2$, whereas carcinoid tumors with intermediate-grade proliferative features have a mitotic activity between 2 and 10 per 2 $mm^2$. Well-differentiated NE neoplasms are not given a Gleason grade.

These tumors were typically seen in younger adults with MEN1 syndrome [52,53]. Even when associated with locally advanced or metastatic disease, a more favorable prognosis was noted with such tumors [50]. Recently, a case report of a tumor fulfilling the criteria of a well-differentiated NE tumor (carcinoid tumor) was reported in a patient with conventional adenocarcinoma treated with androgen-deprivation therapy [54]. It is not clear whether this tumor would represent a second primary tumor or transdifferentiation from the original prostatic adenocarcinoma [54]. Data on the molecular pathogenesis of well-differentiated NE tumors are scarce.

### 3.4. Poorly differentiated prostatic NE carcinomas (small or large cell type)

Poorly differentiated prostatic NE carcinomas are uncommon. These may occur de novo or more frequently in patients who have had androgen-deprivation therapy for an advanced prostate cancer. Presence of distant metastasis at the time of diagnosis of these carcinomas is common. The diagnosis of a poorly differentiated NE carcinoma is essentially based on histopathologic and immunohistochemical features [55]. Although more than 50% of these poorly differentiated prostatic NE carcinomas present as a pure form, the remaining is typically seen in association with a prostatic carcinoma (see below the next section on mixed NE and non-NE carcinoma of the prostate) [15,56]. Two cytomorphologic variants of poorly differentiated prostatic NE carcinomas have been described. The more common variant is the small cell type (Fig. 6), and the much rarer is the large cell type (Fig. 7). The large cell and small cell variants can be admixed in some tumors; however, most cases exhibit either pure small cell or large cell features. The small cell NE carcinomas show identical cytomorphologic features as defined in other small cell NE carcinomas of various organs. The cytomorphology ranges from typical "oat cell" type to intermediate cell type [56]. Some cases may exhibit tumor giant cells with large nuclei and smudgy chromatin; others may show true rosettes and pseudorosettes. Prominent nucleoli and abundant cytoplasmic content should alert the pathologist to the possibility of a large cell NE carcinomas. Evans et al [57] reported the largest series of 7 cases of large cell prostatic NE carcinomas. The mean age of occurrence in this series was around 67 years, and they had a dismal prognosis [58]. These neoplamss contain large tumor cells with more abundant cytoplasm and large nuclei with coarse chromatin pattern and prominent nucleoli. The cell

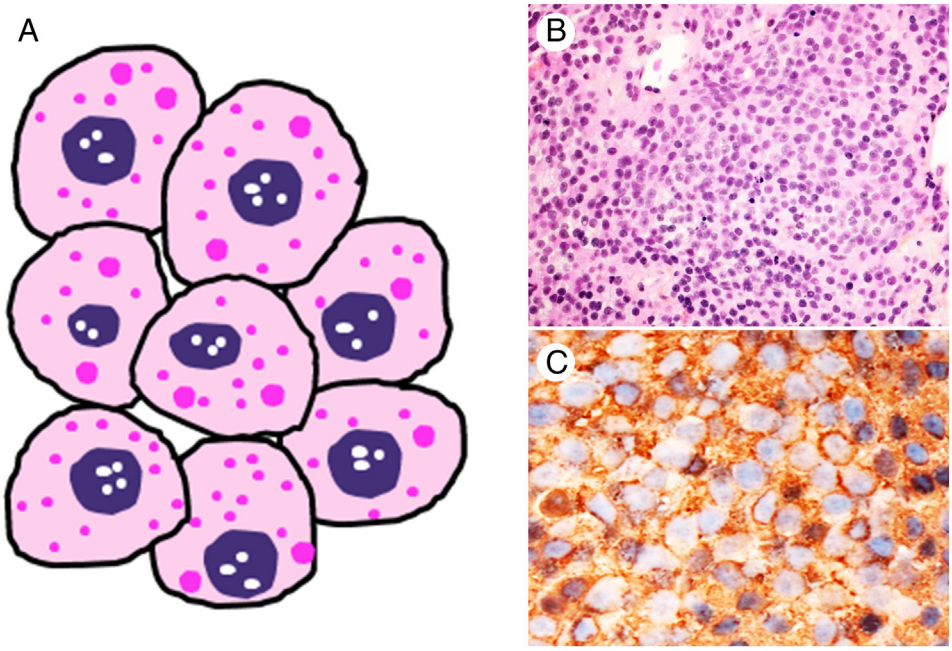


**Fig. 5** Well-differentiated prostatic NE tumors. These tumors are extremely rare in the prostate. A, They are composed of uniform cells with diffuse neurosecretory granules and nuclei with salt and pepper appearance (pink granules represent neurosecretory granules). B, Solid and nested growth patterns are common. C, They are distinguished from poorly differentiated NE carcinoma with their extensive reactivity for NE differentiation markers (chromogranin A) as well as their low proliferative activity.

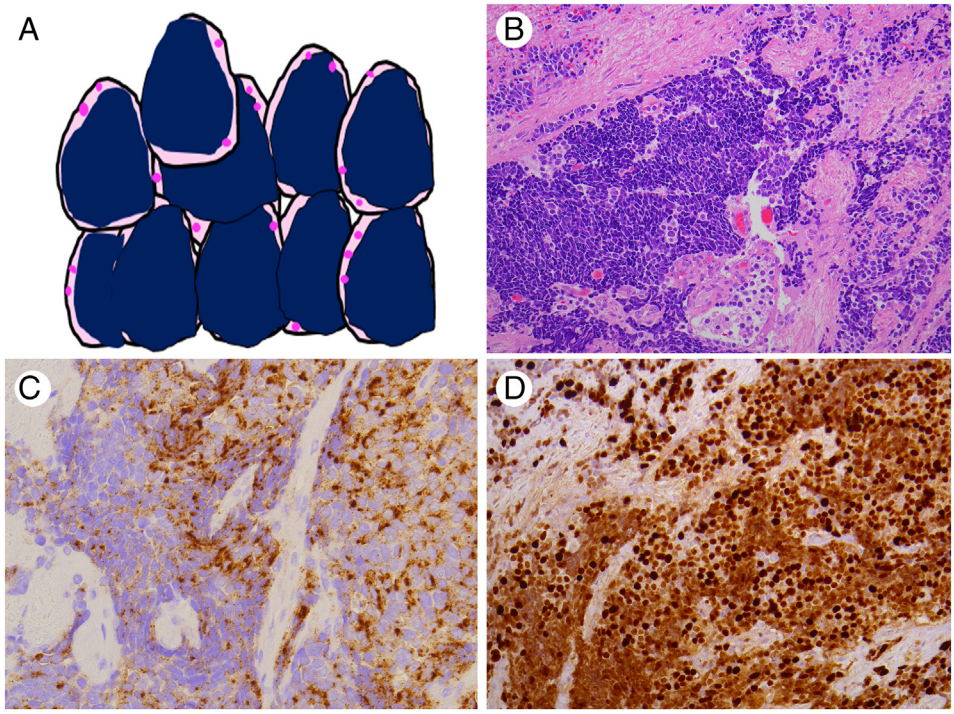


**Fig. 6** Poorly differentiated NE carcinoma of the prostate, small cell type (small cell NE carcinoma). A and B, The small cell NE carcinoma exhibits a cytomorphology ranging from typical "oat cell" type to intermediate cell type with scant cytoplasm and scattered perinuclear neurosecretory granules. Tumor cells often lack prominent nucleoli and show nuclear molding. A, Unlike well-differentiated NE tumors, small cell NE carcinomas contain scattered small neurosecretory granules (pink granules). C, Therefore, perinuclear dot-like chromogranin A immunoreactivity is frequently identified. D, The Ki-67 (MIB-1) labeling index is often very high and almost always exceed 55% of the tumor nuclei.

nests may show peripheral palisading of nuclei. They can exhibit areas of geographic necrosis. Both small cell and large cell NE carcinomas often have a high Ki-67 labeling index exceeding 55% of the tumor nuclei. Both small cell and large cell NE carcinomas are usually positive for at least one NE marker (eg, chromogranin A and synaptophysin), and are often negative for AR, PSA, and PSAP. Focal/variable positivity for AR, PSA, or PSAP can be encountered when the poorly differentiated NE carcinoma component is seen in association with a concomitant prostatic adenocarcinoma (see below the next section on mixed NE and non-NE carcinoma of the prostate). Similar to poorly differentiated NE carcinomas of various sites, poorly differentiated prostatic NE carcinomas can also show thyroid transcription factor-1 (TTF-1) positivity. It is important to note that PSAP expression can be seen in NE tumors of gastrointestinal tract, which are phylogenetically arising from the hindgut—its prototype being the L-cell NE tumors of the rectum [59-61]. In addition, INMS1, FOXA2, and ASCL1 are variably expressed in small cell carcinomas of the prostate [62,63]. In cases where the distinction between a small cell and large cell NE carcinoma is challenging, the immunoprofile of a poorly differentiated NE carcinoma (Rb loss along with p16 positivity and absence of cyclin D1 overexpression) can be used to favor a small cell NE carcinoma over a large cell NE carcinoma in the lung [64]. To our knowledge, the latter has not been validated in poorly differentiated prostatic NE carcinomas.

Up to 47% of small cell NE carcinomas of the prostate show *TMPRSS2-ERG* gene fusion by fluorescence in situ hybridization [65], a frequency similar to those of conventional prostatic adenocarcinomas. Based on the limited evidence, it seems that these molecular alterations are not present in poorly differentiated NE carcinomas of other organs like the lungs and urinary bladder. Identification of this oncogene fusion could potentially be used to distinguish the prostatic origin of a poorly differentiated NE carcinoma [66,67]. On the other hand, almost all de novo (hormone-naive) poorly differentiated prostatic NE carcinomas fail to show immunohistochemical ERG protein expression, because these neoplasms lack AR and the ERG expression is driven by an activated AR. Unlike de novo prostatic small cell NE carcinomas, hormone treatment–induced tumors can show AR transcriptional activity and immunoreactivity for AR [9].

A rare look-a-like of small cell variant of poorly differentiated NE carcinoma is a lesion called small cell–like change [68,69]. This entity is more commonly associated with high-grade prostate adenocarcinomas, intraductal carcinoma, and prostatic intraepithelial neoplasia. Unlike the small cell NE carcinoma, small cell–like change lacks mitotic activity (with corresponding low Ki-67 labeling index) and lacks apoptosis, necrosis, and NE marker expression (Fig. 8). The pathological significance of SCLC is unclear.

Development of poorly differentiated NE carcinoma in the context of castration-resistant prostate carcinoma is becoming

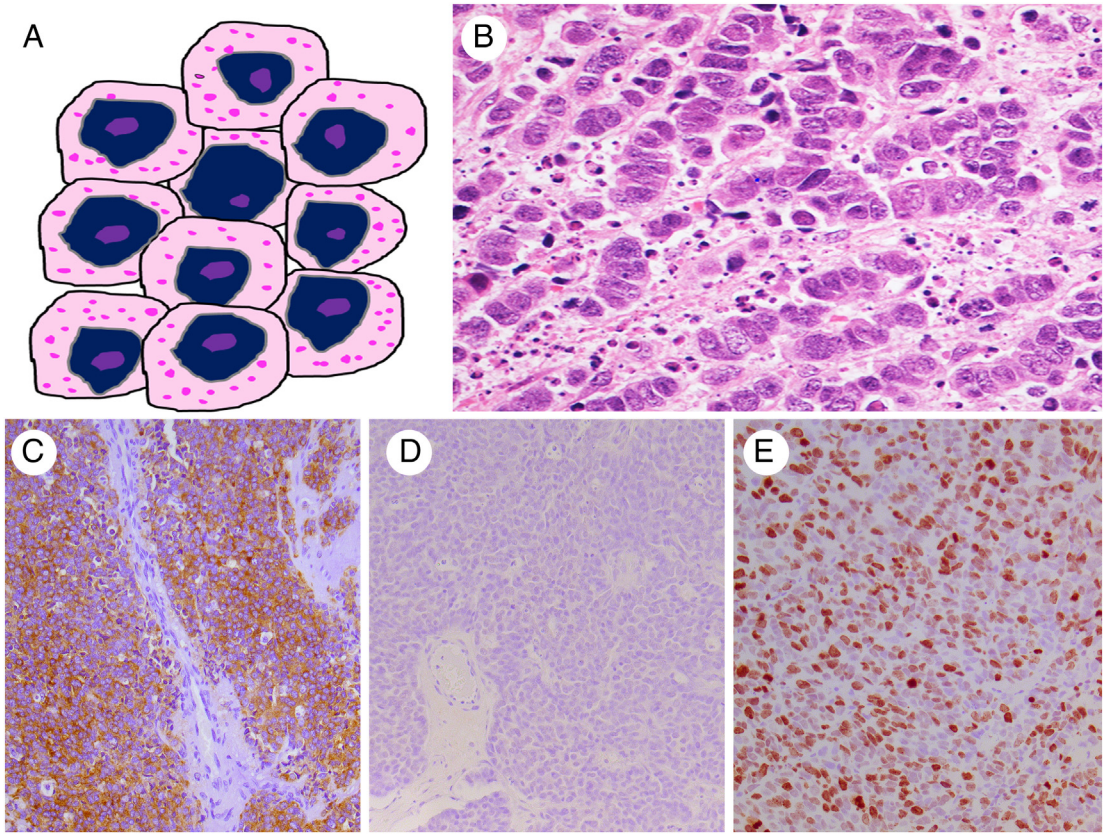


**Fig. 7** Poorly differentiated NE carcinoma of the prostate, large cell type (large cell NE carcinoma). Tumor cells display high nucleocytoplasmic ratio. A and B, Unlike small cell NE carcinoma, large cell NE carcinomas are composed of cells that have larger cytoplasm with variable neurosecretory granules and nuclei with prominent nucleoli (pink granules represent neurosecretory granules [A]). B, These neoplasms often display solid/trabecular growth with increased mitotic activity, necrosis, and apoptotic bodies. The tumor cells are positive for chromogranin A and synaptophysin (C) and are negative for AR (D) and PSA. E, The Ki-67 (MIB-1) labeling index is often high and exceeds 55% of the tumor nuclei.

an increasingly important clinical issue. Recent evidence suggested that androgen ablation therapy–induced small cell prostatic NE carcinoma accounts for 17% of castration-resistant metastatic prostatic cancers [9]. It is thought that the current intensified androgen-deprivation methods used to treat affected patients with metastatic prostate cancer can trigger the occurrence of such manifestations [7]. Further support for this notion comes from the AR-positive LTL331 xenograft model, in which prolonged androgen deprivation resulted in the development of an AR-negative, chromogranin A positive highly proliferative prostatic NE cancer that retained the *TMPRSS2-ERG* fusion [70]. The latter xenograft model represents the counterpart of the previously mentioned PC-310 NE transdifferentiation xenograft model. The androgen deprivation leads to an abrupt change of adenocarcinoma cells with luminal phenotype to a persistent nonproliferative NE population [34]. Some authors suggest that poorly differentiated NE carcinomas arise from a stem cell–like AR-negative precursor, describing such a mechanism as transdifferentiation [71]. More recent studies provided further evidence that in CRPC, there is a divergent evolution of NE phenotype from adenocarcinoma cells associated with the acquisition of genomic and epigenetic changes, which in turn drive the tumor cells selectively toward the AR-wild phenotype, a process also referred to as epithelial plasticity [71].

At the molecular level, poorly differentiated NE carcinomas frequently show *N-MYC* amplification and overexpression with 40% of NE carcinoma versus 5% of conventional acinar adenocarcinoma [72]. In a mouse model of conventional prostate cancer, the induction of *N-MYC* overexpression led to the development of a poorly differentiated carcinoma with similar molecular features of NE carcinomas, including lack of ARs. This would suggest that *N-MYC* amplification is one of the common factors driving the development of NE carcinomas in the background of conventional prostatic adenocarcinomas [73]. Furthermore, about 40% of small cell NE carcinomas have both *N-MYC* and *AURKA* overexpression [74,75]. This would potentially open the door for targeted therapy, in particular using AURKA inhibitors, which disrupt the N-MYC/AURKA complex [76]. Other distinctive common genetic alterations in poorly differentiated NE carcinomas are deletions of the *Rb1* gene and mutation or deletion of *TP53* [71,77]. Aggarwal et al [9] expanded the molecular correlates of androgen ablation therapy–induced small cell NE carcinoma in patients with CRPC. Among these, alterations in DNA repair pathway genes were almost entirely exclusive,

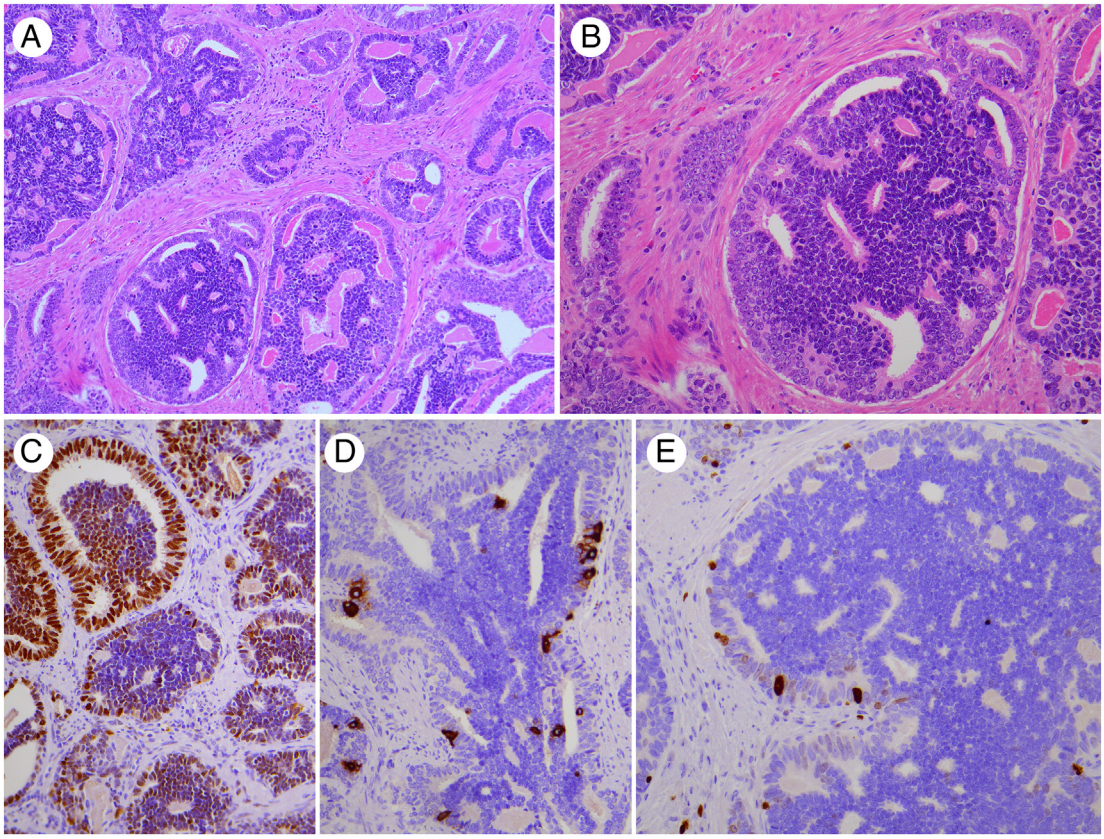


**Fig. 8** Small cell–like change in prostatic adenocarcinoma. A and B, This morphologic change is a potential pitfall that can simulate small cell NE carcinoma. C, AR is variably positive. D, Chromogranin A is negative and only highlights focal divergent NE differentiation. E, The lack of mitotic activity with corresponding low labeling Ki-67 (MIB-1) index is a characteristic finding of small cell–like change.

and they were enriched in overexpression of master regulators including *EZF1*, *ASCL1*, *FOXA2*, *POU3F2*, and *PDX1* [9]. Serine/arginine repetitive matrix 4 (SRRM4) was shown to act as yet another driver of poorly differentiated NE carcinoma and hence a potential therapeutic target for such tumors [78].

### 3.5. Mixed NE and non-NE neoplasms (MiNEN) of the prostate

Lewin [79] first coined the term "mixed endocrine-exocrine tumors," which includes (*a*) composite tumors in which the cells from both components are admixed, (*b*) amphicrine tumors in which the cells that constitute the tumor exhibit both endocrine and exocrine characteristics in the same cell, and (*c*) collision tumors in which there is a clear-cut boundary between the 2 components. Mixed tumors composed of adenocarcinoma and NE carcinoma are labeled as mixed adenoneuroendocrine carcinoma (MANEC) [80,81], a subset of malignancies encompassed by the new umbrella concept of "mixed neuroendocrine–nonneuroendocrine neoplasms" (MiNENs) [82]. The latter terminology has recently been adopted by the fourth edition of WHO classification of endocrine tumors; however, it is not included in the current WHO classification of tumors of most organ systems.

The generic term of MiNEN is conceptually used in the current review. A mixed or composite tumor consists of an exocrine (prostatic adenocarcinoma) and NE neoplasm (eg, large cell NE carcinoma, small cell NE carcinoma, and well-differentiated NE tumor). In our experience, almost all prostatic MiNENs are MANECs. These are composed of prostatic adenocarcinoma and NE carcinoma (either small cell or large cell NE carcinoma, and rarely mixed large and small cell NE carcinomas). In fact, the term MANEC also does not entirely specify individual tumor subtypes. Therefore, the composite elements of mixed tumors should also be defined clearly in all pathology reports.

Unlike prostatic adenocarcinomas with focal divergent NE differentiation or amphicrine features, prostatic MiNENs contain at least 2 morphologically and immunohistochemically distinct tumor populations. To our knowledge, there is no scientific evidence on the minimum amount that defines a mixed tumor. In some organ systems, MANEC requires an arbitrary cutoff of at least 30% of representation for each tumor component, but the biological significance of this 30% threshold has so far not been validated. Furthermore, in prostate pathology, a cutoff has not been well recognized, mainly because the most common diagnostic samples for this type of lesions, such as biopsies or transurethral resections, would not be

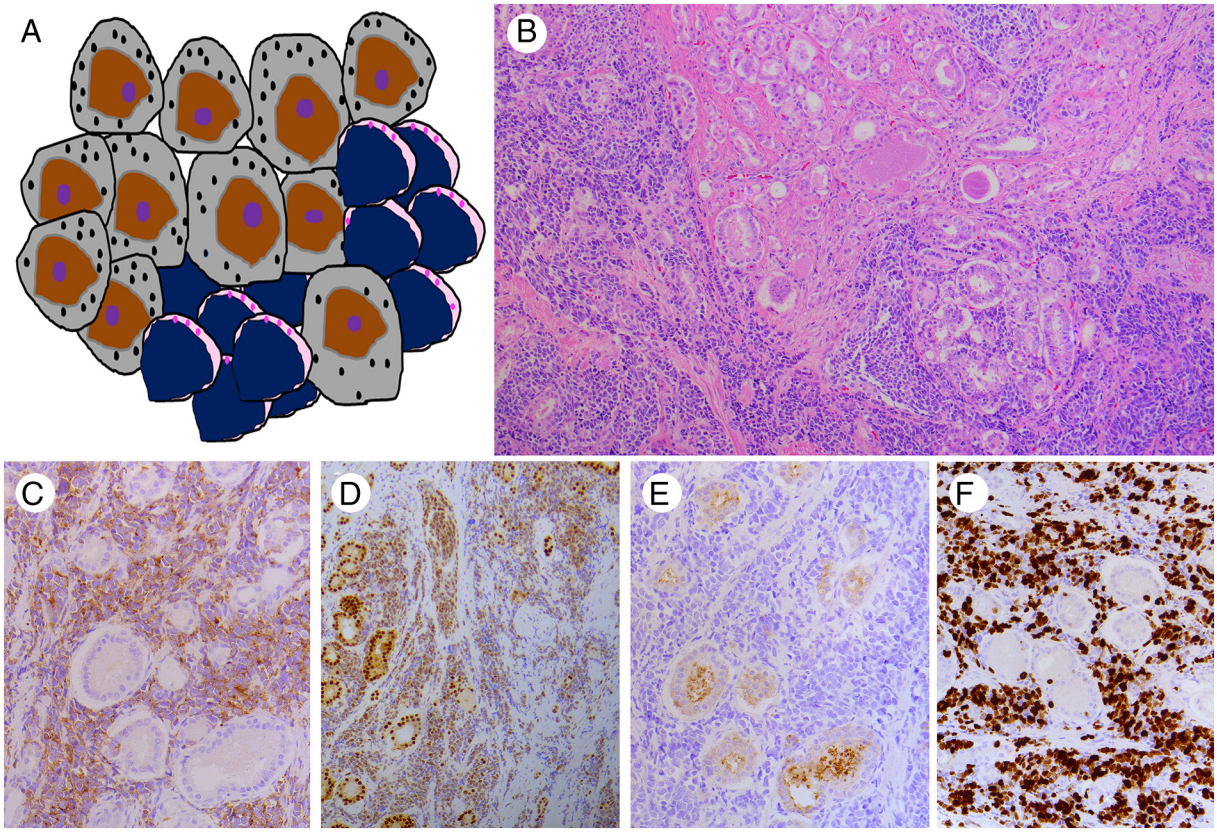


**Fig. 9** Mixed NE and non-NE neoplasm (MiNEN). In the prostate, mixed prostatic adenocarcinoma and small cell NE carcinoma are the most common correlates of MiNEN. A and B, The tumor is often composed of 2 distinct cellular proliferations, each exceeding the arbitrary cutoff of 30% (pink granules refer to neurosecretory granules [A]). C, Unlike the prostatic adenocarcinoma component, the small cell NE carcinoma component is positive for chromogranin A and synaptophysin. Small cell NE carcinoma of the prostate can sometimes be positive for AR, PSA, and PSAP when encountered in the context of MiNEN. D, The illustrated mixed tumor shows variable AR expression in the small cell NE carcinoma, as well as strong reactivity in the adenocarcinoma component. E, In this case, PSA is restricted to the prostatic adenocarcinoma component. F, The Ki-67 (MIB-1) labeling index is very high in the small cell NE carcinoma component.

informative on the actual proportion of each component because of potential sampling bias. When coexisting with conventional prostatic adenocarcinoma, there is generally a sharp demarcation between the NE carcinoma and the conventional adenocarcinoma component (Fig. 9). However, the 2 components are more admixed with each other in some cases; therefore, the use of immunohistochemical biomarkers is required to distinguish these tumors. For hormone-naive MiNENs, a Gleason score is assigned only to the conventional adenocarcinoma component [6]. A large retrospective study on MiNENs of the prostate using the Surveillance Epidemiology and End Result database found that the admixture of a lower-grade adenocarcinoma or lower pathological stage would be associated with a longer survival than admixture with high-grade prostate cancer [83]. Previous smaller studies failed to show this conclusively [3,4].

Molecular-genetic studies have shown that in mixed tumors of the prostate, the poorly differentiated NE and exocrine carcinoma components share the *p53* mutation, implying a common clonal origin [5]. The clonal origin of the 2 components is further supported by studies showing a high proportion of *ERG-TMPRSS2* rearrangements in both components of such tumors of the prostate [65].

The published data on prostatic MANECs are limited; however, the biology of a MiNEN depends on tumor components. Accordingly, therapeutic considerations also vary by tumor subtypes.

### 3.6. Prostatic amphicrine carcinomas

The term “amphicrine” was suggested for the first time by Ratzenhofer in 1977 for cells that displayed both exocrine and endocrine differentiation in the same cell [84,85]. The concept of amphicrine tumor is well established in the gastrointestinal tract [68-75]; however, these were not categorized as pure NE carcinomas. Rare amphicrine tumors were also reported in other organ systems including those arising from the nasal cavity [86], lung [87,88], larynx [89], middle ear [90], skin [91], vulva [92], thyroid [93], and breast [94,95]. Some initial cases published as an amphicrine carcinoma of the prostate were not based on rigid morphologic and immunohistochemical criteria [96]. Wu et al [97] reported a case of a prostatic carcinoma entirely composed of tumor cells with dual

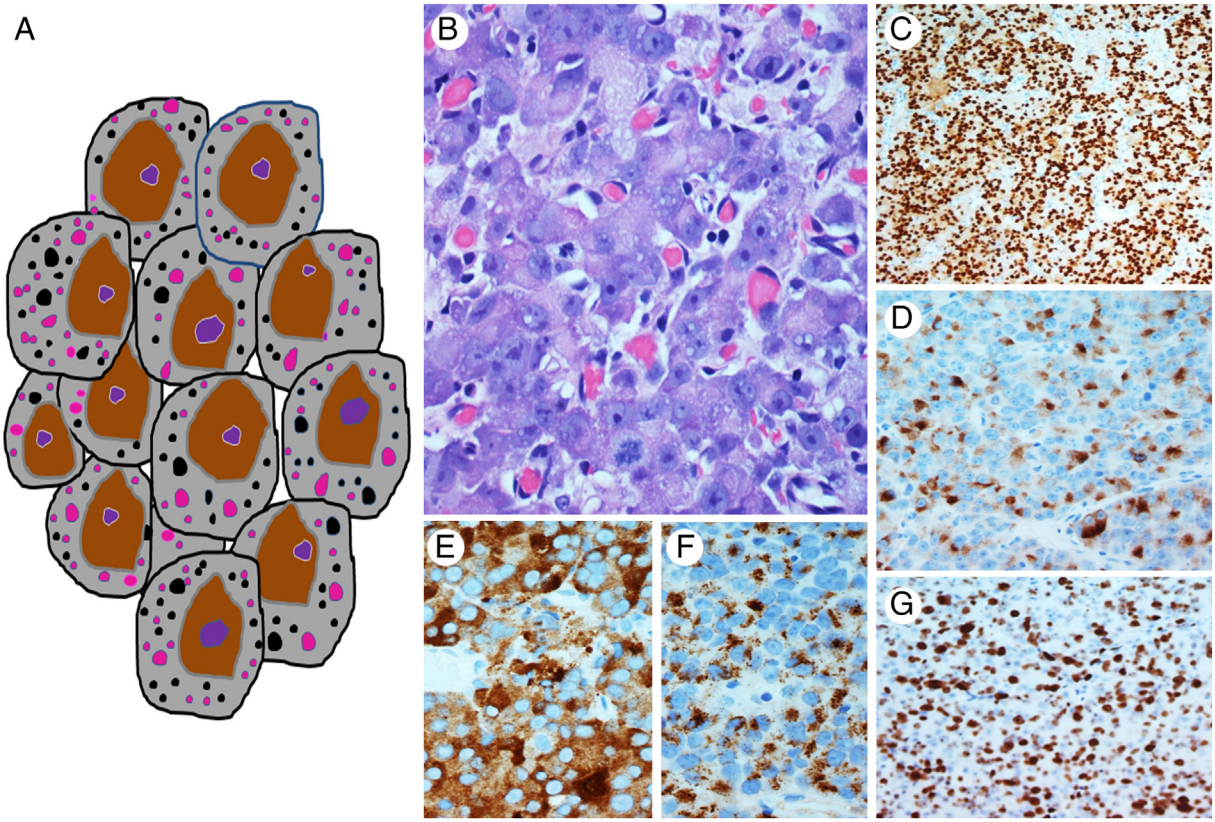


**Fig. 10** Prostatic amphicrine carcinoma. A, These tumors are composed of a single cell type that display both exocrine and NE differentiation (black granules represent exocrine granules; pink granules represent neurosecretory granules). A and B, These tumors often show solid nests with moderate volume of amphophilic cytoplasm, large pale nuclei, mixture of either a single, large centrally placed nucleolus or multiple small, separate nucleoli and absent necrosis. Consistent with the amphicrine phenotype, the monomorphic tumor cells show diffuse or near diffuse positivity for AR (C), PSA (D), synaptophysin (E), and chromogranin A (F). G, These aggressive tumors often show increased Ki-67 (MIB-1) labeling index.

exocrine and NE differentiation that was reported as "hybrid carcinoma," fulfilling the criteria of an amphicrine carcinoma. This hormone-naive tumor with lymph node metastasis at time of diagnosis was entirely composed of tumor cells that were positive for both chromogranin A, AR, and PSA. The "hybrid" expression pattern was also confirmed by transcriptome analysis [97]. Remarkably, several unique oncogene fusions were identified including those involved in the NE pathway. Although the data are limited, amplification and overexpression of the stem cell gene *MS12* in the reported case may suggest its involvement in the stabilization and expansion of this carcinoma with this unique amphicrine phenotype. Androgen-deprivation therapy led to a rapid reduction of his symptoms and a drop in his PSA. Since the report of Wu et al [97], our group have also identified 5 additional aggressive prostate cancers fulfilling the rigid definition of amphicrine phenotype, that is, diffuse expression of one or more NE markers (chromogranin A and synaptophysin) as well as positivity for immunohistochemical biomarkers of exocrine differentiation (eg, PSA, AR, etc) [11]. Some of these tumors were found in hormone-naive patients, whereas others were identified in patients with hormone therapy–resistant prostate cancers. Interestingly, all affected patients had an initial presentation outside the prostate. These tumors have a characteristic morphology and resemble Gleason score 9 or 10 prostatic adenocarcinomas (Fig. 10). They are composed of nests and strands of tumor cells lacking lumen formation, and the tumor nuclei are vesicular with a prominent nucleolus and prominent/high mitotic activity. Because the histomorphology of the amphicrine carcinoma is not immediately suggestive of a poorly differentiated NE carcinoma, these amphicrine carcinomas may be underrecognized or can be mistaken for other NE manifestations [98]. The authors of this review suggest that the use of immunohistochemical biomarkers is helpful in the distinction of an amphicrine phenotype in an aggressive and highly proliferative prostatic adenocarcinoma resembling to those of Gleason score 9 or 10.

### 3.7. Miscellaneous category

As discussed earlier, some prostate cancers with the morphology of a classical small cell or large cell poorly differentiated NE carcinoma may have an aberrant immunoprofile, such as positivity for AR [57]. Such cases might represent a

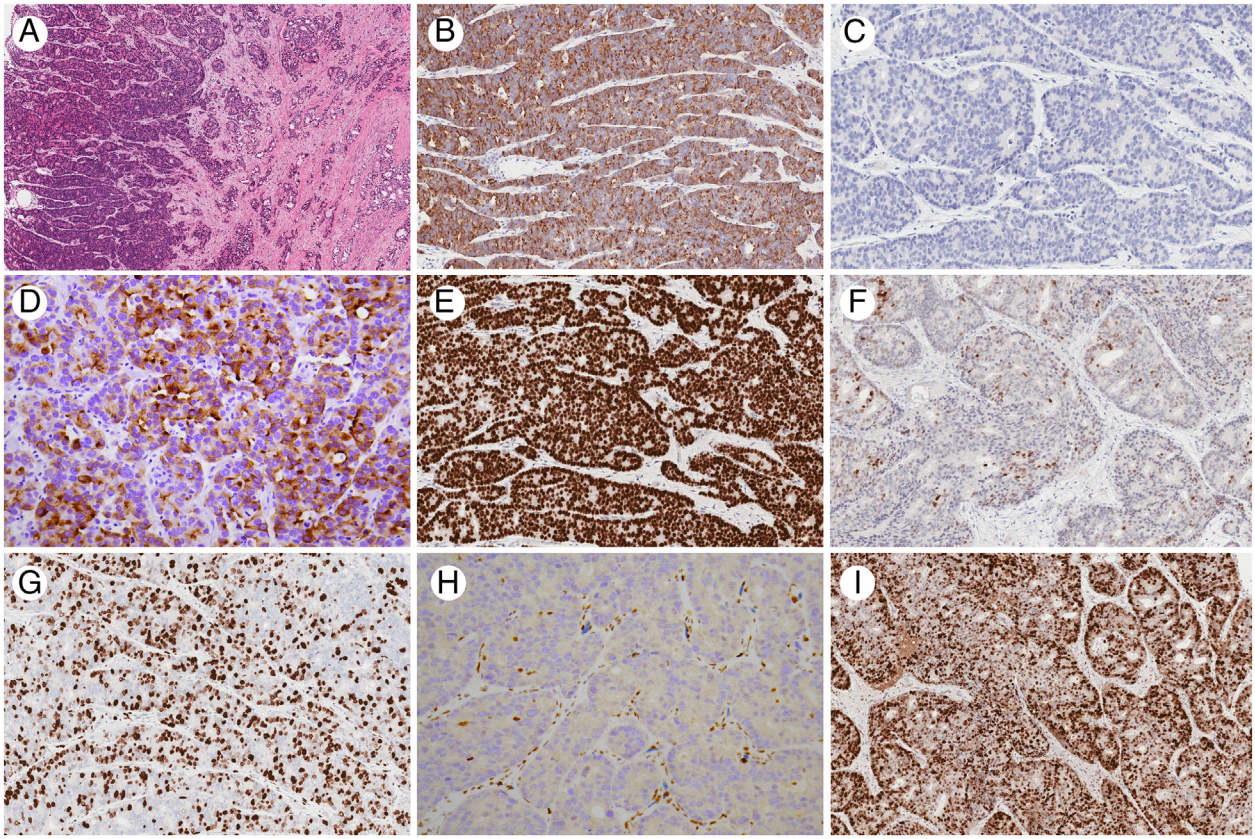


**Fig. 11** Miscellaneous NE manifestations. Not all prostatic NE proliferations follow the common rules of expression profile. This tumor represents a recurrence of a non–small cell prostatic cancer after androgen-deprivation therapy. The detailed clinical and imaging investigations excluded the presence of additional primary source. A, The tumor is composed of cells with variable cytoplasm and display trabecular and cribriform architecture. The tumor is diffusely positive for synaptophysin (B) and chromogranin A and is negative for AR, PSA (C), and PSAP. Patchy serotonin (D), diffuse TTF-1 (clone SPT24; E), and very focal CDX-2 (F) expression is noted in this case. G, The Ki-67 (MIB-1) labeling index exceeds 55%. H, There is global loss of Rb protein in the tumor, and the nontumorous endothelial cells remain positive for Rb. I, p53 overexpression is also identified in this tumor.

transition from conventional adenocarcinoma to amphicrine phenotype or poorly differentiated NE carcinoma, and can be seen in the context of mixed tumors. In fact, the latter may be due to the heterogenous molecular background of castration-resistant prostatic cancers [9]. Although immunohistochemical biomarkers were not systematically investigated in NE neoplasms of the genitourinary tract, the identification of PDX1, which is one of the master regulators in treatment-induced small cell NE carcinomas, is of interest [9]. Similarly, the authors of this review also experienced hormone therapy–induced NE carcinomas demonstrating an unusual combination of transcription factor expression including CDX-2 and TTF-1 (Fig. 11). Although TTF-1 can be expressed in poorly differentiated NE carcinomas of various anatomic sites, the significance of other transcription factors is largely unknown. One can hypothesize that the transdifferentiation in tumor cells may induce expression of transcription factors of various other cell lineages. Under the current morphology-based WHO classification, these would have been considered as small or large cell NE carcinoma. Their designation as poorly differentiated NE carcinoma with aberrant biomarker expression would be more informative; however, this remains an unanswered challenge from a classification perspective. Documentation and follow-up of miscellaneous NE manifestations may provide additional insights into their biological features.

## 4. Conclusions

The classification of NE manifestations of the prostate has gone through various stages from the initial 3 categories to include (*a*) small cell NE carcinoma, (*b*) carcinoid and carcinoid-like tumors, and (*c*) focal NE differentiation in conventional prostate adenocarcinoma to that published in the most recent WHO publication [55,56]. The most recent WHO classification included the same set as 5 different categories comprising (*a*) usual adenocarcinoma with NE differentiation, (*b*) adenocarcinoma with Paneth cell–like NE differentiation, (*c*) well-differentiated NE tumors, (*d*) small cell NE carcinoma, and (e) large cell NE carcinoma [55]. Other classification systems have also been published as well [6,99]. None of these classification systems encompass the entire gamut of prostatic NE

disease that we come across in practice, and we feel that a more comprehensive classification as proposed here (Table) would be more useful. Although the morphologic assessment still remains the basis of the diagnostic workup of most prostatic neoplasms, we believe that the application of ancillary biomarkers is crucial in the accurate classification of prostatic NE manifestations.

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