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Review

The Colorful Palette of Neuroendocrine Neoplasms in the Genitourinary Tract

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Abstract. *Background: Neuroendocrine neoplasms include a heterogeneous group of malignant tumors. Primary neuroendocrine tumors in the genitourinary tract are rare, comprising approximately 1-2% of genitourinary malignancies. Materials and Methods: An extensive search was performed for publications between 2000 and 2018 regarding neuroendocrine tumors of the genitourinary tract. Epidemiological, clinical, histopathological, prognostic and therapeutic data were evaluated. Results: Neuroendocrine tumors of the kidneys are exceedingly rare, mostly well-differentiated. 0.5-1% of all primary bladder malignancies are small cell neuroendocrine carcinomas. Characteristically, prostatic adenocarcinoma with neuroendocrine differentiation occurs in androgen receptor-independent/castrate-resistant cancer. Small cell and large cell neuroendocrine carcinomas are the most aggressive tumors in each location. Conclusion: Due to the rarity and poor prognosis of these tumors, proper pathological diagnosis and early therapy are important. Therapeutic guidelines are not available. Surgery, radiotherapy and/or chemotherapy are possible treatment options; somatostatin analogs are used as standard therapy in case of well-differentiated neuroendocrine tumors.*

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Neuroendocrine neoplasms (NENs) make up a heterogeneous group of malignant tumors with distinct histological features, clinical behavior, and patient outcome. NENs can arise virtually in any organ system, although 85% of NENs affect the gastrointestinal (GI) tract and the lungs. Primary neuroendocrine tumors of the genitourinary (GU) tract are rare, accounting for less than 1-2% of GU malignancies (1, 2). Primary neuroendocrine tumors may develop anywhere in the GU tract; they are most frequently localized in the prostate, but the involvement of the kidneys, urinary bladder, testes, ovaries, and the uterus results in challenging diagnostic and therapeutic dilemmas. Otherwise, the GU tract is a potential site for metastases from other primary neuroendocrine tumors (3). On the basis of the 2016 World Health Organization (WHO) Classification of Tumors of Urinary System and Male Genital Organ classification system, they can be described as well-differentiated neuroendocrine tumors (NET), large cell neuroendocrine carcinoma, small cell neuroendocrine carcinoma, and paraganglioma. The exact classification depends on the site of the origin (Table I) (4). Within this systematic review, the incidence, the pathological features, and prognostic data of NENs of the kidney, urinary bladder, and prostate are discussed together with an emphasis on the main differential diagnostic and therapeutic considerations. The various phenotypes are discussed below separately per organ. The morphological categorization is described by the WHO classification (Table I) (4).

Materials and Methods

PubMed database and clinical trials were searched with publication dates between January 2000 and January 2018. The keywords and the associated results include: The key word 'neuroendocrine genitourinary tumor', gave 656 results, out of which 181 were review papers, 358 pathology studies, and 117 case reports. The keyword 'neuroendocrine genitourinary tumor therapy', gave 314 papers. The search was

Table I. *World Health Organization (WHO) histological classification of neuroendocrine neoplasms of the genitourinary tract in adults (4).*

Kidney	Urinary Bladder	Prostate
Well-differentiated neuroendocrine tumor	Well-differentiated neuroendocrine tumor	Adenocarcinoma with neuroendocrine differentiation
Small cell neuroendocrine carcinoma	Small cell neuroendocrine carcinoma	Well-differentiated neuroendocrine tumor
Large cell neuroendocrine carcinoma	Large cell neuroendocrine carcinoma	Small cell neuroendocrine carcinoma
Paraganglioma	Paraganglioma	Large cell neuroendocrine carcinoma

extended separately for the following organs. For 'neuroendocrine prostate tumor', 1130 papers were identified, and for 'neuroendocrine prostate carcinoma' 594 papers. 301 results were identified for the keyword 'neuroendocrine prostate tumor carcinoma therapy', and 211 for 'neuroendocrine urinary bladder tumor', 172 for 'neuroendocrine urinary bladder carcinoma', and 87 for 'neuroendocrine urinary bladder tumor carcinoma therapy'. For 'neuroendocrine kidney tumor' 570, for 'neuroendocrine kidney carcinoma' 449, and for 'neuroendocrine kidney tumor carcinoma therapy' 154 papers were found. Only publications in English language were included, and also English language abstracts even if the whole paper was written in another language. Basically, reviews papers were excluded unless they were published after the year 2000, and contained data essential for this review. A comprehensive summary regarding the prognosis and potential therapy in case of urological NETs is presented.

Results

Neuroendocrine tumors of the kidney

Neuroendocrine tumors of the kidney are exceedingly rare, and they are classified into well-differentiated tumors, small cell carcinomas and large cell carcinomas (5).

Well-differentiated NET of the kidney. Primary kidney well-differentiated neuroendocrine tumors (formerly carcinoids) are rare. Only about 90 cases are reported in the literature (6). Interestingly, a significant proportion of kidney NETs were associated with horseshoe kidney (18-26% of the patients) (7, 8). There is no gender predilection. The mean age of the patients was 49 years, and approximately 25-50% of the cases were discovered accidentally, and the remaining patients presented with symptoms similar to the ones caused by renal cell carcinoma (RCC), such as pain in the pelvic region, weight loss, fever, palpable mass, and hematuria (3). Carcinoid syndrome is infrequent, and it is presented only in 10-15% of patients with the following symptoms: flush, diarrhea, and generalized edema (9). Radiologically, neither the CT nor the MRI scan can distinguish this tumor from renal cell carcinoma. Somatostatin receptor scintigraphy with octreotide has a high sensitivity for the small and clinically silent renal NETs, and it also has an important role in staging, follow-up, and surveillance of the disease (9, 10). Macroscopically, well-differentiated renal tumors are solitary and well-circumscribed, occasionally with a pseudocapsule. Focal hemorrhage, calcification, cystic changes, and tumor cell necrosis are uncommon (11). The histogenesis of renal NETs are yet unknown. The renal pelvis contains neuroendocrine cells, but not the renal parenchyma. The most popular and acceptable hypothesis is that renal NETs differentiate from neuroendocrine-committed, primitive totipotential cell lines (12). Histologically, polygonal tumor cells with granular amphophilic to eosinophilic cytoplasm can be observed forming vascularized trabeculae or nests. The nuclei are oval-shaped with the typical "salt and pepper" chromatin and minimal pleiomorphism (13). Immunohistochemically, these tumors demonstrate diffuse chromogranin A, synaptophysin, CD56, and cytokeratin labeling (12, 13). In support, no admixture of renal NET and clear cell RCC within the same tumor has been documented; only one case of synchronous renal NET and contralateral multilocular cystic renal neoplasm of low malignant potential has been recorded (12). The prognosis is controversial; some patients survive for only 6 months, some others for many years, even with metastases (14). Renal NET is a slow-growing tumor; patients show a prolonged clinical course, even when they have a metastatic disease that indicates the indolent behavior of renal NETs (13). The first choice of therapeutic management for the localized and even for the metastatic well-differentiated tumors could be surgical resection (5, 15) because these tumors are chemoresistant (12). The prognostic and therapeutic details are presented Table II (10, 13, 16-19).

Small cell neuroendocrine carcinoma of the kidney. Renal small cell neuroendocrine carcinomas (SCNEC) are rare, the approximate number of the reported cases is 50 (6, 20-22). These tumors resemble the small cell carcinoma of the lungs. In renal small cell neuroendocrine carcinoma, the mean age of the patients is 59 years; there is no gender predilection, and the left to right side ratio is 1:1.5. The clinical symptoms are abdominal pain, macroscopic hematuria, and weight loss. Macroscopically, these are large tumors with a range from 100-230 mm, and usually infiltrate the entire kidney (20). The cut surface is soft, whitish, gritty, and necrotic with a solid growth. Infiltration of the renal sinus, renal vein, and perirenal tissue is frequent (21). Microscopically, the tumor consists of poorly differentiated small, round cells that compose sheets and nests. Mitoses, vascular tumor emboli, and extensive necrosis are common (13). The tumor cells show dot-like cytoplasm

Table II. *Neuroendocrine tumors of the kidney: prognostic and therapeutic data from current references.*

	Prognosis	References	Potential therapy	References
Kidney				
Well-diff. NET	Indolent behavior in horseshoe kidney	Motta *et al*. 2004 (16)	Ovarian and hepatic metastases, one year after thecomplete surgery (hysterectomy, nephrectomy, hepatectomy) no recurrence	Gedaly *et al*. 2008 (17)
	45% of cases present with perirenal fat and renal vein infiltration, in 50-60% of patients occured paraaortic lymph node, lung, liver and bone metastases	Romero *et al*. 2006 (10)	Sunitinib in vascular endothelial growth factor and hypoxia-inducible factor 2 positive cases	Finley *et al*. 2011 (18)
	High metastatic rate: age >40 years, tumors >4 cm, T3 stage, mitotic rate >1/10 HPF	Mazzucchelli *et al*. 2009 (13)	OS was 9 months after radical nephrectomy, no local recurrence, no metastasis	Inagaki *et al*. 2013 (19)
SCNEC and LCNEC	75% of the patients died within one year	Lane *et al*. 2007 (6)	Small cell neuroendocrine carcinoma occured 4 years after surgery with local recurrence	Piedra Lara *et al*. 2003 (29)
	Poor prognosis, survival is less than 1 year, with frequent extrarenal extension, regional lymph node, brain, bone, adrenal gland and liver metastases	Mazzucchelli *et al*. 2009 (13) Kuroda *et al*. 2014 (24)	Platinum-based chemotherapy for treatment or palliation	Lane *et al*. 2007 (6)
	One case occured in kidney transplant recipient	Mohd *et al*. 2016 (28)	Surgery in case of tumor thrombus, 7 months OS	Xu *et al*. 2009 (30)
	One case with pulmonary, pancreatic and cardiac metastases	Shimbori *et al*. 2017 (27)	Surgery plus chemotherapy, 17.3 months overall survival	Teegavarapu *et al*. 2014 (31)
			Surgery, platinum-based chemotherapy and radiotherapy	Shimbori *et al*. 2017 (27)

OS: Overall survival.

staining with cytokeratin, and they are variably positive for chromogranin A, synaptopthysin, CD56, and NSE. As seen in the bladder, primary renal SCNEC can coexist with in situ and/or papillary urothelial carcinoma, squamous cell carcinoma, or adenocarcinoma (23). They are highly aggressive tumors, and they are associated with poor prognosis; the median survival is less than 1 year (13, 24).

Large cell neuroendocrine carcinoma of the kidney. Renal large cell neuroendocrine carcinoma (LCNEC) is an extremely rare form of cancer with fewer than 10 cases in the literature (2, 6, 25-27). There is no gender predilection, and the peak age of incidence is between 50 and 60 years. Most patients present in an advanced stage; the main symptoms and signs are pain in the flank, palpable mass, hydronephrosis, and hematuria, and in some cases, the symptoms and signs are induced by the distant metastases (2). Grossly, renal LCNECs have a solid cut surface with necrosis, and the extrarenal extension is common (2, 25). The tumor cells are large with abundant cytoplasm, vesicular chromatin, and prominent nucleoli. There is a brisk mitotic rate, usually more than 10 per high power field (2). For establishing the diagnosis, at least focal positivity of the NE markers is essential (6). The diagnosis can be mistaken for high-grade renal cell carcinoma or urothelial carcinoma. The clinical prognosis of these carcinomas is very poor (2). There is no indication of systematic therapy for renal SCNEC and LCNEC. Surgery, platinum-based chemotherapy, and radiotherapy could be an effective multimodal management (27). See Table II for particular prognostic and therapeutic data about SCNEC and LCNEC (6, 13, 24, 27-31).

Neuroendocrine tumors of the urinary bladder

Neuroendocrine tumors are very rare in this site, and they can be classified as well-differentiated tumors, SCNEC, and LCNEC.

Well-differentiated neuroendocrine tumors of the urinary bladder. Well-differentiated neuroendocrine tumors of the urinary bladder (previously called carcinoids) are extremely rare; there are, approximately, only 25 reported cases in the literature. These tumors usually develop in elderly male patients (mean age: 56 years). Symptoms of the disease are the following: hematuria and irritating voiding difficulties. No association with carcinoid syndrome has been reported in the literature (32, 33). These tumors are usually discovered accidentally (34). Cystoscopy may reveal polypoid structures with submucosal infiltration 3 to 30 mm

in size. The tumor is usually localized to the trigone and the neck of the bladder, but there are several cases in the literature in which the prostatic urethra is involved as well (35). According to other theories, the tumor originates from metaplastic bladder urothelium or from transformed neuroendocrine cells, especially in the region of the trigone (12). The exact cellular origin of bladder NET is still unknown; however, it has been postulated that NETs may arise from NE cells of different kind of reactive lesions (36). Microscopic features are similar to NETs located in other organs. Histologically, the tumor cells are cuboidal or columnar with abundant amphophilic cytoplasm, and they are arranged in an insular, acini, trabecular, or pseudoglandular pattern in a vascular stroma with finely stippled chromatin and inconspicuous nucleoli. Mitotic figures are infrequent, and no tumor cell necrosis can be seen. Typically, the tumor cells are found in the lamina propria and are positive for NE markers (chromogranin A, synaptophysin, and CD56) and cytokeratins (23, 34). In addition, prostate-specific acid phosphatase (PAP) expression was detected. No other prostate marker positivity can be detected (36). Due to the lack of long-term follow-up data, the prognosis cannot be exactly estimated.

Small cell neuroendocrine carcinoma of the urinary bladder. 0.5-1% of all primary bladder malignancies are SCNECs. Its pure form is rare; half of the cases are mixed with urothelial carcinoma, adenocarcinoma, squamous cell carcinoma, and/or sarcomatoid features (37). SCNEC has a slight male predominance with a male-to-female ratio of 3:1. The mean age of the patients is 66 years (23). 80% of the patients have a history of cigarette smoking. Common clinical symptom of this disease is hematuria. Sometimes local irritation, pain in the pelvic region, or urinary obstruction may also occur (38). In most of the cases, macroscopic histological examination reveals large solid, polypoid, or nodular, ulcerated mass with muscle or fat tissue invasion. The fundus, the lateral and posterior walls of the bladder are most commonly involved (39). Macroscopically, SCNEC is not different from urothelial carcinoma. SCNEC usually has a polypoid, solid, or ulcerative appearance with deep invasion of the bladder wall (40). Microscopically, histological features of bladder SCENC are similar to those of small cell carcinoma of the lungs. The tumor is composed of small to intermediate size cells with scanty cytoplasm, inconspicuous nucleoli, and in several cases, the typical salt-and-pepper chromatin can be observed as well (41). Brisk mitotic activity, vascular invasion, and necrosis can also be detected (23). Mitotic count and Ki67 index are important for grading (42). Tumor cells express both epithelial and neuroendocrine markers. Chromogranin A, synaptophysin, neuron-specific enolase, CD57, CD56, protein gene product 9.5, and 'dot-like' cytokeratin positivity are characteristic for this kind of tomur. Chromogranin A is a specific but quite insensitive marker, which is expressed in 30% of the tumors. The Ki67 index is variable, and nuclear accumulation of p53 protein can be observed as well (43-45). The use of TTF-1 to differentiate the tumor from pulmonary small cell carcinoma is dubious as 25-39% of bladder small cell carcinomas also express TTF-1. Several allelic and chromosomal losses, deletions, and gains have already been identified. Some of these affected oncogenes, like *MYC* has a high amplification level in SCNEC of the bladder (43). Genetic trials proved *p53* and *RB1* to be the most frequently altered genes in 90% of patients with small cell carcinoma. Bladder-specific mutations in the TERT promoter have been reported. These genetic results are more likely to refer to urothelial carcinoma rather than small cell lung cancer (46). Bladder SCNEC has an aggressive clinical course (23, 47). CT images of bladder small cell cancer show a heterogeneous broad-based polypoid mass with extensive local invasion (at least T3 or T4 stage) (3). Bladder SCNEC tends to have a better outcome than the small cell carcinoma of prostate (48). Most available treatment options can also be administered in case of small cell carcinoma of the lungs. Early diagnosis of the disease as well as surgery, neoadjuvant, adjuvant, or palliative chemotherapy with or without radiotherapy are the cornerstones of patient care (13, 48-50). Details about prognosis and therapy are shown in Table III (13, 23, 35, 41, 42, 44, 47-60).

Large cell neuroendocrine tumor of the urinary bladder. Large cell neuroendocrine tumor (LCNEC) of the bladder is an extremely rare form of cancer with fewer than 25 reported cases (61). The disease mainly develops in elderly male patients (36). Histologically, LCNEC is identical to large cell carcinoma of the lungs. Tumor cells are large with a polygonal shape, low nuclear to cytoplasmic ratio, coarse nuclear chromatin, prominent nucleoli, and frequent mitotic figures (38, 62). Admixture of LCNEC and other forms of bladder cancer including urothelial carcinoma, squamous cell carcinoma, adenocarcinoma, and sarcomatoid carcinoma can also be detected (63). The genetic background is unknown due to the rarity of the disease (36). Immunohistochemically, the tumor cells show a strong reaction for cytokeratins (AE1/AE3, CAM5.2) and EMA. The expression of NE markers mainly confirm the diagnosis; however, chromogranin A is expressed more frequently in bladder SCNEC than in LCNEC (62). The prognosis of pure bladder large cell carcinoma is similar to small cell cancer (13). The therapeutic options are presented in Table III (13, 61, 63-65).

Neuroendocrine tumors of the prostate

Neuroendocrine differentiation in prostate cancer. Almost all prostate carcinomas (PCA) have focal NE differentiation, but confluent zones with focal NE cells or NE cell clusters (<50 cells) can be detected only in 5-10% of cases. The role and origin of prostatic NE cells are unknown (66). There are some

Table III. *Neuroendocrine tumors of the urinary bladder: prognostic and therapeutic data from current references.*

	Prognosis	References	Potential therapy	References
Urinary bladder				
Well-diff. NET	Lymphatic metastasis in 25% of cases, mixed tpyes NETs with adenocarcinoma are aggressive	Mazzucchelli *et al*. 2009 (13)	Excision	Chen *et al*. 2011 (35)
SCNEC	Aggressive behavior, 1.7 years median survival time, anecdotal long-time survival	Cheng *et al*. 2004, (23) Choong *et al*. 2005(47)	Surgery with adjuvant cisplatin-based chemotherapy	Ghadouane *et al*. 2003 (52)
	12.7 months median OS, better outcome than prostatic SCNEC	Asmis *et al*. 2006 (48)	After cystectomy the median cancer-specific survival was 23 months, combined with preoperative chemotherapy the 5-year survival was 78%	Siefker *et al*. 2004 (53)
	In 40% of cases brain metastasis occured	Moretto *et al*. 2013 (44)	Neoadjuvant chemotherapy before surgery has favourable effect on survival	Siefker *et al*. 2004 (53), Prelaj *et al*. 2016 (51)
	In 28-80% of cases lymphatic, liver, lung and bone metasteses occured	Zheng *et al*. 2015 (41)	Etoposide, cisplatin, carboplatin for pure forms; methotrexate, vincristine, adriamycin, cyclophosphamide, etoposide or cisplatin for mixed types	Manunta *et al*. 2005 (54)
	At the time of diagnosis 95% of cases are present in advanced local stage (pT2 or higher)	Zheng *et al*. 2015 (41), Prelaj *et al*. 2016 (51)	Treated with transurethral resection, adjuvant carboplatin-based chemo- and radiotherapy, 30 months disease-free survival	Tunc *et al*. 2006 (55) Mazzucchelli *et al*. 2009 (13)
			Early cisplatin-based chemotherapy	
			Neoadjuvant platinum-based chemotherapy followed by aggressive surgery	Ruoppolo *et al*. 2010 (56)
			Platinum based chemotherapy followed by local treatment	Macedo *et al*. 2011 (57), Thota *et al*. 2013 (50)
			Cystectomy plus adjuvant chemotherapy and radiotherapy	Guo *et al*. 2012 (49)
			Case with lymphatic, hepatic, adrenal, lung metastases with two different cycles of cisplatin chemotherapy, no resoponse	Cerulli *et al*. 2012 (58)
			Surgery with neoadjuvant or adjuvant chemotherapy and radiochemotherapy (doses from 35 Gy/20, 64 Gy/32 to 70 Gy)	Moretto *et al*. 2013 (44)
			Palliative chemotherapy for metastatic disease	Thota *et al*. 2013 (50)
			Cisplatin-based chemotherapy plus radical cystectomy	Aragón-Tovar *et al*. 2014 (59)
			Surgery/cystectomy alone is inadequat	Erdem *et al*. 2016 (60)
			Transurethral bladder resection is inadequate for therapy	Ghervan *et al*. 2017 (42)
LCNEC	Similar to SCNEC of urinary bladder	Mazzucchelli *et al*. 2009 (13)	Aggressive surgery with neoadjuvant or adjuvant etoposide and platinum-based chemotherapy, surgery alone is not recommended	Evans *et al*. 2002 (65), Coelho *et al*. 2014(61)
	Increased risk for developing of prostate cancer after external beam radiation and brachytherapy	Zakaria *et al*. 2017 (64)	7 months survival after 5 cycles of chemotherapy with etoposide and cisplatin followed by surgery	Colarossi *et al*. 2013 (63)

Table IV. *Neuroendocrine tumors of the prostate: prognostic and therapeutic data from current references.*

	Prognosis	References	Potential therapy	References
Prostate carcinoma				
Adenocc with NED	Metastatic androgen-independent prostate cancer with focal NE differentiation has poor prognosis	Cheville *et al.* 2002 (75)	Aurora A inhibitor in metastatic castrate-resistant and neuroendocrine prostate	clinical trial (77)
	Serum chromogranin A does not correlate with response to chemotherapy	Berruti *et al.* 2005 (95)	Lanreotide with dexamathasone with 7 months PFS	Koutsilieris *et al.* 2001 (96)
	No correlation of neuroendocrine differentiation with clinical outcome	Fine SW 2007 (5)	Lanreotide with ethinylestradiol with 18.5 PFS	Di Silverio *et al.* 2003 (97)
	Ki-67 index as independent prognostic factor	Komiya *et al.* 2009 (66)	Serotonin receptor antagonists	Dizeyi *et al.* 2005 (79)
	AURKA and/or n-MYC amplifications might be a predictive factor	Beltran 2011 (76), Terry and Beltran 2014 (67)	Bombesin-like/gastrin-releasing peptide antagonists in androgen-independent prostate cancer	Stangelberger *et al.* 2006 (78)
			Three courses of cisplatin and irinotecan	Inoue *et al.* 2007 (98)
			mTOR pathway in the management	Garcia *et al.* 2008 (99)
			Somatostatin analogs	Komiya *et al.* 2009 (66)
			High doses of paclitaxel and carboplatin then irradiation (60+10Gy)	Maebayashi *et al.* 2015 (100)
			Etoposide and carboplatin then docetaxel only	Wei *et al.* 2016 (101)
			Intracellular chemokine CXCL12γ as therapeutic target	Jung *et al.* 2018 (102)
Well-diff. NET	Relatively indolent and favorable	Mazzucchelli *et al.* 2009 (13)	Neoadjuvant chemotherapy and radical prostatectomy for metastatic well-differentiated NETs	Tash *et al.* 2002 (82)
SCNEC	Testicle metastasis 2.5 years after androgen deprivation therapy	Schneider *et al.* 2006 (103)	Cisplatin-based chemotherapy plus radiotherapy failed to improve the survival, patient died after 4 months	Benchenkroun *et al.* 2002 (104), Stein *et al.* 2008 (105)
	No difference in prognosis between pure small cell and mixed with adenocarcinoma	Mazzucchelli *et al.* 2009 (13)	Octreotide therapy recived remission	Spieth *et al.* 2002 (106)
	Small cell component usually means a terminal phase	Mazzucchelli *et al.* 2009 (13)	Combination of doxorubicin, etoposide and cisplatin resulted 5.8 months PFS and 10.5 months OS	Papandreou *et al.* 2002 (107)
	Aggressive behavior, poor prognosis with 19 months median cancer-specific survival, 2-year and 5-year survival were 14.3%, 27.5% respectively	Deorah *et al.* 2012 (93)	Metronomic cyclophosphamide and mitoxantrone have favorable effect	Berry *et al.* 2002 (108), Lord *et al.* 2007 (109)
			Cisplatin plus etoposide, progression controlling for 7 months	Yashi *et al.* 2006 (110)
			Four cycles of irinotecan plus cisplatin, after second cycle neuron-specific enolase level was normalized and after the fourth cycle was complete remission	Komiya *et al.* 2009 (66)
			Three course intra-arterial infusion of cisplatin plus ifosfamid, then external beam radiaton	Uemura *et al.* 2013 (111)
			Carboplatin plus docetaxel followed by cisplatin plus etoposide, objective response rate 33%, median survival 16 months	Aparicio *et al.* 2013 (112)

Table IV. *Continued*

Table IV. *Continued*

	Prognosis	References	Potential therapy	References
			Combination of carboplatin, etoposide, cyclophosphamide, doxorubicin and vincristine between 4 and 8 cycles and then locoregional methods	Aparicio *et al*. 2014 (113)
			Systemic chemotherapy alone or combintion with androgen deprivation therapy	Parimi *et al*. 2014 (73)
			For advanced stage disease is platinum-based chemotherapy	Campedel *et al*. 2017 (94)
			Case report with paraneoplastic syndrome of inappropriate antidiuretic hormone secretion and high sensitivity for chemotherapy	Peverelli *et al*. 2017 (114)
			Platinum-based chemotherapy, but response duration is short	Akamatsu *et al*. 2018 (115)
LCNEC	Rapid course, poor prognosis	Evans *et al*. 2006 (95)	Platinum based chemotherapy with 7 months survival	Evans *et al*. 2006 (95)
			Neoadjuvant chemotherapy (taxol, vepesid and cisplatin) with Lupron followed by radical prostatectomy and pelvic lymphadenectomy with 13 months survival	Okoye *et al*. 2013 (116)
			Effects of icaritin in mice model	Sun *et al*. 2016 (117)

OS: Overall survival; PFS: progression-free survival.

potential theories about the origin of NE cells: (1) NE and conventional adenocarcinoma components may arise from one tumor clone with stem cell-like abilities (*i.e*., epithelial and NE differentiation) (67); (2) NE tumor cells may evolve from adenocarcinoma cells by genetic alterations, due to treatment interventions (*i.e*., androgen deprivation therapy, radiation and chemotherapy) or changes in the microenvironment of the tumor cells (*i.e*., hypoxia, cytokines, or hormones); (3) malignant NE phenotype arises from normal prostatic NE cells (67). Reduced activity and/or expression of the androgen receptor (AR) can be observed in NE cells, resulting in a hormone-insensitive cellular population embedded in the tumor, which may lead to the progression of the disease (67-69). NE cells are indistinguishable from tumor cell in PCA; therefore, the identification is based on the expression of NE markers: chromogranin A, serotonin, and somatostatin. Prostate-specific markers (prostate specific antigen - PSA, prostatic acid phosphatase - PAP) positivity can also be found in case of NE cells (5). There is a relationship between the elevated proportion of NE differentiation in castrate-resistant prostate cancer and high serum level of chromogranin A. It could be an indicator in patients without elevated serum PSA level (70, 71). Some data show that more than 50% of all neuroendocrine prostatic carcinoma cases are associated with prostatic adenocarcinomas and clinically with androgen-receptor independence. Therefore, in 2013, the Prostate Cancer Foundation Working Committee on neuroendocrine PCA suggested the terminology of "AR-negative prostate cancer" for neuroendocrine prostatic carcinoma. However, mixed tumors contain AR-positive and also AR-negative cells, and in rare cases, hybrid tumors can be identified where neuroendocrine markers and AR are expressed in the same tumor cells (72). Studies have proven that prolonged androgen deprivation in androgen sensitive metastatic and also in primary PCA results in increased neuroendocrine differentiation (73). Focal NE differentiation develops in 10% to 100% of prostate adenocarcinomas treated by anrogene deprivation therapy (ADT), especially in advanced stage but with relatively low serum PSA (74). The prognosis is controversial (5), but in fact, prostate cancer with focal NE differentiation has poor prognosis (13, 75). In order to better understand the importance of NE differentiation, the molecular mechanisms also have to be studied. Recently, two proto-oncogenes have become the center of attention, namely, cytoplasmic serine/threonine-protein kinase *AURKA (Aurora kinase A)* and nuclear transcription factor n-MYC, which might be responsible for the malignant NE phenotype in prostate cancers (76). Terry and Beltran have found in their

study that the inhibition of *AURKA* blocks the growth of NE cells *in vitro* and *in vivo*. Detection of *AURKA* may lead to further therapeutic options (77). Prostatic neuroendocrine tumors are treated with combined somatostatin analogs that have a high therapeutic index (66). Bombesin/GRP antagonists and serotonin antagonists may be regarded as further therapeutic options (78, 79). Castration-resistant prostate cancer is usually fatal, and successful management is still a problem. Nelson *et al*. have proposed a theory about four different stages of so-called adaptation in prostate cancer on the basis of androgenic ligands and the activity of AR (80).

Well-differentiated neuroendocrine tumor of the prostate. Well-differentiated neuroendocrine tumors of the prostate are extremely rare; only a few cases of them have been reported (81, 82). No specific age group in which prostatic NET develops more frequently can be identified; nevertheless, some authors suggest that it is usually found accidentally in elderly patients, while others report that locally advanced and metastatic diseases are more frequent in younger adults (13, 73). Clinical symptoms are hematuria, burning nocturia, frequent urination, and different symptoms of urinary retention. Macroscopically, the size of the tumor is variable, and sometimes infiltrates the entire prostate. For the diagnosis of pure NET, conventional PCA with NE differentiation need to be excluded, which could be challenging (5). Histological features are similar to NETs of other organs: trabecular, insular, mixed architectural patterns of generally polygonal or spindle-shaped cells, with low-grade cytological features and "salt and pepper" chromatin. The cytoplasm is abundant and eosinophilic, and mitotic figures are uncommon (81, 83). The cells are positive for chromogranin A and synaptophysin, and negative for PSA and PAP. If a tumor represents nested architecture and uniform nuclei with positive staining for PSA and NE markers, a "NET-like" PCA should be considered (73, 74). The prognosis is hard to define because of their rarity, but nowadays, it is considered to be favorable (13).

Small cell neuroendocrine carcinoma of the prostate. Prostatic SCNEC represents approximately 1-5% of all prostate malignancies (5). Local symptoms are similar to those represented in case of conventional PCA, but in a few cases, paraneoplastic syndrome develops, such as Cushing syndrome, hypercalcemia, syndrome of inappropriate antidiuretic hormone secretion, and Eaton–Lambert syndrome (84-86). The serum PSA concentration is variable (87). Prostatic SCNEC may develop in a pure form or can be mixed with acinar PCA (13, 73). At least 25% of patients with advanced PCA may eventually develop SCNEC. The number of NE differentiation in PCA may increase because of the novel AR targeted therapies for castration-resistance PCA (88). Microscopically, SCNEC has similar histological features to small cell carcinoma in other organs with minimal cytoplasm, indistinct cell borders, nuclear molding, extensive tumor cell necrosis, high mitotic rate, and nuclear fragility (73). Approximately 50% of the cases express TTF1, hence the use of TTF-1 expression cannot distinguish between primary prostatic SCNEC and metastatic small cell carcinoma of other organs (73). Chromogranin and synaptophysin staining is intense in 90% and 17% of cases, respectively (5). 24% of cases are diffusely positive for PSA and PAP, which suggests that there is a link between acinar PCA and prostatic SCNEC (89-91). In the diagnostic process, fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction may be useful in order to detect a gene fusion between the ETS family member gene *ERG* and *TMPRSS2* gene. Half of the prostatic small cell cases are positive for *TMPRSS2-ERG* gene fusion by FISH (92). Grading of small cell cancer should not be done according to the Gleason system, although some pathologists still give Gleason score with an additional comment (13). Prostatic SCNEC has one of the most aggressive behaviors of all prostate cancers, often in advanced local stage (93). Small cell carcinomas of the prostate are thought to be identical to small cell carcinomas of the lungs. Therefore, cytotoxic agents given in case of small cell carcinoma of the lungs can be usually administered to patients with small cell carcinoma of the prostate as well (94), but there are also other therapeutic options available.

Large cell neuroendocrine carcinoma of the prostate. Few cases of LCNEC have been reported (5, 95). Histologically, it shows similar features to the ones seen in other organs. Typically, the tumor cells have abundant amphophilic cytoplasm and large nuclei with coarse chromatin and prominent nucleoli. Brisk mitotic activity and geographic necrosis can be noticed as well. The tumor cells are larger than the cells of small cell carcinoma or conventional prostatic adenocarcinoma (73). However, it is difficult to distinguish LCNEC from Gleason 5 + 5 PCA, hence the chance of a misdiagnosis is quite high (95). Immunohistochemically, these tumors are strongly positive for chromogranin A, synaptophysin, CD56, CD57, and P504S/α-methylacyl CoA racemase. A focally positive staining pattern can be identified for PSA and PAP in LCNEC, and they are negative for androgen receptor. Their prognosis is poor, and they are frequently present with distant metastases at the time of their discovery. They might be treated with long-term hormone therapy (95). Table IV contains further prognostic and therapeutic details for all prostatic neuroendocrine tumors (5, 13, 66, 67, 73, 75-79, 82, 93-117).

Discussion

As a result of the rarity of these tumors, there is a diagnostic challenge and therapeutic dilemma. To distinguish between a NET and an undifferentiated tumor of the GU tract can become an exceedingly problematic task, and that is why special

immunohistochemichal stainings, beyond the standard markers, should be ordered in such cases. NE markers have good specificity although their sensitivity is different. Since neuroendicrine tumors are more common in the lungs and the gut than in the GU tract, the possibility of a metastatic involvement from these sites should be considered first. Because the pathologist has limited options, the exclusion of a metastasis in other organs is mainly based on the clinical parameters. The outcome of these tumors is poor; therefore, an exact histological and immunohistochemical verification is needed to prevent misdiagnosis. No guidelines are available regarding the optimum management; thus, different treatment strategies are applied to improve the poor prognosis of the disease. The therapy of renal and bladder NET is based on the management of NET in other sites. There are some important approaches for the management of prostatic NET. Prostatic NETs are mainly AR negative. Data show that advanced prostatic cancer often presents with mixed histological features, with AR-dependent and AR-independent tumor cells; moreover, hybrid tumors can also be detected with both NE markers and AR expressing tumor cells. Neuroendocrine differentiation in prostatic adenocarcinoma characteristically occurs in AR-independent/castrate-resistant prostate cancers. The therapeutic options involve chemotherapy, somatostatin analogs, and bombesin-like antagonists. Somatostatin analogs are the basic therapeutic regimens in case of well-differentiated NETs.

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