



## REVIEW

# Neuroendocrine tumors in the urinary bladder: a literature review

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## Abstract

Neuroendocrine tumors (NETs) can be found in most organs, as well as in the urinary bladder. Some of the clinical and pathologic features of these tumors may be characteristic of the organ of origin, but most of the properties are shared by neuroendocrine neoplasms regardless of their anatomic site. In the bladder, NETs comprise less than 1% of all bladder tumors and can be found in a pure form or intermixed with urothelial carcinoma and its variants. Bladder NETs are classified into 2 subtypes: carcinoid tumor and neuroendocrine carcinoma, which is further subdivided into small cell and large cell neuroendocrine carcinoma.

Characteristics of bladder NETs and its differential diagnosis are discussed herein.

**Key words:** bladder cancer, carcinoid, small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma

## 1. Introduction

The most common cancer of the urinary bladder is urothelial carcinoma, which has a broad spectrum of biological behavior. As such, many studies are being conducted to investigate the connection between different histological growth patterns, cell lineages and biology, as well as the prognosis and therapy of these tumors [1, 2].

Bladder urothelial cancer is known for its divergent differentiation, which is mostly visible in a form of glandular or squamous differentiation; however, its morphologic spectrum remains broad. This also refers to the renal pelvis and ureter. It is important to recognize and report different variants of urothelial carcinoma as well as other neoplasms of the bladder for diagnostic and prognostic reasons, including potentially different therapeutic approaches [1, 2].

Neuroendocrine neoplasms are epithelial tumors with neuroendocrine differentiation characterized by neuroendocrine hormone secretion. They can be found in most organs in the human body, as well as in the bladder. Some of the clinical and pathologic features of these tumors may be characteristic of the organ of origin, but most of their properties are shared by neuroendocrine neoplasms regardless of their anatomic site. In the last decade, these tumors are observed as one tumor group, regardless of the primary site [3].

Many difficulties arise due to the different classifications and nomenclature of neuroendocrine tumors (NETs). Classifications differ in the use of specific terminology and criteria for grading and staging of NETs due to the organ in which they are found. Morphologically similar tumors may be diagnosed differently depending on the site of origin, and some of the nomenclature used in one system may designate different tumor biology based on another system classification.

This causes confusion in therapeutic and prognostic decisions, as well as difficulties in designing studies that include NETs of different origin. It would be extremely useful in predicting outcome, and the determination of therapy, if a single system of nomenclature, grading, and staging could be established for NETs of all anatomic sites (Table 1) [3, 4].

Neuroendocrine differentiation can rarely be seen in an otherwise classic urothelial carcinoma, although it is more often found in high-grade urothelial carcinoma, and connected to a worse therapeutic response and

prognosis. It can also be found as a part of sarcomatoid carcinoma or bladder adenocarcinoma. Rarely, pure neuroendocrine neoplasms can be observed. There are different hypotheses regarding its origin, but it is commonly accepted that it can arise from urothelial cancer stem cells, as well as neuroendocrine cells located in the basal urothelial layer [5]. These cells are also known as enterochromaffin cells and are widely distributed throughout the body. They have been described in the urinary bladder (especially in the trigone), the urethra, and the renal pelvis [6, 7].

The spectrum of neuroendocrine tumors reported in the urinary bladder includes carcinoid and small and large cell neuroendocrine carcinomas. Herein we provide a short literature review of these mentioned entities.

## 2. Carcinoid

Carcinoid is a low-grade neuroendocrine tumor that is exceedingly rare in the bladder. There are about 50 cases described in the literature and if we separate pure neuroendocrine forms, there are less than 15 cases described. It usually affects people between 47 and 69 years, and is located in the trigone or bladder neck [8-11]. It probably arises from isolated neuroendocrine cells located in the basal layer of the urothelium. Patients usually present with clinical signs of hematuria, without signs of carcinoid syndrome [6]. It is often an incidental finding. Cystitis cystica or glandularis and Paneth cell metaplasia may be found along with the tumor (Table 2).

Macroscopically, its largest diameter measures 0.3-1.2 cm, and it is usually a sessile polypoid nodule, tan in color, and covered by urothelium. The most common pattern is the glandular pattern, but acinar, trabecular, and cribriform structures of monotonous small round cells with finely granular cytoplasm and small nucleoli with so-called "salt and pepper" chromatin are also found. Mitoses are rare, and necrosis and the crush effect are absent.

Cells are synaptophysin, chromogranin and neuron-specific enolase (NSE) positive, as well as CD56 in a smaller percentage, as proof of neuroendocrine differentiation. In some studies part of the cells were positive for the b subunit of human chorionic gonadotropin, and in only one case, thyroid transcription factor. Cytokeratin 20 is negative in carcinoid, and cytokeratin 7 staining can be strongly positive in most of the tumorous cells [2, 12, 13]. Cases of carcinoid producing calcitonin have also

**Table 1. Features to report in the pathohistological finding.**

<b>Neuroendocrine differentiation</b>	Pure form	Carcinoid	Mitotic count (on 10HPF) Proliferative activity (Ki-67 or MIB-1) Immunohistochemical positivity for synaptophysin/chromogranin/ CD56 TNM stage
		SCNEC	
		LCNEC	
	Mixed form	- Specification of all the other components (in procentage); urothelial, adenocarcinoma, squamoid, sarcomatoid.... - Designation of the component with the highest grade - TNM stage	

**Table 2: Bladder neuroendocrine tumors.**

<b>Bladder neuroendocrine tumor</b>	Intermixed with other bladder lesions	Reactive	Cystitis cystica or glandularis; Paneth cell metaplasia		
		Tumor	Inverted papilloma	Reported with carcinoid	
			Urothelial carcinoma and its subtypes/ in situ urothelial carcinoma	Reported with carcinoid	
				Reported with SCNEC and LCNEC, usually with high grade urothelial carcinoma	
			Bladder adenocarcinoma/ squamous ca.	Reported with SCNEC	
	Sarcomatoid bladder carcinoma	Usually with SCNEC, but cases with LCNEC also reported			
	Pure NET	Carcinoid	≤ 15 cases described		
		SCNEC	≤ 200 cases described		
		LCNEC	≤ 12 cases described		

NET- neuroendocrine tumor; SCNEC- small cell neuroendocrine carcinoma; LCNEC- large cell neuroendocrine carcinoma

been reported [14].

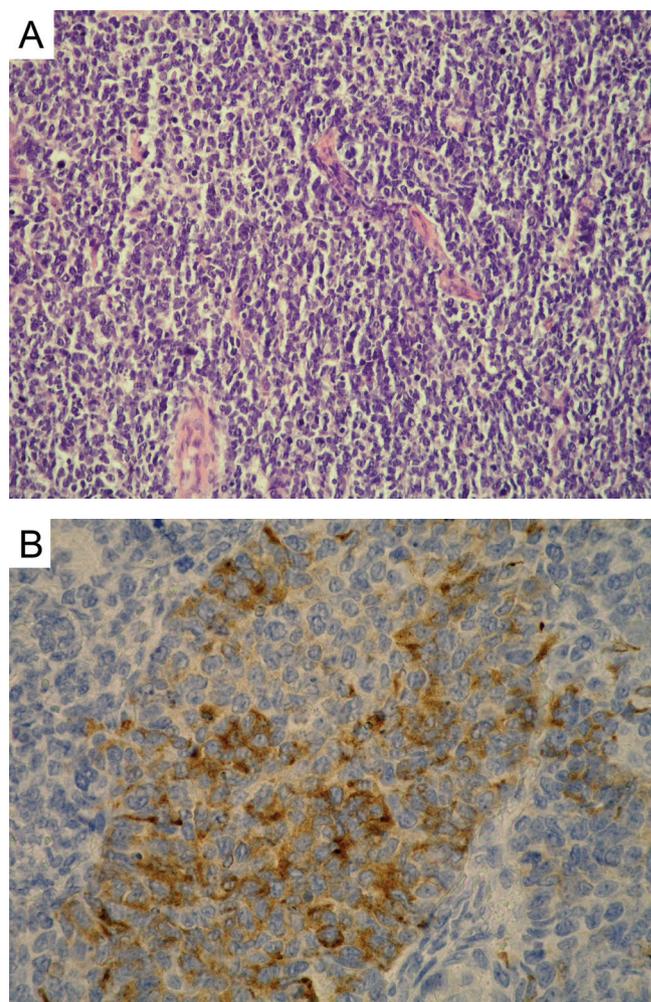
In the differential diagnosis, inverted papilloma, nested variant of urothelial carcinoma, adenocarcinoma, paraganglioma, and a metastatic tumor should be considered. Inverted papilloma and nested urothelial carcinoma can resemble carcinoid because of their rounded polypoid structure, general architecture, and normal urothelium covering. Urothelial tumors lack the “salt and pepper” chromatin, as well as finely granular eosinophilic cytoplasm. Immunohistochemistry can usually help resolve this dilemma. There is a case report describing simultaneous growth of inverted papilloma and carcinoid [15]. Nephrogenic metaplasia (nephrogenic adenoma) shows some similarities to carcinoid tumors in the urinary bladder. Paraganglioma has nests of tumorous cells surrounded by s-100 positive sustentacular cells. Clinical data are crucial in the diagnosis of metastatic carcinoid, as well as in excluding the possibility of direct invasion of carcinoid tumor from the appendix. Primary carcinoid of the appendix is more common than bladder carcinoid [6, 7] (Table 3).

Primary bladder carcinoid is usually small and excision is curative. Some authors emphasize that pure forms of carcinoid tumors in the bladder have a very favorable clinical outcome, but mixed urothelial carcinomas with neuroendocrine differentiation showing focal carcinoid-like histologic features, should be distinguished [13, 16]. However, carcinoid tumors can metastasize to lymph nodes and distal organs, and its behavior is unpredictable [6, 7, 13, 17].

### 3. Small cell neuroendocrine carcinoma

Small cell neuroendocrine carcinomas (SCNEC) of the urinary bladder are uncommon but aggressive neoplasms, representing less than 1% of all vesical tumors. Differentiation of SCNEC from high-grade urothelial carcinoma is based on histomorphological features, but can be difficult in small biopsies and cases with mixed morphology. SCNEC of bladder has been shown to express markers of neuroendocrine differentiation, as well as TTF-1 [18, 19]. Still, urinary bladder is the most common site of extrapulmonary small cell undifferentiated carcinoma [20] (Table 2).

Approximately 400 cases of these tumors have been reported in the literature, with male predominance (male to female ratio 5:1). Mean age of presentation is 66 years. As in carcinoid tumors, most patients present



**Figure 1.** Small cell neuroendocrine carcinoma as a component of sarcomatoid carcinoma of the bladder (100xHE) (A); synaptophysin positive neuroendocrine cells (100x syn) (B)

with hematuria, flank pain, dysuria, obstructive voiding symptoms, weight loss, abdominal pain, and recurrent urinary tract infections. Only rare cases with carcinoid or paraneoplastic syndromes have been reported. Cigarette smoking is an accepted risk factor [20-22]. Macroscopically, a large, solid, polypoid, and sometimes necrotic tumorous mass is found. Histologically the tumor is composed of solid sheets of atypical epithelial cells, with scant cytoplasm and a high nuclear/cytoplasmic ratio in a sparse fibrovascular stroma. Hyperchromatic nuclei with inconspicuous nucleoli are seen and the so-called “salt and pepper” chromatin is also found (Figure 1). Geographic necrosis and high mitotic

**Table 3. Differential diagnosis of bladder neuroendocrine tumors (A, B, C)**

A	CARCINOID	INVERTED PAPILLOMA	INVERTED UC	ADENOCA.	PARAGANGL.	METASTATIC CARCINOID
MORPH.	-small, polypoid -surface covered with urothelium -insular pattern - monotonous small round cells, granular cytoplasm, "salt and pepper" chromatin -no/rare mitoses	-small, polypoid -Surface covered with urothelium - insular pattern, monotonous small round cells - no/rare mitoses	- as inverted papilloma, more polymorphous cells	- growth pattern may simulate, different cytology	- growth pattern may simulate - large, polygonal cells	- the same morphology as bladder primary carcinoid - clinical data are helpful, if adjacent urothelial lesion-bladder primary
IMMUNO.	Syn +, chr+, CD56+ CK7 +/-	CK7+, CK20-, Syn -, chr-, CD56-	CK7+, CK20+, Syn -, chr-, CD56-	CK7+, CK20-, Syn -, chr-, CD56-	Syn +, chr+, CD56+ CK7 -, s-100 + SC	Syn +, chr+, CD56+ CK7 +/-

B	SCNEC	LYMPHOMA	SMALL CELL/UN-DIFFERENTIATED UC	ALVEOLAR RHABDOMYOSARCOMA	METASTATIC
MORPH.	-solid sheets of atypical cells, scant cytoplasm, high nuclear/ cytoplasmic ratio -"salt and pepper" chromatin -frequent mitoses -crush effect	- solid sheets of atypical lymphoid cells, may be scant cytoplasm -may have frequent mitoses	-solid sheets of atypical cells, scant cytoplasm, high nuclear/ cytoplasmic ratio -frequent mitoses	-solid sheets of atypical cells, cells with scant cytoplasm and hyperchromatic nuclei -high mitotic activity	-the same morphology as bladder primary SCNEC - Clinical data are helpful, if adjacent urothelial lesion-bladder primary
IMMUNO.	Syn +/-, chr-/+ , CD56-/+ , TTF-1 +/-, CK7 +/-, LCA-	Syn -, chr-, CD56-, TTF-1 -,CK7 -, LCA+	Syn -, chr-, CD56-, TTF-1 -,CK7+, CK20+/-, LCA-	Syn -, chr-, CD56-, TTF-1 -,CK7-, LCA-, desmin+, SMA+	Syn +/-, chr-/+ , CD56-/+ , TTF-1 +/-, CK7 +/-, LCA-

C	LCNEC	LYMPHOMA	HIGH GRADE UC	METASTATIC
MORPH.	-large polygonal cells in organoid nesting formations, with palisading, rosettes and trabecular pattern. - low nuclear/ cytoplasmic ratio -rough chromatin, prominent nucleoli. -frequent mitoses - multiple areas of necrosis	- solid sheets of atypical lymphoid cells, may be scant cytoplasm -sometimes frequent mitoses	-solid sheets of atypical cells, scant to more abundant cytoplasm -high nuclear/ cytoplasmic ratio -frequent mitoses	-the same morphology as bladder primary SCNEC - Clinical data are helpful, if adjacent urothelial lesion-bladder primary
IMMUNO.	Syn +, chr-/+ , CD56- , TTF-1 +/-, CK7 +/-, LCA-	Syn -, chr-, CD56- ,TTF-1 -,CK7 -, LCA+	Syn -, chr-, CD56- ,TTF-1 -,CK7+, CK20+/-, LCA-	Syn +, chr-/+ , CD56- , TTF-1 +/-, CK7 +/-

SCNEC- small cell neuroendocrine carcinoma; LCNEC- large cell neuroendocrine carcinoma; UC-urothelial carcinoma; Syn-synaptophysin; Chr- chromogranin; TTF-1-thyroid transcription factor; CK7-cytokeratin 7; LCA-leukocyte common antigen; CK20-cytokeratin 20; SC-sustentacular cells

rate, as well as areas of crush artifact are pathognomonic for these tumors. Bladder calculi or chronic cystitis is also described in SCNEC. Histologically they do not differ from their pulmonary counterparts. In about half of these cases, there is an associated urothelial carcinoma or even another bladder cancer subtype (squamous or glandular differentiation). It can also be a component of carcinosarcoma [21-25].

SCNEC shows a positive immunohistochemical reaction to synaptophysin (in 64%) and CD56 (in 71%), while chromogranin reaction is usually weak and focal. NSE is positive in 80% of tumors but is not a specific marker. Proliferation index is always high (over 50%). CK7 is expressed in approximately half of the cases while CK20 is negative. TTF-1 can be positive in about 40% of these tumors, which is important to stress, although positivity does not necessarily suggest a metastatic lung tumor. p53 protein is expressed in approximately half of these cases. Bladder SCNEC can also express c-kit and EGFR in almost 30% of tumors [18, 19].

Comparative genomic hybridization studies have shown frequent genomic alterations, such as deletions of 10q, 4q, 5q, and 13q and gain of 8p, 5p, 6p, and 13q. Cheng et al. described almost identical allelic loss in the small cell carcinoma component compared to adjacent conventional urothelial carcinoma. More recent studies have identified frequent loss of heterozygosity in bladder SCNEC at 9p21 (p16), 3p25-26 (VHL), 9q32-33 (DBC1), and 17p13 (TP53). Quantitative studies on the methylation status of RASSF1, MLH1, DAPK1, and MGMT tumor suppressor genes demonstrated that their promoter regions were commonly methylated. This data suggests a common clonal origin and that SCNEC may originate from a multipotential urothelial stem cell with the ability to differentiate into various tissue types, rather than from a specific neuroendocrine precursor cell [21, 22, 26, 27].

In the differential diagnosis, lymphoma, poorly differentiated urothelial carcinoma, and metastatic SCNEC from another primary should be considered. On the basis of morphology and immunohistochemical profile of the first two tumors a diagnosis should be reached. It is important to distinguish bladder SCNEC from its counterpart of the prostate. Another diagnostic challenge can be alveolar rhabdomyosarcoma, although immunohistochemistry for muscular differentiation is helpful in such cases [28]. Because of morphologic overlap and almost identical immunoprofile, the distinction

between primary and metastatic SCNEC is impossible. Good clinicopathological correlation should resolve this puzzle. In patients with multiple visceral organ involvement including the lung and bladder, it may be difficult to find the primary. Close attention should be made to the overlying epithelium in the bladder to identify any urothelial carcinoma component, and if found, would indicate that the bladder is the primary site. Direct invasion from prostate SCNEC should also be considered and serial slides examined, to search for conventional prostatic adenocarcinoma which suggests prostate primary [22, 23] (Table 3).

Bladder SCNEC is an invasive disease, with most patients diagnosed when invasion of the muscle layer has taken place. Most patients develop metastases to lymph nodes, lung, liver, bone, and brain. Chemotherapy and surgical treatment is recommended when there is any small cell component in the tumor [22, 27, 29].

SCNEC is an aggressive tumor with a poor prognosis and high mortality. The overall 5-year survival rate for reported cases has been estimated to be 8% [23, 24, 30, 31]. There is no significant difference in survival when comparing patients with focal small cell histology and patients with pure SCNEC. It is suggested that tumors with mixed histologic patterns should be classified as small cell carcinoma [22, 23, 27].

#### 4. Large cell neuroendocrine carcinoma

Large cell neuroendocrine carcinoma (LCNEC) of the bladder is a rare, aggressive tumor similar to its counterpart in the lung. It comprises less than 0.5% of all bladder carcinoma. There are about 12 reported cases, with both pure and mixed histology [27]. Macroscopically it is a nodular mass, with a polypoid solid appearance, and is difficult to distinguish from other types of bladder cancers. Microscopically it consists of large polygonal cells forming organoid nested formations, with palisading, rosettes and trabecular pattern. Tumor cells have a low nuclear cytoplasmic ratio, rough chromatin, and prominent nucleoli. Mitoses are frequent and accompanied by multiple areas of necrosis [32-34] (Table 2). LCNEC is described as a pure form or with other variants of urothelial carcinoma, including lymphoepithelioma-like carcinoma, small cell carcinoma, adenocarcinoma and sarcomatoid carcinoma [33, 35-39]. Based on studies of small cell carcinoma, it is hypothesized that LCNEC also originates from common multi-potent stem cells with

divergent differentiation [31].

Because larger studies on LCNEC are lacking, it is hard to determine their immunohistochemical profile. Some, but not all tumors are synaptophysin and chromogranin positive. Focal or diffuse strong CD56 reactivity can be found. TTF-1 and CD57, as well as NSE reactivity is also described [33, 36].

The differential diagnosis includes lymphoma, high-grade urothelial carcinoma, and metastatic neuroendocrine carcinoma from other sites, including the prostate [40]. The first two diagnoses are relatively easy to exclude with proper immunohistochemical analysis. In cases of metastatic LCNEC clinicopathological and imaging correlation is important. The presence of a conventional urothelial carcinoma component indicates a bladder primary (Table 3). As in the lung, large cell neuroendocrine carcinoma may be underreported in the bladder if the diagnosis is not initially considered and appropriate diagnostic workup is not performed [36].

The outcome of LCNEC is similar to SCNEC, with an aggressive clinical course and rapid onset of metastatic disease. It is difficult to make any conclusions about the optimal treatment strategy, as well as prognostic markers due to a small number of reported cases. A recent study on neuroendocrine tumors of the bladder suggests that adjuvant chemotherapy may offer a survival advantage to patients when compared with cystectomy alone [35].

## 5. Conclusion

In summary, we have reviewed available data on neuroendocrine differentiation in bladder tumors, which can be found in a pure form or mixed with different bladder tumor types.

The differential diagnosis of neuroendocrine bladder tumors includes several entities, the majority of which can be readily distinguished using a combination of morphological and immunohistochemical evaluation, as well as clinical data. The major problem is metastatic neuroendocrine tumor versus bladder primary, where associated urothelial lesion is helpful.

Comparative genomic hybridization studies have shown frequent genomic alterations in small cell neuroendocrine bladder carcinoma and some are identical to adjacent conventional urothelial carcinoma. Quantitative studies on the methylation status of tumor suppressor genes demonstrated that their promoter regions were commonly methylated. This data suggests a common

clonal origin of urothelial carcinoma and SCNEC. Further studies are needed to clarify the molecular pathogenesis of neuroendocrine bladder tumors to serve as a basis for diagnostic markers and therapeutic targets. Current nomenclature for neuroendocrine neoplasms should be replaced by more upfront, uniform, and reproducible terminology. Despite the inability to establish a single system of nomenclature, grading, and staging for NETs of all sites, there are common features forming the origin of most systems. Such features are the proliferative rate of the tumor and the extent of local spread. Therefore, it is recommended to use these basic data to stratify NETs and document them in pathology reports.

## Author contributions

BK gave the idea for the article, participated in drafting the article and gave the final approval. MU reviewed the previously published literature, participated in drafting the article and gave the final approval.

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