ANTICANCER RESEARCH *40*: 2439-2447 (2020)
doi:10.21873/anticanres.14213

Review

Urinary Tract Large Cell Neuroendocrine Carcinoma: Diagnostic, Prognostic and Therapeutic Issues

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Abstract. *Large cell neuroendocrine carcinoma (LCNEC) of the urinary tract is a high-grade neuroendocrine tumor with distinct pathological features, usually portending an aggressive clinical behavior in comparison to conventional urothelial carcinoma. Due to its low prevalence, little is known about its clinical management and there is no current standard of care. The aim of this review was to summarize the current knowledge about LCNEC of the bladder, ureter and kidney, with relevance to diagnostic, prognostic and therapeutic issues, through a systematic analysis of clinical, pathological and outcome data retrieved from the literature.*

Primary or metastatic neuroendocrine (NE) tumors may occur throughout the urinary tract. Altogether, primary NE tumors of the urinary tract are rare, accounting for less than 1% of urothelial neoplasms; therefore, they are usually reported as single cases or small case series (1).

According to the 2016 World Health Organization Classification of Tumors of Urinary System and Male Genital Organ, there are four subtypes of primary NE tumors of the urinary tract, spanning from high-grade clinically aggressive neoplasms [namely, small cell neuroendocrine carcinoma (SCNEC), and large cell neuroendocrine carcinoma (LCNEC)], to more indolent well-differentiated neuroendocrine tumor (WDNT), and paraganglioma (2). LCNEC has only recently been recognized as a distinct nosological entity in this classification (2), and this accounts for the small number of published cases of primary LCNECs of the urinary tract (3). Current knowledge of the biological, clinical and prognostic features of this disease is mostly limited and disjointed, resulting in lack of standard of care and effective therapeutic options.

The present study aimed to review available information regarding the pathological and clinical features of urinary tract LCNEC in order to provide reliable evidence for the management of this aggressive tumor.

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Key Words: Large cell neuroendocrine carcinoma, bladder, kidney, ureter, review.

Review Methods

We reviewed clinical and pathological features, type of treatment and clinical outcomes of LCNECs of the bladder, ureter and kidney by systematically searching the English-language literature (case reports and review articles) published up to February 2020 through two databases, PubMed and Google Scholar. Search terms were: large cell neuroendocrine carcinoma, high-grade neuroendocrine tumors, bladder, ureter, kidney, urinary tract. Articles were selected on the basis of their overall scientific quality and relevance to disease. A further check of the appropriateness of the articles based on full-text revision was performed after data extraction.

Cell of Origin

As for the other NE tumors of the urinary tract, there are several theories regarding the etiology and cell of origin of urinary tract LCNEC. The most common hypotheses include origin from (1) multipotent urothelial stem cells that can differentiate into various cell types, (2) pre-existing NE/enterochromaffin cell population in the submucosa or in normal urothelium, (3) urinary tract epithelial metaplasia, and (4) transformation of urothelial carcinoma (UC) cells (4-11). In keeping with some of these theories, molecular

genetic evidence as well as the frequent coexistence of more than one histotype (namely, SCNEC, adenocarcinoma, or UC), suggests a common clonal origin (9, 12, 13); nevertheless, the heterogeneous immunophenotypical profile of urinary NECs provides strong evidence for the multipotent stem cell theory (14).

Another hypothesis is that the NE cells originate in the epithelium of urachal remnants within the bladder (15, 16), since the very first case of bladder LCNEC has been one of probable urachal origin (17).

Bladder LCNEC

Epidemiology. The overall prevalence of bladder LCNEC seems to be less than 0.5% of all bladder UCs (18, 19). Nevertheless, since this tumor has been recently recognized as a distinct entity, it has been suggested that several bladder LCNECs might have gone underdiagnosed or just misdiagnosed as undifferentiated UC (20, 21). Similar to lung tumors, under-diagnosis and consequent under-reporting remain an issue also in bladder cancer (BC) if appropriate diagnostic workup is not performed (22, 23).

Fewer than 40 sporadic cases have been reported in the literature so far, including both pure and mixed histology (6, 11, 15-17, 22, 24-27). According to a recent large retrospective study from the French Genito-Urinary Tumor Group, 23 out of 236 (10%) NE bladder tumors were pure LCNECs, and 16 (7%) were mixed SCNECs and LCNECs (28).

Bladder LCNECs usually affect elderly patients (>60 years), although there is a wide age range at diagnosis (20-84 years, mean 60.8) (Table I) (10), and like their lung counterparts (29) have a male predominance (77.1% *versus* 22.9%) (13, 30, 31).

Similar to most bladder cancers, it has been reported that smoking may be a significant risk factor for LCNEC, as well as for SCNEC (2, 22, 32).

Etiology. On the basis of their results, Bhatt et al. (33) suggested that the personal or family history of cancer may increase the risk of bladder NE cancer, possibly because of genetic predisposition, iatrogenic causes (chemotherapy- or radiotherapy-related factors), or common environmental exposure (*e.g.* smoking). It has been suggested that post-prostate-cancer external beam radiation therapy and high-dose brachyltherapy may trigger this cancer (34).

Clinical features. Clinical presentation is similar to conventional urothelial BC, with gross hematuria being the usual symptom at diagnosis; less frequently, patients complain of dysuria and mucosuria, and in one case there were no symptoms at presentation (6, 31, 35).

Like SCNEC, LCNEC is a biologically aggressive NE tumor, usually associated with dismal prognosis and a high incidence of recurrence and progression despite early treatment (surgical intervention and/or chemotherapy) (6, 10, 17, 18, 25, 36-40); thus, it behaves differently from the other types of NE tumors (carcinoid and paraganglioma) (30). Most clinical studies have analyzed both SCNECs and LCNECs, the latter being a small amount of the whole case series, and reported similar survival and cancer-specific mortality rates in LCNEC compared to SCNEC, ranging from <1 year for advanced disease to >2 years for early disease (11, 15, 20-22, 41, 42). Bhatt et al. reported a 5-year survival rate of 17% for their study population, which consisted of 14 SCCs and only 4 LCNECs (33); these data might not be entirely reliable due to the rarity of bladder LCNEC. Moreover, several authors have reported recurrence-free survival rates up to 11 years of follow-up (11, 20, 43-46).

As for SCNEC, current findings suggest that a significant association exists between cancer specific survival (CSS) and stage, with a 10-year CSS of 67% and 24% in stage pT1/pT2 and pT3/T4 at cystectomy, respectively (5, 47, 48). Available data from the reported cases of bladder LCNEC, however, reveal that a disease remission, either partial or complete, has been achieved in more than half of the patients, and that only 50% of them presented with stage I-II LCNEC (Table I). Therefore, this tumor's outcome might not be significantly affected by stage at diagnosis. Interestingly, no significant differences in cancer-specific survival (CSS) have been reported between patients with high-grade NE carcinoma (HGNEC) and UC when matched for prognostic clinicopathological features in a large series (41).

LCNECs may present as either pure tumors or mixed forms with varying amounts of conventional urothelial and/or variant histology carcinomatous components, including carcinosarcoma in one case (43). Some authors reported that the presence of pure LCNEC may be associated with poorer prognosis compared to mixed forms (13, 24, 32). In keeping with previous studies (20, 31), Martin et al pointed out that 50% of patients in each group of pure and mixed LCNEC died of the disease (9/18 and 6/12, respectively); therefore, pure histology seems to not portend a worse outcome,

Distant metastases have been reported, either at diagnosis or later in the course of disease, with liver and lung being the most common sites (Table I) (6, 11, 21, 40, 44). Both brain and skin metastases of bladder LCNEC have also been described (6, 36, 38, 40).

Imaging. Staging and localization of distant metastases is achieved through imaging studies including contrast-enhanced computed tomography (CT), positron emission tomography (PET) with 18FDG, PET/ CT scans and/or magnetic resonance imaging (MRI) (49-51). 111In-DTPA-octreotide scintigraphy (Octreoscan) is a specific imaging

Table I. *Clinical and pathological features of bladder LCNECs.*

Age, years (range, mean)	20-84, 60.8
Gender (n, %)	
Male	27, 77.1%
Female	8, 22.9%
Size,cm (range, mean)	1-9, 4.0
Histotype (n, %)	
Pure LCNEC	21, 58.3%
Mixed form	15, 41.7%
Stage	
I-II	8, 27.6%
III-IV	21, 72.4%
Main sites of metastasis (n, %)	
Lung	5, 38.5%
Liver	4, 30.7%
Retroperitoneum	2, 15.4%
Brain	1, 7.7%
Skin	1, 7.7%
Follow-up	
Complete or partial remission	16, 51.6%
Dead of disease	15, 48.4%

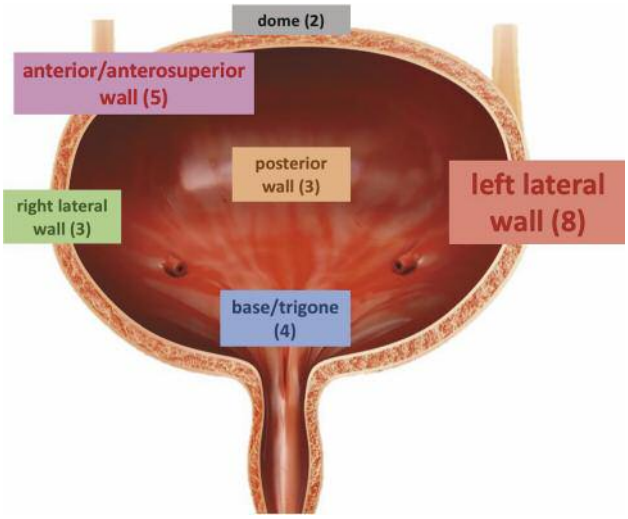

Figure 1. *Sites of occurrence of bladder LCNECs.*

method for detecting NE tumors due to their ability to secrete ectopic hormones (31). Its main advantage over CT scan and MRI is that it can cover all regions of the body (21, 43).

Gross features. Grossly, NE carcinomas of the bladder may appear as a nodular/polypoid lesion in most cases, and less often as a flat or ulcerative lesion (2, 20). Therefore, the distinction from other types of BCs is not straightforward (52).

In all reported cases, there was a single tumor, ranging in size from 1 to 9 cm (mean size, 4 cm). The most common location of LCNEC was on the left lateral wall of the bladder (8/25, 32%); less frequent locations were the anterior/anterosuperior wall, the base/trigone, the posterior and right lateral wall, with bladder dome being the less frequent one (Figure 1) (30, 31, 53).

Morphology. Morphological criteria for the diagnosis of bladder LCNEC are the same as its pulmonary, renal and ureteral counterparts (13). Neoplastic cells are arranged in sheet-like, palisading, trabecular or organoid nested growth patterns; single cells are large, polygonal, with abundant cytoplasm and low nuclear to cytoplasmic ratio. Nuclei are polymorphic, often large, oval, featuring coarse, granular or vesicular chromatin, and often prominent nucleoli. Occasional bizarre cells may be seen (39). Macroscopic or microscopic necrosis and/or frequent apoptotic bodies, as well as brisk mitotic activity (>10 mitoses/10 high power fields), and rosettes have been reported more often than in bladder SCNEC (3, 6, 13, 21, 27, 41, 54).

Interestingly, as for the lung, bladder LCNEC displays high variability in cell size as well as no clear nuclear or cell size cutoff between LCNEC and SCC (41, 55). It has, therefore, been suggested that classifying all HGNECs as a single disease entity with case-to-case noting on its morphology might prevent the use of subjective criteria in distinguishing between small and large cells (20, 41).

In almost half of the cases, bladder LCNEC cells are mixed with urothelial carcinoma and/or variant histology forms, namely lymphoepithelioma-like carcinoma, SCNEC, squamous cell carcinoma, adenocarcinoma or sarcomatoid carcinoma (11, 15, 18, 20, 22, 25, 27, 43, 56).

Immunohistochemistry. As a NE tumor, LCNEC expresses markers such as synapthophysin, chromogranin A, CD56 as well as epithelial markers, namely pan cytokeratins, CAM 5.2, and EMA (57), paralleling ultrastructural evidence of NE differentiation (58). Either immunohistochemical or ultrastructural NE profile is required for this diagnosis; electron microscopy studies often reveal the presence of membrane-bound electron-dense cytoplasmic granules measuring 100 to 200 nm in diameter, which are characteristic of NE cells (59), however it is an expensive and obsolete technique.

The above-mentioned immunohistochemical stains have a combined sensitivity and specificity of 96 and 100%, respectively, to allow the distinction from UC. However, it has been reported that chromogranin A has a reduced sensitivity for LCNEC compared to SCNEC (40 *versus* 80%, respectively) (13).

According to the literature reports, CD56, synapthophysin and chromogranin A are expressed in the large majority of cases (100%, 92.6% and 85.2%, respectively) (Table II). In a series of 12 cases of LCNECs of the bladder, these 3 NE

Table II. *Immunohistochemical features of bladder LCNECs.*

Marker	Rate of positive cases (%)
Chromogranin A	23/27 (85.2%)
Synaptophysin	25/27 (92.6%)
CD56	14/14 (100%)
Neuron-specific enolase	12/13 (92.3%)
Cytokeratins	11/12 (91.7%)

markers were positive in all cases (53), possibly due to the clonal code of the antibodies used. Further NE markers that may be positive in LCNECs of the bladder are CD57 and NSE (22, 27), the latter being highly sensitive but less specific than the above-mentioned antibodies, namely chromogranin A (41).

LCNEC is a high proliferating tumor, with a Ki67 index up to 100% (3); however, a Ki67 index of >40% has been shown to be 80% sensitive and 86% specific in distinguishing LCNEC and UC, which usually features a Ki67 proliferation rate as high as 25% (15, 31, 41, 54).

TTF1 is a transcriptional factor that is frequently expressed in adenocarcinoma and NE tumors of the lung, as well as in thyroid tumors; it has been reported in a subset of extrapulmonary SCNECs as well, including bladder primaries (22, 60, 61). Tumor cells of bladder LCNECs were positive in 7/10 of the reported cases (70%), therefore this antibody is not useful for the distinction between primary and metastatic LCNECs.

Cell cycle proteins such as p53 and p16 are usually expressed at higher levels by bladder HGNECs compared to conventional UCs (41, 62, 63). Bladder HGNECS are also p63 negative in a significantly higher number of cases in comparison to UC; the combined use of p16 and p63, however, has shown to be highly sensitive yet not specific in obtaining the differential diagnosis (41, 62, 64).

Interestingly, a cutaneous metastasis of bladder LCNEC has been reported to be CK20-positive (38). The authors suggested that this can be a proof of the similarities between bladder NEC and conventional UC; in clinical practice, however, this may be a confounding issue in the differential diagnosis with Merkel cell carcinoma, a peculiar cutaneous CK20+ NE tumor.

Differential diagnosis. The differential diagnoses of bladder LCNECs include SCNEC, poorly differentiated high-grade UC or prostate carcinoma, secondary involvement of the bladder by NE carcinoma from other sites, malignant lymphoma, malignant melanoma, paraganglioma/pheochromocytoma, lympho-epithelioma-like carcinoma, neuroblastoma, alveolar rhabdomyosarcoma and metastatic Merkel cell carcinoma (53). In small specimens, bladder LCNEC must be distinguished from chronic cystitis whereby inflammatory cells with scant cytoplasm may resemble tumor cells (20). Immunohistochemistry, and electron microscopy if available, is useful in the distinction of LCNEC from non-NE lesions, but is of limited value in differentiating lesions expressing NE markers, regardless of their histotype, grade and organ of origin. Therefore, it is important to carefully assess prior prostate cancer history, since LCNEC in the bladder may directly ensue from the prostate (39). Metastatic LCNECs most frequently arise from lungs or intestines (11, 52), and in these cases clinicopathological and imaging correlation plays a pivotal role.

A further issue in differential diagnosis is the occurrence of mixed forms whereby LCNEC is combined with conventional UC or other UC variants (see above); such cases support a bladder primary.

Treatment. Due to its rarity, the optimal therapeutic strategy of LCNEC of the bladder is debated and no standard treatment exists. A single center study reported a difference in five patients treated with adjuvant chemotherapy *versus* surgery alone in terms of disease-free survival rates (116 *versus* 2 to 29 months, respectively) (41). Chemotherapeutic regimens have been mostly extrapolated from those used for their pulmonary counterparts, therefore neoadjuvant or adjuvant etoposide and platinum-based drugs are the treatment of choice (31, 33, 65). They are usually administered after surgery along with or as an alternative to radiotherapy in a multimodal approach (6, 11, 15, 26, 44). Some authors advocate the use of the Ki-67 proliferative index or concordant gene expression profiles to predict single patient's chemosensitivity (66-68), while others suggest to compare treatments strategies between LCNECs of different organs (66).

Although surgery alone is not recommended in these cases, it plays a pivotal role in the correct management of these patients. In a large series of 35 bladder LCNECs from the Surveillance, Epidemiology, and End Results (SEER) database, 97.1% underwent surgery (20, 30). All patients treated with TUR and/or chemotherapy, without cystectomy, died of the disease in few months (<1 to 8) (26, 54, 66, 69). Therefore, a bladder-sparing protocol seems to be less effective than radical surgery, but data remain conflicting (11, 43, 45).

Due to the potential aggressive behavior of bladder LCNEC, prompt diagnosis and early treatment with radical cystectomy and (neo)adjuvant chemotherapy may provide long-term control of a localized tumor and an extended overall survival (44).

Renal LCNEC

Primary LCNEC of the kidney is extremely rare, with less than 10 cases having been reported in the English literature so far (70-75, Table III).

Table III. *Clinical and pathological features of renal LCNECs.*

Article	Age	Gender	Presenting symptoms	Size (cm)	Side	Histology	Treatment	N+/M+	Outcome, months
Lane *et al*., 2007	58	M	Flank pain, haematuria	18	Right	Pure form	RN	N+	DOD, 2
Ratnagiri *et al*., 2009	40	F	None	NA	Right	Pure form	RN	None	A&W, 12
Dundr *et al*., 2010	56	M	Left abdominal and lower back pain, weight loss, digestive symptoms	14	Left	Pure form	RN	M+ (liver, lung)	DOD, 7
Palumbo *et al*., 2014	79	M	None	3,5	Left	Mixed form (high-grade UC)	RN	NA	DOD, 4
Wann *et al*., 2014	23	M	Weight loss, palpable left loin mass	10	Left	NA	RN, CHT (CDDP+ETP)	None	A&W, 6
Shimbori *et al*., 2017	59	M	Gross haematuria	11,6	Right	Pure form	RN,CHT (CBCDA+ CPT-11)	M+ (heart, lung, pancreas, bone)	NA

A&W: Alive and well; CBCDA: carboplatin; CDDP: cisplatin; CHT: chemotherapy; CPT-11: irinotecan; DOD: died of disease; ETP: etoposide; NA: not available; RN: radical nephrectomy.

Table IV. *Clinical and pathological features of ureteral LCNECs.*

Article	Age	Gender	Presenting symptoms	Size (cm)	Side	Histology	Treatment	TNM	Outcome, months
Oshiro *et al*., 2013	78	M	Left hydronephrosis	2.3	Left	Pure form	LN, PC	T3cN0cM0	A&W, 9
Dai *et al*., 2016	74	F	Right lower back pain and hydronephrosis	3	Right	Pure form	LN, PC	NA	A&W, 25
Choi *et al*., 2019	58	F	Right hydronephrosis	4	Right	Pure form	RN, CHT (VNR+IFO+ CDDP), RT	T3cN0M+	DOD, 9
Wang *et al*., 2020	62	M	None	2.5	Right	Mixed form (UC)	RN, PC, CHT (ETP+ CBCDA), RT	T3N+M0	A&W, 15

CBCDA: Carboplatin; CDDP: cisplatin; CHT: chemotherapy; ETP: etoposide; IFO: ifosfamide; LN: left nephroureterectomy; PC: partial cystectomy; RN: right nephroureterectomy; RT: radiotherapy; VNR: vinorelbin.

Most affected patients are male adults, with a mean age of 52.5 years (range=23-79 years). Main symptoms are not specific, namely flank and/or abdominal pain, weight loss and haematuria (Table III); occasionally, the tumors present at metastatic stage (70). Renal LCNEC is usually associated with dismal prognosis, but complete remission has been achieved in 2 out of 6 cases, both of them being at a local stage.

Grossly, renal LCNECs have a solid tan-to-grey cut surface with necrosis, and extrarenal extension is common (70, 73).

Interestingly, an NE component has been described in primary renal tumors such as chromophobe renal cell carcinoma (RCC) (76), and mucinous tubular and spindle cell carcinoma (77, 78), although it seems not to significantly affect prognosis.

The differential diagnosis of renal LCNEC includes high-grade RCC or UC, which are both negative to NE markers, and primary or metastatic NE tumors including carcinoid, small cell neuroendocrine carcinoma and Merkel cell carcinoma (79). In contrast to LCNECs, primary or metastatic low-grade NE tumors have a low mitotic index, cytological uniformity, an organoid architectural pattern, and lack necrosis. Primary and metastatic SCNECs are characterized by a smaller cell size, although scattered large cells can be found. Since RCC is the most common recipient of tumor-to-tumor metastasis, it may occur that NE carcinomas from other sites may metastasize to renal primaries (80), including angiomyolipoma (81); in such a case, the differential diagnosis with a primary mixed NEC can be challenging in the absence of proper clinical information.

As for their bladder counterpart, there is no standard of care for renal HGNEC; effective disease control may be achieved through surgery, platinum-based chemotherapy, and radiotherapy (75) in order to delay the occurrence of metastatic tumors.

Ureteral LCNEC

NE tumors rarely occur in the ureter; indeed, only 4 cases have been reported so far (Table IV) (59, 82-84). Usual presenting symptoms are ureteral obstruction or gross hematuria (85), as well as hematuria and leukocyturia in the urine sediment; since these tumors are unilateral, the occurrence of oligoanuria in a binephric patient should raise suspicion of a bladder primary causing bilateral ureteral obstruction rather than an upper urinary tract lesion. For the same reason, serum creatinine concentration usually shows a slow increase in the context of a previously normal renal function (59, 86).

Ultrasonography as well as intravenous and retrograde urography are first-level imaging techniques in these cases, but may show low sensitivity, unlike helical CT or MRI, which are the methods of choice in the detection of upper urinary lesions and in differentiating them from other causes of upper tract obstruction, such as urolithiasis (85, 86). Macroscopically, ureteral NE tumors are sessile lesions whose sizes range from 2,3 to 4 cm, and are diagnosed at an advanced stage (stage III in 3/4 cases reported, Table IV).

Since all the four reported cases of ureteral LCNECs have been described by Asian authors, one might assume that in this ethnic group the prevalence of ureteral LCNEC is higher than in other ethnic groups; however, the number of cases is too little to draw such conclusion.

Conclusion

LCNEC of the urinary tract is a rare disease, recently categorized as a distinct diagnostic entity. In this site LCNEC has peculiar clinical and prognostic features, while it shares morphological and immunophenotypical characteristics with its pulmonary and extrapulmonary counterpart. Due to the low number of cases, most studies have been focusing on both small and large cell NECs, therefore issues still exist regarding the prognosis and therapeutic approach of LCNECs of the bladder, ureter and kidney. Further studies on large homogeneous series are warranted in order to elucidate these issues.

Conflicts of Interest

The Authors acknowledge no conflicts of interest regarding this study.

Authors' Contributions

FS: study concept and design, data acquisition and analysis, manuscript preparation; MC, BC: data acquisition and analysis, quality control of data; ST: data analysis and interpretation; GC, LC: quality control of data, manuscript review and editing.

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Received March 23, 2020
Revised April 1, 2020
Accepted April 2, 2020