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TOPIC PAPER

Update of the International Consultation on Urological Diseases on bladder cancer 2018: non-urothelial cancers of the urinary bladder

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Abstract

Purpose To provide a comprehensive update of the joint consultation of the International Consultation on Urological Diseases (ICUD) for the diagnosis and management of non-urothelial cancer of the urinary bladder.

Methods A detailed analysis of the literature was conducted reporting on the epidemiology, etiology, diagnosis, treatment and outcomes of non-urothelial cancer of the urinary bladder. An international, multidisciplinary expert committee evaluated and graded the evidence according to the Oxford System of Evidence-based Medicine modified by the ICUD.

Results The major non-urothelial cancers of the urinary bladder are squamous cell carcinoma, adenocarcinoma, and neuroendocrine tumors. Several other non-urothelial tumors are rare but important to identify because of their aggressive behavior when compared to urothelial bladder tumors. Radical cystectomy and urinary diversion, preceded by neoadjuvant radiation or chemotherapy in some of these tumors, is the main method or treatment for resectable disease. Adjuvant therapy is not usually successful and no novel targeted or immunotherapeutic agents have been identified to provide benefit. Patients with small cell neuroendocrine tumors of the bladder should be offered chemotherapy before surgery. Because non-urothelial cancers are usually locally advanced and/or metastatic at the time of diagnosis, 5-year survival is generally poor.

Conclusions Non-urothelial cancers of the urinary bladder are rare and mostly lack established protocols for treatment. The prognosis of most of these tumors is poor because they are usually advanced at the time of diagnosis. A multimodal treatment approach should be considered to improve outcomes.

Keywords Bladder cancer · Non-urothelial · ICUD · Update

Introduction

Pure non-urothelial bladder cancers comprise a small minority of about 5% of all bladder cancers. These are distinct from urothelial tumors with a variant histologic component. They are comprised of several histologic subtypes that are generally thought to have a worse prognosis compared to urothelial tumors. However, once corrected for stage and other patient-related factors, a significant proportion of non-urothelial tumors may have prognosis similar to that of

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urothelial tumors. Diagnosis, evaluation and staging of non-urothelial bladder cancers use approaches that are similar to all bladder cancers. In some subtypes, unique features that would entail special diagnostic techniques may include identification of Schistosoma eggs in the bladder wall, or serum, or urinary catecholamine analysis in bladder pheochromocytoma. Special radiologic studies and immunostaining may also be necessary to demonstrate the tumor subtypes.

Management of non-urothelial cancers is largely based on experience from retrospective case series and some prospective data. The rarity of these tumors makes it difficult to conduct randomized trials to assess ideal therapeutic strategies. The mainstay of therapy has been surgical resection with chemo- or radiation therapy in some cases. In this manuscript, with the help of a broad international collection of experts from urology and pathology, we have analyzed the available data and developed a set of consensus recommendations to help provide guidance in the management of the complicated collection of disease entities that represent non-urothelial bladder tumors. Most of the consensus statements are based on lower levels of evidence due to the data quality and hence relies heavily on the opinion of the expert panel.

Materials and methods

A detailed analysis of the literature was conducted reporting on non-urothelial cancer of the urinary bladder. An international, multidisciplinary expert committee evaluated and graded the published evidence according to the Oxford System of Evidence-Based Medicine modified by the International Consultation on Urological Diseases (ICUD).

Squamous cell carcinoma (SCC)

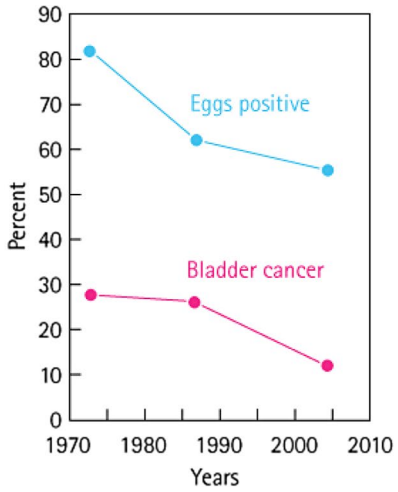
Squamous cell carcinoma (SCC) may occur de novo, or in individuals who have been infected with the parasite *Schistosoma haematobium*.

SCC not associated with schistosomiasis

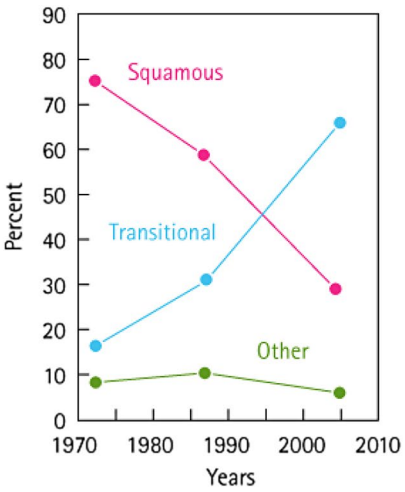
Often referred to as non-bilharzial SCC, this represents the most common non-urothelial bladder malignancy, accounting for 2–5% of cases in most contemporary cystectomy series [1, 2]. These tumors are most often diagnosed during the seventh decade of life and demonstrate less of a male predominance than urothelial carcinoma [3]. Chronic bladder irritation and inflammation are known risk factors for the development of SCC. Keratinizing squamous metaplasia, which clinically presents as leukoplakia, often develops as a result of chronic irritation and has a documented association with squamous carcinoma [4, 5]. Although a risk factor for SCC, currently available evidence is insufficient to support squamous metaplasia as a preneoplastic lesion in the bladder. In contrast to urothelial carcinoma, the relationship between SCC and cigarette smoking is not clear [6]. Other etiologic factors such as human papilloma virus (HPV) infection, radiation, and cyclophosphamide therapy, were investigated with no firm conclusions [7–9]. The presenting symptoms in patients with non-bilharzial SCC are not distinguishable from urothelial carcinoma. Hematuria is the main clinical feature in 63–100% of patients. Irritative bladder symptoms are reported in two-thirds of patients [10, 11]. SCC is often locally advanced at the time of diagnosis [12]. Pretreatment imaging studies may demonstrate hydronephrosis in 33–59% of cases [10]. Pure SCC of the bladder has a poor prognosis, with most patients succumbing within 1–3 years of diagnosis. Surgery (radical cystectomy, lymph node dissection, and urinary diversion) is the main method of treating this disease because of the poor outcomes of radiation (16.7% 5-year overall all survival) and chemotherapy alone [10, 13, 14]. Several screening protocols utilizing annual cystoscopy, urine cytology, and in some random bladder biopsy have been advocated in patients at risk of developing SCC [15].

SCC associated with schistosomiasis

SCC is also prevalent where urinary *Schistosoma haematobium* is endemic. It is often referred to as schistosoma-related SCC or bilharzial SCC (B-SCC). The highest incidence of SCC of the bilharzial bladder occurs in Egypt (Fig. 1). With a mean age at presentation of 46 years, the mean age of B-SCC patients is 10–20 years younger than that seen with non-bilharzial SCC [16]. The male to female ratio is 5:1. The process of migration of the parasite eggs through the bladder wall provokes a chronic inflammatory response that is thought to lead to the development of B-SCC. The clinical presentation of B-SCC is similar to conventional SCC in most respects and imaging studies may frequently demonstrate calcifications in the bladder and distal ureters [17]. Most patients present for treatment at an advanced stage, and 25% of cases are inoperable when first seen [16]. Interestingly, the vast majority of tumors were low grade, a factor that may account for the low incidence of lymph node positivity [18]. As in the case of non-bilharzial SCC, the treating physician could consider radical cystectomy for patients with resectable tumors and use multimodality therapy including radiation with concomitant chemotherapy as a useful alternative for unresectable bladder tumors or in cases where bladder preservation is desired [19, 20]. There is also some evidence that treatment with preoperative radiotherapy improves disease-free survival over radical cystectomy alone [21]. Bilharzial SCC can be prevented through parasitic control, mass treatment of the population, and early detection of the disease [22]. While no current data support the use of immunotherapy in SCC of



The decline in the relative frequency of both bladder carcinoma and its bilharzial association during 37 year (1970–2007)



The change in the relative frequency of histological types of bladder carcinoma during 37 years (1970–2007)

Fig. 1 Successful control of schistosomiasis and the changing epidemiology of bladder cancer in Egypt (with permission from *BJU International* vol. 107(2):206–2011)

the bladder, it appears that drugs active in the PD-1 pathway are independent of histology, and may play a role in future treatment of all types of bladder carcinoma [23].

Consensus statement	Level of evidence
Squamous cell carcinoma	
Patients with long-term indwelling catheters and chronic irritative symptoms or hematuria should undergo evaluation for possible development of SCC	B
Patients with localized non-bilharzial SCC should be offered radical cystectomy with wide resection and regional lymphadenectomy as primary treatment	B
Radiation therapy for non-bilharzial SCC should be reserved for palliation	C
Chemotherapy can be offered in metastatic disease	C
Radical cystectomy should be offered as the primary therapy for patients with bilharzial SCC	B
Neoadjuvant radiation therapy with or without chemotherapy could improve survival following radical cystectomy	B

Adenocarcinoma of the bladder

Adenocarcinomas are malignant tumors with glandular features. Adenocarcinomas of the urinary bladder are broadly divided into primary vesical tumors which originate de novo within the urinary bladder, tumors arising from the urachal remnant, and metastatic or local extension of tumors arising in other organs [24].

Primary adenocarcinoma of the urinary bladder constitutes 0.5–2% of all bladder malignancies and shows highest incidence in the fifth or sixth decade of life with a male-to-female ratio of 2:1–3:1. An important variant of primary bladder adenocarcinoma is clear cell adenocarcinoma which resembles clear cell tumors of the female genital tract. Bladder adenocarcinoma occurs more frequently in females (female-to-male ratio of 2:1), and in middle-aged and elderly patients, and has been more commonly described in the bladder neck, in the trigone, in a diverticulum or in a Mullerian duct cyst [25].

Urachal epithelial tumors are uncommon tumors arising from the urachal vestiges (Table 1). They are less common than non-urachal adenocarcinoma. They are also more common in males with a male-to-female ratio of 2:1–3:1. The etiology in unknown, but the tumor arises from metaplasia of urachal epithelium. Most patients present with hematuria. Other symptoms include umbilical or pelvic pain, mass, and weight loss. Patients may be asymptomatic. Grossly, the tumors are located in the dome and/or anterior wall, in the muscularis propria. They may be calcified on imaging and/or associated with urachal cysts or remnants.

The majority of bladder adenocarcinomas present with locally advanced or metastatic disease with a recent review of the SEER database from 2004 to 2013 reporting that only 35% of these tumors were organ confined and only 24% were low grade [26]. The standard treatment for all localized primary bladder adenocarcinomas is radical cystectomy with

Table 1 Criteria for the diagnosis of urachal adenocarcinoma

(A) Mandatory criteria
Location of the tumor in the bladder dome and/or anterior wall
Epicenter of the carcinoma in the bladder wall
Absence of widespread cystitis cystica and/or cystitis glandularis beyond the dome or the anterior wall
Absence of a known primary elsewhere
(B) Optional criteria
Presence of urachal remnants in association with the tumor

pelvic lymph node dissection, but some urachal adenocarcinomas may be amenable to partial cystectomy. Radical cystectomy confers a higher survival than TURBT alone which is associated with low 5-year survival rates. Primary radiotherapy and systemic therapies for primary bladder adenocarcinomas have limited effectiveness. The data are insufficient to support neoadjuvant therapies for adenocarcinoma of the bladder; however, the use of adjuvant radiation therapy may improve survival in some patients [27]. Intravesical therapies have no role in the management of adenocarcinomas of the bladder and novel therapies are under investigation [28]. While there is a large discordance in overall 5-year survival rates between 11 and 55%, the prognosis is believed to be poorer than for urothelial cancers and age at diagnosis, grade, and stage of tumor has been the most consistent predictors of survival in patients with bladder adenocarcinoma [29].

Adenocarcinoma in exstrophy patients

Patients with exstrophy of the urinary bladder are at a high risk of developing adenocarcinomas and the risk may be 27 times higher than the general population [30]. While the majority of these obvious anomalies are corrected in the neonatal period, delayed presentation due to adverse socioeconomic conditions is not uncommon [31]. Patients who undergo early repair or urinary diversion may also not be immune from the development of an adenocarcinoma [32]. Malignancies most often occur in the fourth and fifth decades of life and surveillance cystoscopy with biopsy has been recommended [33]. However, the role of routine surveillance cystoscopy is not universally accepted and a high index of suspicion with early investigation of symptomatic patients may be an alternative approach.

Secondary bladder adenocarcinomas

Secondary adenocarcinomas of the bladder include tumors that are metastatic to the bladder or involve the bladder through direct local extension of tumors of adjacent organs. Primary sites of such tumors include the colon, rectum, prostate, lung and breast. Secondary adenocarcinomas, though uncommon, may be more frequent than primary adenocarcinomas of the urinary bladder [34]. The majority of metastatic tumors will have evidence of additional site metastasis, either at the time of presentation or in follow-up. Most such tumors are identified through imaging and cystoscopy, and transurethral resection is the primary treatment for diagnosis and symptom control. Systemic chemotherapy based on the primary tumor histology may be considered as additional therapy. However, surgical resection for metastasis has not been used. Partial or total cystectomy, en bloc with the primary tumor, is the most appropriate management for these locally invading tumors [35]. Survival after surgical resection of secondary bladder adenocarcinoma depends on the primary disease pathology [36].

Consensus statement	Level of evidence
Adenocarcinoma	
The diagnosis of a primary bladder adenocarcinoma should be made after ruling out a primary at common sites of adenocarcinomas unless the tumor is suspected to be urachal in origin	B
Radical cystectomy is the primary treatment for non-urachal adenocarcinomas	B
Adjuvant radiation or chemotherapy may be considered for locally advanced disease	C
Limited resection with partial cystectomy and umbilectomy with lymph node dissection may be sufficient treatment for urachal tumors	C
Exstrophy patients who have not undergone a cystectomy are at a higher risk of bladder adenocarcinoma and should be carefully followed	B
Local resection, en bloc, with a primary in the bowel may be considered for adenocarcinomas invading the bladder from adjacent organs	B

Neuroendocrine tumors of the urinary bladder

Small cell carcinoma

Small cell carcinoma of the bladder (SCCB) is a malignant neuroendocrine neoplasm of the urothelium that histologically mimics its pulmonary counterpart. It often coexists with conventional urothelial carcinoma, adenocarcinoma, or squamous cell carcinoma. SCCB is a rare disease, accounting for 0.5–0.7% of all bladder tumors. It most commonly presents in the seventh decade with a mean age of presentation of 66 years and a male:female ratio of 2:1–5:1. Occasionally, patients have paraneoplastic syndromes with hypercalcemia, Cushing syndrome, hypophosphatemia, or a neurologic disorder [37, 38].

At cystoscopy, SCCB cannot be distinguished from bladder urothelial carcinoma by its gross appearance. Lymphoma, poorly differentiated urothelial carcinoma, poorly differentiated squamous cell carcinoma, and metastatic small cell neuroendocrine carcinoma from another primary should be considered. It is also important to distinguish SCCB from small cell carcinoma originating in the prostate. The identification of urothelial components, including urothelial carcinoma in situ, would strongly support a primary bladder origin [39, 40]. SCCB is an aggressive disease. After initial diagnosis on transurethral resection of bladder tumor (TURBT), thorough staging including chest CT should be performed to rule out a primary lung small cell carcinoma.

For primary SCCB, a number of different treatment strategies and their combinations including initial chemotherapy followed by local control with radical or partial cystectomy or sometimes radiotherapy. Because patients with SCCB may frequently have micrometastatic disease at diagnosis that is not detectable on imaging studies, the treatment paradigm emphasized initial systemic chemotherapy. TURBT alone should be used cautiously or not at all given the aggressiveness of SCCB. In contrast to urothelial carcinoma, chemotherapy for SCCB is typically cisplatin (or carboplatin) and etoposide. Neoadjuvant chemotherapy was associated with improved survival outcome [41]. Several reports presented cases of SCCB that were well controlled with local radiation treatment. However, most of the patients in those reports also received chemotherapy and the effect of radiation alone could not be isolated [42]. Similar to pulmonary small cell carcinoma, SCCB is often detected at advanced stage and has a dismal prognosis (10% 5-year survival) [43]. In addition, brain metastases are strongly associated with more advanced stage disease, indicates poor prognosis, and some studies suggested that there might be a potential benefit of prophylactic cranial irradiation in patients with SCCB [44].

Large cell neuroendocrine carcinoma

LCNEC is a tumor of rare incidence that occurs mostly in men. The age of diagnosis ranges from 61 to 87 years (mean 74 years), and most tumors appear as a nodular mass with a polypoid solid appearance and are difficult to distinguish from other types of bladder cancers. The differential diagnosis of primary urinary bladder LCNEC includes metastatic LCNEC, most frequently from lungs or intestines, local extension of poorly differentiated prostatic carcinomas, high-grade urothelial carcinoma, small cell neuroendocrine carcinoma, and some types of lymphoma. There is no standard evidence-based chemotherapy for LCNEC. Akamatsu et al. reported on a subject that underwent chemotherapy with carboplatin and etoposide with radical cystectomy for muscle invasive LCNEC and had no recurrence for 16 months. Most patients with LCNEC present with high stage disease and have a poor prognosis [45].

Well-differentiated neuroendocrine tumor ("carcinoid tumor")

Well-differentiated neuroendocrine carcinoma (WDNET or carcinoid tumor) of the bladder is recognized as a distinct entity of neuroendocrine neoplasms that is potentially malignant with histologic features similar to carcinoids found at other anatomic locations. Some patients can have metastases to regional lymph nodes or distant metastases. WDNET of the urinary bladder is a very rare neoplasm that occurs predominantly in elderly patients with a slight male predominance [46]. WDNET often appeared as small polypoid or smooth-surfaced submucosal nodules by cystoscopic examination. Differential diagnostic considerations include paraganglioma, nested variant of urothelial carcinoma, and metastatic prostate carcinoma [47]. The treatment for localized disease is similar to the treatment of carcinoids at other body sites and primarily involves surgical resection with clinical follow-up and the prognosis of WDNET is excellent [48].

Consensus statement	Level of evidence
Neuroendocrine tumors	
Patients with locoregional pure small cell carcinoma of the bladder should initially be offered treatment with cisplatin-based neoadjuvant chemotherapy prior to radical cystectomy	B

Bladder sarcoma

Malignant soft tissue tumors represent the most common histologic subtype of the non-epithelial bladder tumors. Half of bladder sarcomas are leiomyosarcoma, 20% are rhabdomyosarcoma, and the remainder is angio-, osteo-, and carcinosarcoma [49]. Most patients with leiomyosarcoma present with hematuria. A majority of the tumors are high grade and may attain very large size before recognition. The preferred treatment for localized disease is radical cystectomy with negative margin resection. In the largest series to date, encompassing 24 patients, high-grade sarcomas experienced 50% disease-related mortality vs. 0% of those with low grade [50]. Metastatic sarcomas are treated with multimodality (surgery, radiation therapy, and chemotherapy) protocols. Doxorubicin and ifosfamide are the most active single agents available [51].

Rhabdomyosarcoma of the bladder in the adult is rare. Treatment generally involves the use of neoadjuvant chemotherapy followed by complete resection, which is often radical cystectomy. Radiotherapy is very useful for achieving local control after surgery and chemotherapy [52].

Very few cases of bladder angiosarcoma have been reported so no consensus on treatment has been achieved. The cancer is aggressive and radical cystectomy followed by chemotherapy and radiotherapy is recommended. Complete tumor resection and negative margins are important although long-term survival in uncommon [53].

Paraganglioma

Paragangliomas of the urinary bladder are extra-adrenal neoplasms derived from neural crest cells. Tumors arising within the adrenal medulla are termed pheochromocytoma

and those outside the adrenal, paraganglioma. Bladder paraganglioma accounts for 0.05% of bladder tumors and occurs in young adults (mean age 43 years). It may be derived from embryonic rests of chromaffin cells in the detrusor sympathetic plexus. It accounts for 10% of extra-adrenal paraganglioma. Malignancy was demonstrated in 10% and characterized by local invasion, regional lymph node metastases, or distant spread.

Bladder paraganglioma may be hormonally active and presents with attacks of paroxysmal hypertension, headaches, palpitations, blurred vision, and sweating associated with the act of micturition. If the disease is suspected, cystoscopy should be performed under adrenergic blockade in the operating room. The gross appearance is often a solitary, submucosal, or intramural nodule. Biopsy should be avoided. The diagnosis depends on CT scan or MRI for anatomical location and the extent of the lesion. Isotopic scanning using ^{131}Iodine metaiodobenzylguanidine (MIBG) is the study of choice for localizing small pheochromocytomas with more than 90% specificity [54]. Positron emission tomography has been recently used with high sensitivity as well. Surgical treatment with partial or radical cystectomy is the recommended treatment and should be employed under the same precautions as in adrenal pheochromocytoma with controlled adrenergic blockade.

Consensus statement	Level of evidence
Paraganglioma and pheochromocytoma	
Suspected paragangliomas of the bladder should undergo examination with adrenergic blockade in an operative setting	C
MIBG scanning can be used as confirmatory radiographic evaluation for paraganglioma of the bladder	C
Partial or radical cystectomy should be used as primary curative therapy for paraganglioma of the bladder	C

Bladder pseudotumors

Bladder pseudotumors (also known as inflammatory pseudotumor or pseudosarcomatous myofibroblastic proliferation) are rare and may resemble malignancy [55]. The etiology and histogenesis remain unclear. Some of these lesions present as "postoperative spindle cell tumors". It may be difficult to distinguish them from leiomyosarcoma or sarcomatoid urothelial carcinoma on a histopathologic basis. Pseudotumors may infiltrate deep into the muscularis propria but invasion does not indicate tumor aggressiveness [56]. Local recurrence or distant metastases are rare following complete tumor excision. If the diagnosis is clear, transurethral resection or partial cystectomy is sufficient. Radical cystectomy may be required if the diagnosis is difficult to distinguish from bladder sarcoma.

Melanoma

Primary bladder melanoma is very rare with only 30 cases reported [57]. It affects the urethra more than the bladder. Ages of patients with primary bladder melanoma range from 34 to 84 years without sex predominance. Macroscopic hematuria is the usual presenting symptom. The disease generally has a poor prognosis, with two-thirds dying within 3 years [58]. Treatment is surgery, usually in the form of radical or partial cystectomy. Secondary melanoma of the bladder is found in patients with widespread metastatic melanoma of the skin and is treated with systemic therapy targeted to the primary disease.

Lymphoma

Bladder lymphoma is usually a part of metastatic spread of systemic disease [59–61]. Primary extra-nodal lymphoma of the bladder is very rare. Most bladder lymphomas are the extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue origin (MALT) [60, 61]. Primary lymphoma is more common in women [61]. It is mostly localized and of low grade with good prognosis [60]. Other high-grade lymphomas such as diffuse large B-cell lymphoma may occur [59, 61]. Local radiation is the recommended treatment with a high recurrence-free survival [60, 61].

Consensus statement	Level of evidence
Lymphoma	
Primary or secondary bladder lymphoma should be treated primarily with local radiation and/or chemotherapy	C

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

Ethical statement I testify on behalf of all co-authors that our article submitted to *World Journal of Urology* has not been published in whole or in part elsewhere, is not currently being considered for publication in another journal, and that all authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves jointly and individually responsible for its content.

Human or animal statement This research does not involve human or animal subjects. This work is a review of the literature. No institutional review board was required because no active research was preformed.

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