Review – Bladder Cancer

Current Management of Urachal Carcinoma: An Evidence-based Guide for Clinical Practice

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Article info

Abstract

Urachal carcinoma is a rare urological disease. The shortage of data about diagnosis and surgical treatment in literature makes it hard for clinicians to make a decision. Indeed, urachal carcinoma is an aggressive disease that requires prompt staging and treatment to ensure the best outcome for patients. We reviewed the last evidence about the management of urachal carcinoma to provide an easy-to-use guide for clinical practice.

Patient summary: Urachal carcinoma is a rare malignancy. The literature on this challenging disease remains limited. Herein, we provide a practical guide for its management from diagnosis to treatment, which in most cases requires surgical intervention or chemotherapy.

1. Introduction

The urachus is an embryonic remnant that during fetal life connects fetal bladder to allantois and in adult life results in a fibrous cord known as the umbilical ligament, connecting the bladder dome to the umbilicus. Failure of its closure process may allow islets of cells to proliferate, leading to malignancy. Urachal carcinoma (UrC) is a rare malignancy accounting for <1% of all bladder cancers, the prevalence of which in the general population remains unknown [1]. The median age of presentation for UrC is 52–59 yr (range 46–71 yr); in general, this disease affects a younger population than urothelial bladder cancer [2].

UrC is often considered a highly aggressive cancer with a poor prognosis. In the largest series to date, the reported 5-yr overall survival (OS) was about 50% and the 5-yr cancer-

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specific survival (CSS) was about 35% [3]. Being a rare disease, it lacks large series and/or perspective trials in the literature, and most of the evidence comes from case reports, small case series, and retrospective analyses.

The aim of this review is to summarize the most recent evidence on UrC, focusing on its surgical management, and to provide an easy-to-use guide for clinicians (Fig. 1).

2. Clinical findings and diagnosis

2.1. Signs and symptoms

The most common histological type of UrC is adenocarcinoma. It often presents with gross or microscopic hematuria in 73% of cases, sometimes associated to abdominal

Clinical presentation
Hematuria, mucosuria, umbilical discharge, dysuria, abdominal pain

Diagnostic work up
Cystoscopy + ultrasonography (US) + CT scan (CT)

Diagnostic Criteria
- Tumor in dome or anterior bladder wall
- Tumor growth in the bladder wall
- Absence of urothelial bladder neoplasia
- Absence of primary adenocarcinoma of different origin
- Absence of intestinal metaplasia/cystitis glandularis

Diagnosis of urachal cancer
Staging

Localized   **Locally advanced**   **Metastatic**

Treatment

PARTIAL / RADICAL CYSTECTOMY
- Open / Lap / Robot assisted
- Urachus excision
- Umbilectomy
- Extended bilateral PLND

Adjuvant chemotherapy if PSM

CHEMOTHERAPY
- Cisplatin + 5-FU
- FOLFOX6
- Cytoreductive surgery

CHEMOTHERAPY
- Cisplatin + 5-FU
- FOLFOX6
- Surgery, if resectable single metastatic site

Follow-up
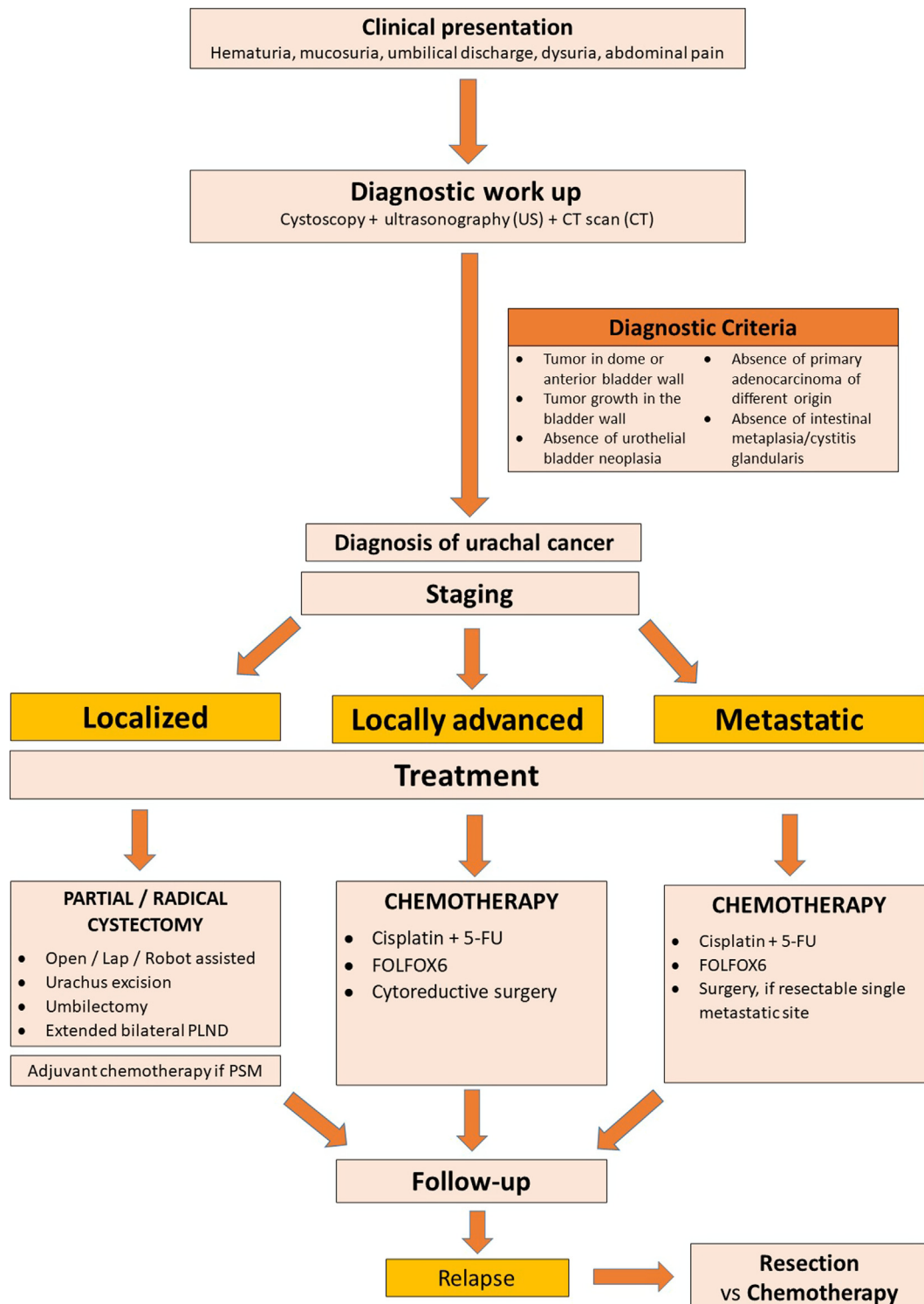
Relapse   **Resection** vs **Chemotherapy**

Fig. 1 – Management of urachal carcinoma. CT = computed tomography; 5-FU = 5-fluorouracil; PLND = pelvic lymphadenectomy; PSM = positive surgical margin.

pain, dysuria, and mucosuria (10–14%) [2]. Seldom, UrC may present other unspecific urinary symptoms (eg, pollakiuria, pyuria, or recurrent urinary tract infections) or umbilical discharge, and an abdominal palpable mass may be found. Systemic nonspecific symptoms may occur (fever, weight loss, and nausea), especially in more advanced stages.

2.2. Diagnostic workup

Diagnosis is based on the medical history and physical examination, and a cystoscopy is mandatory as it represents the most sensitive diagnostic tool (up to 90%) [4]. Indeed, this procedure allows the identification of tumor localization faithfully, which is often described as a broad-based ulcerative mass in the dome or the anterior wall of the bladder. Nevertheless, up to 8% of patients remain asymptomatic; therefore, diagnosis is made incidentally in these cases [2].

Diagnostic workup may include imaging. Ultrasonography can show a supravesical inhomogeneous mass located in the midline, sometimes associated with calcifications that are considered pathognomonic. A computed tomography (CT) scan or magnetic resonance imaging (MRI) is useful for evaluating the mass and performing clinical staging, detecting possible organ invasion, lymph node enlargement, or distant metastasis [3,5].

Urinary UroVysion FISH has recently been studied as a potential tool for the diagnosis of UrC [5]. It has been found to be positive in a high proportion of pathologically confirmed UrC cases, with sensitivity and specificity of 71.43% and 94.61%, respectively [6]. These promising findings seem to support the use of UroVysion to differentiate UrC from a benign urachal cyst.

Preoperative pathological sampling cannot always be achieved. A transurethral resection (TUR) of the mass can be technically challenging in most cases, and it might carry a risk of bladder rupture. Moreover, it has been reported that, while having high specificity, a TUR is affected by a suboptimal negative predictive value (50%) [6]. Thus, percutaneous biopsy has been evaluated as an option to differentiate an infected urachal cyst from UrC when imaging remains inconclusive [7]. Nevertheless, current diagnostic tools might not be enough, and surgical removal can be

indicated on the basis of clinical suspicion and in the absence of a pathology confirmation [6].

Diagnostic criteria have been suggested to standardize the UrC diagnosis. These include the following [8]:

1. Tumor located in the dome or anterior bladder wall.
2. Tumor growth in the bladder wall.
3. Absence of atypical intestinal metaplasia and cystitis/glandularis beyond the dome/anterior wall.
4. Absence of a urothelial bladder neoplasia.
5. Exclusion of a primary adenocarcinoma of a different origin.

Recently, the role of 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT has also been shown in identifying metastatic sites that are undetectable with other imaging tools, especially during follow-up. However, 18F-FDG PET/CT does not seem to yield additional information compared with CT, which still remains the most reliable tool for initial diagnosis and staging [9].

Serum biomarkers have been investigated for UrC. For example, elevated carcinoembryonic antigen serum levels (>3 ng/ml) were found in 59% of UrC cases, and these were associated with worse survival outcomes. Additionally, elevated serum levels of CA19-9 and CA125 were reported in 50.8% and 51.4% of UrC cases, respectively [10]. Despite these intriguing findings, additional studies are needed to recommend their routine use in clinical practice.

2.3. Staging systems

Different staging systems have been proposed to stratify the aggressiveness and prognosis of UrC (Table 1). The TNM system has a limited role, whereas the *Mayo* staging was reported to be superior to the *Sheldon* staging based on its simplicity and higher prognostic value in multivariable models [2]. Overall, 59–66% of cases present at diagnosis with extension beyond the bladder, without fulfilling surgical resection criteria [2].

3. Treatment

The treatment and oncological outcomes vary depending on the stage of the disease (Table 2) [3,4,11,12].

Table 1 – Staging systems of urachal carcinoma

	Stage		Sheldon staging system [2]	Mayo staging system [2]		TNM staging system
Localized disease	I		Tumor is limited to the urachal mucosa	Tumor is confined to the urachus and/or bladder	T1	Tumor invades the subepithelial connective tissue
	II		Invasion confined to the urachus itself (not beyond muscle layer)	Extension beyond the muscular layer of the urachus and/or bladder	T2	Invasion of the muscular layer of the urachus or bladder
Locally advanced disease	III	IIIA	Local extension to the bladder	Metastasis to regional lymph nodes	T3	Invasion of the perivisceral soft tissue, prostate, uterus, or vagina
		IIIB	Local extension to abdominal wall			
		IIIC	Invasion of the peritoneum			
		IIID	Invasion of the local viscera other than the bladder			
Advanced disease	IV	IVA	Metastasis to lymph nodes	Metastasis to nonregional lymph nodes or other distant sites	T4	Invasion of the abdominal wall and metastasis to lymph nodes or other distant sites
		IVB	Distant metastasis			

TNM = tumor, node, metastasis.

Table 2 – Overview on recent outcomes of surgical treatment for urachal carcinoma

Reference	No. of cases	Stage (% of cases)	Surgical treatment (% of cases)	Perioperative chemotherapy, n (% of cases)	Oncological outcomes	Negative prognostic factors
Shao et al (2022) [4]	59	TNM stage T1–2: 13.5 T3: 64.4 T4: 22.1	Open EPC (72.4) Open PC (17.3) Open RC (17.3)	18 (30.5)	Median OS: 52.8 mo 3-yr CSS: 69.1% 5-yr CSS: 62.1%	• High stage (≥pT3) • PSM
Yu et al (2021) [3]	203	Mayo stage I–II: 77 III: 11.4 IV: 11.4	Open or robotic EPC ± LND (82.8) Open RC ± LND (17.3)	65 (32)	5-yr OS: 88.3% 5-yr CSS: 83.1% 5-yr RFS: 63.9%	• High stage (Mayo ≥III, Sheldon ≥IIIc) • PSM • LVI
Duan et al (2020) [11]	62	Sheldon stage III: 80.7 IV: 19.3	EPC (87) or RC (13) ± LND	18 (29)	Median DFS: 32.7 mo Mean OS: 114.6 mo	• Sheldon stage, tumor size for DFS • Sheldon stage, peritoneal metastasis, LN recurrence for OS
Mylonas et al (2017) [12]	420	TNM stage T1–2: 34.2 T3: 29.5 T4: 30.5	Excision/local (20.7) EPC ± LND (52.4) Open RC ± LND (9.8)	NR	Median OS: 57 mo Median CSS: 105 mo 5-yr OS: 51% 5-yr CSS: 57%	• Grade • Stage

CSS = cancer-specific survival; DFS = disease-free survival; EPC = extended partial cystectomy; LN = lymph node; LND = lymphadenectomy; LVI = lympho-vascular invasion; NR = not reported; OS = overall survival; PSM = positive surgical margin; RC = radical cystectomy; RFS = recurrence-free survival; TNM = tumor, node, metastasis.

3.1. Surgery

Surgery represents the mainstay of treatment for localized disease. Excision of the urachus and the umbilicus, and partial/radical cystectomy, combined with extended bilateral pelvic lymphadenectomy (PLND), are usually offered [2]. The most commonly employed surgical approach is the open one, with laparoscopy as a safe and feasible alternative [4].

The prognostic role of lymph node metastasis in OS has recently been shown [3,11,13]. However, the therapeutic role of PLND remains controversial, as previous evidence suggests that it does not improve OS, while carrying a higher complication rate and lymph node positivity of only 17% [1,2]. To the best of our knowledge, PLND is not a predictor of OS; however, the prognostic impact of lymph node metastasis and the accuracy of PLND to assess the pathological stage should encourage clinicians to perform this procedure [11,13]. Recent findings confirm the impact of omphalectomy in improving OS and CSS in these patients [11,13]. An umbilical-sparing management approach might be considered in patients with localized disease [14]. However, the lack of strong evidence should discourage clinicians from performing this procedure routinely.

The main goal in surgical treatment of UrC is to achieve negative surgical margins, especially after partial cystectomy. Indeed, the prognostic impact of positive surgical margins (PSMs) on OS and CSS has consistently been demonstrated [3,15].

More recently, it has been shown that robot-assisted partial cystectomy might represent a feasible and safe procedure to treat UrC [16,17], as it offers the same rate of PSMs as the open approach, with lower perioperative morbidity. Furthermore, new technological tools, such as intraoperative indocyanine green fluorescence, have been tested to facilitate the targeting of surgical landmarks and identification of surgical margins [18].

3.2. Chemotherapy

Advanced stages have a poor prognosis, and perioperative chemotherapy has a limited role. Neoadjuvant chemotherapy treatment could be employed in cases of unresectable disease only when achieving a response may lead to surgical consolidation with a negative margin resection [19].

Recently, its effectiveness in decreasing overall mortality and cancer-specific mortality has been shown in a metastatic cohort, especially in younger patients (≤70 yr) [20]. Commonly employed regimens are 5-fluorouracil and cisplatin or FOLFOX6 (folinic acid, 5-fluorouracil, and oxaliplatin), with gemcitabine increasingly being included in therapeutic protocols [12]. To better standardize chemotherapy regimens, a recent study has demonstrated higher effectiveness of platinum-based chemotherapy than that without platinum in disease control, while there is no significant difference in progression-free survival and OS between groups using fluorouracil and paclitaxel as first-line regimen [21].

Chemotherapy associated with cytoreductive surgery has also been evaluated, demonstrating satisfactory long-term oncological outcomes [22]. Furthermore, UrC local recurrence occurs in about 15–18% of patients after primary treatment [23,24], and chemotherapy should be considered a suitable option to control the relapse when not surgically resectable [24]. However, the benefit of these treatment modalities has yet to be evaluated in adequately powered studies.

3.3. Radiotherapy

Radiotherapy is rarely employed in UrC management: a Surveillance, Epidemiology, and End Results (SEER)-based population study shows that it has been used in only 10% of patients [12]. The limited available evidence on the use of radiotherapy in this setting suggests it to be ineffective as local treatment [23].

4. Metastatic disease

UrC is usually diagnosed at advanced stages, with >20% of patients having distant metastasis at presentation [2]. Moreover, up to 59% of patients may manifest metastasis at some point in the evolution of disease [24], with the lung, bone, peritoneum, and liver being the most commonly involved organs [2,23]. Obviously, the presence of metastasis is associated with a worse prognosis, and chemotherapy is considered the best option of treatment to prolong OS [2]. Surgical resection of metastasis in slow growing disease may be considered, but only in single organ resectable metastasis, after disease control with systemic chemotherapy [19].

In the precision-medicine era, systemic treatment may be shifted toward molecular-targeted therapy. Recently, UrC has been characterized in its genetic signature through a genome-wide analysis. The main common genetic and molecular mutations have been identified, such as KRAS, BRAF, and NRAF, which could be useful in potential treatment tailoring [25,26]. Furthermore, from a molecular standpoint, UrC may show mutation in epidermal growth factor receptor (EGFR) as colon cancer, and the response to EGFR inhibitors such as gefitinib or cetuximab has already been shown in two single reports [2,27]. Immune and targeted therapies for UrC seem to be promising, but their role remains to be determined [19,28].

5. Conclusions

UrC is a rare clinical entity, but its management can represent a clinical challenge, given the limited evidence in the literature. The importance of accurate clinical staging is the first step to establish a tailored treatment plan. Surgery remains the mainstay of treatment for nonmetastatic disease, via open, laparoscopic, or more recently, robotic-assisted techniques. Treatment for metastatic and advanced disease relies on systemic chemotherapy, but no standardized protocols have been established.

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