Management of urachal cancer: A consensus statement by the Canadian Urological Association and Genitourinary Medical Oncologists of Canada

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Cite as: *Can Urol Assoc J* 2020;14(3):E57-64. http://dx.doi.org/10.5489/cuaj.5946

Published online July 23, 2019

Introduction

The urachus is a fibrous remnant of the allantois. After birth, it remains throughout life as the medial umbilical ligament running from the apex of the bladder to the umbilicus but without any further physiological role. First described by Begg in 1931, urachal cancer is a rare pathology representing less than 1% of bladder cancers.[1] Usually located on the serous side of the bladder apex, these tumors are classically silent because of their extravesical and extraperitoneal location. Therefore, most patients present with local invasion or metastatic disease and, thus, are detected at a higher stage.

Based on its rarity, there have been no large, prospective, randomized trials in urachal cancer and there are no evidence-based guidelines on the management of this disease. The existing evidence in the medical literature is derived from case series.

In this article, led by the Genitourinary Medical Oncologists of Canada (GUMOC), we aim to review the literature of this rare disease in order to establish a Canadian consensus statement on the management of urachal cancer. To our knowledge, there is no other consensus statement available.

Methodology

We performed a search of Pubmed, Embase, and Cochrane using the following keywords: urachus cancer, urachus carcinoma, carcinoma of the urachus, cancer of the urachus, urachal cancer.

Guidelines from the European Association of Urology (EAU), the National Comprehensive Cancer Network (NCCN), and provincial guidelines from the British Columbia Cancer Agency (BCCA) were reviewed. Only the BCCA guidelines mention urachal cancer.

The first draft was written and reviewed by the project leaders (ZH and NB) and disseminated to GUMOC members for a primary review. The updated version was resubmitted to the group, as well as key Canadian representatives in the fields of urologic oncology, radiation oncology, pathology, and to a patient advocate. Consensus was obtained within the group by the revision of the summary statements until a unanimous agreement was achieved (either by email exchanges or in-person discussions at the annual GUMOC meeting).

Guidelines for recommendations are described using the World Health Organization (WHO) modified Oxford Centre for Evidence-based Medicine grading system. The level of evidence was described according to the following: Level 1: systematic review of randomized controlled trials (RCT); Level 2: individual RCT, including low-quality RCT; Level 3: controlled cohort; Level 4: case-control studies or case series; Level 5: expert opinion, mechanism-based reasoning.[2]

Data source

From 1960, approximately 300 publications are available. Because of the scarcity of this entity, there are no prospective or phase 3 studies. For the purpose of this article, we included reviews and case series of 10 or more individuals

with urachal cancer, with the exception of articles regarding molecular biology and emerging therapies that included fewer patients. Interestingly, the last two years have seen the publication of two important, informative papers. First, the largest population-based study using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was published. This study comprises data from 18 cancer registries based on the 2010 census of the U.S. population and contained 420 patients with urachal cancers.[3] Second, a meta-analysis including most of the already described and published case series with a total of 1010 patients is now available.[4]

Background

Anatomy

The urachus is a fibrous remnant of the allantois, a canal located at the bladder apex that drains the urinary bladder of the fetus.[5] It extends upward from the anterior dome of the bladder toward the umbilicus and measures 3–10 cm in length and 8–10 mm in diameter.[6] The urachus normally regresses during fetal life but the lumen of the urachus persists in approximately one-third of adults and traverses the bladder wall as a midline tubular or cystic structure of little clinical significance.[7,8] The urachus comprises three different tissue layers: an epithelial canal lined by urothelium, submucosal connective tissues, and an outer layer of smooth muscle. Urachal neoplasms can arise in any of these layers and can be epithelial or mesenchymal. Moreover, the epithelium often demonstrates focal glandular metaplasia, providing a morphological basis for the development of intestinal-type tumors.[1]

Epidemiology

The predominant histological type of bladder cancer in North America and Europe is urothelial (transitional cell) carcinoma in over 90% of cases. Adenocarcinoma of the bladder represents only 1.4%. Among these rare cases of adenocarcinoma of the bladder, urachal cancer represents 10–40%. The estimated annual incidence of this tumor in the general population is reported to be one in five million individuals.[9] It is important to differentiate urachal adenocarcinoma from non-urachal adenocarcinoma of the bladder, as the surgical approach is different for these two entities (extended partial cystectomy opposed to radical cystectomy for the latter). Furthermore, although the biology of adenocarcinoma of the urachus vs. bladder is perceived to be similar, this has not been adequately studied in the literature.

Patients with urachal cancer are more likely to be male with a male to female ratio of 1.44:1 in the SEER database and 60% males in the meta-analysis.[3,4] Based on 17 reports, the median age at diagnosis is 52 years (range 20–90 years), which is younger than non-urachal adenocarcinomas (median age 69).[4,9-14]

In the largest series, five-year overall survival is about 50%.[9,10,12,13] The poor prognosis is mainly explained by advanced stage at presentation due to the relative lack of symptoms in localized disease, difficulty of identification through cystoscopy, and the absence of clear consensus in the investigation and treatment of localized and advanced disease.[5] Despite a younger age of presentation and a prognosis as stated above, urachal cancers are associated with a superior survival compared to non-urachal adenocarcinomas.[13,15]

Histology

Adenocarcinoma is the most common histological subtype of urachal cancer, representing 90% and 82.4% of the cases in the Mayo clinic series (420 patients) and in the SEER database, respectively.[3,10] Adenocarcinoma subtypes include mucinous adenocarcinoma, reported most frequently,[12] adenocarcinoma not otherwise specified, and adenocarcinoma with signet ring cell morphology. Other histological subtypes are relatively uncommon and include squamous cell carcinoma, urothelial carcinoma, and sarcoma.[7,10] More than one histological subtype can be present in the same patient.[12] Overall survival seems to be different for the different histologies of urachal cancer favouring the urothelial cell subtype. In the SEER database, urothelial cell carcinomas subtype had lower cancer-specific mortality than those with signet cell tumors (hazard ratio [HR] 6.14; 95% confidence interval [CI] 2.14–17.6; p<0.001), adenocarcinoma not otherwise specified (HR 3.09; 95% CI 1.21–7.84; p=0.001), and mucinous adenocarcinoma subtypes (HR 3.01; 95% CI 1.21–7.5; p=0.01).

Immunohistopathology

There are no specific markers to confirm or disprove urachal cancer. Moreover, there is a resemblance of these cells to gastric and colonic mucosa that may confuse the diagnosis. Indeed, a theory holds that progenitor cells for urachal tumors arise from enteric remnants left behind during embryologic development.

First, significant overlap seems to be present between adenocarcinomas of enteric, ovarian and urachal origin in regard to cytokeratin 7 (CK7), cytokeratin 20 (CK20), and CDX2 staining. However, CK7 tends to be negative in colonic or gastric signet cell cancers to the contrary of urachal cancer, which is typically CK7-positive.[16]

Other potential markers include 34BE12 and beta catenin. Gopalan et al performed immunohistochemistry (IHC) using CDX2, CK7, CK20, beta-catenin, and 34BE12

on 15 adenocarcinomas of the urachus and compared them to 81 colonic adenocarcinomas. All cases stained positive for CK20 and CDX2, while half of them stained positive for CK7. Approximately two-thirds of patient tumors stained with 34BE12, and in the majority of these, only focal staining was seen. More than 90% of the urachal tumors showed strong and diffuse cytoplasmic membranous reactivity for beta-catenin without nuclear staining. In comparison, 25% of colonic adenocarcinoma showed cytoplasmic membranous reactivity with focal or diffuse nuclear accentuation, and only 11% showed rare or focal cytoplasmic reactivity with 34BE12. The authors conclude in this review that immunostains do not unequivocally discriminate a urachal from a colorectal carcinoma but diffuse positivity for 34BE12 would support a diagnosis of urachal carcinoma, while a diffuse nuclear immunoreactivity for beta-catenin would militate against it.[17]

Molecular biology

Until 2016, little to no data was accessible in the medical literature regarding the biology of this particular tumor. In 2016, Modos et al reported on mutational hotspots, specifically KRAS, NRAS, BRAF, EGFR, and PIK3CA genes in 22 urachal carcinoma samples.[18] These five genes were selected because of the similarity between urachal carcinoma and colorectal adenocarcinoma. They found 11 mutations in 10 of 22 patients. KRAS was the most frequently affected (27%), followed by BRAF (18%) and NRAS (5%). Unfortunately, no correlation was found between mutational status and clinicopathological characteristics, including signet ring cell differentiation, presence of calcification, clinical stage, tumor grade, and the presence of lymph nodes or distant metastases and survival. Of interest, KRAS mutations were only present in non-metastatic cases. Other smaller case series looked at mutational status of KRAS in urachal carcinoma. Sirintrapun et al observed that three of seven cases presented with KRAS mutation, while Alexander et al found a mutation in one of five cases.[19,20] On the basis of these small series, KRAS mutations may be more frequent in urachal carcinoma (similar to colorectal carcinoma) in contrast to urothelial carcinoma, where they are not commonly described. Similarly, BRAF mutations are rare in urothelial carcinoma and adenocarcinoma of the bladder, but are present in 18% of urachal carcinoma in the series described by Modos et al.[18]

Clinical manifestations

Macroscopic or microscopic hematuria is a frequent clinical presentation in about 80% of patients and implies that the tumor has transgressed the muscularis mucosae and invaded the urothelial surface.[10] Other, less frequent symptoms at presentation include bacteriuria, mucinuria, pain, abdominal mass, and umbilicus infection.[5,12] The median tumor size based on the largest diameter is reported to be 3.0–6.3 cm. Unfortunately, since the ligament lies outside the bladder, many patients present with locally advanced disease. For example, in the series of 151 urachal and 1374 non-urachal adenocarcinomas of the bladder patients by Wright et al, only 20% of the patients presented with localized disease.[13] The tumor can extend toward nearby organs and metastases occur mainly in the pelvic lymph nodes, retroperitoneal lymph nodes, lungs, and bones. There are no accurate statistics as to the frequency of metastatic sites, however, in a series by Ashley et al with 66 patients, systemic metastasis occurred in 39 patients at some point in the evolution of the disease (13 patients at diagnosis and 26 during followup). Liver, pulmonary, and bone were the most common.[10]

Diagnostic modalities

Different modalities used to establish the diagnosis include cytology, imaging, and cystoscopy. Cystoscopy can identify a visible mass in about 80% of patients, whereas urine cytology will be positive in only 38%.[10,12] Urine cytology may be negative because of the extravesical location of the tumor.

Radiographic imaging with computed tomography (CT) scan provides strong supportive information of the diagnosis. On CT scan, urachal carcinoma may appear solid, cystic, or a combination of the two. Low-attenuation components are seen in 60% of cases, reflecting mucin content. Additionally, calcification within the tumor occurs in 50–70% of cases and may be punctate, stippled, or curvilinear and peripheral.[6] Therefore, the presence of a midline mass on the bladder dome, whether solid or cystic, especially with small calcifications, is considered highly suspicious, if not pathognomonic, for urachal cancer.[21]

With magnetic resonance imaging (MRI), the tumor is reported to be inhomogeneous and to show high intensity on T2-weighted images. Above all, MRI has the advantage of multiplane imaging and may be more useful than CT to determine the involvement of adjacent organs, such as the bladder. In conclusion, both CT and MRI may be used in the clinical evaluation to clarify the diagnosis for the former and evaluate locoregional extension for the latter.[22]

Finally, biomarkers such as CEA, CA-125, CA 19-9 may be elevated in 40–60% of patients; however, they are nonspecific and can be elevated in cancers of other origins. The response in these markers frequently correlates with radiographic response.[21]

Staging

Currently, there is no validated staging system for urachal cancer. Different staging approaches have been described, namely Sheldon, Mayo, and modified TNM staging systems. The first two are the most commonly used.[9,10,12]

Table 1. Sheldon staging system of urachal cancer

Stage		Sheldon staging system
I		Urachal cancer confined to urachal mucosa
II		Urachal cancer with invasion confined to urachal itself
III	A	Local urachal cancer extension to bladder
	B	Local urachal cancer extension to abdominal wall
	C	Local urachal cancer extension to peritoneum
	D	Local urachal cancer extension to viscera other than bladder
IV	A	Metastatic urachal cancer to lymph nodes
	B	Metastatic urachal cancer to distant sites

Sheldon first described a staging system in 1984 (Table1) and it remains the most reported classification, although was never officially validated. Ashley et al from the Mayo Clinic described a second system based on 66 patients (Table 2). They found the Sheldon staging system to be more complex and overspecified with its eight categories, four of which were occupied by ≤2 patients,[10] while the Mayo system was found to be more balanced in terms of patient distribution. Regardless, both systems predicted cancer-specific mortality equally well, as shown in Table 3.[10]

In a more recent publication, a second team from the Mayo Clinic chose to adapt the more universal TNM staging system to urachal cancer (Table 4).

Consensus statement: The group favors the use of the modified TNM staging system. However, all three staging systems give relevant information of prognostic utility and should be obtained for every patient, when feasible *(Level of evidence 4, Grade C).*

Diagnosis

Diagnostic criteria

The criteria for diagnosis of urachal carcinoma most agreed upon are those described by Sheldon et al[23] and Mostofi et al.[24] These include: 1) tumor in the dome of the bladder; 2) absence of cystitis cystica and cystitis glandularis; 3) predominant invasion of the muscularis or deeper tissues with a sharp demarcation between the tumor and surface bladder urothelium, which is free of glandular or polypoid proliferation; 4) presence of urachal remnants within the tumor; 5) extension of tumor into the bladder wall with involvement of the space of Retzius, anterior abdominal wall, or umbilicus; and 5) no evidence of a primary neoplasm elsewhere.[17] In 2016, Paner et al published an update in the pathological diagnosis and classification of epithelial neoplasms of urachal origin.[15] They found the original criteria above too restrictive and proposed modified criteria. Indeed, urachal remnants were reported in only 15–62.5% of cases.[17] Cystitis cystica and cystitis glandularis were identified focally in 17–21% of cases and while the majority of urachal tumors were situated at the dome, 4% of the cases could be in the anterior wall.[17,25]

Table 2. Mayo staging system of urachal cancer

Stage	
I	Tumor confined to urachus and/or bladder
II	Tumor extending beyond the muscular layer of urachus and/or bladder
III	Tumor infiltrating the regional lymph node
IV	Tumor infiltrating non-regional lymph nodes or distant sites

Table 3. Cancer-specific survival in patients with urachal carcinoma as per Sheldon and Mayo clinical staging system

Stage	5-year cancer-specific survival	10-year cancer-specific survival
I	63%	57%
II	55%	46%
III	19%	0%
IV	8%	0%

Based on proposals from Paner et al, the group supports use of the following modified criteria: 1) location of the tumor in the dome or anterior wall; 2) epicenter of the tumor in the bladder wall; 3) absence of widespread adenomatous changes and widespread cystitis cystica/cystitis glandularis

Table 4. Modified TNM staging system of urachal cancer by Mayo Clinic

T stage	
Tis	Tumor localized to the urachal mucosa with no invasion to the basal membrane (carcinoma in situ)
T1	Tumor with invasion through the basal membrane
T2a	Tumor invades deep muscle (outer half)
T2b	Tumor invades the superficial muscle of the bladder (inner half)
T3	Tumor invades perivesical fat, abdominal wall muscle (in cases of extravesical urachal tumors)
N stage	
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes
M stage	
M0	No distant metastasis
M1	Distant metastasis

in the bladder wall; 4) absence of urothelial neoplasia in the bladder; and 5) absence of a known primary elsewhere.

Prognostic factors

The five prognostic factors more frequently described and most validated include: stage of the disease, presence of positive margins after surgery, pathological tumor grade, presence of positive lymph nodes, and type of surgery. The latter refers to complete en bloc resection of the urachus and the umbilical cord vs. an incomplete resection.

Several studies have shown that the presence of an advanced stage is associated with a poor prognosis.[13,14] Using the TNM staging system reported above, Molina and al from Mayo Clinic showed that median survival is more than 10 years for stage I and 7.5 years for stage II. It then decreases significantly to 1–2 years and less than one year for stages III and IV, respectively.[12]

Second, the ability to achieve negative margins has a strong impact on survival. In the study by Ashley et al, presence of positive margins was associated with a hazard ratio of cancer-specific mortality of 3.8 (p<0,001).[10]

Third, tumor grade remains one of the most important prognostic factors in multivariate analysis. In the study by Pinthus et al, patients with a well-differentiated operated primary tumor had up to 90% long-term disease-specific survival compared to patients with poorly differentiated tumors who all died.[9]

Fourth, the additional finding of lymph node metastasis, occult or not, has been associated with adverse prognosis on multivariate analysis in different series. Again, in the study by Ashley et al, presence of lymph node metastasis was associated with a hazard ratio of cancer-specific mortality of 5.1 (p<0.001).[10]

Consensus statement: The five main prognostic factors in urachal cancers that should be evaluated for every patient include: stage of the disease, surgical margin status, pathological tumor grade, presence of positive lymph nodes, and type of surgery *(Level of evidence 4, Grade C)*.

Treatment

Surgery

The recommended treatment for localized urachal cancer is en bloc surgical removal of the umbilicus with the urachal ligament and partial cystectomy. This intervention is associated with the highest median survival when compared to cystectomy without umbilectomy.[12,26,27] Herr et al reported the survival of 50 patients operated in their institution for urachal carcinoma. They found that en bloc resection of the urachal tumor and urachus combined with partial cystectomy cured 70% of the patients with clinically localized urachal cancer.[11] In another series, although en bloc resection was not statistically associated with survival (p=0.09), 13 of the 16 long-term survivors after resection were in the group treated with en bloc resection and umbilectomy.[26]

The large meta-analysis included the surgical treatment for 957 patients[4]: 66% had partial cystectomy while 12% underwent radical cystectomy. In 67% of the patients, umbilectomy was performed. These data suggest that en bloc surgical removal of the umbilicus with the urachal ligament concurrently to partial cystectomy is commonly performed and may be associated with better outcome based on retrospective series.[4]

As for extensive pelvic lymphadenectomy, it does not seem to improve survival over that of the aforementioned surgery and seems to be associated with more complications, as reported in the majority of the literature.[14] Only 38% patients in the meta-analysis had lymphadenectomy and 17% of these cases had positive lymph nodes. In the SEER database, lymphadenectomy seems to be associated with radical cystectomy as 8%, 44.1%, and 78% of patients who underwent local excision, partial, and radical cystectomy, respectively, had documented lymph node removal. In total, only 13.4% had positive lymph nodes.[3] Although pelvic lymphadenectomy is advocated in patients with urachal cancers, its therapeutic role, as well as the template of dissection, needs to be further defined and studied.

Finally, there is no apparent survival advantage associated with complete cystectomy vs. partial cystectomy.[27] According to Siefker-Radtke et al, complete cystectomy with en bloc resection of the urachal ligament and umbilicus should be considered only if necessary to obtain negative margins or if partial cystectomy would result in inadequate bladder capacity and function.[21]

Consensus statements:

- **En bloc surgical removal of the umbilicus, urachal ligament, and partial cystectomy with pelvic lymphadenectomy is the preferred intervention. Radical cystectomy with en bloc resection of the urachal ligament and umbilicus should be considered in selected cases when negative bladder surgical margins is not possible with a partial cystectomy** *(Level of evidence 4, Grade C)*.
- **In patients with a positive margin and/or incomplete surgical procedure, consideration should be given to second-look surgery** *(Level of evidence 5, Expert opinion)*.
- **In the case of oligometastatic disease or localised recurrence, surgical resection can be discussed on a case-by-case basis** *(Level of evidence 5, Expert opinion)*.

Radiotherapy

Urachal tumors are not particularly radiosensitive and radiotherapy is rarely used. In the SEER database, only 10% of patients (total 414 patients) received radiotherapy, 29 in combination with surgery (13 stage IV, 10 stage III, and five stage II disease) and 13 as monotherapy (of which 11 were stage IV).[3] It is sometimes used postoperatively for positive margins or for localized inoperable disease, but without any strong evidence to suggest improved curability.[21]

Consensus statement: Surgery should be the preferred modality in localized disease. When patients are considered unfit for surgery, radiotherapy can be considered, but the benefits are unclear. Radiation therapy can be considered for postoperative positive margins, especially if second-look surgery is not deemed feasible. Palliative radiation can be considered for incurable disease *(Level of evidence 5, Expert opinion)*.

Chemotherapy

No recommendations exist with respect to the use and type of chemotherapy in the perioperative setting (neoadjuvant or adjuvant).

However, there are some case reports of patients who have received postoperative chemotherapy due to positive margins, lymph node or peritoneal involvement, or unresected umbilicus and a high likelihood of relapse.[21]

In advanced disease, it is difficult to draw any conclusions regarding the best chemotherapy regimen from published series, as types of treatment used are heterogeneous and the number of patients small. There is certainly a medical need to determine the optimal and more effective treatments, as five-year overall survival for metastatic disease is less than 20%. Despite this, the main drug used is cisplatin alone or in combination, such as cisplatin-methotrexate-vinblastine (CMV), methotrexate-vinblastine-doxorubicin-cyclophosphamide (MVAC), cisplatin-5-FU-gemcitabine, or others. Additional reported drugs include paclitaxel, cisplatin, and ifosfamide.[5,21,28] Because of a certain resemblance to colonic cancer in terms of immunohistochemistry, elevation of CEA and production of mucin by the tumor, regimens described in recent published case reports are derived from those often offered in gastrointestinal cancers —FOLFOX and FOLFIRI.[29,30]

In the large meta-analysis, the authors compared the efficacy of cisplatin-based, 5-FU-based, 5-FU+cisplatin combination and other chemotherapies. A total of 74 patients were analyzed. The response rate was higher in the 5-FU and the 5-FU+cisplatin groups (44% and 43%, respectively) in contrast to the non-5-FU group having a lower response rate (9%). The combination of 5-FU+cisplatin also had the lowest progression rate and, thus, seems to be have the best outcomes in this report. In this paper, regimens using these two drugs included: 5-FU+leucovorin, gemcitabine, cisplatin; 5-FU+IFN-a, cisplatin; 5-FU+oxaliplatin; and 5-FU+cisplatin.[4]

Other case series are available and presented in Table 5. They all include a smaller number of patients due to this diagnosis rarity. Hong et al recently reported a retrospective study of 21 patients with non-transitional cell bladder carcinoma including four urachal cancer patients. The overall response rate was 33% and the median survival 13 months. Within the study, 11 patients received gemcitabine-cisplatin, six 5-FU-cisplatin, one paclitaxel-cisplatin, one MVAC, one CMV, and one VIP (etoposide-ifosfamide-cisplatin).[31]

In another prospective study by Galsky et al, 20 patients, including six urachal cancer patients, received ifosfamide, paclitaxel, and cisplatin. Overall, 35% achieved major response and the median survival time of patients with adenocarcinoma was 24.8 months.[32]

Finally, another major series by Siefker-Radtke et al reported a 33% overall response rate when using a platinum-based

Table 5. Chemotherapy regimens and response to chemotherapy in urachal carcinoma patients

Authors	N (total)	Number of urachus adenocarcinoma only	Regimens	Response rate (%)	Mean survival time (months)
Jung et al (2014)[28]	10	10	24 different regiments. Most common: 5-FU, gemcitabine, and taxane-based	16.7	Unknown
Hong et al (2009)[31]	21	5	GP†; FP; TP; MVAC; CMV; VIP. TC‡; EP; BOMP; VI; paclitaxel	29§/9¶	13
Galsky et al (2007)[32]	20	6	Ifosfamide, paclitaxel, and cisplatin	35	24.8 (adeno)/8.9 (no-adeno)
Molina et al (2007)[12]	10	10	5-FU, FP 5-FU, lomustine+vincristine; TP; platinum and etoposide, MVAC	56	20.4
Siefker-Radtke et al (2003)[26]	20	20	Emory††, 5-FU, α-interferon, cisplatin, MVAC, paclitaxel-based‡‡, ifosfamide-based§§	33	20

†First-line chemotherapy regimen. ‡Second-line or third-line chemotherapy regimen. §Response rate of first-line chemotherapy. ¶Response rate of second-line chemotherapy. ††5-FU, leucovorin + gemcitabine + cisplatin. ‡‡Paclitaxel + carboplatin, paclitaxel + cisplatin, paclitaxel+ methotrexate + cisplatin, and paclitaxel alone. §§Ifosfamide, cisplatin + gemcitabine, 5-FU, 5-fluorouracil. Adeno: adenocarcinoma; BOMP: bleomycin + vincristine + mitomycin + cisplatin; CMV: methotrexate + vinblastine + cisplatin; EP: etoposide + cisplatin; FP: 5-FU + cisplatin; GP: gemcitabine + cisplatin; MVAC: methotrexate + vinblastine + doxorubicin + cisplatin; no-adeno: non-adenocarcinoma; TC: paclitaxel + carboplatin; TP: paclitaxel + cisplatin; VI: VP-16 + ifosfamide; VIP: VP-16 + ifosfamide + cisplatin.

regimen. Of the 20 patients who received chemotherapy, four partial or complete responses were observed, including three following a protocol based on 5-FU and cisplatin.[26]

The latest publication is by Jung et al and demonstrates the heterogeneity of treatments with 10 urachal cancer patients receiving a total of 24 different schemes of palliative chemotherapy. Regimens with a base of 5-FU, taxane, and gemcitabine were the most common and the overall response rate of all chemotherapeutic regimens was 16.7%.[28]

Targeted therapy

Because of the similarity previously described between urachal and colorectal cancer, the use of epidermal growth factor receptor (EGFR) inhibitors as in colorectal cancer would theoretically be feasible. On this subject, very little but nonetheless interesting data is available. In a phase 1 study of gefitinib published in 2005, one patient with urachal cancer was included and had a transient 55% decrease in tumor size.[33] Recently, Collazo-Lorduy et al published a report with a patient with metastatic urachal cancer in whom targeted exome sequencing revealed EGFR amplification and wild-type KRAS.[34] The patient was treated with cetuximab as a single agent, providing him with a response lasting more than eight months. Subsequently, targeted exome sequencing was performed on nine other specimens finding mitogen-activated-protein-kinase (MAPK) pathway mutations in four of nine cases, but no EGFR amplification. Moreover, two cases harbored APC mutations. To conclude, EGFR inhibitor therapy is certainly of interest in these cases, however, further evaluations of the genetic features of this disease are warranted and may lead to more rational targeted approaches in the future.

Immunotherapy

Immunotherapy changed the paradigm of treatment of many cancers in the last few years. Unfortunately, to our knowledge, there are no cases of urachal cancer treated with checkpoint inhibitors that have been published so far. However, it was recently shown that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with anti-PD1 therapy.[35] Interestingly, Sirintrapun et al evaluated microsatellite instability (MSI) in seven cases with urachal cancer.[19] Three cases showed MSI, one with MSH2 and MSH6 and two with PMS2 loss. Further evaluation of a larger cohort is certainly desirable to explore possibility of treatment with immune compounds.

Consensus statements:

- **The benefit of adjuvant chemotherapy is unknown at this time and is not recommended on a routine basis. The optimal regimen in this setting has not been defined.**
- **In the absence of high-level evidence, we suggest FOLFOX as the preferred regimen. The chemotherapy regimen can be tailored to immunohistopathological findings, especially if urothelial carcinoma features on histology is present** *(Level of evidence 4, Grade C).*
- **Given the rarity of this tumor, patients with this diagnosis should be discussed at a multidisciplinary forum and every effort should be made for the patient to be seen or discussed in collaboration with specialists who have some experience with this cancer. Ideally, a molecular profile should be obtained to identify potentially biological pathways and actionable targets to guide treatment. Finally, participation in clinical trials, where possible, is encouraged.**

Conclusions

Urachal cancer is a rare entity with a poor prognosis when presenting with advanced stage. Collaborative efforts are warranted in order to improve patient outcomes and formalize treatment modalities. Examples include the establishment of a national or international clinical database and standardization of treatment approaches in reference cancer institutions. Better knowledge of this tumor's molecular features may also improve pathological definition and define targeted approaches for this advanced disease

Competing interests: Dr. North has been an advisory board member for Astellas; has received grants/honoraria from Astellas, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Janssen, and Sanofi. Dr. Canil has been an advisory board member for AstraZeneca, Bayer, BMS, Eisai, Janssen, Merck, Novartis, and Pfizer; has received travel grants from Amgen and Sanofi; has received consulting honoraria from Janssen; and has participated in clinical trials supported by Astellas, AstraZeneca, Eisai, Janssen, and Roche. Dr. Wood has been an advisory board member (with no compensation) for Astellas, Pfizer, and Novartis; and has participated in clinical trials supported by Aragon, AstraZeneca, BMS, Exelixis, Merck, Pfizer, and Roche. Dr. Hotte has been an advisory board member for AstraZeneca, BMS, Merck, and Pfizer; and has participated in clinical trials supported by AstraZeneca, BMS, Merck, and Takeda. Dr. Sridhar has attended advisory boards for Astellas; has received grants/honoraria from Astellas, Janssen, and Sanofi; and has participated in clinical trials for Agenisys, Imclone, OGX, Roche, and Sanofi Aventis. Dr. Soulières has been an advisory board member for Novartis and Pfizer; and has participated in clinical trials supported by Merck and Pfizer. Dr. Latour received a grant for a PD1 study in urothelial carcinoma from Roche. Dr. Taussky has received honoraria from Bayer and Sanofi. Dr. Kassouf has received grants/honoraria from Amgen, Astellas, and Janssen. Dr. Blais has received consultancy fees from AstraZeneca, Bayer, BI, BMS, Merck, Novartis, Pfizer, Roche, Sanofi, and Servier. Dr. Hamilou reports no competing personal or financial interests related to this work.

This work was funded by the Urachal Cancer Research Fund.

This paper has been peer-reviewed.

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