

Urachal adenocarcinoma. Analysis of 8 years in a third level medical facility

Adenocarcinoma de uraco. Análisis de 8 años en un centro hospitalario de tercer nivel de atención

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Abstract

Background: Urachal cancer is one of the rarest and aggressive malignant diseases of the bladder; its incidence was 0.2% of all bladder cancers in 2012. It occurs in advanced stages, among stage IV tumors 58% die at 22 months. It is originated from urachal, an embryological structure that is present in 32% of the adult population. **Objective:** To present a case series of urachal cancer in a third level medical facility. **Method:** Case series. Clinical data from patients with urachal cancer during 2011 to 2019 were analyzed. The variables included were age, gender, smoking, clinical stage, treatment, and evolution. Descriptive statistics, measures of central tendency and dispersion were used. **Results:** There were seven patients; three men and four women; the mean age was 54.4 years. The most frequent histological type was mucinous adenocarcinoma. Partial cystectomy was performed with bilateral pelvic lymphadenectomy in three (42.8%) patients, radical cystectomy plus bilateral pelvic lymphadenectomy in the remaining four (57.2% patients). **Conclusions:** Urachal cancer is rare, clinical manifestations occur late. Hematuria is the most frequent clinical sign. The medium term prognosis is bad.

Key words: Urachal carcinoma. Cystectomy. Lymphadenectomy. Chemotherapy. Radiotherapy.

Resumen

Antecedentes: El cáncer de uraco es una de las enfermedades malignas de la vejiga más raras y agresivas. Su incidencia en 2012 era del 0.2% de todos los cánceres de vejiga. Se presenta en estadios avanzados, con una mortalidad del 58% a 22 meses para el estadio IV. Se origina a partir del uraco, una estructura embriológica que está presente en el 32% de la población adulta. **Objetivo:** Presentar las características clínicas de una serie de casos de cáncer de uraco en una unidad de tercer nivel de atención médica. **Método:** Serie de casos. Se analizaron los resultados clínicos obtenidos de pacientes con cáncer de uraco de 2011 a 2019. Las variables incluidas fueron edad, sexo, tabaquismo, estadio clínico, tratamiento y evolución. Se utilizó estadística descriptiva, con medidas de tendencia central y dispersión. **Resultados:** Fueron siete pacientes, tres hombres y cuatro mujeres, con una edad media de 54.4 años. El tipo histológico más frecuente fue adenocarcinoma tipo mucinoso. Se realizó cistectomía parcial con linfadenectomía pélvica bilateral a tres pacientes (42.8%), y cistectomía radical más linfadenectomía pélvica bilateral en los otros cuatro (57.2%). **Conclusiones:** El cáncer de uraco es una

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enfermedad rara. Sus manifestaciones son tardías y el signo clínico principal es la hematuria. El pronóstico es malo a mediano plazo.

Palabras clave: Carcinoma de uraco. Cistectomía. Linfadenectomía. Quimioterapia. Radioterapia.

Introduction

Bladder cancer is the seventh most frequently diagnosed cancer in the male population from all over the world. Its incidence is 9.0% for men and 2.2% for women, and mortality is 3.2% for men and 0.9% for women^{1,2}.

Urachal cancer is one of the rarest bladder cancers³; it accounts for 0.01% of all malignant tumors, 0.7% of bladder cancers and 35% of bladder adenocarcinomas. Since its presentation is generally at advanced stages, its prognosis is poor in the short term^{3,4}. It arises in the urachus, a structure that originates from the allantois and that runs from the bladder dome to the umbilicus, present during embryonic development, which involutes from the third trimester of gestation on, but that can persist in 32% of adult population⁵⁻⁷. It consists of three histological layers: smooth muscle outer layer, submucosal connective tissue intermediate layer and luminal-type internal layer. Of the above, the epithelial cells that make up each layer give rise to urachal carcinoma⁸. Among urachal carcinomas, 90% are adenocarcinomas^{9,10}, are predominant in males at a 5:1 ratio, and usually appear between the fifth and sixth decades of life. Their characteristic localization is on the bladder dome^{10,11}.

Prognosis depends on the clinical stage at which it is found at the time of diagnosis; when the tumor is limited to the urachus and bladder (stages I and II), 10-year overall survival is 95%, and for metastatic disease, overall survival is less than one year. These data make for urachal cancer treatment to have to be aggressive⁹⁻¹².

The purpose of this research work is to inform about the form of presentation, treatment and evolution of urachal cancer in a tertiary care hospital.

Method

Case series. Medical records of patients with urachal cancer were reviewed for the 2011-2019 period. Patients with histopathology-confirmed urachal cancer, of both genders and of all ages, were included. The variables that were considered were gender, age at diagnosis, tobacco consumption, clinical symptoms,

histological and immunohistochemical results, initial surgical treatment in addition to adjuvant treatment, overall survival and recurrence.

Regarding tobacco use, medical records only reported whether patients smoked or not. The Sheldon System was used for clinical classification (Table 1), and Anderson Cancer Center Medical Diagnostic Criteria (Table 2) were used for diagnosis. The statistics that were used were descriptive, with measures of central tendency and dispersion for ordinal variables, and frequencies and percentages for nominal variables, on SPSS v. 23 statistical program for Windows. This work meets the ethical criteria in matters of research: value, it has scientific and clinical importance; scientific validity, it is original, suitable and feasible; the researchers have experience in the topic; equitable selection of subjects, all met the selection criteria; favorable risk-benefit ratio; independent evaluation; there is no conflict of interests or funding for the performance of the work; no informed consent letter was required because it is a record-review study; and regarding the enrolled subjects, their autonomy and anonymity are respected. The protocol was duly registered before the research committee of the participating medical unit.

Results

There were seven patients with urachal cancer in the study period. Mean age was 54.42 years, with a minimum of 35 and a maximum of 70, and a standard deviation of 13.15 years. Among them, 4 (57.2%) were women and 3 (42.8%) were men; 4 (57.2%) were smokers and 3 (42.8%) were non-smokers. The predominant symptom was hematuria in all cases, followed by mucinuria in 5 (71.4%), and pain and umbilical tumor in 3 (42.8%).

According to Sheldon's classification, one patient (14.3%) was at stage II; 4 (57.2%), at IIIA; one (14.3%), at IIIB; and one (14.3%), at IV. As for histological type, all patients had adenocarcinomas, out of which 4 (57.2%) were of the mucinous subtype, and the remaining 3 (42.8%), of the non-mucinous type. All patients tested positive for cytokeratin 7 and cytokeratin

Table 1. Sheldon classification system

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- Stage I: urachal cancer confined to urachal mucosa.
 - Stage II: invasion confined to the urachus.
 - Stage IIIA: urachal cancer with local extension to the bladder.
 - Stage IIIB: urachal cancer with extension to the abdominal wall.
 - Stage IIIC: urachal cancer with extension to the peritoneum.
 - Stage IIID: urachal cancer with extension to a viscera other than the bladder.
 - Stage IVA: metastasis to lymph nodes.
 - Stage IVB: distant metastasis.
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Table 2. M.D. Anderson Cancer Center criteria for the diagnosis of urachal cancer¹⁴

Main criteria:

Location in the bladder dome or elsewhere in the midline of the bladder

Sharp demarcation between tumor and normal surface epithelium

Supportive criteria:

Enteric type histology

Absence of urothelial dysplasia

20 (Table 3), and 2 (28.6%), for carcinoembryonic antigen. Urachal adenocarcinoma histopathological results are shown in figures 1 and 2.

All seven patients underwent surgical treatment: 3 (42.8%), partial cystectomy with omphalectomy and bilateral pelvic lymphadenectomy, and 4 (57.2%), radical cystectomy with omphalectomy and bilateral pelvic lymphadenectomy.

Adjuvant treatment was administered to six patients: 4 (66.6%) received chemotherapy, and 2, (33.4%) radiotherapy.

At the time of study closure (in 2019) there was recurrence of the disease in two patients (28.6%); in one (14.3%), it was on the liver at 5 years, and in the other, it was a local recurrence at 4 years from disease onset (Table 4).

An overall survival of 72 months is reported in two patients of this series, 64 months in one, 24 months in one, 6 months in one and 4 months in two (Fig. 3).

Discussion

Urachal cancer is a rare disease, and its prognosis is poor in the short term. There are currently less than 400 cases reported in English-language medical literature, most of which correspond to case reports and literature reviews^{2,11-13}.

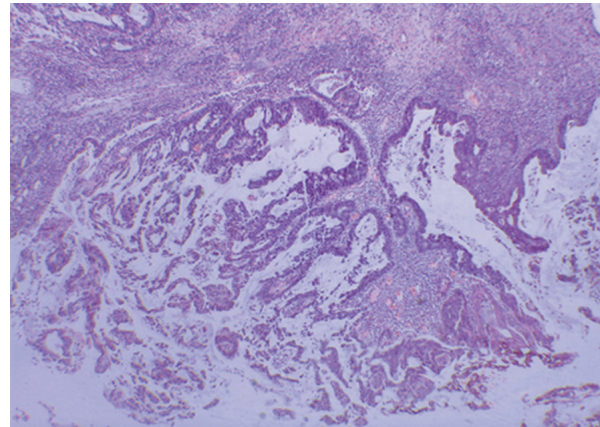


Figure 1. Urachal cancer well-differentiated cells with glandular proliferation (10x).

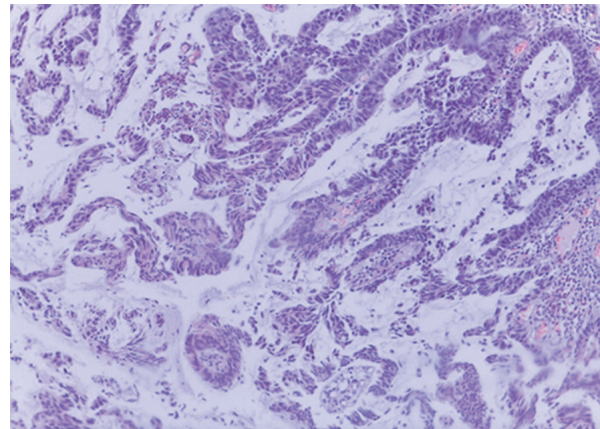


Figure 2. Glandular proliferation with well-differentiated cells (10x).

Age at presentation in this series was in the sixth decade of life (54.42 years), which is consistent with the world literature, which reports that the age at presentation of these tumors is between the fifth and sixth decades of life^{2,3,10,14}. It occurs more frequently in men than in women, at a 5:1 ratio, and the incidence is 9.0% for men and 2.2% for women^{8,14-19}, which differs from the results of this study, in which predominance in women was found.

In the world literature, some authors report a relationship between tobacco use and the development of urachal cancer, while other authors affirm that smoking does not lead to its development^{9,11,18}. In this series, most patients who were smokers were men; however, the influence of tobacco use on patients could not be determined because they were only investigated with regard to whether they smoked or not, and the amount and time of tobacco use was not determined in any record.

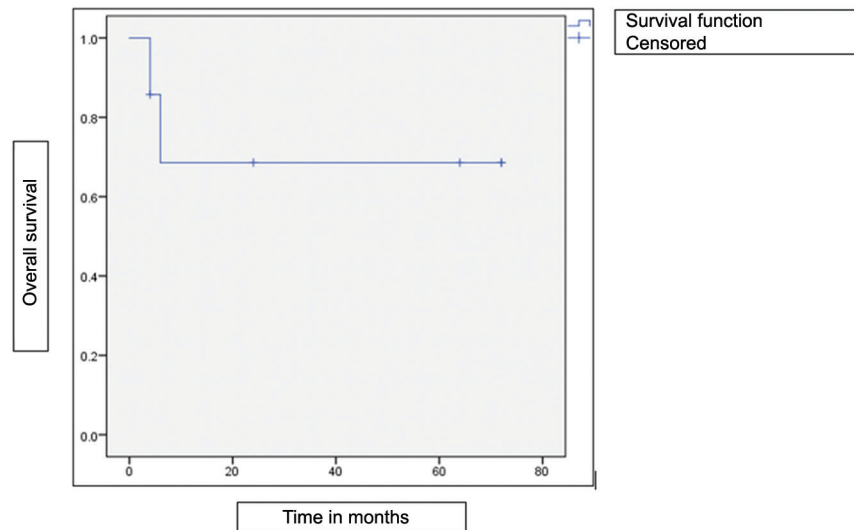


Figure 3. Overall survival of the population included in the study.

Table 3. Cases of urachal cancer

Case	Gender	Age	Smoking	Symptoms	Sheldon	Histology	CK7, CK20	CEA
1	W	43	-	Hematuria, mucinuria, dysuria, pain, tumor	IIIA	Mucinous	+	-
2	W	60	+	Hematuria, mucinuria		Non-mucinous	+	-
3	W	48	-	Hematuria, dysuria, pain, tumor		Non-mucinous	+	+
4	M	56	+	Hematuria, mucinuria		Mucinous	+	-
5	M	35	+	Hematuria, dysuria, pain, tumor		Mucinous with signet ring cells	+	-
6	M	69	+	Hematuria, mucinuria, dysuria		Non-mucinous	+	-
7	W	70	-	Hematuria, mucinuria		Mucinous	+	-

CEA: carcinoembryonic antigen; CK: cytokeratin.

Table 4. Treatment and evolution of included patients

Surgery	Ct	Rt	Recurrence	Survival
PC + BPL	Yes	No	Liver	72 months
PC + BPL	No	No	No	72 months
PC + BPL	No	Yes	Local	64 months
RC + BPL	Yes	No	No	4 months*
RC + BPL	Yes	No	No	6 months*
RC + BPL	No	Yes	No	24 months
RC + BPL	Yes	No	No	4 months

BPL: bilateral pelvic lymphadenectomy; Ct: chemotherapy; PC: partial cystectomy; RC: radical cystectomy; Rt: radiotherapy.

*Deceased patient.

As for urachal cancer clinical presentation, the symptoms are, in order of frequency, gross hematuria (73%), poorly localized abdominal pain (14%),

intermittent dysuria (13%), mucosuria (10%), lower urinary tract irritative symptoms (40%), palpable tumor at lower abdomen (17%), bacteriuria (8%) and mucous or bloody umbilical discharge (2%)^{13,17}. In our patients, symptom presentation was similar: gross hematuria in 100%, hypogastric pain of moderate intensity in 42.8%, mucosuria in 71.5%, umbilical tumor in 42.8% and mucous-bloody fluid discharge from umbilical scar in 28.6%. However, given that symptoms occur at late stages, this is a disease of late diagnosis and poor prognosis.

In addition to M.D. Anderson Cancer Center criteria (Table 2), for urachal cancer diagnosis we used cystoscopy with biopsy of the bladder tumor as an essential diagnostic procedure, which provides us with an orientation for clinical staging due to the possibility for the lesion to be located inside the bladder^{18,19}.

Computed tomography is the most important imaging test for urachal carcinoma diagnosis, given that it is also used for clinical staging of the disease and provides an image on local extent and lymph node status and possible distant spread. One of the signs regarded as pathognomonic of urachal cancer is the presence of tumor activity on the midline of the bladder and peripheral calcifications on the tumor^{14,18}. All patients were evaluated with computed tomography.

At the time of diagnosis, patients were at advanced stages, 71.4% at Sheldon stage III and 14.2% at stage IV, which is consistent with the literature and is due to the fact that the disease is asymptomatic at initial stages. Only 14.28% of patients were at Sheldon stage II.

As for histological classification, urachal adenocarcinoma is divided into five subtypes: intestinal, mucinous, signet ring cell, mixed and non-specific^{11,13}. In this study, all patients had tumors of the adenocarcinoma type and, as regards subtype, the most common was mucinous, with 57.2%, followed by non-mucinous with 42.8%^{3,6,11,13}.

In the consulted literature, immunohistochemistry for cytokeratin 7 and 20 was positive in 60% of urachal adenocarcinoma cases. Immunohistochemistry negativity for cytokeratin 7 favors the development of colonic cancer in these patients^{4,20,21}. In this study, immunohistochemistry results were positive for cytokeratin 7 and 20 in all patients. In addition, carcinoembryonic antigen was positive in 28.6% of patients.

Standard treatment for non-metastatic urachal cancer is surgical and is based on clinical stage at diagnosis; it can be partial or radical cystectomy, plus omphalectomy and bilateral pelvic lymphadenectomy, taking into account that radical prostatectomy must be carried out in men^{4,9,10,15}. In this series, 42.8% of patients underwent partial cystectomy, and 57.2%, radical, plus omphalectomy-bilateral pelvic lymphadenectomy, with radical prostatectomy in the case of men (Table 3).

Currently, the role of chemotherapy and adjuvant radiotherapy is not entirely clear, but there are studies that demonstrate response in some cases¹².

Adjuvant treatment with chemotherapy is based on regimens consisting of cisplatin + paclitaxel + ifosfamide, 5-fluorouracil + doxorubicin, methotrexate + 5-fluorouracil + epirubicin + cisplatin, irinotecan, and paclitaxel + methotrexate + cisplatin. However, the effectiveness of a standard regimen in the treatment of urachal carcinoma has not been demonstrated; there are only sparse reports of cases with response to chemotherapy regimens. Studies are currently being carried out to assess the use of neoadjuvant

and adjuvant chemotherapy in the treatment of urachal cancer in order to have better treatment strategies and more favorable results for this disease^{19,22,23}.

Treatment with adjuvant chemotherapy was started with a cisplatin plus gemcitabine regimen in 4 patients (57.2%), and in 2 (28.6%), radiotherapy with 30 Gy, divided in 10 fractions.

As for prognosis, when the disease is diagnosed confined to the urachus and bladder, survival is higher than 10 years, but for metastatic disease it is lower than one year¹¹.

Recurrence of the disease was documented in 28.6% of patients; in 14.3%, it was in the liver, and in the other 14.3%, it was local recurrence at 5 and 4 years.

In conclusion, urachal cancer is a rare, indolent disease that manifests itself late, the main clinical sign of which is hematuria and that has a poor prognosis in the medium term. At the time of study closure it is not possible to determine 10-year mortality in this group of patients because some do not complete the follow-up time.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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