ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 34 (2016) 388–398

UROLOGIC ONCOLOGY

Review article

Clinical, prognostic, and therapeutic aspects of urachal carcinoma—A comprehensive review with meta-analysis of 1,010 cases

Tibor Szarvas, Ph.D.[a,b,1,*], Orsolya Módos, M.D.[a,1], Christian Niedworok, M.D.[b], Henning Reis, M.D.[c], Attila Szendröi, M.D.[a], Marcell A. Szász, M.D.[d], Péter Nyirády, M.D.[a]

[a] *Department of Urology, Semmelweis University, Budapest, Hungary*
[b] *Department of Urology, University of Duisburg-Essen, Essen, Germany*
[c] *Institute of Pathology, University of Duisburg-Essen, Essen, Germany*
[d] *2nd Department of Pathology, Semmelweis University, Budapest, Hungary*

Received 4 March 2016; received in revised form 22 April 2016; accepted 23 April 2016

Abstract

Background and objectives: Urachal carcinoma (UrC) is a rare and poorly investigated disease. Our current knowledge is mainly based on single-institutional studies. Despite growing interest in UrC, the included case numbers in recently published studies are still low. Therefore, we aimed to provide a comprehensive meta-analysis on the clinical, prognostic, and therapeutic aspects of UrC.

Methods: A systematic Medline/PubMed search was performed on UrC using the terms "urachal carcinoma," "urachal cancer," and "urachus." Original articles and reviews in English language with case numbers >10 were selected.

Results: The vast majority (91%, 489/532) of UrCs are diagnosed at later stages (Sheldon ≥III) when the tumor invades the urinary bladder. About 21% (136/646) of UrC patients have distant metastasis at first presentation. Although for patients with non–metastatic UrC surgical treatment provides an acceptable disease control, the systemic treatment of patients with progressed/metastatic UrC—in lack of prospective clinical trials—are less well established. Comparing cisplatin-based and 5-FU-based therapies in 74 published UrC cases, we found the latter to be superior in terms of radiographic response rates (9% vs. 44%, $P = 0.043$), but the combination of these 2 therapies provided the lowest progression rate (14%) with a similarly high response rate (43%).

Conclusions: Owing to the lack of evidence-based guidelines, the therapy of UrC remains challenging. Given the infrequency of UrC, large prospective studies comparing different systemic therapies can hardly be conducted. Our metadata indicates that 5-FU-containing chemotherapy regimens are more effective than cisplatin-based treatment modalities, whereas their combination seems to provide the strongest antitumor effect. Nevertheless, in the lack of evidences from prospective clinical trials, therapeutic decision-making necessarily remains on an individual basis. In this situation, targeted therapies may provide a reasonable alternative. Therefore, better understanding of the molecular background of UrC is needed to rationalize treatment decisions in UrC.

Keywords: Urachal carcinoma; Urachal cancer; Urachus; Prognosis; Therapy; Chemotherapy

1. Introduction

The urachus is a remnant of embryonic development, a tubular structure that connects the fetal bladder to the allantois. As the main excretory organ in fetus, the urachus removes the nitrogenous waste from the bladder. During the fourth and fifth month in embryonic life, the urachus gradually degenerates into a rudimentary fibromuscular closed canal, which is known in adults as the median umbilical ligament and stretching between the dome of urinary bladder and the umbilicus. Failure of complete urachal lumen closure may lead to various anomalies including malignant transformation. Autopsy studies suggested that in one-third of adults the urachus canal partly persists [1].

[1] Equally contributed.

[*] Correspondence address: Department of Urology, University of Duisburg-Essen, Hufelandstr 55, 45147 Essen, Germany. Tel.: +49-201-723-4547; fax: +49-201-723-4686.

E-mail address: sztibusz@gmail.com (T. Szarvas).

http://dx.doi.org/10.1016/j.urolonc.2016.04.012

Urachal carcinoma (UrC) was first described by Begg [2]. It is an extremely rare but highly malignant entity representing 0.35% to 0.70% of all bladder cancers [3–4]. The rarity of UrC has limited the available evidence to some single-institution studies with low case numbers, hardly providing enough power for statistical evaluation. However, in the last decade, the number of publications on UrC increased from an average of 3 (between 1980 and 2005) to ~10/year (between 2006 and 2015), the included case numbers remained low. In addition to single institutional studies, population-based analyses represent an alternative approach to achieve higher case numbers. However, such studies inherent of their registry-based, multicentric, retrospective nature cannot provide full details on clinical, histological, and therapeutic data. Therefore, for the most comprehensive evaluation of epidemiologic, prognostic, and therapeutic aspects of UrC, the combination of population-based and single-institutional studies applying a meta-analytic approach seems to be the most appropriate way to draw firm conclusions.

The aim of this review is to provide a timely and comprehensive overview on the clinical, prognostic, and therapeutic aspects of UrC. Therefore, we performed a systematic PubMed search using the following search terms: "urachal cancer" and "urachal carcinoma" resulting in the identification of 29 studies. Overall, 5 studies were excluded, 3 because of biased patient selection and other 2 because of non-English publication. The final selection left 24 studies with an overall number of 1,010 UrC patients. For comparative analysis of survival, studies with low statistical power (including less than 20 cases) were excluded. Studies applying characteristic patient selection (e.g., some studies with a focus on chemotherapy, included only patients who presented with metastasis) have been used only for those analyses they were conducted for.

2. Definition of UrC

To date, no consensus has been reached regarding the diagnostic criteria of UrC. Most scientists and clinicians apply the criteria proposed by Sheldon et al. [5] and Mostofi et al. [6] and revised by Gopalan et al. [3]. These include the following characteristics: (1) tumor is located in the dome/anterior wall of the bladder, (2) epicenter in the bladder wall, (3) absence of cystitis cystica and cystitis glandularis, and (4) lack of known primary adenocarcinoma (ADC) elsewhere. Herr et al. [7] suggested to use the location at the bladder dome as the only criteria for UrC. However, in a later study with a partly overlapping cohort, only 34% of dome-based tumors proved to be "real" UrCs [3]. Later, investigators at MD Anderson Cancer Center in Texas, developed a less restrictive approach for diagnosis suggesting to consider any enteric-type ADCs with sharp demarcation between tumor and surface epithelium in the bladder as UrC unless proven otherwise [8]. These criteria, however, are not applicable for the rarely occurring non-glandular type of UrC. To solve this problem, Paner et al. [9] proposed criteria for pathologic confirmation of non-glandular UrCs (see histology section).

3. Clinical parameters and diagnosis

Our summary including 1,010 patients shows that UrC is more frequent in men (59%, 604/1,010) than in women (41%, 406/1,010) [3,4,10–31].

Based on published data of 17 studies with patient numbers higher than 20, the median age was 52 years (range: 20–90 years (Table 1). In addition, some case reports described UrC in children and newborns (in ages of 12 years and 4 months) [32,33].

The most frequent symptom of UrC is macroscopic or microscopic hematuria reported in 73% (394/540) of patients followed by abdominal pain in 14% (54/396), dysuria in 13% (29/229), and mucosuria in 10% (35/353) (Table 1). Other less frequent clinical presentations included pollakisuria, pyuria, urinary tract infection, umbilical discharge (e.g., blood, urine, and mucus), vaginal discharge, and nonspecific symptoms (nausea, vomit, diarrhea, weight loss, or fever) (Table 1). In studies with at least 20 patients, the median tumor size (defined as the largest diameter) was found between 3.0 and 6.3 cm with a range of 0.8 to 12 cm.

In addition to medical history and physical examination, cystoscopy is the most important diagnostic tool for UrC. From the 276 UrC cases with available data on cystoscopy 245 proved to be positive (89%). In addition, cystoscopy is useful in specifying the localization of the tumor in the dome or anterior wall. The tumor may present as a broad-based ulcerative mass but—because of the intramural spreading—in early stages is often covered with normal mucosa. In these cases, pressing the suprapubic area can cause mucus eruption that uncovers the hidden tumor.

In addition, imaging methods are indispensable for diagnosis. Ultrasonography most frequently shows a supravesical, inhomogeneous and irregular mass in the midline. Like other mucinous ADCs, mucin-producing UrCs often contain calcification that can be detected by computed tomography (CT)-/magnetic resonance imaging-scan or ultrasonography [34]. Calcification at the bladder dome/midline is therefore considered to be pathognomic. However, our summary based on 142 published cases with available data on calcification, revealed only 45 cases (32%) to be positive, indicating that calcification with appropriate location is not a necessary finding in UrC. Additionally, CT and magnetic resonance imaging might provide information about the local extension and lymph node (LN) or distant metastasis. However, only half of the bladder wall invasions can be detected by CT, showing its limited value in estimating tumor invasion [17]. The combination of positron emission tomography with CT, however, was

Table 1
Patients characteristics and pretreatment findings

Studies (n = 24)	N	Men	Women	Men (%)	Median age (range)	Hematuria	Abd. pain	Palp.tu	Mucosuria	Dysuria	Calcif.	Cystoscopy pos.	Cytology pos.
Johnson et al. [4]	14	9	5	64	55 (38–76)								
Grignon et al. [25]	24	13	11	54	52 (X)	22/24			4/24				
Henly et al. [26]	38	28	10	74	57 (28–88)	30/38	8/38	1/38	6/38			34/38	6/12
Santucci et al. [30]	17	8	9	47	55 (25–77)								
Dandekar et al. [27]	21	9	12	43	x								
Siefker-Radtke et al. [23]	42	22	20	52	47 (23–76)								
Thali-Schwab et al [17].	25	13	12	52	48 (21–69)	13/22	3/22	1/22	2/22	1/22	18/25		
Asley et al. [10]	66	46	20	70	61 (57–64)	53/66	16/66	6/66	6/66	8/66	9/26	54/66	13/32
Pinthus et al. [20]	40	23	17	58	51 (x- 82)								
Wright et al. [28]	151	83	68	55	x								
Molina et al. [11]	49	33	16	67	58 (42–76)	42/49	4/49	8/49	8/49			45/53	
Chen et al. [13]	14	9	5	64	52 (24–75)	13/14	0/14	1/14	1/14	6/14	5/14	12/14	
Gopalan et al. [3]	24	15	9	63	52 (26–68)	17/24	0/24	1/24	1/24	1/24			
Bruins et al. [12]	152	88	64	58	58 (20–90)								
Yazawa et al. [15]	10	8	2	80	55 (31–70)	8/10						10/10	2/8
Meeks et al. [14]	65	42	23	65	51 (x)	49/65							7/34
Cho et al. [16]	17	13	4	76	46 (x)	12/17	1/17	1/17	1/17	1/17			
Kim et al. [21]	41	24	17	59	x	32/41	10/41	7/41		8/41	3/35	31/35	
Chen et al. [31]	17	10	7	59	50 (37–77)	14/17		2/17		1/17	7/15	16/17	1/5
Jung et al. [22]	28	19	9	68	46 (26–67)	18/28	3/28	3/28	0/28	3/28	3/27	15/19	0/16
Amin et al. [29]	55	23	32	42	49 (24–83)	6/25	3/25	8/25	3/25				
Niedworok et al. [24]	26	15	11	58	48 (32–73)	15/26	3/26						1/5
Dhillion et al. [18]	46	30	16	65	53 (28–82)	29/46	6/46		3/46				
Hayashi et al. [19]	28	21	7	75	52 (46–57)	21/28						28/28	
				604/1010		394/540	54/396	39/341	35/353	29/229	45/142	245/276	30/102
Sum	1010	604	406	59%	52 years	73%	14%	11%	10%	13%	32%	89%	29%

found to provide accurate information on staging before surgery [13].

Some serum markers have proven to be helpful in the diagnosis and monitoring of UrC. As UrC-ADC and colorectal ADC exhibits considerable histopathological similarities, carcinoembryonic antigen and carbohydrate antigen 19-9 as well as cancer antigen 125 serum levels have been detected to be increased in UrC-ADC [19,23]. Especially but not exclusively in the rare case of squamous cell UrC also squamous cell carcinoma-related antigen has been described as being helpful in disease monitoring [19,23].

Urinary cytology has no significant value in the detection of UrC, as only 29% (30/102) of published cases proved to be positive (Table 1). This is most probably related to the fact that UrC is primarily an extravesical cancer that arises in the muscle wall or outside of the bladder and grows inwards. Therefore, many diagnostic symptoms including hematuria and also positive urine cytology may occur first when the tumor has already invaded the intravesical cavity.

Generally, all urachal masses are recommended to be surgically removed to avoid UrC. However, in many cases urachal remnants contain no malignancy. To avoid overtreatment in these patients, Meeks et al. [14] assessed the preoperatively available variables such as preoperative biopsy (by transurethral resection), urine cytology and imaging. Although these variables provided excellent specificity and positive predictive values for the detection of UrC, their negative predicting value hardly reached 0.6, showing that 40% of UrCs would be missed if therapeutic decision would base on these parameters [14]. Therefore, to date, there are no reliable preoperative methods for the diagnosis of UrC.

4. Histopathology

The most common histological type of UrC is ADC. Several studies used glandular differentiation as a criterion for UrC, which in consequence virtually increase the rate of glandular UrCs to nonglandular UrCs. To avoid this misinterpretation, we considered only those studies that included also nonglandular UrCs for the calculation of the rate of glandular to nonglandular UrCs. By doing so, 90% (360/401) of all UrCs were found to be ADCs. In the literature, urachal ADCs referred to represent ~30% of all vesical ADCs [3,11,14]. However, the largest population-based study so far identified a much lower rate of UrC-ADCs among all vesical ADCs of 10% [28]. This latter data appears to be more realistic when considering the possible biases owing to overrepresentation of rare diseases in referral centers. In addition, diagnostic criteria for UrC are debated and some investigators consider all ADCs at the bladder dome as UrC that may also lead to an overrepresentation of UrCs among ADCs of the bladder [28].

In the literature, the most commonly encountered ADC pattern in UrC is the mucinous/colloid type followed by the ADC type not otherwise specified. Other rare patterns include the signet ring cell type, clear cell type, hepatoid type and mixed patterns [35]. However, it seems to be important to distinguish between different histomorphological patterns of UrC-ADC for (differential) diagnostic reasons, their clinical significance remains unclear. Even more important is to differentiate urachal ADCs from primary (nonurachal) ADCs of the bladder, as these 2 entities are treated differently. Muscle-invasive nonurachal ADCs are treated with radical cystectomy in contrast to UrC-ADCs that are usually treated with extended partial cystectomy.

5. Staging systems

Several types of stage classifications were suggested, but the most often used are the Sheldon and the Mayo staging systems (Table 2) [5]. Data on Sheldon staging were available in case of 532 UrC patients showing an uneven distribution of cases. Only 3 cases were staged as Sheldon I (0.6%), 40 were Stage II (8%), 363 Stage III (68%), and 126 stage IV (24%) [3,10,12,14,18–20,24,26,27,30,31] (Table 3). Overall, 6 studies classified a total number of

Table 2
Staging systems for UrC

Sheldon staging	
Stage I	Urachal cancer confined to urachal mucosa (no invasion beyond urachal mucosa)
Stage II	Urachal cancer with invasion confined to urachus itself
Stage IIIA	Local urachal cancer extension to bladder
Stage IIIB	Local urachal cancer extension to abdominal wall
Stage IIIC	Local urachal cancer extension to peritoneum
Stage IIID	Local urachal cancer extension to viscera other than bladder
Stage IVA	Metastasis to regional lymph node
Stage IVB	Metastatic urachal cancer to distant sites
Mayo staging	
Stage I	Tumor confined to urachus and/or bladder
Stage II	Tumor extending beyond the muscular layer of urachus and/or the bladder
Stage III	Tumor infiltrating the regional lymph node
Stage IV	Tumor infiltrating non-regional lymph nodes or other distant sites

Table 3
Pathological parameters

Studies (n = 24)	All patients	Adeno[a]	Nonadeno[a]	G1	G2	G3	Sheldon I	Sheldon II	Sheldon III	Sheldon IV	Mayo I	Mayo II	Mayo III	Mayo IV	R1	R0	N+[b]	M+
Johnson et al. [4]	14	14	0															
Grignon et al. [25]	24	24	0															
Henly et al. [26]	38	36	2				2		31	5								9
Santucci et al. [30]	17	14	0				0	1	14									2
Dandekar et al. [21]	21	21	0															
Siefker-Radtke et al. [23]	42	42	0				0		27	12					5	14	5	7
Thali-Schwab et al. [17]	25	25	0														2	8
Asley et al. [10]	66	61	5				0	5	42	19	28	19	6	13	18	39	10	13
Pinthus et al. [20]	40	25	15	12	11	11	1	5	22	0					12	7		
Wright et al. [28]	151	151	0															46
Molina et al. [11]	49	44	3															
Chen et al. [13]	14	13	1				0	1	10	3							0	3
Gopalan et al. [3]	24	24	0				0	2	20	2					1	23	1	1
Bruins et al. [12]	152	143	9	13	38	34	0	22	85	45					15	76	15	30
Yazawa et al. [15]	10	10	0														2	1
Meeks et al. [14]	65	62	0												7	52	8	
Cho et al. [16]	17	17	0	0	23	8					3	12	1	0	5	12	1	
Kim et al. [21]	41	38	3				0	0	33	8	18	14	4	5	4	21		
Chen et al. [31]	17	14	2				0	2	11	4					1	15	2	1
Jung et al. [22]	28	27	1	3	6	1					10	13	2	3				3
Amin et al. [29]	55	55	0															
Niedworok et al. [24]	26	26	0	5	12	9	0	0	18	6	8	9	1	6	5	17		7
Dhillion et al. [18]	46	46	0				0	0	27	19	6	21	1	18				
Hayashi et al. [19]	28	28	0				0	2	23	3								2
		360/401	41/401	33/186	90/186	63/186	3/532	40/532	363/532	126/532	73/221	88/221	15/221	45/221	73/349	276/349	41/239	136/646
Sum	1010	90%	10%	18%	48%	34%	0.6%	8%	68%	24%	33%	40%	7%	20%	21%	79%	17%	21%

[a] As several studies selected only glandular differentiated (adenocarcinomas of the urachus), we considered only those studies which cohorts included also nonglandular urachal carcinomas.
[b] LN positivity rate was calculated only in cases treated with lymph node dissection.

221 patients according to the Mayo staging system and found 73 UrCs to be stage I (33%), 88 stage II (40%), and 15 stage III (7%) whereas 45 were stage IV (20%) tumors [10,16,18,19,21,22,24] (Table 3).

Comparing the stage distribution of UrC cases by using the Sheldon and Mayo staging criteria, a characteristic difference can be observed. When using the Sheldon staging system, most patients are classified into stage III and far less patients into other stages. In contrast, Mayo staging system provides a more balanced distribution of UrC patients between stages and provides therefore a more applicable risk-stratification. In all, 4 independent studies with an overall number of 179 UrC patients compared the prognostic value of these 2 staging systems and consequently found that both systems are able to significantly predict patients' prognosis [18]. However, the Mayo staging was reported to be superior to Sheldon staging based on its simplicity and higher prognostic value in multivariable models [10,21].

The applicability of TNM classification for UrC is limited as it does not arise from the bladder surface urothelium. However, recently Dhillon et al. [18] suggested a prognostic relevance for the TNM classification also for UrC.

UrC is often referred as a cancer typically diagnosed in progressed tumor stages when LN or distant metastases are present in a considerable proportion of patients. By lymphatic dissemination UrC usually metastasizes into the pelvic LNs and by hematogenous dissemination into distant organs, especially lung, bone, or peritoneum [13]. The 24 summarized studies with reported status of distant metastasis at initial diagnosis included 646 patients and revealed 136 patients (21%) with primary metastatic disease (Table 3). As the pathological evaluation provides the most reliable detection of LN metastases, we calculated the occurrence of LN metastasis only in those cases when LN dissection (LND) was performed. Of the 239 reported patients, 41 (17%) had pathologically confirmed LN metastases. Interestingly, UrC patients with nodal involvement discovered at surgery had a similar poor prognosis (less than 20% survival at 5-years) as those with clinically apparent distant metastases [12,23]. This suggests that LND might be beneficial for UrC patients. In contrast to this assumption, studies reported so far found no survival benefit for those patients who underwent LND [10,12,24]. It is, however, important to note that—in the lack of randomization—decisions on the performance of LND were done on a rather subjective and individual basis, therefore these comparisons cannot be considered as reliable.

6. Survival

UrC is often referred as a highly malignant cancer with a devastating prognosis. However, Wright et al. [28] comparing the survival between urachal and nonurachal (primary) ADCs of the bladder found higher overall and cancer-specific survival rates for UrC patients. In addition, a recent study compared the cancer-specific survival rates between urachal and urothelial bladder cancer at progressed stages and found better survival for UrC [18]. Based on these, UrC seems to have a more favorable prognosis compared to both primary (nonurachal) ADC and urothelial carcinoma of the bladder.

The 5-year overall survival rates in the largest series were found to be ~50% [11,12,23,28]. Several parameters have been analyzed for their prognostic value including age, sex, Sheldon stage, Mayo stage, tumor grade, LN status, presence of distant metastasis, positive surgical margin, tumor size, presence of signet ring cell differentiation, mucin production, peritoneal involvement, performance of umbilectomy/LND/partial vs. radical cystectomy and Eastern Cooperative Oncology Group (ECOG) performance status (Table 4). Heterogeneity of the included parameters in multivariable models, different cut-off values for dichotomization of staging, grading or other continuous variables (such as tumor size and patients' age) as well as different study end-points (disease-specific vs. overall survival) makes a direct comparison between various studies difficult. A further obstacle is the low number of patients and at the same time a large number of tested variables resulting in over-fitted models. Therefore, we restricted our comparative analysis only to those studies including at least 25 patients. After this restriction, 10 studies comprising 620 UrC patients remained in the comparison [10,12,18–24,28].

In univariable analyses, patients' age and sex did not influence survival. Sheldon staging >IIIB or >IIIC rather than >IIIA was found to be significantly associated with poor patients' survival. Similarly, Mayo staging >II was consequently found to be associated with shorter survival. Furthermore, Mayo staging was found to be superior to Sheldon staging in the prediction of survival [10,21]. Tumor grading proved to be associated with prognosis in the univariable but not in multivariable models [10,12,20,22,23,28]. The presence of LN and distant metastases were consequently associated with poor prognosis [12,23,28]. Information on surgical margin status was available in 4 studies and was constantly identified as a significant risk factor, underlining the importance of the complete tumor resection [10,12,23,24]. However, the performance of radical cystectomy compared with partial cystectomy provided no survival benefit [10,24]. Tumor size and the presence of signet ring differentiation were controversially reported as prognostic factors [10,21,22], whereas mucinous tumor phenotype had no prognostic effect on survival [12,21]. ECOG performance status was tested in one study and was identified as an independent prognosticator for survival [22].

In multivariable analyses, Sheldon stage >IIIB, Mayo stage >II, presence of LN or distant metastases, positive surgical margin and ECOG performance status were

Table 4
Prognostic factors of UrC

		Bruins et al. [12]				Ashley et al. [10]				Kim et al. [21]				Jung et al. [22]				Niedworok et al. [24]		
	n	152				66				41				28				26		
	Median OS	45%				–				–				–				46%		
	Median DSS	–				45%				56%				–				–		
		UV		MV		UV		MV		UV		MV		UV		MV		UV		MV
		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)
	Age	N.A.	NS	–	–	1.2(0.6–2.4)	NS	–	–	1.0(0.9–2.8)	NS	–	–	N.A.	NS	–	–	0.5 (0.2–1.4)	NS	–
	Sex (female)	N.A.	NS	–	–	1.1(0.4–1.9)	NS	–	–	–	–	–	–	N.A.	NS	–	–	2.4 (0.9–8.9)	NS	–
Sheldon	> III A	N.A.	S	–	NS	–	–	–	–	–	–	–	–	–	–	–	–	4.3 (0.9–19.8)	NS	2.2 (0.5–11.2)S
	> III B	N.A.	S	5.1(2.5–10.3)	S	–	–	–	–	–	–	–	–	–	–	–	–	2.5 (0.8–8.1)	NS	–
	> III C	–	–	–	–	–	–	–	–	4.6(1.5–14.1)	S	3.4(0.9–12.7)	–	–	–	–	–	–	–	–
Mayo	< II	–	–	–	–	–	S	–	NS	11.9(3.8–37.4)	S	18.3(4.0–84.3)	S	N.A.	S	2.3(1.8–43.9)	S	–	–	–
Grade		N.A.	S	–	NS	3.6(1.7–7.7)	S	3.7(1.7–7.9)	S	–	–	–	–	N.A.	S	1.5(0.4–5.5)	NS	1.1 (0.4–3.2)	NS	–
LN+		N.A.	S	1.7(1.2–2.6)	S	1.5(0.7–2.8)	S	–	NS	–	–	–	–	–	–	–	–	–	–	–
M+		N.A.	S	5.3(2.8–9.9)	S	3.3(1.6–6.8)	S	–	NS	–	–	–	–	–	–	–	–	–	–	–
R+		N.A.	S	5.2(1.2–21.9)	S	4.7(2.2–9.8)	S	3.8(1.9–7.5)	S	–	–	–	–	–	–	–	–	6.1 (1.7–22.0)	S	4.7 (1.2–17.9)S
Size+		–	–	–	–	1.5(0.7–3.0)	NS	–	–	4.9(1.1–22.0)	S	6.6(1.3–33.1)	S	N.A.	NS	–	–	–	–	–
Signet ring		N.A.	S	–	NS	1.4(0.4–4.5)	NS	–	–	–	–	–	–	–	–	–	–	2.1(0.7–6.6)	NS	–
Mucinous		N.A.	NS	–	–	–	–	–	–	3.8(1.3–10.3)	S	2.7(0.9–8.6)	NS	–	–	–	–	–	–	–
Part CE/radCE		–	–	–	–	2.1(0.9–4.5)	NS	–	–	–	–	–	–	–	–	–	–	–	–	–
Umilectomy/noUBE		–	–	–	–	3.0(1.3–6.8)	S	–	NS	–	–	–	–	–	–	–	–	1.3(0.4–4.4)	NS	–
no LND/LND		–	–	–	–	1.5(0.7–2.8)	S	–	NS	–	–	–	–	–	–	–	–	0.8(0.3–2.8)	NS	–
ECOG		–	–	–	–	–	–	–	–	–	–	–	–	N.A.	S	15.3(1.8–43.9)	S	–	–	–
Adjuvant therapy		–	–	–	–	1.6(0.7–3.6)	NS	–	NS	–	–	–	–	–	–	–	–	–	–	–

Abbreviations: CE = cystectomy; LND = lymph node dissection; MV = multivariable; NS = non significant; S = significant; UBE = umbilectomy; UV = univariable.

Table 5
Primary surgical treatment

Studies (n = 24)	All patients	Partial CE	Radical CE	TURB	Umbilectomy	LND*
Johnson et al. [4]	14	11	1	0	–	–
Grignon et al. [25]	24	16	4	1	–	–
Henly et al. [26]	38	30	4	2	34	–
Santucci et al. [30]	17	14	0	2	–	–
Dandekar et al. [27]	21	10	9	0	–	–
Siefker-Radtke et al. [23]	42	28	7	0	19	19
Thali-Schwab et al. [17]	25	–	–	–	–	–
Asley et al. [10]	66	46	14	0	32	20
Pinthus et al. [20]	40	28	4	0	–	–
Wright et al. [28]	151	71	17	19	–	45
Molina et al. [11]	49	43	3	0	42	12
Chen et al. [13]	14	8	3	0	–	–
Gopalan et al. [3]	24	20	3	1	11	14
Bruins et al. [12]	152	81	20	17	–	43
Yazawa et al. [15]	10	5	4	0	9	9
Meeks et al. [14]	65	59	0	0	50	51
Cho et al. [16]	17	16	1	0	16	3
Kim et al. [21]	41	29	5	3	–	–
Chen et al. [31]	17	12	2	1	13	5
Jung et al. [22]	28	–	–	–	–	–
Amin et al. [29]	55	40	0	3	32	–
Niedworok et al. [24]	26	21	4	0	–	10
Dhillion et al. [18]	46	33	7	0	29	–
Hayashi et al. [19]	28	12	5	0	–	17
	1010	633/957	117/957	49/957	287/429	248/647
Sum		66%	12%	5%	67%	38%

[a]LND (lymph node dissection) and umbilectomy rate was calculated only for those patients who were treated with primary surgical therapy (partial or radical cystectomy and transurethral resection).

identified as independent prognostic factors (Table 4). Further validation of these findings is necessary.

7. Therapy

The recommended treatment for nonmetastatic UrC is surgery. Both partial and radical cystectomy can be considered as they provide similar oncological results [10,12,20,23]. However, organ preserving partial cystectomy provides higher quality of life and should therefore be preferred. As positive surgical margin is one of the most significant risk factors in UrC [10,12,24], en bloc resection with complete removal of urachal remnant and the umbilicus is essential for prolonged survival. To see whether these recommendations are followed in the clinical practice, we performed a summary on surgical treatment based on the initially selected 24 studies (Table 5). Data on surgical treatment were available for 957 patients. The majority (66%, 633/957) of patients was treated with partial cystectomy followed by radical cystectomy (12%, 117/957) and transurethral resection (5%, 49/957). Data on umbilectomy were published in 429 patients. In 287 (67%) of these cases, the removal of umbilical ligament with umbilicus has been performed (Table 5). These data are in accordance with the recommendations of the most authors; however, the importance of umbilectomy has to be clearly highlighted to further encourage its performance.

However, the prognostic effect of LND as an integral part of radical or partial cystectomy is controversial [10,24]. The removal of pelvic LN may be recommended considering the fact that LN positivity (without distant metastasis) showed a similar negative effect on survival as the presence of distant metastasis [12,23]. Therefore, the timely pathological detection of LN positivity may be essential for adequate staging, which in turn could influence treatment decisions. We found data on lymphadenectomy in 545 UrC patients. Of these, LND was performed in 248 cases (38%), reflecting current uncertainty regarding the benefit of lymphadenectomy. On the other hand, LN positivity was found in only 17% of cases. This relative low rate of LN positivity highlights the need for larger patient cohorts for the valid prognostic analysis of the potential benefit of lymphadenectomy and might explain why LND was not found to be prognostic in former studies.

As UrC is usually detected at progressed tumor stages, the rate of distant metastatic cases at diagnosis is relatively high (>20%). In addition, postoperative recurrence or metastatic progression are also frequent. In lack of effective radiotherapy, chemotherapy is the only treatment option to potentially prolong survival. However, the 5-year overall survival rate for UrC patients with metastatic disease is less than 20% clearly highlighting the need for more effective

Table 6
Chemotherapies and radiographic response

	CR/PR		SD		PD		Total
	n	%	*n*	%	*n*	%	*n*
Cisplatin-based	2	9	10	45	10	45	22
5-FU based	7	44	4	25	5	31	16
Combined (cisplatin + 5-FU-based)	6	43	6	43	2	14	14
Other (no cisplatin or 5-FU)	5	23	6	27	11	50	22
Total	20	27	26	35	28	28	74

CR = complete response; PD = progressive disease; PR = partial response; SD = stabile disease.

systemic therapy regimens [10,12]. Considering the low incidence of UrC, it is not surprising that no large-scale clinical studies have been performed to identify effective drugs for UrC. Therefore, most of the data are available from case reports using several various chemotherapy combinations and some studies with low case numbers not providing enough statistical power. Therefore, we summarized the available data to compare the efficacy of the most often used chemotherapeutic agents.

Cisplatin-based combination therapies (methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine-cisplatin) are the first-line chemotherapies in urothelial carcinomas of the bladder and are often used in UrC. Based on the obvious histological and clinical similarity between urachal and colon ADC, chemotherapies applied in colon cancer such as 5-fluorouracil (FU) can also be considered for the treatment of UrC. Promising results have been published with the combination of 5-FU, leucovorin, gemcitabine, and cisplatin suggesting 30% to 40% radiographic response rates, but long-term survival rates are awaited from this study [23]. As presently the most often used drugs for the treatment of UrC are cisplatin and 5-FU, in our meta-analysis we compared the efficacy of cisplatin-based, 5-FU-based, 5-FU+cisplatin combination and "other" chemotherapies. Because of the large number of various chemotherapy combinations, we disregarded the use of other agents in addition to cisplatin or 5-FU. Furthermore, considering the heterogeneous treatment history and patients' base-line performance status as well as the usually short follow-up time, we decided to consider only radiographic response but not survival as an end-point. Finally, we excluded cases where data on radiographic response were not available. These restrictions left an overall number of 74 UrC patients (Table 6). Of them, 22 were treated with platinum-based, 16 with 5-FU-based, and 14 with cisplatin-5-FU combination chemotherapy, whereas 22 patients received "other" chemotherapies including neither cisplatin nor 5-FU. The response rates were the highest in the 5-FU and cisplatin-5-FU group (44% and 43%, respectively), whereas the lowest progression rate was found in patients who were treated with cisplatin-5-FU combination (14%). The lowest response rate was found in the cisplatin-based chemotherapy group (9%) (Fig.). Taking together, our meta-analysis on a relative large number of patients shows that the most effective treatment may be combination of 5-FU with cisplatin, which performs significantly better than cisplatin-based therapies (Fisher's exact test: $P = 0.043$). In addition, the 5-FU-cisplatin combination provided similar response rates as 5-FU alone (43% vs. 44%) and the combination therapy had lower progression rates as 5-FU alone (14% vs. 31%). Therefore, the combination of 5-FU with cisplatin seems to provide the highest benefit for UrC patients. This finding is in line with former findings [23]. Effectively used 5-FU-platinum treatments included the following combinations: (1) 5-FU + leucovorin, gemcitabine, cisplatin, (2) 5-FU + IFNa, cisplatin, (3) 5-FU + oxaliplatin, and (4) 5-FU + cisplatin.

Currently, systemic treatment of cancer is shifting from empirical, cytotoxic therapies toward rationale-based targeted therapies. These new modalities are especially hopeful for rare diseases, where large-scale clinical studies cannot be conducted. To date, there are only few, however, promising data on the efficacy of targeted therapies in UrC.

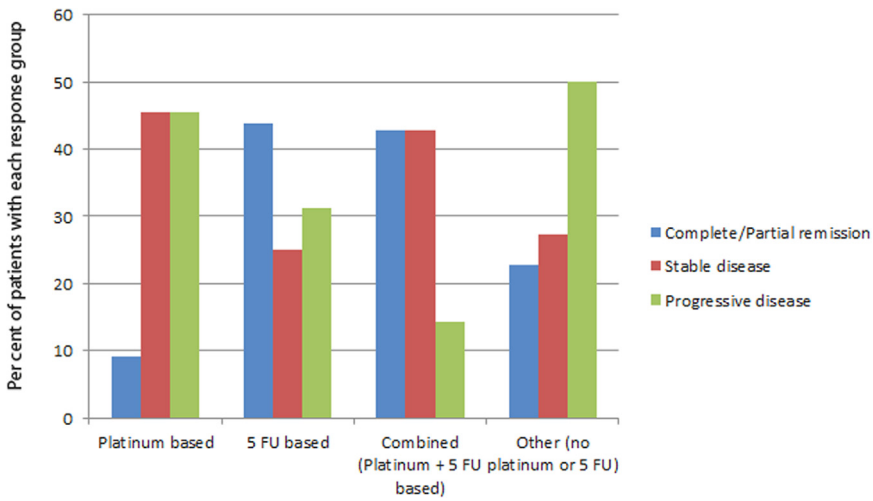

Fig. Radiographic response of UrC to different chemotherapies (Refer to Table 6 for more details). (Color version of figure is available online.)

Testa et al. [36] reported a necrotic involution of the tumor and a significant improvement of abdominal pain in a patient with metastatic UrC who was treated with second-line multikinase inhibitor (sunitinib) following failure of platinum-containing combination chemotherapy.

Epidermal growth factor receptor (EGFR)-inhibitors are commonly used in colorectal cancer. The only available study assessing an EGFR-inhibitor (gefitinib) in UrC included 7 types of different solid tumors and reported the strongest size decrease in the one single case of UrC included in this study. The shrinkage of UrC was associated with decreasing proliferation index suggesting efficacy of EGFR-inhibitors in UrC [37]. For the prediction of these targeted therapies including gefitinib, cetuximab, and panitumumab, mutation analysis of the EGFR pathway members is recommended. In this context, it is important that KRAS mutations seem to be frequent in UrC [38,39]. Furthermore, also microsatellite instability was observed in a high rate (~43%) of UrCs [38]. As microsatellite instability was formerly found to be associated with poor response to 5-FU treatment in colorectal cancer, the presence of microsatellite instability represents a contraindication for 5-FU treatment in colorectal cancer [40]. These data should be kept in mind when considering 5-FU based or EGFR-targeting chemotherapy for UrC patients.

8. Conclusions

In localized UrC partial cystectomy with en bloc resection and complete removal of umbilical ligament mostly provide a long-term disease-free survival. Our metadata—including the highest number of analyzed cases so far—confirmed that 5-FU-based chemotherapies are superior to cisplatin-based regimens in terms of radiographic response, whereas the combination of 5-FU with cisplatin provides the most favorable response in metastatic UrC.

Targeted therapies tailored to molecular features of UrC provide a promising alternative to or in combination with chemotherapy. Therefore, significant efforts need to be put into molecular characterization of UrC with a focus on therapeutically relevant alterations.

Acknowledgments

We would like to thank Prof. Elek Dinya for his help in the statistical analyses.

References

[1] Duncan T Wilcox, Pasad P Godbole, Martin A Koyle, Pediatric urology—Surgical complications and management ISBN:978-1-4051-6268-5, 2008.
[2] Begg RC. The urachus: its anatomy, histology and development. J Anat 1930;64:170–83.
[3] Gopalan A, Sharp DS, Fine SW. Urachal carcinoma: a clinicopathologic analysis of 24 cases with outcome correlation. Am J Surg Pathol 2009;33:659–68.
[4] Johnson DE, Hodge GB, Abdul-Karim FW, Ayala AG. Urachal carcinoma. Urology 1985;26:218–21.
[5] Sheldon CA, Clayman RV, Gonzalez R, Williams RD, Fraley EE. Malignant urachal lesions. J Urol 1984;131:1–8.
[6] Mostofi FK, Thomson RV, Dean AL. Mucous adenocarcinoma of the urinary bladder. Cancer 1955;8:741–58.
[7] Herr HW, Bochner BH, Sharp D, Dalbagni G, Reuter VE. Urachal carcinoma: contemporary surgical outcomes. J Urol 2007;178:74–8.
[8] Siefker-Radtke A. Urachal carcinoma: surgical and chemotherapeutic options. Expert Rev Anticancer Ther 2006;6:1715–21.
[9] Paner GP, Barkan GA, Mehta V, et al. Urachal carcinomas of the nonglandular type: salient features and considerations in pathologic diagnosis. Am J Surg Pathol 2012;36:432–42.
[10] Ashley RA, Inman BA, Sebo TJ, et al. Urachal carcinoma: clinicopathologic features and long-term outcomes of an aggressive malignancy. Cancer 2006;15(107):712–20.
[11] Molina JR, Quevedo JF, Furth AF, Richardson RL, Zincke H, Burch PA. Predictors of survival from urachal cancer: a Mayo Clinic study of 49 cases. Cancer 2007;110:2434–40.
[12] Bruins HM, Visser O, Ploeg M, Hulsbergen-van de Kaa CA, Kiemeney LA, Witjes JA. The clinical epidemiology of urachal carcinoma: results of a large, population based study. J Urol 2012;188:1102–7.
[13] Chen ZF, Wang F, Qin ZK, et al. Clinical analysis of 14 cases of urachal carcinoma. Chin J Cancer 2008;27:252–5.
[14] Meeks JJ, Herr HW, Bernstein M, Al-Ahmadie HA, Dalbagni G. Preoperative accuracy of diagnostic evaluation of the urachal mass. J Urol 2013;189:1260–2.
[15] Yazawa S, Kikuchi E, Takeda T, et al. Surgical and chemotherapeutic options for urachal carcinoma: report of ten cases and literature review. Urol Int 2012;88(2):209–14.
[16] Cho SY, Moon KC, Park JH, Kwak C, Kim HH, Ku JH. Outcomes of Korean patients with clinically localized urachal or non-urachal adenocarcinoma of the bladder. Urol Oncol 2013;31:24–31.
[17] Thali-Schwab CM, Woodward PJ, Wagner BJ. Computed tomographic appearance of urachal adenocarcinomas: review of 25 cases. Eur Radiol 2005;15:79–84.
[18] Dhillon J, Liang Y, Kamat AM, et al. Urachal carcinoma: a pathologic and clinical study of 46 cases. Hum Pathol 2015;46:1808–14.
[19] Hayashi T, Yuasa T, Uehara S, et al. Clinical outcome of urachal cancer in Japanese patients. Int J Clin Oncol 2016;21:133–8.
[20] Pinthus JH, Haddad R, Trachtenberg J, et al. Population based survival data on urachal tumors. J Urol 2006;175:2042–7.
[21] Kim IK, Lee JY, Kwon JK, et al. Prognostic factors for urachal cancer: a bayesian model-averaging approach. Korean J Urol 2014;55:574–80.
[22] Jung HA, Sun JM, Park SH, Kwon GY, Lim HY. Treatment outcome and relevance of palliative chemotherapy in urachal cancer. Chemotherapy 2014;60:73–80.
[23] Siefker-Radtke AO, Gee J, Shen Y, et al. Multimodality management of urachal carcinoma: the M. D. Anderson Cancer Center experience. J Urol 2003;169:1295–8.
[24] Niedworok C, Panitz M, Szarvas T, et al. Urachal carcinoma of the bladder—impact of clinical and immunohistochemical parameters on patients' prognosis. J Urol 2015 10.1016/j.juro.2015.11.067. [Epub ahead of print].
[25] Grignon DJ, Ro JY, Ayala AG, Johnson DE, Ordóñez NG. Primary adenocarcinoma of the urinary bladder. A clinicopathologic analysis of 72 cases. Cancer 1991;67:2165–72.
[26] Henly DR, Farrow GM, Zincke H. Urachal cancer: role of conservative surgery. Urology 1993;42:635–9.
[27] Dandekar NP, Dalal AV, Tongaonkar HB, Kamat MR. Adenocarcinoma of bladder. Eur J Surg Oncol 1997;23:157–60.

[28] Wright JL, Porter MP, Li CI, Lange PH, Lin DW. Differences in survival among patients with urachal and nonurachal adenocarcinomas of the bladder. Cancer 2006;107:721–8.
[29] Amin MB, Smith SC, Eble JN, et al. Glandular neoplasms of the urachus: a report of 55 cases emphasizing mucinous cystic tumors with proposed classification. Am J Surg Pathol 2014;38:1033–45.
[30] Santucci RA, True LD, Lange PH. Is partial cystectomy the treatment of choice for mucinous adenocarcinoma of the urachus? Urology 1997;49:536–40.
[31] Chen D, Li Y, Yu Z, et al. Investigating urachal carcinoma for more than 15 years. Oncol Lett 2014;8:2279–83.
[32] Kim SO, Kwon D, Choi C, Baek HJ, Park K, Ryu SB. A case of spontaneous rupture perforation of leiomyosarcoma in the urachus of a young boy. Int J Urol 2007;14:960–2.
[33] Tareen F, McDowell DT, O'Sullivan M, Mortell A. Urachal carcinoid —a new presentation. Eur J Pediatr Surg 2013;23:e1–2.
[34] Monteiro V, Cunha TM. Urachal carcinoma: imaging findings. Acta Radiol Short Rep 2012, http://dx.doi.org/10.1258/arsr.2011.110018.
[35] Williamson SR, Lopez-Beltran A, Montironi R, Cheng L. Glandular lesions of the urinary bladder:clinical significance and differential diagnosis. Histopathology 2011;58:811–3.
[36] Testa I, Verzoni E, Grassi P, Colecchia M, Panzone F, Procopio G. Response to targeted therapy in urachal adenocarcinoma. Rare Tumors 2014;6:5529.
[37] Goss G, Hirte H, Miller WH Jr, et al. A phase I study of oral ZD 1839 given daily in patients with solid tumors: IND.122, a study of the Investigational New Drug Program of the National Cancer Institute of Canada Clinical Trials Group. Invest New Drugs 2005;23:147–55.
[38] Sirintrapun SJ, Ward M, Woo J, Cimic A. High-stage urachal adenocarcinoma can be associated with microsatellite instability and KRAS mutations. Hum Pathol 2014;45:327–30.
[39] Modos O, Szarvas T, Reis H, et al. Mutation analysis of EGFR signal transduction pathway in urachal carcinoma. Eur Urol Suppl 2015;14:e1215.
[40] Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 2003;349:247–57.