Urachal Cancer in Germany and the USA: An RKI/SEER Population-Based Comparison Study

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Abstract

Introduction: Urachal cancer (UrC) is a rare but aggressive cancer. Due to its low incidence, structured epidemiological data have only rarely been reported. To date, no valid data on UrC are available for the German population. *Methods:* Data on incidence and relative 5-year survival of urachal lesions (ICD-10: C67.7) were collected from all population-based cancer registries in Germany, provided by the Robert Koch-Institut (RKI). Data were anonymized and included age, sex, and general histology (ICD-O-3). For comparison, a similar inquiry of the "Surveillance, Epidemiology, and End Results program" (SEER-18) database for the USA was conducted. *Results:* From 2011 to 2015, a total of 154 and 152 cases of UrC were reported for Germany (RKI) and the USA (SEER-18 area), respectively. Age-standardized incidence was 0.32/1,000,000 age-standardized cases/year in both cohorts, and elderly persons were more often affected. The major histological type was adenocarcinoma (64.9 and 81.6%). Relative 5-year survival was 54.8% (CI: 45.0–64.6) in Germany (RKI) and 64.4% (54.1–72.1) in the USA (SEER-18 cohort). *Discusssion/Conclusion:* The collected data demonstrate low incidence rates and similar epidemiological and clinicopathological characteristics of UrC for both registries. This is the first report of structured epidemiological data for UrC for the German population.

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Introduction

The urachus is present during embryological development and usually degenerates to a fibromuscular canal known as the median umbilical ligament. In up to 32% of adults, however, microscopic residues of urachal remnants can be detected as the source of cancer development [1, 2]. Urachal cancer (UrC) can then occur in the region of the urachus in the midline from the bladder dome to the umbilicus. Despite the fact that urothelium lines most urachal remnants, adenocarcinomas present the majority (>90%) of UrC, and the mucinous subtype is the most common histologic subtype (57%) [3]. Further

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Table 1. Data of UrC (2011–2015) in the RKI (Germany) area compared to the SEER-18 (USA) area

Histology	SEER-18 (USA, 2011–2015)			RKI (Germany, 2011–2015)		
	Total, n (%)	m, n (%)	f, n (%)	Total, n (%)	m, n (%)	f, n (%)
8000–8009: unspecified neoplasms	0 (0)	0 (0)	0 (0)	10 (6.5)	6 (6.5)	4 (6.5)
8010–8049: epithelial neoplasms, NOS	5 (3.3)	2 (2.4)	3 (4.3)	9 (5.8)	6 (6.5)	3 (4.8)
8050–8089: squamous cell neoplasms	6 (3.9)	3 (3.6)	3 (4.3)	1 (0.6)	0 (0)	1 (1.6)
8120–8139: transitional cell carcinomas	16 (10.5)	10 (12)	6 (8.7)	33 (21.4)	27 (29.3)	6 (9.7)
8140–8389, 8440–8499: adenocarcinomas	124 (81.6)	68 (82)	56 (81.2)	100 (64.9)	52 (56.6)	48 (77.4)
Other	1 (0.7)	0 (0)	1 (1.4)	1 (0.6)	1 (1.1)	0 (0)
Total	152 (100)	83	69	154 (100)	92	62
Median age, years (range)						
Total cohort	61 (19–92)	61 (29–92)	60 (19–91)	64 (18–90)	66.5 (18–90)	60.5 (26–86)
Adenocarcinomas	60 (19–91)	61 (29–89)	60 (19–91)	56 (22–90)	60.5 (22–90)	60 (26–86)
Urothelial carcinomas (TCC)	78.5 (59–92)	75.5 (59–92)	80 (68–88)	73 (43–88)	75 (50–88)	73 (43–85)
Age-standardized incidence, per 1,000,000/year	0.32	0.37	0.28	0.32	0.41	0.24
Age-specific incidence						
0–14 years	0	0	0	0	0	0
15–29 years	0.04	0.02	0.07	0.07	0.11	0.03
30–44 years	0.18	0.16	0.20	0.25	0.21	0.29
45–59 years	0.53	0.66	0.42	0.47	0.56	0.38
60–74 years	1.05	1.23	0.90	0.99	1.38	0.64
>75 years	0.57	0.67	0.48	1.01	1.73	0.56
Relative 5-year survival (2011–2015), % (CI)						
Total cohort	64.4% (54.1–72.1)			54.8% (45.0–64.6)		
Adenocarcinomas	65.9% (54.9–74.5)			55.6% (46.5–69.3)		

RKI, Robert Koch-Institut; SEER, Surveillance, Epidemiology, and End Results program; UrC, urachal cancer; NOS, not otherwise specified; TCC, transitional cell carcinoma; n, number; CI, confidence interval.

histological subtypes include the intestinal, not otherwise specified (NOS), mixed, and signet ring cell type [4].

UrC often present in late stages of disease, and hematuria is the most common initial symptom due to infiltration into the bladder cavity. Therapeutic options include (partial) cystectomy with *en bloc* resection of the median umbilical ligament and umbilicus in local disease and mostly 5-fluorouracil-based chemotherapy regimes in advanced cases [5–7]. Recently, molecular studies have allowed more insights in the genetic background of UrC, which seems to be a distinct molecular entity [8–17].

Due to the rarity, only few single-center reports (including our data) and population-based epidemiological studies on UrC exist [3, 7, 18–26]. For European populations, epidemiological characteristics of UrC have only been reported for The Netherlands and Ireland [22, 24]. We, therefore, collected data of UrC from the population-based cancer registries in Germany, which was provided by the Robert Koch-Institut (RKI). To improve comparability, we compared out results with the data provided by the US-SEER program ("Surveillance, Epidemiology, and End Results program").

Material and Methods

For Germany, we analyzed data from federal state run population-based cancer registries, whose data are regularly pooled at the Centre for Cancer Registry Data at the RKI in Berlin. Since 2009, population-based cancer registration in Germany is nationwide. Thus, for the calculation of incidence rates for the period of 2011–2015, data from all 16 federal states could be used. The short timeframe of reported data was chosen to give an overview of the current epidemiological situation, which is sufficiently covered in large registries even for rare diagnoses. We also did not aim to show trends as data from before 2009 would be difficult to interpret.

Data were evaluated for all primary tumor cases documented with the ICD-O-3 topography code for urachus (C67.7). Subgroup

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Table 2. Grading of urachal carcinomas in the RKI (Germany) area compared to the SEER-18 (USA) area

	Total cohort				Male				Female			
	total, n (%)	ADC, n (%)	UC, n (%)	Other, n (%)	Total, n (%)	ADC, n (%)	UC, n (%)	Other, n (%)	Total, n (%)	ADC, n (%)	UC, n (%)	Other, n (%)
SEER-18 (USA)												
Low-grade (G1)	20 (13.2)	18 (14.5)	1 (6.3)	1 (8.3)	15 (18.1)	13 (19.1)	1 (10)	1 (20)	5 (7.2)	5 (8.9)	0 (0)	0 (0)
Intermediate-grade (G2)	48 (31.6)	43 (34.7)	2 (12.5)	3 (25)	25 (30.1)	23 (33.8)	0 (0)	2 (40)	23 (33.3)	20 (35.7)	2 (33.3)	1 (14.3)
High-grade (G3–G4)	46 (30.3)	35 (28.2)	8 (50)	3 (25)	19 (22.9)	14 (20.6)	4 (40)	1 (20)	27 (39.1)	21 (37.5)	4 (66.7)	2 (28.6)
n/a	38 (25)	28 (22.6)	5 (31.3)	5 (41.7)	24 (28.9)	18 (26.5)	5 (50)	1 (20)	14 (20.3)	10 (17.9)	0 (0)	4 (57.1)
Total	152 (100)	124	16	12	83 (100)	68	10	5	69 (100)	56	6	7
RKI (Germany)												
Low grade (G1)	7 (4.5)	7 (7.1)	0 (0)	0 (0)	2 (2.2)	2 (3.9)	0 (0)	0 (0)	5 (8.1)	5 (10.4)	0 (0)	0 (0)
Intermediate grade (G2)	45 (29.2)	39 (39.4)	3 (9.1)	3 (13.6)	24 (26.1)	20 (39.2)	3 (11.1)	1 (7.1)	21 (33.9)	19 (39.6)	0 (0)	2 (25)
High grade (G3–G4)	68 (44.2)	37 (37.4)	25 (75.8)	6 (27.3)	43 (46.7)	19 (37.3)	20 (74.1)	4 (28.6)	25 (40.3)	18 (37.5)	5 (83.3)	2 (25)
n/a	34 (22.1)	16 (16.2)	5 (15.2)	13 (59.1)	23 (25)	10 (19.6)	4 (14.8)	9 (64.3)	11 (17.7)	6 (12.5)	1 (16.7)	4 (50)
Total	154 (100)	99	33	22	92 (100)	51	27	14	62 (100)	48	6	8

RKI, Robert Koch-Institut; SEER, Surveillance, Epidemiology, and End Results program; n/a, not available; ADC, adenocarcinoma; UC, urothelial carcinoma/transitional cell carcinoma.

analyses were performed by histology, sex, and age (shown in Table 1).

An analogous inquiry of the SEER-18 database (USA) run by the National Cancer Institute for the same time period was conducted [27]. The database provides population-based data on cancer incidence and survival from 8 US states and 10 additional regions (2000–2016), representing approximately 28% of the US population.

For calculation of 5-year relative survival, the observed 5-year survival was divided by the expected survival, which is defined by the survival in the general population with an identical age and sex distribution. Expected survival was estimated according to the Ederer II method [28] using population life tables for Germany and the USA, stratified by calendar period, age, and sex. We used the period method, which provides an estimate for the prognosis of patients diagnosed in the most recent years (2011–2015) [29], using data from 2006 to 2015. For these analyses, data from 12 federal states from Germany could be used. The same data were used to calculate Kaplan-Meier estimates for observed survival.

Incidence rates were given as incident cases by 1 million inhabitants. Age-standardized rates were calculated using the European standard population [30]. Only anonymized epidemiological data were used and the institution's ethic committee (University of Duisburg-Essen) approved the study (17-7341-BO).

Results

From 2011 to 2015, the total incidence rate for UrC was 0.32/1,000,000 age-standardized cases/year for Germany (RKI) and for the SEER area (USA). Within this

period, 154 cases (n = 62 female [40%]; n = 92 male [60%]) of UrC were reported for Germany (RKI), while SEER data showed 152 cases (n = 69 female [45%], n = 83 male [55%]) in the covered US population. Patient ages at time of report ranged from 15 to >75 years for both areas. The highest age-specific incidence figures were detected in patients from 60 to 74 years in the USA (SEER-18 area) and in patients ≥60 years in Germany (RKI) (shown in Table 1).

The most frequent tumor type was adenocarcinoma (RKI: n = 100 [65%]; SEER: n = 124 [82%]) followed by urothelial carcinoma (RKI: n = 33 [21%]; SEER: n = 16 [11%]). Other and unspecified histological types were rarely detected (shown in Table 1). More information and distribution of grades for both cohorts are summarized in Table 2 and visualized in Figure 1.

Due to the rarity of other cancer types, relative 5-year survival was calculated for the whole cohort and for adenocarcinomas (shown in Table 1) only. Kaplan-Meier survival curves for both regions are shown in Figure 2 including confidence intervals (CI).

Discussion

UrC is a rare cancer, and reported incidence rates vary in the literature [3, 7, 18–24, 26]. In concordance with these reports, our results demonstrate low rates of UrC in Ger-
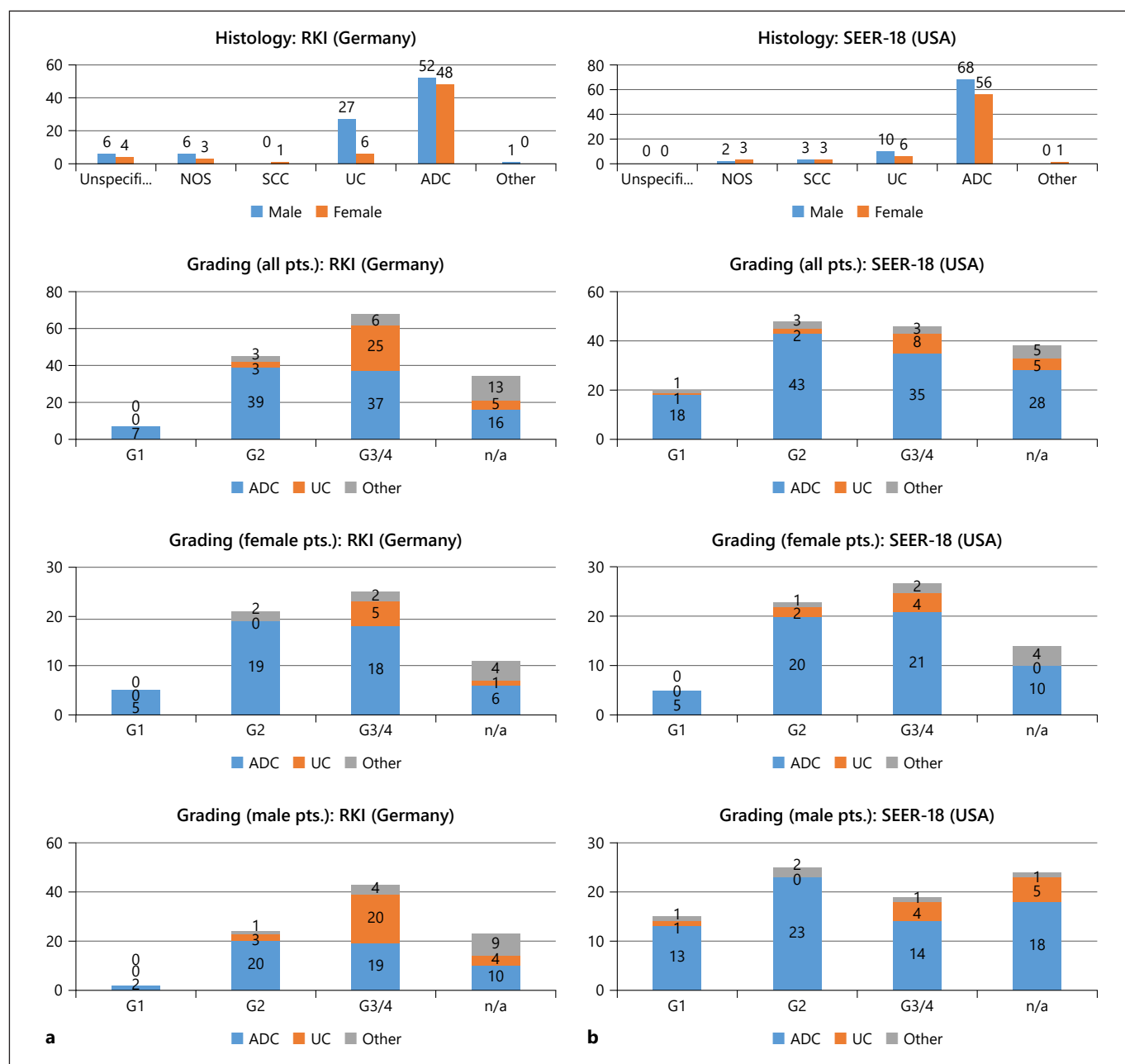
Fig. 1. Distribution of histologic subtypes and grading of UrC. In row (**a**), histological subtypes and grading in the total cohort and female/male patients are shown for Germany (RKI) and in (**b**) for the USA (SEER-18 area). Unspecified, histological subtype not specified; NOS, epithelial neoplasm, not otherwise specified; SCC, squamous cell carcinoma; UC, urothelial carcinoma (transitional cell carcinoma); ADC, adenocarcinoma; pts., patients; UrC, urachal cancer; RKI, Robert Koch-Institut; SEER, Surveillance, Epidemiology, and End Results program.

many (RKI) and the USA (SEER-18 area) of approximately 0.3/1,000,000 age-standardized cases/year in both regions.

It is interesting to note that the studies reporting data from Western countries show similar percentages of UrC compared to bladder cancer (BC) cases. For North Amer-

ica, 1 study reported figures from Canada (Ontario) with 40 UrC cases in a period of 25 years (~0.1% UrC/BC), while 2 other studies were performed in SEER areas (USA) reporting 151 and 420 UrCs in a period of 30 and 25 years [19, 20, 25]. For the European population, 2 stud-
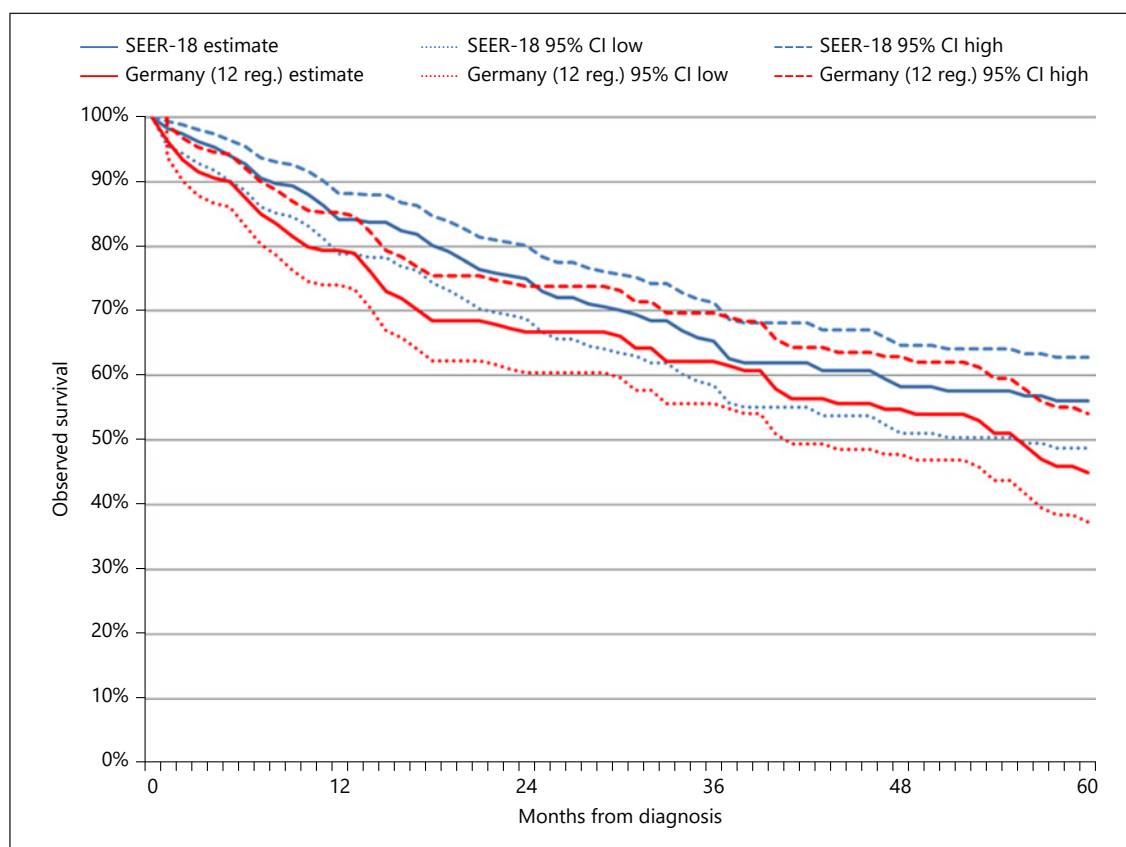
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Fig. 2. Kaplan-Meier survival analysis for UrC in Germany (RKI) compared to the SEER-18 (USA) area. UrC, urachal cancer; RKI, Robert Koch-Institut; SEER, Surveillance, Epidemiology, and End Results program; CI, confidence interval.

ies were published from The Netherlands (0.2% UrC/BC) and Ireland (0.3% UrC/BC) with 152 and 26 UrC cases in a period of 28 and 18 years, respectively [22, 24]. In the present study, the estimated ratio is ~0.2 UrC/BC. In contrast, higher proportions of UrC (approx. 2-fold) than BC cases have been reported for the Japanese population (0.4–0.6%) [18, 26, 31]. The reason for this phenomenon remains unclear and warrants further investigation. Potentially, this may lead to the identification of yet unknown genetic and/or environmental factors, which could result in further elucidation of the etiology of UrC.

Apart from these differences, UrC is generally a cancer of elderly and male patients (Table 1; Fig. 1). In a recent review of the clinicopathological characteristics of 1,010 UrC cases, the median patient age, however, was 52 years [7]. It is important to note that 96% of UrC in this study were adenocarcinomas. While it has been reported that urachal adenocarcinomas occur earlier than both bladder adenocarcinomas and bladder urothelial carcinomas [20, 32], to the best of our knowledge, no larger data set was available on

the median age of urothelial UrC prior to the present study. We detected that urachal adenocarcinomas in median occur more than 15 years earlier than their urothelial counterpart (shown in Table 1) and that urothelial UrC get diagnosed later at about the same age as urothelial BC.

In addition, there is a considerable variation in reported 5-year survival rates, which ranges from only 6% to more than 60% [3, 7, 18, 20]. However, it has to be kept in mind that the studies span several decades with advances in the surgical and medical treatment of UrC. In our study, we detected relative 5-year survival rates in the total cohorts of 54.8% (CI: 45.0–64.6) in Germany (RKI) to 64.4% (CI: 54.1–72.1) in the USA (SEER-18) (shown in Table 1; Fig. 2). The figures are in line with reported outcomes in modern series [3, 7]. As many potentially influencing factors exist that are not captured in the present data set, the reasons for the survival difference in the cohorts remain speculative.

In the literature, another point of debate is the prognostic role of grading in UrC. In general, no standardized

and specific grading system has been suggested for UrC. However, as UrC show the same histopathological subtypes as colorectal and bladder adenocarcinomas, grading is usually performed in a similar and comparable approach. In the present study, UrC tended to have a higher grade in the German cohort (RKI) than the SEER-18 population (USA) (shown in Fig. 1; Table 2). This applies to both female and male patients. However, when only urachal adenocarcinomas are considered, a predominance of moderately differentiated (G2) tumors can be seen both in the German and the US cohorts (shown in Fig. 2). In contrast, the reported urothelial UrC are concentrated in the less or un-differentiated group (G3/4; high-grade), especially in the German cohort (RKI), thus shifting the total group toward less differentiated grades.

Our study has some limitations, which are inherent to the study setup. Our collected data lack detailed information on staging. However, as UrC is not a primary BC and develops in the bladder wall up to the umbilicus along the midline, we feel the TNM system is not appropriate for staging, and we usually use the systems proposed by Sheldon et al. [33] and Ashley et al. [2] (Mayo system). In addition, no therapeutic data were available.

Conclusion

Apart from these limitations, we report structured epidemiological data for UrC in Germany (RKI) for the first time. We showed that UrC in Germany exhibits similar incidence rates and clinicopathological characteristics compared with reports from other European and North American countries with minor differences. Population-based cancer registries are a valuable source to improve our understanding of such rare tumor entities like UrC.

Statement of Ethics

Conflict of Interest Statement

Funding Sources

Author Contributions

H.R., K.K., and T.H. designed the study; H.R., K.K., T.H., T.S., B.H., and K.W.S. analyzed and interpreted the data; H.R., T.H., and K.K. wrote the manuscript; and H.R., K.K., T.H., T.S., B.H., and K.W.S. proofread the manuscript.

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