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Clinical-bladder Cancer

Estimation of the incidence of urachal cancer: A systematic review and meta-analysis of registry-based studies

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Abstract

Background: Urachal cancer (UrC) is a rare disease with limited availability of representative incidence and clinical data. Although, the prevalence is accounting for less than 1% of bladder tumors, the 5-year survival rate is around only 50% for patients with resectable tumors, and even worse for patients with metastatic disease. Due to the lack of comprehensive prospective studies, our current knowledge of UrC is still limited.

Objective: The present study aimed to summarize the available registry-based studies with unselected UrC patients to evaluate its incidence and clinicopathological characteristics.

Material and methods: We conducted a systematic literature search of registry-based UrC publications on the 15th of May 2023 in 5 databases, which identified 4,748 publications. After duplicate removal and selection by 2 independent investigators, 6 publications proved to be appropriate for the final meta-analysis. Estimated incidence and clinicopathological parameters were extracted.

Results: Estimated incidence ranged between 0.022 and 0.060/ 100.000 person-years, with the highest occurrence in Japan and the lowest in Canada, while the random effect model calculated an overall incidence rate of 0.04 (95%CI: 0.03−0.05) 100.000 person-years. The median age at first diagnosis was 60 years (range: 58−64). The female to male ratio was 2:3. Lymph node or distant metastases were present in 9% and 14% of patients. The predominant tumour type was adenocarcinoma (86%) followed by urothelial carcinoma (12%) and squamous cell carcinoma (2%). The 5-year survival rate was 51.0% with 95%CI: 45.2−57.4.

Conclusions: Our study provides an up-to-date comparison of estimated incidence rates between 6 countries of 3 continents based on rigorously selected registry-based studies. The results suggest low incidence rates for UrC with considerable geographic differences. The present meta-analysis provides unbiased registry-based data on the incidence, clinicopathological parameters and survival of UrC.

Keywords: Urachal cancer; Urachus carcinoma; Incidence; Epidemiology; Registry; Adenocarcinoma; Bladder cancer

1. Introduction

Urachal cancer (UrC) is an exceptionally rare cancer arising from the urachal remnant, a residual structure extending between the bladder dome and the umbilicus. Due to its close proximity to the urinary bladder, UrC frequently invades the bladder, resulting in the primary symptom of haematuria. Consequently, although UrC is not a urological cancer, it is predominantly diagnosed within urological patient care settings [1−5]. Due to the absence of extensive prospective studies, our current knowledge on UrC especially regarding its aetiology, incidence, molecular features, and therapeutic sensitivity is still limited.

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In terms of incidence of UrC, most papers refers either to the published registry-based study by Wright *et al.* [6] or to the study by Pinthus *et al.* [7]. Both studies are important contributions to the field but their validity regarding the incidence may be limited. Wright and his colleagues assessed the survival rate of patients with urachal and non-urachal adenocarcinoma cases of the bladder using database of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, which covers incidence and survival data for 30% of the US. population. The authors focused only on the adenocarcinoma cases, therefore the study did not include further UrC histological types, such as squamous cell carcinoma (SQ) and urothelial histology (UC), and thus most probably underestimates the incidence of UrC [6]. The study published by Pinthus *et al.* identified and reported all histological types of UrC using the data of the Ontario Cancer Registry. However, for the later analyses of clinicopathological and survival data, authors excluded 22 UrC cases with non-adenocarcinoma histology [7]. Interestingly, this study described the lowest incidence of 0.022 / 100.000 person-years so far for UrC.

Providing more accurate incidence values is crucial for various reasons. Incidence data play a vital role in the planning and execution of clinical trials, informing health policies for resource allocation decisions. Additionally, when comparing incidence rates across different geographic areas and populations, scientists can discern patterns that may indicate the presence of intrinsic or extrinsic risk factors. This comparative analysis contributes to the discovery of the aetiology of the disease.

In the present systematic review and meta-analysis, we aimed to summarize the results of studies with clinically and histologically unselected UrC patients in order to evaluate the incidence of UrC. Most of the information on UrC originates from case reports, single institutional case series and registry-based studies. Case reports are not suitable for assessing incidence data as they provide information on individual cases rather than population-level statistics. Similarly, institutional case collections have inherent limitations for incidence analysis, as they are based on a specific healthcare setting and may not represent the entire population at risk. Therefore, inclusion of case reports and institutional case series can introduce biases and lead to inaccurate calculations of the incidence of UrC. In contrast, registry-based studies reporting the occurrence of UrC in a defined population size and are therefore appropriate sources of incidence calculations. Therefore, we focused exclusively to registry-based studies with well-defined inclusion criteria and population areas.

2. Material and Methods

2.1. Academia Europaea translational medicine working group

The Academia Europaea (4,800 members, https://www.ae-info.org/) established its Translational Medicine Working Group (AE-TMWG) on 1 January, 2023 to promote the early utilization of scientific results for community benefit [8,9]. The AE-TMWG admits and supports scientific projects that may have a major future public health impact in the field. The present project was endorsed unanimously by the AE-TMWG at its meeting on 27 January 2023 and the project was continuously discussed at its regular meetings.

2.2. Meta-analysis

The inclusion criteria were defined based on the Condition, Context, Population (CoCoPop) framework, (*Condition: Urachal carcinoma, Context: any, Population: whole population*). Original articles and conference abstracts reporting registry-based UrC case identification were included. Despite available demographic data, studies solely in non-English language, and those with fewer than 10 cases were excluded from the present study. Detailed information on eligibility criteria for article or abstract identification have been prospectively provided at PROSPERO under the following identification number: CRD42023427238.

The systemic search was performed on the 15th of May 2023 in the electronic databases of PubMed, Embase, The Cochrane Library, Scopus and Web of Science to retrieve registry-based studies with UrC patients using the following search key: urach* AND (cancer OR carcin* OR neoplasm* OR malign*), which identified an overall number 4748 publications. The publications appearing in 2 or more databases were removed using EndNote 20 (Clarivate Analytics, Philadelphia, PA, USA), while the selection process was conducted using Rayyan [10]. Duplicate removal and article selection based on title and abstract was performed by 2 independent researchers (CO and AK). Title and abstract selection identified 17 registry-based articles or conference abstracts that met the eligible inclusion criteria. As a secondary outcome, we also analyzed patients' survival when overall survival was available, however, the availability of survival data was not mandatory for the overall inclusion. The following parameters were extracted: country and time period of data collection, year of publication, UrC / bladder cancer ratio, estimated inhabitants of the region or country of data collection in the study period, median age, sex, AJCC/TNM stage, Sheldon stage, grade, presence of metastases, surgical treatment, resection margin positivity, administration of chemo- or radiotherapy. The present study was prepared according to the PRISMA guidelines.

2.3. Statistical analysis

For the meta-analysis of incidence rate (IR), the IR with 95% confidence interval (CI) was used for the effect size measure. To calculate the incidence rate, the number of patients with UrC, the population size (the number of

people at risk) and the length of observation (the time period) were extracted from each selected study. We assumed considerable between-study heterogeneity; thus, the random-effects model was used to pool the incidence rates. Forest plot was used to graphically summarize the results of estimated incidence rates. To analyse the survival curves, we digitalized the available plots using the software and reconstructed the raw data with the R package IPDfromKM [11]. We used the Kaplan−Meier method to visualize the survival curves and the log-rank test for the comparison of survival between different countries. For the meta-analysis of survival curves, we used the method proposed by Combescure (2014) and estimated the median survival time and 5-year OS rate by this model [12]. To evaluate the risk of bias in each included article or conference abstract, the Joanna Briggs Institute checklists for prevalence studies was used (https://jbi.global/sites/default/files/2020-08/Checklist_for_Prevalence_Studies.pdf) by 2 independent authors (CO and AK). All statistical analyses were performed with R version 4.1.0 using meta, IPDfromKM, survival, MetaSurv and survminer packages [13].

3. Results

3.1. Study characteristics

After removing duplicates/triplicates, 2,693 publications remained for further selection. The title and abstract selection resulted in a good overlap between the 2 investigators (k = 0.867), and the full-text selection resulted in 58 publications (Supplementary Figure S1 and S2). Seventeen registry-based study met the inclusion criteria (k = 0.879) (Supplementary Table S1) [7,14−28]. However, only 6 studies were selected to assess of UrC incidence, while studies with overlapping datasets mainly used the UrC cases from SEER database were excluded from the final analysis. The present study included a total of 1,629 UrC patients and calculated estimated incidence data from three European countries (Ireland, the Netherlands and Germany), two American countries (Canada and the United States), and one Asian dataset from Japan (Table 1).

3.2. Incidence rate analysis

The estimated incidence rate for UrC was between 0.022 and 0.060 /100.000 person-years. The lowest estimated incidence rates were observed in Canada (0.022) and the United States (0.030), followed by similar incidence rates in Ireland (0.033), Germany (0.038) and the Netherlands (0.046), while the highest rates were reported from Japan (0.060) (Table 1) (Fig. 1A). The overall estimated incidence rate of UrC was 0.04 /100.000 person-years.

3.3. Patients' characteristics

Patients' characteristics are summarized in Table 2. To avoid histology-related selection bias, the study by Pinthus *et al.* was excluded from the evaluation of clinical parameters, as it only included urachal adenocarcinomas, while non-adenocarcinomas were excluded. The median age of UrC patients was 60, and in general, a higher proportion of males was found within the cohorts (60% male *vs.* 40% female), the largest difference was observed in the Japanese cohort (66% male *vs.* 34% female). Comparison of tumor stages was difficult due to the different classification systems used in different studies. According to the Sheldon staging system, stage III was the most common finding (56%), however data are only available for the Netherlands and US cohorts. Lymph node and distant metastases at diagnosis were detected in 9% and 14% of patients, respectively. Adenocarcinoma was the most frequently diagnosed histological type, in 86%, while urothelial and squamous histology occurred in 12% and 2%, respectively. Partial cystectomy was performed in 69% of patients, while radical cystectomy and transurethral resection of the bladder were performed in only 12% and 20% of patients, respectively. Positive resection margin was detected in 13% of patients. Chemotherapy was applied in 27% of patients, and radiotherapy in 9%.

3.4. Survival outcomes

Data on 5-year survival were available from four studies (US, Japan, Germany, and the Netherlands) (Fig. 1).

The 5-year OS rate for the entire cohort of 1,123 UrC patients was 51.0%, with 95%CI: 45.2−57.4 (Fig. 2A). UrC patients from Japan had the most favourable 5-year OS rate compared to other cohorts, however this difference did not reach the significance level ($P = 0.220$). The median survival time for the whole cohort was 62.9 months with 95%CI: 52.0−82.8 months (Fig. 2B).

4. Discussion

Available data on the incidence, clinicopathological parameters and survival in unselected UrC cohorts is largely limited. There are only few unbiased, non-overlapping registry-based studies, which probably provide the most representative characteristics for UrC. Therefore, in the present study we performed a systematic review and meta-analysis focusing only on registry-based studies to assess the epidemiological and clinical characteristics of UrC in different countries.

Currently, no identified environmental or genetic risk factors shed light on the aetiology of UrC, leaving it essentially undetermined. However, cancer registry studies offer a valuable means to observe geographical variations in the occurrence and clinicopathological characteristics of UrC, which may help to identify risk factors potentially enhancing our understanding of their underlying pathophysiology. Our meta-analysis focusing exclusively to unselected registry studies, provides a representative and thus most probably unbiased summary of incidence data. Based on this

Table 1
Selected registry-based studies to assess the incidence of urachus carcinoma.

Study	UrC patients	Authors (ref)	Published		Occurrence	Incidence	Database	Period		Habitants
Country	number of UrC patients		y	PMID	UrC/BC ratio	100.000 person-years	Registry- or population-based	range	y	estimated during the study period
1. Ireland	26	*Collins et al. (15)*	2016	27746878	0.3%	0.033	National Cancer Registry in Ireland	1994−2011	18	4.4M
2. Netherlands	152	*Bruins et al. (16)*	2012	22901574	0.2%	0.046	Netherlands Cancer Registry	1989−2009	21	15.7M
3. Germany	154	*Hager et al. (17)*	2020	32784300	0.2%	0.038	Robert Koch Institute	2011−2015	5	81.3M
4. Canada	62	*Pinthus et al. (7)*	2006	16697798	<0.1%	0.022	Ontario Cancer Registry	1976−2002	27	10.3M
5. Japan	456	*Nagumo et al. (18)*	2019	31793080	0.4%	0.060	Hospital-based cancer registry (University of Tsukuba)	2008−09 / 2012−2015	2/4	127.5M
6. USA	841	*Dursun et al. (14)*	2022	35509235	no data	0.030	The National Cancer Database	2004−2016	13	216.1M

analysis, the overall estimated incidence of UrC is 0.04 / 100.000 person-years, meaning that 4 new UrC cases can be detected in a population of 10 million. However, our analyses revealed substantial difference between countries and even more between continents ranging between 0.022 and 0.060 / 100.000 person-years. The lowest incidence was found in Canada (0.022) followed by the US (0.030), while in Europe slightly higher values (ranging between 0.033 and 0.046 / 100.000 person-years) were noted and the highest estimated incidence was detected in Japan with 0.060 / 100.000 person-years [7,14−18]. These results, show meaningful heterogeneity in the incidence of UrC between various countries, with the highest incidence in Japan (as its confidence interval is completely not overlapping with the confidence interval of the overall). However, this is the only registry-based study has been published from Japan, previous research summarizing the published literature on UrC in Japan concluded that the incidence of UrC is higher in Japan compared to western countries, which is in line with our present observation [29]. Confirmation of the elevated incidence UrC in the Japanese population holds the potential for uncovering its underlying risk factors through subsequent research. Furthermore, differences in diagnostic procedures, treatment approaches, and insurance systems may additionally influence the incidence across different countries.

When considering clinicopathological parameters which were available in at least three independent studies, we could compare age, lymph node and distant metastases and histological types. Age at diagnosis ranged between 58 and 64 years, thus the median age is lower compared to urothelial carcinomas of the bladder, which represent 69 years in men and 71 years in women [30]. The lymph node and distant metastasis rate ranged between 6%−11% and 12% −26%, respectively. Interestingly, the distribution of histological subtypes was different between the studies, which may suggest different pathophysiological backgrounds for UrC in different geographic regions. The highest rate of adenocarcinomas of 94% was found in the Netherlands, while the lowest rate was detected in Germany with only 58% [16,17].

Treatment data was available from Ireland, the Netherlands, and the US, which revealed differential treatment patterns between these countries. In Ireland, only 31% of patients received the recommended surgical treatment of partial cystectomy, while 35% received radical cystectomy [15]. In the Netherlands 53% of patients were treated with partial and only 13% with radical cystectomy, while a high rate of patients (20%) received radiotherapy, and only 7% underwent chemotherapy [16]. In the US., the highest rate of patients was treated by partial cystectomy (60%), while only 8% received radical surgery. In addition, a relative high rate (30%) of US. patients received chemotherapy [14]. A study, based on the SEER database assessing only metastatic UrC cases, described those patients who received chemotherapy were younger (median age: 62 *vs.* 73 years)

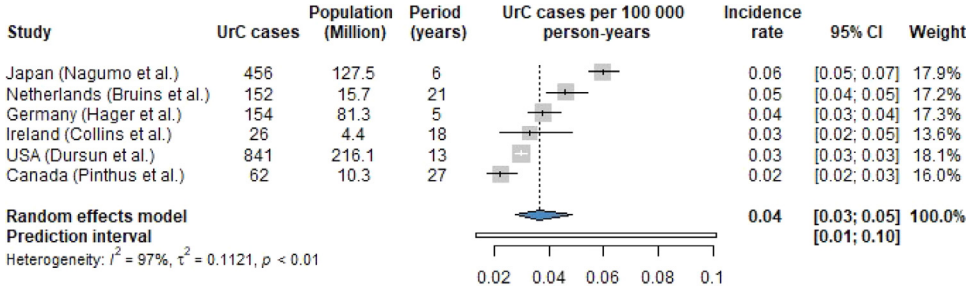

Fig. 1. Forest plot presentation of the estimated incidence rates of urachal cancer in different countries.

and more frequently underwent radical surgery (19% *vs.* 8%). The application of chemotherapy significantly increased overall survival; however, the survival benefit could only be detected in the population of younger (<70 years) patients [31]. These results highlight the importance of age as a potential factor for treatment decision.

The higher administration rate of chemotherapy in the US cases compared to the Netherlands is rather surprising when considering the higher metastatic, Sheldon stage IV rate in the Netherlands cohort [14,16]. These data reflect meaningful differences in the treatment patterns of UrC between countries and may be the result of the missing treatment recommendations. Despite this therapeutic heterogeneity the 5-year overall survival rates seem to be similar between the US, Germany and the Netherlands suggesting that different treatment approaches have only minor influence on UrC patients' survival [14,16,17]. The Japanese survival rates seem to be more favourable, which may be associated with the fact that the Japanese patients were diagnosed with the lowest distant metastasis rate among the included studies [18]. This suggests an earlier diagnosis in these patients and suggests that the early diagnosis has a more significant impact on patient' survival

Table 2
Patients' characteristics.

Variables	Country Authors	Ireland N = 26 *Collins et al.*	Netherlands N = 152 *Bruins et al.*	Germany N = 154 *Hager et al.*	Japan N = 456 *Nagumo et al.*	US. N = 841 *Dursun et al.*	US. N = 841 *Limonnik et al.*	Overall
Age	Median	na	58	64	61	58		60
Sex *n* (%)	Male	16 (62)	88 (58)	92 (60)	301 (66)	480 (57)		977 (60)
	Female	10 (38)	64 (42)	62 (40)	155 (34)	361 (43)		652 (40)
AJCC/TNM* stage *n* (%)	T1	na	na	na	69* (15)	127 (15)		127 (25)
	T2	na	na	na	201* (44)	124 (15)		124 (24)
	T3	na	na	na		92 (11)		92 (18)
	T4	na	na	na	48* (11)	169 (20)		169 (33)
Sheldon stage *n* (%)	I	na	0	na	na	na	43 (5)	43 (6)
	II	na	22 (14)	na	na	na	57 (7)	79 (10)
	III	na	85 (56)	na	na	na	349 (41)	434 (56)
	IV	na	45 (30)	na	na	na	177 (21)	222 (29)
Grade *n* (%)	G1	na	na	7 (5)	na	111 (13)		118 (16)
	G2	na	na	45 (29)	na	263 (31)		308 (42)
	G3	na	na	68 (44)	na	247 (29)		315 (43)
Metastases *n* (%)	LN+	na	15 (10)	na	48 (11)	73 (6)		136 (9)
	M+	3 (12)	40 (26)	na	49 (11)	114 (14)		206 (14)
Histology *n* (%)	AdenoCA	15 (58)	143 (95)	100 (65)	363 (80)	717 (85)		1338 (86)
	UC	7 (27)	7 (5)	33 (21)	49 (11)	86 (10)		182 (12)
	SQ	1 (4)	0	1 (1)	14 (3)	13 (2)		29 (2)
Surgery *n* (%)	Partial CE	8 (31)	81 (53)	na	na	508 (60)		597 (69)
	CE	9 (35)	20 (13)	na	na	71 (8)		100 (12)
	Excision/TURB	4 (15)	17 (11)	na	na	151 (18)		172 (20)
Margin *n* (%)	Positive	Na	15 (10)	na	na	100 (12)		115 (13)
Treatments *n* (%)	ChT	6 (23)	10 (7)	na	na	256 (30)		272 (27)
	RT	4 (15)	30 (20)	na	na	59 (7)		93 (9)

AdenoCa = adeno carcinoma histology, CE = cystectomy, ChT = chemotherapy, LN+ = lymph node metastasis, M+ = metastasis, RT = radiotherapy, SQ = squamous histology, TURB = transurethral resection of the bladder, UC = urothelial histology, US = United states of America.

* : TNM stage, ˚: same cohort, na: not available information.

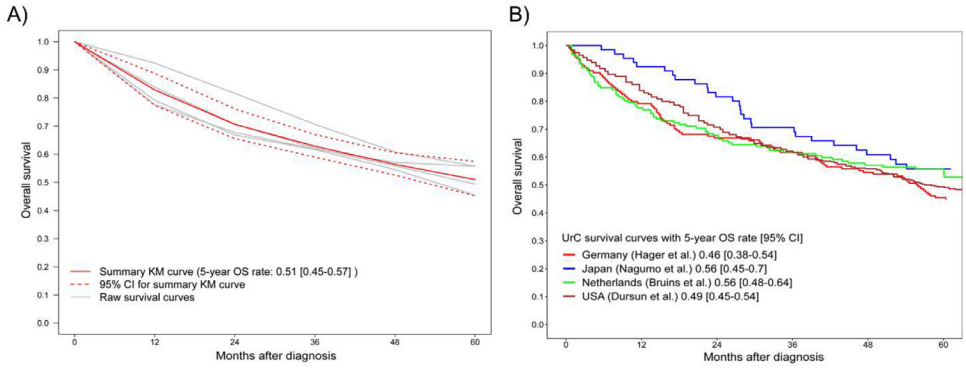

Fig. 2. Kaplan-Meier curves of overall survival for patients with urachal cancer (A) and overall survival curves stratified by different countries ($n = 1{,}123$, $P = 0.220$) (B).

then the differences in the applied therapies. In addition, also the time span of compared data between the studies has to be taken into account as diagnostic and therapeutic strategies might have shifted during the observation period.

This study has several limitations. Although, our systematic search identified a sufficient number of publications, many of these studies used the SEER database with overlapping populations and study periods and therefore had to be excluded. Despite our focus on unbiased registry-based studies, the data collection methods and thus data quality as well as the available parameters may be different in various countries and registries, which limits their comparability. Additionally, due to the complexity of the diagnostic procedure, UrC may be underdiagnosed and underreported, potentially resulting in lower case numbers than the actual reality. Furthermore, we were not able to age-standardize cancer incidence rates from different countries. Finally, searching for possible reasons for the incidence differences found among various countries was beyond the scope of this manuscript; therefore, statements in this regard are necessarily to be considered as hypothesis-generating. Despite these limitations, our approach probably provides the most accurate data for an incidence evaluation available to date.

5. Conclusions

In conclusion, performing a systematic review and meta-analysis on registry-based studies, we found important differences in the estimated incidence, histology, and treatment patterns between various countries. The incidence seems to be the highest in Japan, which may point to differences in the pathobiology of UrC in this country. However, the rate of distant metastasis and patients' survival seems to be more favourable in Japan. The notable variations in the treatment approaches for UrC among different countries can be attributed to the absence of established treatment recommendations. This emphasizes the need for the development of comprehensive treatment guidelines to provide clear directives and standards for managing UrC.

Declaration of competing interest

The authors declare no potential conflicts of interest.

CRediT authorship contribution statement

Csilla Olah: Writing – original draft, Conceptualization. **András Kubik:** Writing – original draft, Conceptualization. **Péter Mátrai:** Methodology, Formal analysis. **Marie Anne Engh:** Writing – review & editing, Methodology. **Viktória Barna:** Writing – review & editing. **Péter Hegyi:** Writing – review & editing, Methodology. **Henning Reis:** Writing – review & editing, Conceptualization. **Péter Nyirády:** Writing – review & editing. **Tibor Szarvas:** Writing – original draft, Conceptualization.

Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2024.03.011.

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