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Incidence and survival of rare urogenital cancers in Europe

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ABSTRACT

Background: The RARECARE project aims at increasing knowledge of rare cancers in Europe. This manuscript describes the epidemiology (incidence, prevalence, survival) of rare urogenital cancers, taking into account the morphological characterisation of these tumours. **Methods:** We used data gathered by RARECARE on cancer patients diagnosed from 1995 to 2002 and archived in 64 European population-based cancer registries, followed up to December 31st, 2003 or later.

Results: The annual number of males that develop penile cancer in the EU is estimated at 3100, which is equivalent to an age standardised rate (ASR) of 12 per million males. The 5-year relative survival rate is 69%, while squamous cell carcinoma is the predominant morphological entity. Each year around 650 persons in the EU develop cancer of the urethra and 7200 develop cancer of the renal pelvis or ureter (RPU). The ASR for cancer of the urethra and RPU is 1.1 (males 1.6; females 0.6) and 12 (males 16; females 7) per million inhabitants, respectively. The 5-year relative survival rate for cancer of the urethra and RPU is 54% and 51%, respectively. Transitional cell carcinoma is the predominant morphological entity of cancer of the urethra and RPU.

Conclusions: In view of the low number of cases and the fact that one third to one half of the patients die of their disease, centralisation of treatment of these rare tumours to a select number of specialist centres should be promoted.

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1. Introduction

In this review we have identified three main groups of rare urogenital cancers: cancer of the penis, cancer of the urethra and cancer of the upper urinary tract (renal pelvis and ureter).

Cancer of the penis is the rarest cancer of the male genital tract, especially in Islamic countries and Israel.¹ Compared to

Europe and North America, the incidence is higher in Asia, Africa and South America. The highest rate world-wide was reported for Brasilia (Brazil) during 1998–2001 and amounted to an age standardised rate (ASR) of 40 per million males.

Risk factors for the development of penile cancer are multifactorial. The presence of phimosis has been shown to be strongly associated with the risk of developing penile

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cancer in a number of studies.^{2,3} Circumcision is known to protect against penile cancer.⁴ Neonatal circumcision may be an explanation for the very low penis cancer incidence in Israel and Islamic countries, where the vast majority of the male population is circumcised in the neonatal period. In contrast, those circumcised after infancy have a higher risk, similar to those not circumcised.⁵ The mechanism for the protection conveyed by early circumcision is multi-factorial. From a pure anatomical perspective circumcision may prevent roughly one third of penile cancers as about one third of penile cancer is cancer of the foreskin. The remaining cancers mostly originate in the glans penis.

Parkin and Bray estimated that 40% of penile cancers are attributable to infection with human papilloma virus (HPV).⁶ HPV-16 and HPV-18 are the most common types involved.⁷ Uncircumcised males generally have a higher HPV prevalence,⁸ which is probably caused by a reduced clearance of the HPV infection in comparison to circumcised men.⁹ Circumcision may therefore protect against HPV associated disease by enhancing the resolution of infection. Other risk factors include HIV infection, cigarette smoking, history of trauma and chronic balanitis.

Cancer of the urethra occurs in both sexes and its aetiology is multifactorial. HPV infection may also be a risk factor for cancer of the urethra, but HPV prevalence in the male urethra is much lower than in the penis.¹⁰ Wiener reported the presence of oncogenic genotypes HPV-16 and HPV-18 in 59% of female patients with urethral carcinoma.¹¹ There seems also to be a correlation with recurrent urinary tract infections, clean intermittent catheterisation and cancer of the urethra.¹² In addition, a history of sexually transmitted diseases and urethral strictures appear to increase the risk of urethral cancer.

The main risk factors for cancer of the renal pelvis and ureter are smoking, long-term use of analgesics and laxatives, as well as several occupational exposures.^{13,14} Comparative population-based studies regarding the age standardised incidence of cancer of the renal pelvis, ureter and urethra are not known to us. Moreover, these subsites are not included in Globocan or Cancer Incidence in Five Continents.^{1,15}

This manuscript describes the epidemiology (incidence, prevalence, survival) of rare urogenital cancers in Europe, taking into account the morphological characterisation of the tumours. With this extra information we were able to define cancer entities with clinical relevance. The present study benefits from a large population-based series of data, collected in the framework of the EC funded project 'Surveillance of rare cancer in Europe' (RARECARE).¹⁶ For the first time, prevalence will be provided for these cancers. For rare diseases prevalence is a crucial indicator, since the EU Directive on orphan drugs bases the definition of rare diseases on prevalence.¹⁷

2. Patients and methods

For this study we selected data regarding rare urogenital cancers from the RARECARE database.¹⁸ Rare urogenital cancers that are described in this article include epithelial cancers of the penis (ICD-O-3 topography code C60), the urethra (C68.0), as well as the renal pelvis (C65) and the ureter (C66). The renal pelvis and the ureter (RPU) were analysed together.

The following morphology groups were distinguished for penis: squamous cell carcinoma (ICD-O-3 morphology codes 8020–8022, 8050–8084, 8123) and adenocarcinoma (8140–8147, 8190, 8200–8201, 8210–8211, 8230–8231, 8255–8263, 8310, 8323, 8440, 8480–8490, 8504, 8510, 8512, 8514, 8525, 8542, 8550–8576, 8940). For the urethra and RPU we distinguished transitional cell carcinoma (8020–8022, 8031, 8050, 8082, 8120, 8122, 8130–8131), squamous cell carcinoma (8051–8076, 8123) and adenocarcinoma (8140–8141, 8143, 8147, 8190, 8200–8201, 8211, 8221, 8230–8231, 8255, 8260–8263, 8290, 8310, 8320, 8323, 8430, 8480–8490, 8510, 8512, 8514, 8525, 8542, 8560, 8570).

The analysis was carried out on 5016 epithelial cancers of the penis diagnosed in Europe during 1995–2002, 1059 epithelial cancers of the urethra as well as 11,669 epithelial cancers of the RPU. The incidence analysis considered cases incident from 1995 to 2002 from 64 cancer registries (CRs) covering 32% of the population of the 27 Member States of the EU (EU27). The CRs were grouped by country and the countries were grouped into regions: Northern Europe (Iceland, Norway, Sweden), United Kingdom and Ireland (England, Scotland, Wales, Northern Ireland, Republic of Ireland), Central Europe (Belgium, Austria, France, Germany, The Netherlands, Switzerland), Eastern Europe (Poland, Slovakia), and Southern Europe (Italy, Malta, Portugal, Slovenia, Spain).

Incidence rates were estimated as the number of new cases occurring in 1995–2002 divided by the total person-years in the general population (male and female) in the CR areas considered, over the same period. For age-standardised rates (ASRs), the European population was used.

All CRs had vital status information available up to December 31st, 2003 or later. The prevalence per million was estimated at the index date of January 1st, 2003. The counting method based on CR incidence and follow-up data, was applied to CR data from 1988 to 2002.¹⁹ Only data from 22 registries from 12 countries, covering the whole 15-year period with geographical representation of the five defined regions and assumed to be representative for the EU27 as a whole, were used for prevalence estimation in EU27. The completeness index method was used to estimate complete prevalence, and involved adding the estimated number of surviving cases diagnosed prior to 1988 to those counted in 1988–2002.²⁰ The expected number of new cases per year and of prevalent cases in Europe (EU27) was estimated by multiplying the crude incidence and prevalence rates to the 2008 European population (497.5 million) provided by EUROSTAT.

We estimated relative survival rates (RSRs) in the period 2000–2002 by the Hakulinen method, as the ratio of observed survival to the expected survival in the general population of the same age and sex.²¹ Relative survival was estimated by the period approach.²²

Overall, 1.2% of the penis cancers, 1.6% of urethra and 1% of the cases of RPU were 'death certificate only' (DCO). For 3–6% of the cases an unspecified morphology code was registered, while 94% of the penis cancers, 93% of urethra cancers and 92% of RPU cancers were microscopically verified. 1–1.5% of the cases were censored before five years of follow-up.

Table 1 – Incidence of rare urogenital cancers in Europe according to sex and age group, 1995–2002.

Entity	Total		Sex						Age group								Estimated number of cases arising in EU27 per year*
			Male			Female			<55 years		55–64 years		65–74 years		75+ years		
	Observed number of cases in 1995–2002	Crude rate per million	SE	ASR	SE	ASR	SE	Rate per million	SE	Rate per million	SE	Rate per million	SE	Rate per million	SE		
Epithelial tumours of the penis	5016	6.2	0.1	11.7	0.2			1.8	0.1	12.6	0.4	18.7	0.5	27.4	0.7	3101	
Squamous cell carcinoma and variants of penis	4611	5.7	0.1	10.8	0.2			1.7	0.1	11.9	0.4	17.1	0.5	24.2	0.7	2851	
Adenocarcinoma and variants of penis	40	0.0	0.0	0.1	0.0			0.0	0.0	0.1	0.0	0.1	0.0	0.3	0.1	25	
Epithelial tumours of the urethra	1059	1.3	0.0	1.6	0.1	0.6	0.0	0.2	0.0	2.1	0.2	4.7	0.3	7.6	0.4	655	
Transitional cell carcinoma of urethra	678	0.8	0.0	1.2	0.1	0.2	0.0	0.1	0.0	1.3	0.1	3.3	0.2	5.0	0.3	419	
Squamous cell carcinoma and variants of urethra	170	0.2	0.0	0.2	0.0	0.1	0.0	0.0	0.0	0.4	0.1	0.7	0.1	1.0	0.1	105	
Adenocarcinoma and variants of urethra	108	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.2	0.1	0.3	0.1	0.7	0.1	67	
Epithelial tumours of the renal pelvis and ureter	11,669	14.5	0.1	16.5	0.2	7.3	0.1	1.8	0.1	26.5	0.6	60.3	0.9	73.6	1.1	7215	
Transitional cell carcinoma of the renal pelvis and ureter	10,355	12.9	0.1	14.8	0.2	6.4	0.1	1.6	0.1	23.9	0.5	54.9	0.9	63.1	1.1	6403	
Squamous cell carcinoma and variants of the renal pelvis and ureter	215	0.3	0.0	0.3	0.0	0.2	0.0	0.0	0.0	0.4	0.1	1.0	0.1	1.5	0.2	133	
Adenocarcinoma and variants of the renal pelvis and ureter	191	0.2	0.0	0.3	0.0	0.1	0.0	0.1	0.0	0.5	0.1	1.0	0.1	0.7	0.1	118	
ASR = age standardised rate (per million). SE = standard error.																	
* Including areas not covered by the RARECARE database.																	

Table 4 – One- and five-year survival rates of rare urogenital cancers in Europe; period survival analysis 2000–2002.

Entity	Cases analysed	Duration					
		1 year			5 years		
		Observed survival	Relative survival		Observed survival	Relative survival	
	N	%	%	SE	%	%	SE
Epithelial tumours of the penis	1555	81.8	85.7	1.1	54.6	68.9	1.6
Epithelial tumours of the urethra	340	67.9	71.5	2.8	41.8	53.8	3.5
Epithelial tumours of the renal pelvis and ureter	4021	71.8	74.8	0.8	41.1	51.3	1.0

3.2. Prevalence

Table 3 shows the observed prevalence proportion at 2, 5, and 15 years of follow-up and the estimated complete prevalence in EU27 (index date January 1st, 2003). About 82,000 persons were alive in the EU27 at the beginning of the year 2008 with a past diagnosis of rare urogenital cancers: 27,500 males with cancer of the penis, 4300 persons with cancer of the urethra and 50,000 with cancer of RPU. Of the total

prevalence (all rare urogenital cancers combined), 20% and 41% were diagnosed within 2 and 5 years before the prevalence date, respectively. The difference between the 2 and 5 year prevalence (21%) represents the proportion of cases in the 3rd–5th year after diagnosis, presumably undergoing clinical follow-up. The remaining fraction of 59% represents long-term survivors, which are probably cured, and 18,000 of these (22% of the total) were those surviving more than 15 years after diagnosis.

Table 5 – Five-year period survival rates of rare urogenital cancers in Europe according to site, sex, age group and region, 2000–2002.

		Cases analysed	Five-year relative survival	
		N	%	SE
<i>Epithelial tumours of the penis</i>				
Sex	Male	1555	68.9	1.6
Age	<65	681	73.3	1.9
	65+	888	64.8	2.5
European region	Northern	313	72.4	3.7
	Central	388	70.8	3.4
	Eastern	116	52.6	6.0
	Southern	293	68.4	4.0
	UK and Northern Ireland	570	69.7	2.8
	Total	1555	68.9	1.6
<i>Epithelial tumours of the urethra</i>				
Sex	Male	239	53.2	4.2
	Female	105	56.0	6.2
Age	<65	109	66.7	5.2
	65+	239	47.7	4.3
European region	Northern	73	55.1	7.9
	Central	116	55.6	6.2
	Eastern	9	43.0	19.6
	Southern	65	61.0	8.4
	UK and Northern Ireland	94	46.5	6.6
	Total	340	53.8	3.5
<i>Epithelial tumour of the renal pelvis and ureter</i>				
Sex	Male	2477	53.1	1.3
	Female	1560	48.4	1.6
Age	<65	1116	57.8	1.6
	65+	2932	48.1	1.2
European region	Northern	711	53.8	2.3
	Central	1189	48.4	1.9
	Eastern	253	49.3	4.0
	Southern	773	58.2	2.3
	UK and Northern Ireland	1201	48.7	1.8
	Total	4021	51.3	1.0

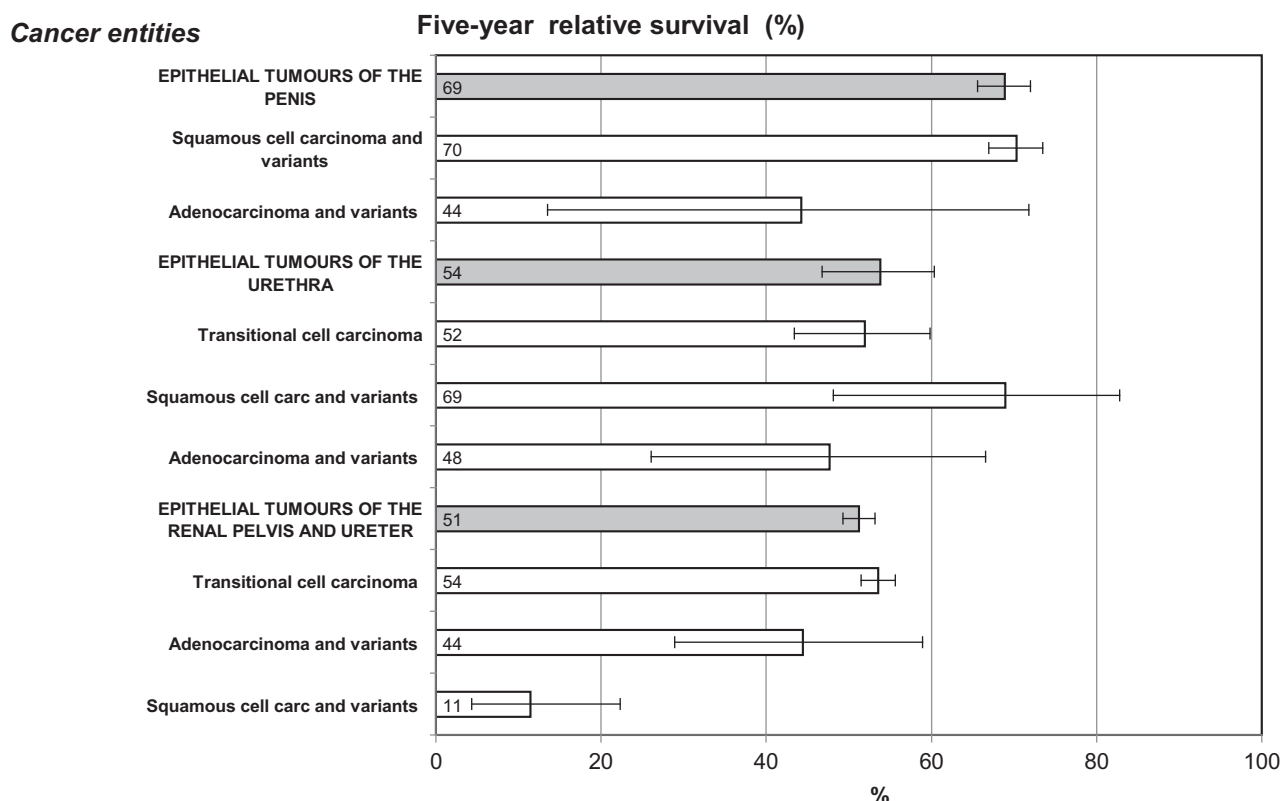


Fig. 1 – Five-year relative survival rates (and 95% confidence intervals) of rare urogenital cancers in Europe by entity.

3.3. Survival

Table 4 presents the period survival for the years 2000–2002 for rare urogenital cancers. Both observed and relative survival, together with the estimated standard error of relative survival, are shown at one and five years after diagnosis.

The 1 and 5-year relative survival rate (RSR) of penis cancer was 86% and 69%, respectively. Throughout Europe there is limited variation in the survival of penis cancer, with the exception of Eastern Europe, where the 5-year RSR (53%) is clearly below the European average (Table 5). Survival of adenocarcinoma of the penis (44%) is much lower than survival of squamous cell carcinoma of the penis (70%), but the confidence intervals overlap (Fig. 1).

The 1 and 5-year RSR of cancer of the urethra were 71% and 54%, respectively, while the rates for cancer of the RPU were 75% and 51%, respectively. For cancer of the urethra there is some regional variation within Europe in the 5-year RSR (range 43–61%), but this was not statistically significant (Table 5). For cancers of the RPU geographical variation in RSRs is limited (range in 5-year RSR 48–58%). Elderly patients (65 or older) have a lower RSR than younger patients, while women with cancer of the RPU have a somewhat lower RSR than males (48% versus 53%, Table 5). For cancers of the urethra, the 5-year RSR of squamous cell carcinoma is highest (69%), followed by transitional cell carcinoma (52%) and adenocarcinoma (Fig. 1). However, due to small numbers the confidence intervals of the three entities overlap. For cancers of the RPU the results are opposite to the urethra, with the low-

est survival rate for squamous cell carcinoma (only 11%) and the highest for transitional cell carcinoma (54%).

4. Discussion

The annual number of males that develop penile cancer in the EU is estimated at 3100, which is equivalent to an ASR of 6 per million males + females or 12 per million males. The 5-year relative survival rate is 69%, while squamous cell carcinoma is the predominant morphological entity. Each year around 650 persons in the EU develop cancer of the urethra and 7200 develop cancer of the renal pelvis or ureter. The ASR for cancer of the urethra is 1.6 and 0.6 per million males and females, respectively, while the ASR for cancer of the RPU is 16.5 and 7.3 per million males and females, respectively. The 5-year relative survival rate for cancer of the urethra and RPU is 54% and 51%, respectively. Transitional cell carcinoma is the predominant morphological entity of cancer of the urethra and RPU. The RSR of squamous cell carcinoma of the RPU is significantly lower than that of transitional cell carcinoma of the RPU.

The incidence of penile cancer in Europe is intermediate compared to the high rates (ASR 20 per million males or higher) in some South-American (Brazil, Colombia) and African countries (Uganda) and very low rates (ASR 3 per million males or lower) in Israel and several Islamic countries (Bahrain, Pakistan, Egypt, Turkey, Kuwait).¹ Also in several Asian populations (Korea, Japan) very low rates exist. As HPV infection is an important risk for penile cancer and

circumcision is protective, the intermediate position of Europe can be explained by moderate rates of HPV-infection in a generally uncircumcised male population.²³

The 5-year RSR of penile cancer in this study in Europe (69%) was slightly lower than in the USA (74%).²⁴ However, in a previous European study the 5-year relative survival of cases with penis cancer diagnosed during 1995–1999 (74%) was equal to the rate in the USA, with rates ranging from 63% in Scotland, Malta and Slovenia to 88% in the Netherlands.²⁵ As in the latter country, there is one specialised hospital for the treatment of penile cancer which treats patients from all over the country, the high survival rate in this country advocates the centralisation of the treatment of penile cancer. Centralisation in the United Kingdom also improved outcomes.²⁶ However, we do not possess detailed information about centralisation in other countries, nor do we have information about centralisation in the RARECARE database, so also other factors may be involved. Survival in Eastern Europe (52%) in the present study is significantly lower than in other European regions (range 68–72%), possibly due to patient delay in Eastern Europe, which results in unfavourable stages.²⁷ Unfortunately, stage data were not available in this study.

For cancer of the renal pelvis, ureter or urethra comparison with other registries may be biased by differences in registration and classification practices. In the 9th edition of the International Classification of Diseases and the 1st edition of the International Classification of Diseases for Oncology these cancers are grouped together with kidney cancer and many registries still report these cancers combined. However, as far as can be concluded from these combined data, cancer of the renal pelvis, ureter and urethra is rare everywhere.

The male to female incidence ratio of cancer of the urethra was 2.9. This high ratio is probably related to the longer length of the male urethra (15–20 cm versus 3–4 cm in females). Population-based incidence data for cancer of the urethra are scarce. Schwarz reported an ASR in the USA of 4.3 per million males and 1.5 per million females, with rates in blacks being twice as high as in whites.²⁸

Our study reported a higher incidence of transitional cell carcinoma of the RPU in males than in females. The male to female ratio of cancer of the RPU was 2.3 in our study, which is much lower than the male to female ratio for bladder cancer in the EU (4.7).¹⁵ Although the epithelium of the bladder is little different from the epithelium of the renal pelvis and ureter, the different male-to-female ratio suggests a different importance of the various etiological factors. Smoking is the most important factor for bladder cancer and as smoking patterns in Europe still show large differences between males and females, bladder cancer is much more common in males than in females. Although smoking is also a risk factor for cancer of the renal pelvis and ureter, the long-term use of analgesics and laxatives,^{13,14} which is a strong risk factor for cancer of the renal pelvis and ureter and which is probably as widespread among females as among males, reduces the male to female ratio.

Upper tract urothelial neoplasms, comprising cancers of the renal pelvis and ureter, are rare with ASRs reported for the USA of 17 per million for cancer of the RPU.²⁹ Many European cancer registries do not report detailed incidence data for cancer of the renal pelvis and ureter. In Belgium in 2006,

the ASR for cancer of the RPU was 18 per million for males and 8 for females.³⁰ ASRs in the Netherlands for 2004–2008 are roughly the same: 15 and 7 for cancer of the RPU in males and females, respectively.³¹ The rates in these countries are slightly higher than the European average in our study, but almost equal to the rates we found for Central Europe.

In the Netherlands, a relative survival rate for upper tract urothelial neoplasms of 45% was reported for invasive cases diagnosed during 1998–2007, ranging from 77% for TNM-stage I to 10% for TNM-stage IV.³¹ SEER reported a RSR of 89% for localised tumours and 16.5% for distant lesions²⁹ and a RSR of 56% for all cancers of the ureter combined,²⁴ compared to 51% for cancer of the RPU in Europe. Like in Europe, survival of transitional cell carcinoma in the USA is 2% higher than all cancers combined. Differences in survival between countries may be explained by differences in stage at diagnosis, but also by differences in treatment outcome, which – in the case of rare tumours – may be effected by timely and appropriate referral of patients to centres of expertise and reference networks.¹⁶ Survival of squamous cell carcinoma and adenocarcinoma of the RPU was clearly poorer than that of transitional cell carcinoma. Our study lacks data about stage, but several studies have pointed out that the stage distribution of squamous cell carcinoma and adenocarcinoma of the RPU is relatively unfavourable in comparison to transitional cell carcinoma, with a consecutive poor survival.^{32,33} Therefore, the most likely explanation for our finding is that the poor survival of squamous cell carcinoma and adenocarcinoma of the RPU is related to a less favourable stage distribution. However, the reason for this unfavourable stage distribution is unclear. Possibly transitional cell carcinoma causes bleedings in an earlier stage and therefore is discovered earlier. Diagnostic delay may also be the reason for the lower survival of cancer of the RPU in females, which is also known for bladder cancer survival in females.³⁴

The definition of cancer entities is in some ways arbitrary. According to the definition as developed by RARECARE experts, several interesting rare urogenital cancers were not included in this paper. Among others, this is the case for melanoma of the genitals (included in ‘melanoma of mucosa’) and scrotal carcinoma (included in ‘epithelial tumours of skin’). Especially the latter cancer has drawn the attention of researchers in the past because of its distinct aetiology and occupational hazards (chimney sweepers).³⁵ However, a recent Dutch study of Verhoeven et al. (unpublished data from the Comprehensive Cancer Centre South and Comprehensive Cancer Centre the Netherlands) suggests that the occupational hazards no longer influence the risk of scrotal cancers, which would justify the RARECARE grouping of scrotal skin cancers with other skin cancers. A second study from the Netherlands revealed that scrotal cancers are very rare and that the incidence was stable during the past two decades.³⁶

In summary, in this study we present for the first time epidemiological data of rare urogenital cancers throughout Europe. In view of our observation that roughly one third to one half of the patients with these cancers do not survive their illness and that these are very rare cancers, centralisation of treatment to a select number of specialist centres should be promoted. Besides, further collaborative research

into aetiology and treatment seems necessary to reduce the occurrence and to improve the treatment outcome of patients with these rare cancers.

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Conflict of interest statement

None declared.

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