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Original article

Penile cancer − Incidence, mortality, and survival in Saxony, Germany

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Abstract

Objective: Penile cancer is a rare disease in Europe and North America. Cancer registry data were used to estimate the incidence, mortality, and survival of penile cancer in Saxony, Germany.

Methods: Data on incidence were analyzed for the period 1961 to 2012 and mortality for the period 1990 to 2012. Trend analyses of incidence and mortality were performed using joinpoint regression. Survival rates for primary penile cancer (ICD-10 C60) were estimated; overall, by T stage, UICC stage, and by year of diagnosis for the years 1963 to 2012.

Results: Age-standardized incidence increased from 1.2 per 100,000 in 1961 to 1.8 per 100,000 in 2012, with a statistically significant increase between 2003 and 2012 (annual percent change: 4.66; 95% confidence interval, CI 0.62−8.86). There was a statistically significant negative trend in mortality between 1990 and 2012 (annual percent change: −3.46, 95% CI −5.21 to −1.67). A total of 430 new cases of penile cancer were registered between 2003 and 2012, with 63% of all penile cancers occurring in men aged 60 to 79 years. Almost half of those cases were located at the glans penis. The overall relative 5-year survival for the years of diagnosis 2003 to 2012 was 72.4% (95% CI 64.8%−80.0%). Relative 5-year survival decreased with higher UICC stages (I: 96%, 95% CI 84.7%−107.3%; II: 86.3%, 95% CI 71.0%−101.5%; III: 39.6%, 95% CI 19.9%−59.3%; IV: 20.3%, 95% CI 2.4%−38.2%).

Conclusion: The incidence of penile cancer in Saxony has increased in recent years, while mortality has decreased. However, survival rates have remained constant over time.

Keywords: Penile cancer; Incidence; Mortality; Survival; Saxony; Germany

Abbreviations: ESR, European Standardized Rate; WSR, World Standardized Rate; HPV, human papillomavirus; SCC, squamous cell carcinomas; CCR, Common Cancer Registry; NCR, National Cancer Registry; TNM, Tumor-Node-Metastasis Classification of Malignant Tumors; UICC, Union for International Cancer Control; APC, annual percent change; DCO, death certificate only; STIKO, the German Standing Committee on Vaccination

1. Introduction

Penile cancer is a rare disease in Europe and North America [1,2]. Age-standardized (world standardized rate [WSR]) incidence in Europe between 1998 and 2002 ranged from 0.5 per 100,000 in Finland to 1.1 per 100,000 in Denmark, Portugal, and Iceland [3]. The incidence and mortality of cancers of the penis and other male genital organs has been low and stable over time in the Nordic countries, with an age-standardized (WSR) incidence of approximately 0.9 per 100,000 since the 1960s and a

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mortality rate of just above 0.2 per 100,000 since the 1970s [1]. The overall incidence (US standard population) of primary, malignant penile cancer from 1973 to 2002 in the United States was 0.69 per 100,000, with a statistically significant decrease over time: 0.84 per 100,000 in 1973−1982 to 0.69 per 100,000 in 1982−1992 to 0.58 per 100,000 in 1993−2002 [2]. Although the incidence rate of penile cancer in most Western countries is less than 1 per 100,000, incidence rates greater than this are observed in India, Southeast Asia, Latin America, and in Eastern and Southern Africa [4]. One of the world's highest penile cancer incidence rates is found in Brazil, with an incidence rate of 3.3 per 100,000 recorded in Goiânia [4]. An increase in penile cancer mortality was also reported in Brazil, with a statistically significant annual percent change (APC) of 1.4% during the period 1996 to 2010 [5].

Relative survival rates for patients with penile cancer and other male genital organs were stable over time in Finland and Sweden and increased in Norway and Denmark during the 1980s [1]. The relative 5-year survival rate was 80% in Norway, 74% in Denmark, 70% in Sweden, and 62% in Finland for patients diagnosed between 1999 and 2003 [1]. In the United States, relative 5-year survival of penile cancer decreased from 72% in 1990−1995 to 63% in 2002−2007 [6]. As penile cancer is a rare disease, only few data have been available on incidence, mortality, and survival of penile cancer patients in Germany [7,8].

Most malignant lesions of the penis are squamous cell carcinomas [9−11]. Penile cancer is most prevalent in men aged 60 years and older [2,9,11]. Some insight into the risk factors associated with penile cancer has been gained in recent years, however, many aspects of this malignancy are still poorly understood. The following risk factors for the development of penile cancer have been investigated: living alone, not currently being married, no circumcision in childhood, phimosis, poor genital hygiene, chronic balanitis, tobacco consumption, high number of sexual partners, genital warts, and infection with high-risk human papillomavirus (HPV) [12−17]. There is distinct geographic variation in the distribution of penile cancer, with higher incidence rates in the developing world [4]. This may point toward an association with socioeconomic status, prevalence of infection with HPV as well as religious and cultural beliefs.

The Common Cancer Registry (CCR) registers epidemiological data of tumor cases for Berlin and the 5 federal states of Brandenburg, Mecklenburg-Western Pomerania, Saxony-Anhalt, Saxony, and Thuringia. The CCR replaced the National Cancer Registry, which was established in 1952/1953 in the former German Democratic Republic. After German reunification in 1989/1990, the legal situation became uncertain, with notification no longer being required by law and the rate of notifications therefore decreasing. In 1993, the reporting of cancer cases to the CCR became mandatory again [18,19].

The entire population of the federal state of Saxony, which had 4.3 million residents in 2003 and 4.1 million residents in 2012, is covered by 5 population-based regional clinical cancer registries. All 5 clinical cancer registries transfer a defined epidemiological dataset to the CCR on a regular basis. Rarely, office-based physicians directly report to the CCR. As a further data source, the CCR receives all death certificates within its catchment area. The overall completeness of cancer registration in Saxony was estimated to be above 95% for the diagnosis years 2007 and 2008 [20].

The objective of this analysis was to examine the epidemiology of penile cancer (ICD-10 C60) in Saxony, Germany. Trends in incidence (1961−2012), mortality (1990−2012), and survival (1963−2012) of penile cancer in Saxony were investigated using data from the CCR as well as from the Federal German Statistical Office.

2. Methods

Incidence and survival in Saxony were estimated using CCR data, while data on mortality rates were obtained from the Federal German Statistical Office. To allow for comparison with international data, incidence rates were standardized with the European (European Standardized Rate [ESR], old European population) as well as the world populations (World Standardized Rate [WSR]) for the years 1961 to 2012. Incidence estimates include death certificate only (DCO) cases unless otherwise stated. Mortality rates standardized with the European (ESR) and world populations (WSR) for the years 1990 to 2012 were calculated. To provide insight into the past decade, cases documented between 2003 and 2012 were analyzed in greater detail with regards to age and tumor localization. Trend analyses for incidence and mortality for the respective periods were performed using joinpoint regression. The period 1990 to 1994 was excluded from the incidence trend analysis as these years were characterized by under-reporting of cases following German reunification. A sensitivity analysis including the period 1990 to 1994 was also conducted. APC and the respective 95% confidence intervals (CIs) were estimated to investigate changes in trends for the respective time periods.

Penile cancer cases were classified according to the International Classification of Diseases for Oncology (ICD-O) [21]. Only cases with malignant, primary tumors were included in the analyses. T stage was classified as T1, T2, T3, and T4, as well as Union for International Cancer Control (UICC) I, II, III, and IV according to the International Tumor-Node-Metastasis (TNM) Classification of Malignant Tumors and the classification of the UICC [22]. For stages T1 to T4, tumor patients were classified according to the degree of local invasion, i.e., whether the tumor infiltrated subepithelial connective tissue (T1), the corpus spongiosum or cavernosum (T2), the urethra (T3) or other nearby structures such as the pubic bone, the scrotum, or

the prostate (T4). For the UICC stages, tumor patients were classified according to whether the cancer was confined to the glans or the prepuce (I), had invaded the shaft or corpora (II), had spread to the inguinal lymph nodes (III), or had distantly metastasized (IV). The UICC classification takes the size of the tumor (T), the degree of spread to regional lymph nodes (N), and the presence of metastases (M) into account.

The 1-year and 5-year relative survival rates were estimated for the years of diagnosis 1963 to 1972 (period: 1968–1972), 1980 to 1989 (period: 1985–1989), and 2003 to 2012 (period: 2008–2012) using the period analysis approach based on life table survival estimates [23,24]. For the years of diagnosis 2003 to 2012, survival was stratified by T stages and UICC stages. Estimates of survival included only primary tumors.

Trend analyses were performed with the Joinpoint Regression Program (Version 4.2.0.2, Statistical Research and Applications Branch, National Cancer Institute, Bethesda, MD). For the survival analyses, the program "R" and the module "periodR" were used [24].

3. Results

The age-standardized incidence rate (ESR) of penile cancer in Saxony increased from 1.2 per 100,000 in 1961 to 1.8 per 100,000 in 2012 (Table 1, Fig. 1). There was a statistically significant positive trend in incidence for the period 2003 to 2012 (APC: 4.66, 95% CI 0.62–8.86), while no statistically significant trend was found for the period 1961 to 2003 (APC: 0.08, 95% CI −0.41 to 0.57). The sensitivity analysis, which included the years 1990 to 1994, showed similar results, although the shift in the incidence trend occurred earlier, in 1997. No statistically significant trend was found for the period 1961 to 1997 (APC: −0.28, 95% CI −0.93 to 0.37), although a statistically significant positive trend was found for the period 1997 to 2012 (APC: 3.10, 95% CI 1.09–5.16).

During the years 2003 to 2012, 430 incident cases of penile cancer were reported, including 7 DCO cases (1.6%). The crude incidence rate was 2.1 per 100,000 and the age-standardized incidence rate (ESR) 1.5 per 100,000. The incidence rate (ESR) increased from 0.9 per 100,000 in 2003 to 1.8 per 100,000 in 2012 (Table 1, Fig. 1). During this period, most incident penile cancers occurred in men aged 60 to 79 years (63%) and only a few men were diagnosed with penile cancer before age 50 years (7%) (Table 2). Almost half of all penile cancer cases (47%) were located at the glans penis (C60.1) followed by prepuce (C60.0, 19%), penis unspecified (C60.9, 15%), overlapping lesions of penis (C60.8, 10%), and body of penis (C60.2, 9%) (Table 2).

The age-standardized mortality rates (ESR) varied over the years, decreasing after a peak in the early 1990s (Table 1, Fig. 1). A statistically significant negative trend in mortality was found for the period of 1990 to 2012 (APC: −3.46, 95% CI −5.21 to −1.67) (Fig. 1). During 2003 to 2012, 100 deaths due to penile cancer were reported, resulting in a crude mortality rate of 0.5 per 100,000 and an age-standardized

Table 1
Incidence ($n = 1\,634$), 1961–2012 and mortality ($n = 352$), 1990–2012 of primary penile cancer patients (ICD-10 C60), Saxony.

Y	Incidence per 100,000			Mortality per 100,000		
	Crude	ESR	WSR	Crude	ESR	WSR
1961	1.1	1.2	0.7			
1962	1.2	1.1	0.7			
1963	0.9	0.9	0.6			
1964	1.4	1.3	0.9			
1965	1.4	1.3	0.9			
1966	1.3	1.1	0.8			
1967	1.1	0.9	0.7			
1968	0.8	0.7	0.5			
1969	1.3	1.2	0.9			
1970	1.3	1.1	0.7			
1971	1.5	1.3	1.0			
1972	1.4	1.2	0.8			
1973	1.1	1.1	0.7			
1974	1.2	1.2	0.8			
1975	1.4	1.1	0.8			
1976	2.0	1.7	1.1			
1977	1.2	1.1	0.8			
1978	1.3	1.2	0.8			
1979	1.5	1.4	0.9			
1980	1.4	1.3	0.9			
1981	1.2	1.3	0.9			
1982	0.9	0.8	0.6			
1983	1.0	1.0	0.7			
1984	1.1	1.1	0.7			
1985	1.2	1.3	0.9			
1986	1.0	0.9	0.6			
1987	1.2	1.2	0.8			
1988	0.9	1.0	0.7			
1989	1.3	1.4	0.9			
1990	1.5	1.4	0.9	0.4	0.3	0.2
1991	1.3	1.3	0.9	0.8	0.8	0.5
1992	0.9	0.8	0.6	0.9	0.9	0.6
1993	0.8	0.7	0.5	0.6	0.6	0.4
1994	0.9	0.8	0.6	0.5	0.5	0.3
1995	1.0	1.0	0.7	0.2	0.2	0.2
1996	1.1	1.0	0.7	0.5	0.5	0.4
1997	0.9	0.8	0.6	0.5	0.5	0.3
1998	1.7	1.5	1.1	0.4	0.4	0.2
1999	1.2	1.0	0.7	0.4	0.3	0.2
2000	1.3	1.2	0.8	0.5	0.5	0.3
2001	1.5	1.3	0.9	0.6	0.5	0.3
2002	1.8	1.6	1.1	0.6	0.5	0.3
2003	1.1	0.9	0.6	0.5	0.4	0.2
2004	1.6	1.2	0.8	0.4	0.3	0.2
2005	1.3	1.0	0.6	0.4	0.4	0.2
2006	2.2	1.5	1.0	0.5	0.4	0.2
2007	2.4	1.7	1.2	0.2	0.2	0.1
2008	2.3	1.6	1.1	0.6	0.5	0.3
2009	2.6	1.8	1.3	0.6	0.4	0.2
2010	2.1	1.5	1.1	0.7	0.4	0.3
2011	2.4	1.5	1.0	0.4	0.3	0.2
2012	2.9	1.8	1.2	0.5	0.3	0.2

ESR = standardized with the old European population; WSR = standardized with the World population.

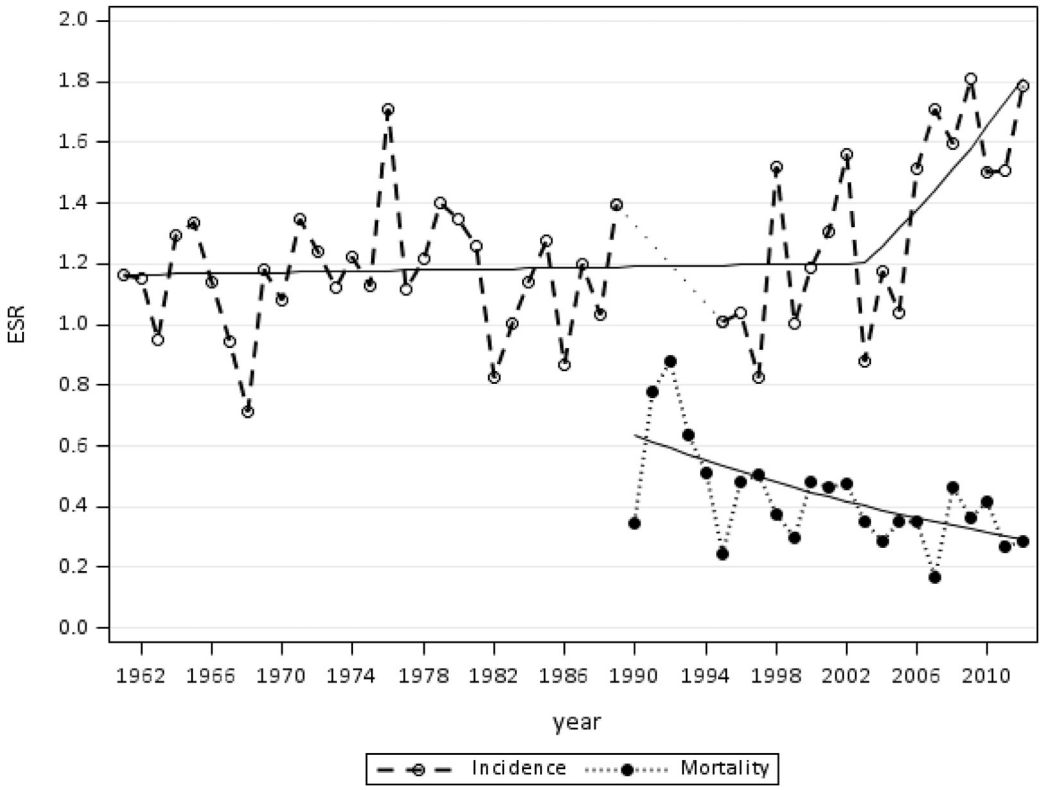

Fig. 1. Standardized incidence and mortality rates of penile cancer per 100,000, Saxony, age-standardized (ESR): 1,577 cases of penile cancer (including DCO cases) for the years 1961−2012 and 252 cases of death for the years 1990−2012 from primary penile cancer*. (*Joinpoint regression results indicated as solid lines; the years 1990−1994 were excluded from the incidence analysis.)

mortality rate (ESR) of 0.4 per 100,000. The mortality rate (ESR) decreased slightly from 0.4 per 100,000 in 2003 to 0.3 per 100,000 in 2012 (Table 1, Fig. 1).

The overall 5-year relative survival was 72.9% (95% CI 61.5%−84.3%) for the years of diagnosis 1963 to 1972 and 70.3% (95% CI 58.5%−82.1%) for the years of diagnosis 1980 to 1989 (Table 3). Survival analysis for the years of diagnosis 2003 to 2012 included 373 cases, excluding the 7 DCO cases and the 50 cases that died before 2008. The overall relative 1-year and 5-year survival rates for this period were 87.1% (95% CI 82.3%−91.9%) and 72.4% (95% CI 64.8%−80.0%), respectively (Table 3).

Survival estimations by T stage were performed for the years of diagnosis 2003 to 2012. A total of 343 cases with data on T stage were included in the analysis, while for the analyses by UICC stage, 287 cases with information on UICC were included. The relative 5-year survival by T stage was 85.8% (95% CI 75.3%−96.3%), 58.8% (95% CI 43.7%−73.9%), 52.5% (95% CI 31.0%−73.9%), and 16.9% (95% CI 0.0%−59.6%) for T1, T2, T3, and T4, respectively (Table 4). The relative 5-year survival rates by UICC stages were 96.0% (95% CI 84.7%−107.3%), 86.3% (95% CI 71.0%−101.5%), 39.6% (95% CI 19.9%−59.3%), and 20.3% (95% CI 2.4%−38.2%) for stages I, II, III, and IV, respectively (Table 4). The relative 1-year survival rates for T stages and UICC stages were also estimated. The survival rates decreased with more advanced stages (Figs. 2 and 3).

Table 2
Distribution of primary penile cancer patients ($n = 430$) by age and localization of tumor, Saxony, years of diagnosis: 2003−2012, ICD-10 C60.

Characteristic		*n*	%
Age			
<50		32	7
50−59		66	15
60−69		132	31
70−79		138	32
>80		62	14
Total		430	100
Localization by ICD-O			
C60.0	Prepuce	81	19
C60.1	Glans penis	202	47
C60.2	Body of penis	37	9
C60.8	Overlapping lesions of penis	45	10
C60.9	Penis, unspecified	65	15
Total		430	100

ICD-O = International Classification of Diseases for Oncology.

4. Discussion

Incidence, mortality, and survival of penile cancer patients in Saxony were estimated using epidemiological cancer registry data. The incidence rate (ESR) of penile

Table 3
Relative survival of primary penile cancer patients by years of diagnosis (ICD-10 C60), Saxony.

Years of diagnosis	Period	Number of penile cancer cases	1-year relative survival rate, % (95% confidence interval)	5-year relative survival rate, % (95% confidence interval)
1963−1972	1968−1972	244	88.3 (81.9−94.7)	72.9 (61.5−84.3)
1980−1989	1985−1989	215	80.9 (73.3−88.5)	70.3 (58.5−82.1)
2003−2012	2008−2012	373	87.1 (82.3−91.9)	72.4 (64.8−80.0)

cancer increased from 1.2 per 100,000 in 1961 to 1.8 per 100,000 in 2012. During the period 2003 to 2012, the incidence rate (ESR) increased statistically significantly from 0.9 per 100,000 in 2003 to 1.8 per 100,000 in 2012. This doubling of the incidence rate may be due to changes in health behavior or sexual behavior in the former East Germany following reunification. It is however also possible that this trend is an artifact due to improved reporting and documentation of penile cancer cases by office-based urologists, clinicians, and cancer registries over the years.

Findings from other countries are inconsistent. NORDCAN data showed that the standardized incidence rate (ESR) of cancers of the penis and other male genital organs (ICD-10 C60, C63) has been stable since the 1960s (approximately 1.4 per 100,000) [25]. Increasing trends in the incidence of penile cancer were reported in the Netherlands, with a statistically significant increase in the incidence rate (ESR) from 1.4 per 100,000 in 1989 to 1.5 per 100,000 in 2006 (APC: 1.3, 95% CI 0.1−2.6) [26]. A study in Denmark estimated that the overall age-standardized incidence rate (WSR) increased from 1.0 to 1.3 per 100,000 person years from 1978−1979 to 2006−2008, with a significant average APC of 0.8 (95% CI 0.17−1.37) [27]. In England, the age-standardized incidence rate (ESR) increased gradually from 1.1 per 100,000 in 1979 to 1.3 per 100,000 in 2009 [28]. In contrast, the incidence (US standard population) in a study in the United States decreased from 0.8 per 100,000 in 1973−1982 to 0.6 per 100,000 in 1993 to 2002 [2].

The age-standardized mortality rate (ESR) of penile cancer (ICD-10 C60) in Saxony peaked in the early 1990s and decreased statistically significantly to 0.3 per 100,000 in 2012. In the Nordic countries, the mortality rate (ESR) of cancers of the penis and other male genital organs has remained just above 0.3 per 100,000 since the 1970s [25]. In England, age-standardized mortality rates (ESR) of penile cancer fell from 0.4 to 0.3 per 100,000 between 1979 and 2009 [28]. From 1998 to 2003, according to the SEER database, the age-adjusted mortality rate (US standard population) was 0.2 per 100,000 in the United States [29].

The overall relative 5-year survival of penile cancer in Saxony was 72.9% for the years of diagnosis 1963 to 1972 and 70.3% between 1980 and 1989. For the years of diagnosis 2003 to 2012, the survival rate was 72.4%. In a pooled analysis from epidemiological registries covering 12 out of 16 German federal states and the Münster administrative district of North Rhine-Westphalia, a population of 33 million, during the years 2002 to 2006, a 5-year relative overall

Table 4
1-year and 5-year survival (observed and relative) of primary penile cancer patients overall and by UICC stages and T stages, Saxony, diagnosis: 2003−2012, ICD-10 C60.

	Number of penile cancer cases	1-year observed survival rate, % (95% confidence interval)	5-year observed survival rate, % (95% confidence interval)	1-year relative survival rate, % (95% confidence interval)	5-year relative survival rate, % (95% confidence interval)
Overall					
	373	84.3 (79.7−88.9)	61.2 (54.8−67.7)	87.1 (82.3−91.9)	72.4 (64.8−80.0)
UICC stage					
I	120	98.6 (96.0−101.3)	80.8 (71.3−90.3)	101.6 (98.9−104.3)	96.0 (84.7−107.3)
II	93	88.0 (79.7−96.4)	72.2 (59.4−84.9)	91.4 (82.8−100.1)	86.3 (71.0−101.5)
III	47	74.2 (58.8−89.6)	34.1 (17.1−51.1)	76.7 (60.8−92.6)	39.6 (19.9−59.3)
IV	27	55.1 (35.4−74.8)	18.9 (2.2−35.6)	56.5 (36.3−76.7)	20.3 (2.4−38.2)
T stage					
1	197	95.3 (91.7−99.0)	71.3 (62.6−80.0)	98.4 (94.6−102.2)	85.8 (75.3−96.3)
2	90	72.2 (60.6−83.8)	50.7 (37.7−63.7)	74.7 (62.7−86.7)	58.8 (43.7−73.9)
3	47	74.2 (58.8−89.6)	45.0 (26.6−63.4)	76.7 (60.8−92.7)	52.5 (31.0−73.9)
4	9	69.2 (33.7−104.7)	13.8 (0.0−48.9)	70.6 (34.4−106.8)	16.9 (0.0−59.6)

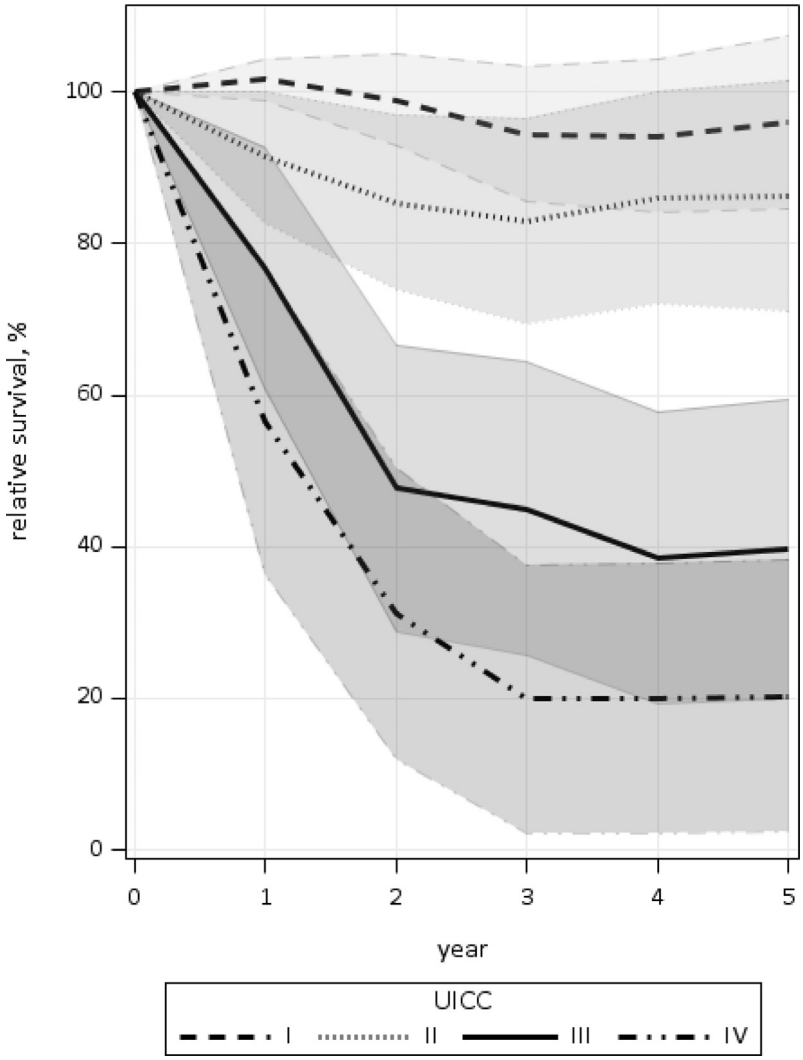

Fig. 2. Relative survival of primary penile cancer ($n = 343$) by UICC, Saxony, period: 2008−2012, diagnosis: 2003−2012.

survival rate of 65.5% for penile cancer was estimated [8]. Based on the European RARECARE database for the period 2000 to 2002, the 5-year relative survival in the Central European Region (including Germany) was 70.8% [30]. In the European network EUNICE, the total 5-year relative survival of penile cancer patients for central and southern Europe increased over time from 69.4% in 1990−1995 to 76.3% in 1996−2001 and 72.3% in 2002−2007 [6]. Survival may improve in the future due to improved treatment options becoming available in recent years. These include the introduction of novel targeted therapies [31].

Findings on incidence, mortality, and survival are inconsistent internationally. When interpreting findings, possible improvements in the documentation of cases over the years, as well as demographic changes such as the aging male population, also need to be taken into account. The introduction of the HPV vaccine may lead to a decrease in penile cancer incidence in the future. The lead-time benefit would however be several decades [32]. In Germany, STIKO recently introduced an official recommendation for boys between the ages of 9 and 14 years to be vaccinated with the HPV vaccine, additionally to the existing recommendation for girls of the same age [33,34].

Since penile cancer is a rare disease, a limitation of our study was the low number of cases included in the analyses, particularly the survival analysis stratified by T stage.

5. Conclusion

This study provides valuable data on a rare disease using cancer registry data in Germany. It shows higher estimates of incidence, slightly higher mortality, and higher 5-year

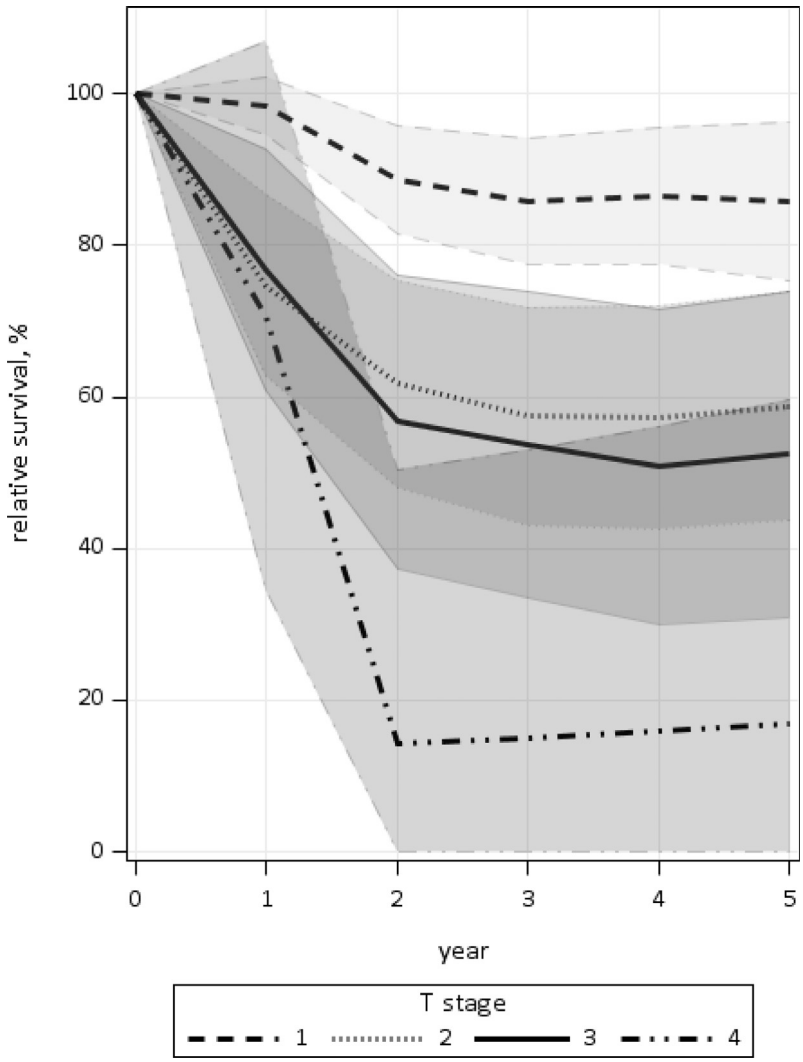

Fig. 3. Relative survival of primary penile cancer ($n = 240$) by T stage, Saxony, period: 2008–2012, diagnosis: 2003–2012.

relative survival compared to studies on penile cancer in other countries.

Conflict of interest

The authors declare that they have no conflicts of interest.

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