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Original Article

Rising incidence rates and unaltered survival rates for primary upper urinary tract urothelial carcinoma: a Dutch population-based study from 1993 to 2017

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Aim

To assess trends in the incidence, disease management and survival rates for upper urinary tract urothelial carcinoma (UTUC) in the Netherlands.

Materials and methods

Patients diagnosed with primary UTUC in the Netherlands between 1993 and 2017 were identified through the population-based Netherlands Cancer Registry (NCR). Patient and tumour characteristics, as well as information on treatment and vital status, were retrieved from the NCR. Age-standardized incidence rates were calculated, stratified by age, gender, calendar period and disease stage. Relative survival served as an approximation for cancer-specific survival.

Results

We identified 13 314 patients with primary UTUC. The age-standardized incidence rate increased from 2.0 in 1993 to 3.2 per 100 000 person-years in 2017, without change in gender distribution. The increase in incidence held for all disease stages except organ-confined (T1–T2) disease. The most prominent increase was in superficial (Tis/Ta) and metastatic (M+) UTUC, which increased from 0.6 to 1.2 and 0.1 to 0.4 per 100 000 person-years, respectively. The 5-year relative survival did not change over time: 57.0% (95% confidence interval 55.9–58.1). Applied treatments were largely the same over the study period, although fewer radical nephroureterectomies and more kidney-sparing surgeries were performed in the most recent years. The use of peri-operative intravesical chemotherapy modestly increased.

Conclusion

Between 1993 and 2017, the age-standardized incidence of primary UTUC in the Netherlands has increased by more than 50%, but the relative survival of UTUC patients remained unchanged. Preventive measures against exposure to risk factors, early detection of disease, and more efficacious treatment methods are needed to improve outcomes of patients with UTUC.

Keywords

upper urinary tract, urothelial carcinoma, incidence, survival, treatment, epidemiology, #utuc, #uroonc

Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a rare entity, with an incidence of 1–2 cases per 100 000 person-years in Western countries [1]. It is less common than urothelial carcinoma of the bladder (UCB); only 5% to 10% of all urothelial carcinomas are located in the upper urinary tract (UUT).

The principal environmental risk factor for developing UTUC is tobacco use [2]. Genetic factors also play a role as UTUC is the second most commonly diagnosed extra-colonic cancer within the spectrum of Lynch syndrome [3]. Haematuria and flank pain are the most frequent presenting symptoms, although many patients present without symptoms [3–5]. CT urography is recommended as the standard diagnostic and staging method, and this has replaced intravenous

pyelography [6,7]. To obtain a histological diagnosis and more definite risk stratification, the European Association of Urology (EAU) recommends a diagnostic ureterorenoscopy with biopsy of the tumour [1]. Although ureterorenoscopy techniques have improved, accurate tumour staging by diagnostic biopsies carries a high risk of understaging. Rojas et al. [8] reviewed 137 biopsies obtained by ureterorenoscopy in 81 patients and showed that the radical nephroureterectomy (RNU) specimen was discordant for tumour stage in 57% of cases. Hence, preoperative risk stratification of patients with suspected UTUC remains a challenge.

Radical nephroureterectomy with bladder cuff excision is the recommended treatment for patients with non-metastatic UTUC. For low-risk UTUC, however, kidney-sparing surgery (KSS) seems to be a feasible alternative [9]. After RNU, 22–47% of patients develop UCB within the first 2 years. A single postoperative intravesical instillation with chemotherapy significantly reduces the risk of future UCB and is therefore recommended in current clinical guidelines [1]. In contrast to UCB, (neo)adjuvant chemotherapy is rarely applied in UTUC patients, although the improved survival shown after adjuvant chemotherapy following RNU from the recently reported POUT trial might change that in the future [10].

To determine whether there has been any progress in the clinical management and outcomes of patients with UTUC, we performed a population-based study and evaluated trends in the incidence, disease management and survival of patients diagnosed with UTUC in the Netherlands between 1993 and 2017.

Material and Methods

Patients diagnosed with primary UTUC between 1993 and 2017 were identified through the Netherlands Cancer Registry (NCR). The NCR is a nationwide population-based registry held by the Netherlands Comprehensive Cancer Organization since 1989. The NCR receives notifications of newly diagnosed cancers from the nationwide network and registry of histo- and cytopathology (PALGA). Annual linkage to the national hospital discharge registry is performed to identify non-histologically confirmed cancers. Patient, tumour and treatment information is retrieved from patients' electronic patient files by staff well trained in data management. The vital status of patients is updated each year by linkage to the Personal Records Database, which keeps information on vital status of all Dutch residents.

Information on patient and tumour characteristics, as well as applied therapies, was extracted from the NCR. The diagnosis of UTUC was defined as International Classification of Disease for Oncology (ICD-O-3); C65.9 (renal pelvis) and C66.9 (ureter) [11]. Tumour stage was defined according to the 7th edition of the International Union Against Cancer TNM classification, as this did not change between 1993 and 2017 [12]. Patients with histology other than UCC were excluded (n = 327). For patients diagnosed with bilateral metachronous UTUC, only the primary tumour was included in the analysis.

Included patients were categorized into six disease stage groups, based on pathological TNM stage, supplemented with clinical TNM stage if histological confirmation of the primary tumour or metastasis could not be retrieved: (i) superficial (Tis-TaN0M0); (ii) organ-confined (T1–T2N0M0); (iii) non-organ-confined (T3-T4N0M0); (iv) nodal metastatic (N+); (v) distant metastatic (M+); and (vi) unknown (TxNxMx). Five calendar periods were defined based on the date of diagnosis; 1993–1997, 1998–2002, 2003–2007, 2008–2012 and 2013–2017. Treatment methods were identified and grouped: RNU; KSS; surgery not otherwise specified; radiotherapy only; chemotherapy only; palliative chemotherapy plus radiotherapy; immunotherapy; instillation topical therapy UUT only; other therapy; and no therapy. The group 'no therapy' consisted of patients who received active surveillance or best supportive care. As information on applied therapies was not recorded until 2005, analyses involving applied therapies were limited to patients diagnosed from 2005 onwards. It should be noted that during the period 2005–2008 a transition from general terminology for treatment to more specified terminology took place.

Statistical Analysis

Age-standardized incidence rates using the 1976 European standard population expressed as the number of new cases per 100 000 person-years (European standardized rate [ESR]), were calculated and analyzed according to year of diagnosis, gender, age at diagnosis, and stage of disease. Trends in incidence were presented by 3-year moving averages. The estimated annual percentage of change (EAPC) was calculated to evaluate changes over time.

Follow-up was defined as time from the date of primary diagnosis until date of death, emigration or last follow-up. Relative survival was calculated as an approximation of disease-specific survival and was defined as the ratio of observed and expected survival [13]. Expected survival was calculated by the Ederer II method, using age, sex and calendar year-specific life tables of the Dutch general population [14]. Relative survival rates were age-standardized by the International Cancer Survival Standard [15].

To evaluate trends in survival over time, relative survival was modelled using a generalized linear model, assuming a Poisson distribution for the observed number of deaths. The significance of linear trends was obtained with P_{trend} values from a likelihood ratio test comparing a model including the midpoint of the five calendar periods and a model without calendar periods. Statistical analyses were performed using SAS version 9.4 and STATA version 16.1.

Ethical approval

This study was approved by the Privacy Review Board of the NCR (K17.177 IKNL).

Results

Patient and Tumour Characteristics

We identified 13 314 patients with diagnosed primary UTUC. The median age at diagnosis had increased from 70 to 72 years over the 1993–2017 period (Table 1). Gender distribution had remained unchanged, with a 2:1 male to female ratio across all five time periods. Histological proof of the primary UTUC had been obtained in 94.8% of the 1823 patients diagnosed during the 1993–1997 period, vs 83.9% of the 3876 patients diagnosed during the 2013–2017 period. The proportion of histologically proven metastases had increased from 0.6% to 4.7%. Overall, the decrease in histologically proven primary or metastatic UTUC was 6%. The distribution of low-, intermediate- and high-grade UTUC changed over time, with more high grade/carcinoma *in situ* in recent years.

Incidence

The ESR of UTUC had increased from 2.0 in 1993 to 3.2 per 100 000 person-years in 2017, equivalent to an EAPC of 1.8% ($P < 0.01$). Figure 1 shows the incidence rates of UTUC from 1993 to 2017 in the Netherlands, visualized as 3-year moving averages. In absolute numbers, this increase corresponded to a doubling of UTUC diagnoses, from approximately 400 in 1993 to 800 in 2017. This trend was irrespective of gender. The increase in incidence was most prominent in patients with urothelial carcinoma of the ureter, i.e. EAPC ureter 2.4% ($P < 0.01$) vs renal pelvis 1.5% ($P < 0.01$; Fig. S1). The incidence of UTUC in patients younger than 60 years had remained stable over time but had increased in the older age groups (Fig. S2). Stage-stratified analyses showed a statistically significant increase in incidence across all tumour stages, except for organ-confined disease (Fig. 2). The increase in the ESR was most prominent for metastatic UTUC: from 0.1 to 0.4 (EAPC 5.5%; $P < 0.01$). For superficial UTUC, the ESR increased from 0.6 in 1993 to 1.2 (EAPC 2.7%; $P < 0.01$) in 2017, with a steep increase from 2004 onwards. The age-standardized incidence rates based on the more recent 2013 European standard population, second edition, are visualized in Figs S3–S6.

Treatment

Between 2005 and 2017, RNU remained the most applied treatment method (Table 2), although the proportion of patients who received RNU decreased from 72.3% of the 2181 patients (2005–2008) to 62.9% of the 3876 patients (2013–2017). The proportion of patients who received KSS more than doubled from 2005, from 6.0% to 13.6%. The number of lymph node dissections performed in combination with RNU remained limited: 9.3% (2005–2008) vs 11.8% (2013–2017).

Table 1 Patient and tumour characteristics of 13 314 patients diagnosed with upper urinary tract urothelial carcinoma between 1993 and 2017 in the Netherlands.

Variable	1993–1997 *N* = 1823	1998–2002 *N* = 1985	2003–2007 *N* = 2419	2008–2012 *N* = 3211	2013–2017 *N* = 3876
Median (IQR) age, years	70 (63–76)	70 (62–77)	71 (63–77)	72 (64–79)	72 (65–78)
Gender, %					
Male	66.8	67.5	66.4	67.6	67.2
Female	33.2	32.5	33.6	32.4	32.8
Diagnosis, %					
Histologically proved UTUC	94.8	93.2	89.7	87.0	83.9
Histologically proved metastases	0.6	0.8	1.5	2.9	4.7
Urinary cytology	2.8	3.4	4.9	5.1	5.9
Clinical assessment	1.9	2.7	3.9	5.0	5.5
Location of UTUC, %					
Renal pelvis	57.1	58.6	56.9	56.9	54.2
Ureter	42.9	41.4	43.1	43.1	45.8
Disease stage, %					
Superficial (Tis–Ta)	30.6	30.5	28.9	33.0	36.1
TaG1	34.4	26.9	22.9	26.8	27.5
TaG2	44.3	48.1	52.2	50.4	47.2
TaG3/Tis	6.5	11.1	12.3	13.9	16.8
Unknown	14.8	13.9	12.6	8.9	8.5
Organ-confined (T1–T2)	32.4	28.6	29.3	25.3	19.9
Non-organ-confined (T3–T4)	19.7	21.2	20.4	18.7	18.6
Nodal metastases (Tany N + M0)	5.6	7.9	8.1	9.0	8.3
Distant metastases (Tany Nany M+)	5.3	7.2	9.3	9.2	11.8
Unknown (TxNxMx)	6.4	4.6	4.0	4.8	5.2

IQR, interquartile range; UTUC, upper urinary tract urothelial carcinoma.

Fig. 1 European standardized rates and absolute number of patients diagnosed with primary upper urinary tract urothelial carcinoma (UTUC) in the Netherlands from 1993 till 2017 (3-year moving average). EAPC, estimated annual percentage of change; ESR, European standardized rate.

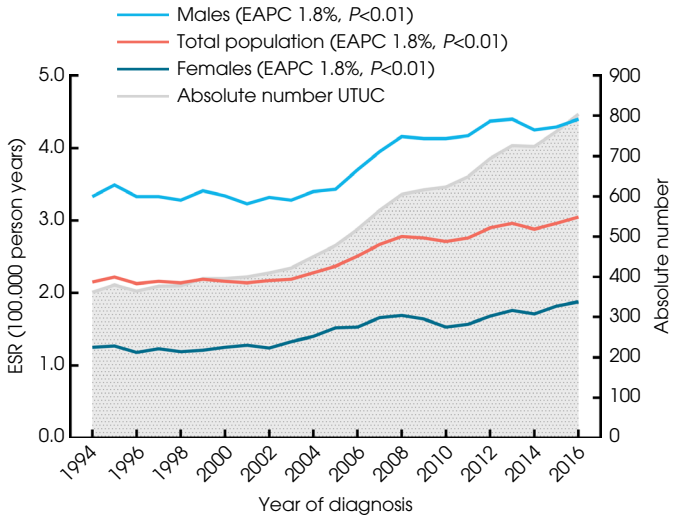
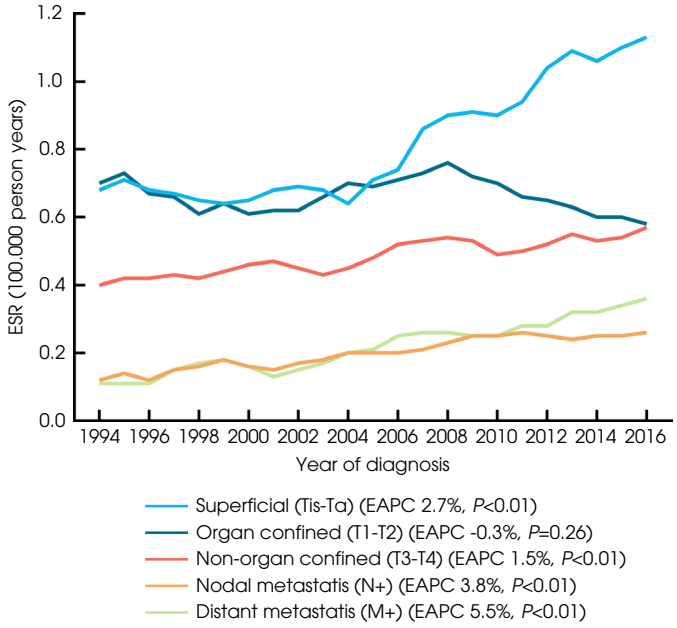


Fig. 2 European standardized rates of patients diagnosed with primary upper urinary tract urothelial carcinoma (UTUC) in the Netherlands from 1993 till 2017 stratified by disease stage (3-year moving average). EAPC, estimated annual percentage of change; ESR, European standardized rate.



(Neo)adjuvant chemotherapy was rarely applied, but the use of postoperative intravesical instillations with chemotherapy had considerably increased, from 2.2% (2005–2008) to 9.7% (2013–2017).

Survival

The 5-year relative survival was 57.0% (95% CI 55.9–58.1) and had not changed over time (P_{trend} = 0.05; Fig. 3). Tumour stage-specific analysis showed no improvement in survival of patients diagnosed with superficial (P_{trend} = 0.96) or organ-confined (P_{trend} = 0.82) disease from 1993 to 2017, with 5-year relative survival of 85.7% (95% CI 83.9–87.3) and 69.6% (95% CI 67.6–71.6), respectively. For patients diagnosed with non-organ-confined UTUC, the 5-year survival had modestly improved from 35.6% (CI 29.8–41.4) to 43.6% (CI 37.7–49.3; P_{trend} = 0.05). The 1- and 3-year survival for patients diagnosed with nodal metastatic UTUC had increased from 36.3% (95% CI 26.5–46.3) to 57.8% (95% CI 52.3–62.9; P_{trend} = 0.03) and 16.5% (95% CI 9.2–25.6) to 31.9% (95% CI 24.7–39.2; P_{trend} < 0.01), respectively. For distant metastatic disease, the 1-year relative survival had increased from 11.3% (95% CI 5.9–18.6) to 24.3% (95% CI 19.4–29.4; P_{trend} = 0.29). Tumour grade-specific analysis for superficial UTUC showed a difference in the 5-year survival, as seen in Fig. 4.

Discussion

In this nationwide, population-based study on 13 314 primary UTUC patients in the Netherlands, we found a significant increase in age-standardized incidence, from 2.0 to 3.2 cases per 100 000 person-years from 1993 to 2017. The literature on the incidence of UTUC is sparse, and studies are often not population-based and mostly reflect different time periods, which hampers adequate comparison with the results of the present study. An Australian study reported a stable age-standardized incidence rate between 2001 and 2011 [16]. Another study from Australia confirmed this observation and also did not find an increase in incidence for the period 1977–2003 [17]. Using the Surveillance, Epidemiology, and End Results (SEER) database, Raman et al. [18] reported a slight increase from 1.88 in 1973 to 2.06 cases per 100 000 person-years in 2005 in the USA. Based on this SEER database, a more recent study covering the period from 2004 to 2016 showed a decrease from 1.3 to 1.1 cases per 100 000 person-years. However, pTa and pTis UTUC were not included [19]. Two other population-based studies, one conducted in the UK and one in Denmark, describing the periods 1985–2009 and 1944–2003, respectively, also found an increase in UTUC incidence [20,21]. The most recent publication on trends in the incidence of UTUC was based on the Norwegian cancer registry, which reported a similar trend over time to that found in our study; an increase in incidence from 3.21 to 4.71 per 100 000 person-years during the period 1999 to 2018 [22].

Although the ageing of the population contributes to the increase in the absolute number of patients diagnosed with

Table 2 Distribution of applied therapies by calendar period in patients diagnosed with primary upper urinary tract urothelial carcinoma in the Netherlands between 2005 and 2017.

Variable	2005–2008 *N* = 2181		2009–2012 *N* = 2584		2013–2017 *N* = 3876	
	N	%	*N*	%	*N*	%
Radical nephroureterectomy	1576	72.3	1884	72.9	2439	62.9
Plus neoadjuvant chemotherapy	12	0.8	22	1.2	48	2.0
Plus adjuvant chemotherapy	43	2.7	31	1.6	43	1.8
Plus intravesical chemotherapy	34	2.2	46	2.4	236	9.7
Plus lymph node dissection	146	9.3	171	9.1	287	11.8
Kidney-sparing surgery	131	6.0	183	7.1	529	13.6
Surgery, not otherwise specified	108	5.0	9	0.3	19	0.5
Radiotherapy only	31	1.4	49	1.9	66	1.7
Chemotherapy only	44	2.0	88	3.4	170	4.4
Palliative chemotherapy + radiotherapy	17	0.8	17	0.7	33	0.9
Immunotherapy	–	–	–	–	4	0.1
Instillation topical therapy UUT only	13	0.6	13	0.5	30	0.8
Other therapy	12	0.5	30	1.2	70	1.8
No therapy	249	11.4	311	12.0	516	13.3

UUT, upper urinary tract.

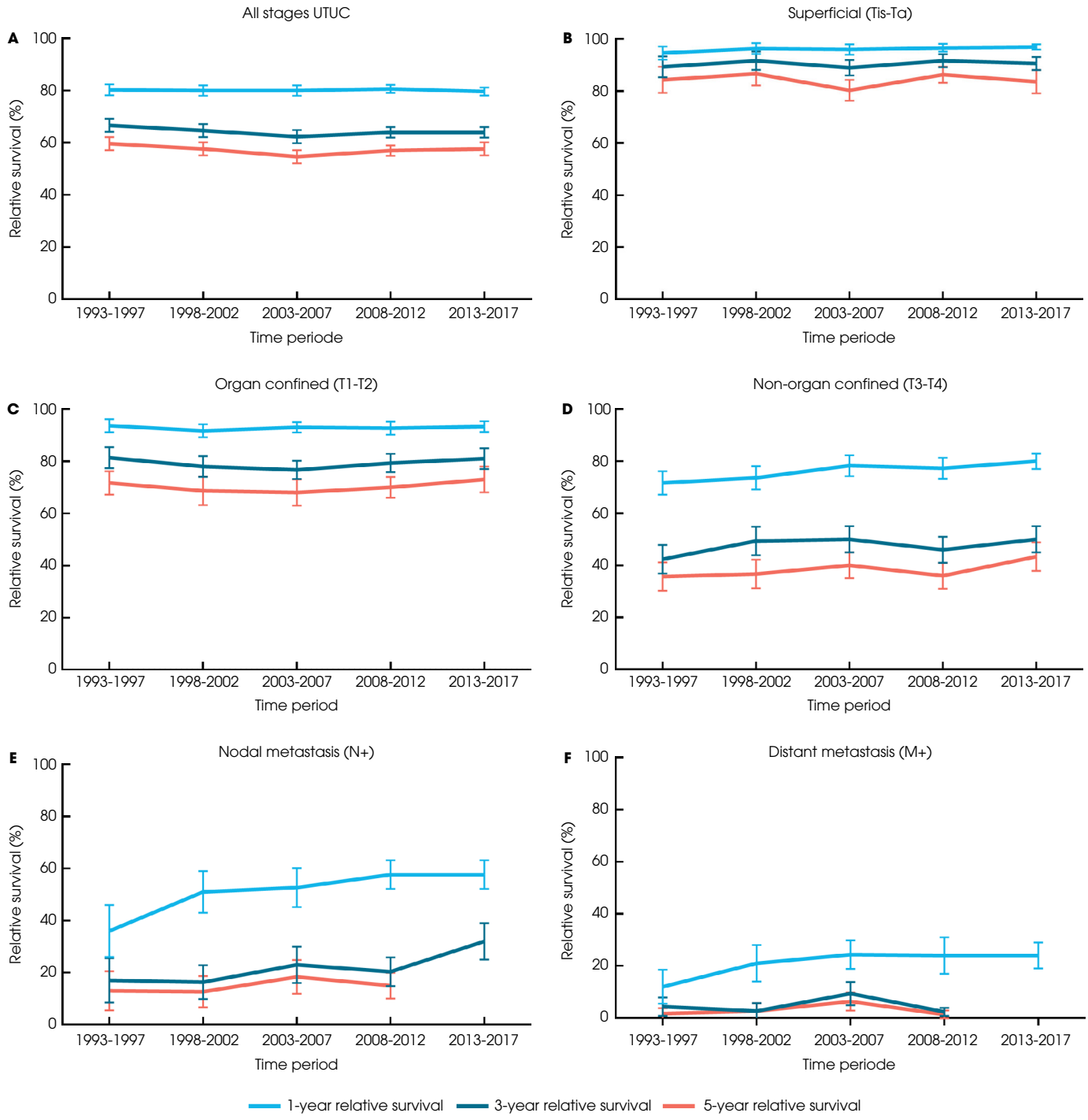
UTUC, ageing does not explain the increase in the age-adjusted incidence. As smoking is the most important risk factor for both UTUC and UCB, and smoking habits have declined over the last decades, one would have expected a decrease in the trends in incidence for UTUC, as described for UCB [23]. However, an explanation for the discrepancy in trends in incidence between UCB and UTUC might be that UTUC develops more slowly than UCB, as the UUT has no storage function whereas the bladder has; consequently, the urothelium of the UUT is less intensely exposed to carcinogenic toxins and incidence rates may lag behind on those of UCB.

The most important factor affecting the rising incidence of UTUC is the more extensive use of cross-sectional imaging in clinical practice. As approximately one-third of UTUCs are incidental findings, the degree of abdominal imaging in clinical practice directly impacts incidence numbers [24]. In addition, the sensitivity of CT urography for the detection of UTUC has been shown to be superior to conventional intravenous pyelography (96% vs 50–61%) [25–27]. In 2011, the EAU recommended CT imaging as the preferred diagnostic method for UTUC instead of intravenous pyelography [28]. The release of the first EAU guidelines on UTUC in 2004 had probably already raised awareness of this disease [29]. Hence, growing awareness, improved imaging techniques, and consensus in the diagnostic evaluation for UTUC might have contributed to the increase in incidence.

The better diagnostic accuracy of CT imaging of the UUT, in combination with enhanced quality of flexible diagnostic ureterorenoscopy and selective urinary cytology, might also be an important contributor to the stage migration from organ-confined towards a higher proportion of diagnosed superficial UTUC from approximately 2005 onwards [7,30]. After the introduction of multidetector CT (MDCT) urography, correct staging of UTUC improved from 59.5% to 87.5% [31,32]. The increase in the incidences of nodal and metastatic disease, also reported by Ruvolo et al., might also be attributed to better diagnostic accuracy of CT imaging, as recommended by the EAU since 2011 [19,28,29]. For detecting lymph node involvement, MDCT has a reported sensitivity of 87.5% and specificity of 98% [33]. For fluorodeoxyglucose-postitron-emission tomography/CT, the sensitivity rate of 50%, as reported for MDCT for detecting distant metastases, even improved to 85% [34]. The observed 'grade' migration towards a higher proportion of patients diagnosed with TaG3/Tis tumours might be explained by a better awareness among pathologists and urologists of tumour grade as a prognostic factor for this stage category [35]. With the applicability of KSS in recent years, it has become more important to find concordance on tumour grade for superficial tumours prior to treatment. For carcinoma *in situ*, however, detection by imaging and ureterorenoscopy remains challenging and a paradigm shift is needed [36].

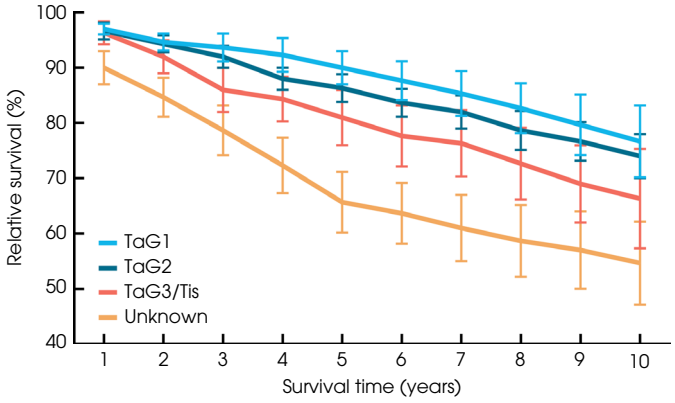
The 5-year relative survival had not improved over the 25-year time period in the Netherlands. This is in line with reported findings in other countries. An Australian population-based study including 722 patients described a stable 5-year relative survival of 30% (2001–2006) and 36% (2007–2011) [16]. A nationwide study from the UK, which included patients diagnosed between 1985 and 2010, showed a decline in the 5-year relative survival from 60% to 48% [20]. Eylert et al. speculated that this might be explained by a sharp rise in incidence for patients >80 years, and that more deaths were probably attributed to UTUC since more cross-

Fig. 3 The 1-, 3- and 5-year relative survival, including 95% confidence intervals (CI), of patients diagnosed with primary upper urinary tract urothelial carcinoma (UTUC) stratified by time period (panel **A**) and stratified by disease stage; (**B**) superficial (Tis-Ta) disease; (**C**) organ-confined (T1–T2) disease; (**D**) non-organ-confined (T3-T4) disease; **E**) nodal metastatic (N+) disease; **F**) distant metastatic (M+) disease.



sectional imaging was used. Adibi et al. [37] also described a stable 5-year cancer-specific survival from 1983 to 2007 in patients all treated by RNU. A Canadian study reported a similar relative 5-year survival to that observed in the present study (i.e. 57% in both studies) in 830 UTUC patients between 1995 and 2004 [38]. Contrary, the 5-year cancer-specific survival in Norway improved between 1999 and 2018 from 57.4% to 65.4% [22]. Although information on adjuvant

Fig. 4 Relative survival, including 95% CIs, of patients diagnosed with primary superficial upper urinary tract urothelial carcinoma (UTUC) stratified by tumour grade WHO 1973; TaG1, TaG2, TaG3/Tis and unknown.



treatment regarding UTUC was limited, the authors stated that this improvement might be explained by the increased use of peri-operative chemotherapy and the introduction of immunotherapy in recent years. A conclusion that cannot be confirmed within our cohort.

One might expect that the observed shift towards superficial UTUC should have improved the survival for the entire cohort in our study. However, the concomitant increase in patients diagnosed with advanced UTUC and the increased number of high-grade superficial UTUCs has seemingly compensated for this expected gain. The increased incidence in the older age groups might also have contributed to this lack of improvement in survival as with increasing age the survival decreases. Older patients are less likely to undergo surgical treatment, and are often not eligible for chemotherapy. Notably, due to an increase in the absolute number of patients diagnosed with UTUC, an increasing number of deaths is attributed to UTUC annually. The improved stage-specific survival we found for non-organ-confined, nodal and distant metastatic UTUC patients is probably the result of stage migration [39]. As imaging techniques have become more sensitive for the detection of small metastases before they become clinically apparent, both (micro-)metastatic and non-metastatic patients are staged more accurately. This stage shift eventually leads to an improved survival in all three stage groups.

Our finding that treatment approaches had remained largely the same is in line with the unchanged survival rate. The shift to more KSS in recent years can probably be ascribed to the discrimination of low- and high-risk UTUC recommended by the EAU guidelines since 2011, in combination with improved equipment and techniques for performing KSS [28]. In combination with the improved detection of superficial, low-grade tumours, promising recent techniques, such as chemoablation and laser vaporization of UTUC, will most likely increase the use of KSS [40,41]. The significant increase we found in the use of peri-operative intravesical chemotherapy in recent years, is in line with the 2015 EAU guidelines on UTUC, which recommended a postoperative bladder installation of chemotherapy to reduce the risk of a future intravesical recurrence [42–44].

The present study has some limitations. The NCR allows us to evaluate trends over time in incidence, treatment and survival of a rare entity as UTUC. Data in the NCR are collected by well-trained data managers applying (inter)national coding rules leading to a high quality and uniform registration. However, information on causes of death is not available in the NCR. Thus, we could not calculate cancer-specific survival rates, and had to resort to the relative survival as an approximation of the cancer-specific survival. As smoking is an important risk factor for the development of UTUC, the relative survival might slightly be overestimated as background mortality due to smoking is underestimated. On the other hand, UTUC as cause of death might have been wrongfully scored as death from kidney cancer on death certificates, which would also have affected survival rates. We had to limit the analyses concerning changes in treatment to the period from 2005 onwards because specific treatment information in the NCR was only available from that time point. Lastly, within the NCR, tumours with predominantly UCC are registered as UCC, regardless of the presence of a minor component of aberrant histology component. Therefore, this would have had a negligible influence on survival.

In conclusion, the age-standardized incidence of UTUC in the Netherlands has increased by more than 50% over the past decades. A stage shift towards superficial UTUC has occurred. A concomitant increase was also seen in the proportion of patients with advanced disease. Improved quality and increased utilization of imaging techniques for the UUT might have contributed to these observed trends. The relative survival has not improved, which corresponds to the overall lack of changes in therapies, although more patients received KSS and peri-operative intravesical chemotherapy in recent years. Effective prevention strategies, earlier detection and new, more effective treatment methods are required to achieve progress in the care for UTUC patients.

Disclosure of Interests

J. L. Boormans reports consultancy work for MSD, Janssen, Ambu and Ismar Health Care, during the conduct of the study, and received a research grant from Decipher Biosciences. All other authors report no conflict of interest.

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Abbreviations: EAPC, estimated annual percentage of change; EAU, European Association of Urology; ESR, European standardized rate; KSS, kidney-sparing surgery; MDCT, multidetector CT; NCR, Netherlands Cancer Registry; RNU, radical nephroureterectomy; SEER, Surveillance, Epidemiology, and End Results; UCB, urothelial carcinoma of the bladder; UTUC, upper urinary tract urothelial carcinoma; UUT, upper urinary tract.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. European standardized rates of 13 314 patients diagnosed with primary UTUC in the Netherlands from 1993 till 2017 stratified by tumour location; renal pelvis versus ureter (3-year moving average).
Fig. S2. European standardized rates of 13 314 patients diagnosed with UTUC in the Netherlands from 1993 till 2017 stratified by age (3-year moving average).

Fig. S3. European standardized rates and absolute number of patients diagnosed with primary UTUC in the Netherlands from 1993 till 2017 (3-year moving average).
Fig. S4. European standardized rates of patients diagnosed with primary UTUC in the Netherlands from 1993 till 2017 stratified for stadium (3-year moving average).
Fig. S5. European standardized rates of patients diagnosed with primary UTUC in the Netherlands from 1993 till 2017 stratified by tumour location; renal pelvis versus ureter (3-year moving average).
Fig. S6. European standardized rates of patients diagnosed with primary UTUC in the Netherlands from 1993 till 2017 stratified by tumour location; renal pelvis versus ureter (3-year moving average).