Prognosis is deteriorating for upper tract urothelial cancer: data for England 1985–2010

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Objective

- To ascertain current trends in the incidence and mortality rates for upper tract urothelial cancer (UTUC) and identify any relationship with age, stage at presentation, social deprivation and treatment method.

Patients and Methods

- We used national databases to collect the data: incidence, stage and survival data from the National Cancer Data Repository (NCDR) and British Association of Urological Surgeons (BAUS) audit database; mortality data from the Office for National Statistics (ONS); and treatment method data from the Hospital Episodes Statistics (HES).

Results

- The incidence of UTUC is increasing (from 1985 to 2009 it increased by 38% in men and 77% in women). It affects mainly those aged >60 years, and diagnoses are increasingly made in those aged >80 years. Diagnoses at advanced stage have increased from 45 to 80%.
- Mortality has risen faster than incidence; the overall 5-year survival rate has dropped from 60 to 48%. Survival is worst in stage IV disease and in patients aged ≥80 years; when analysed by age or stage group, survival rates are unchanged.
- Nephroureterectomy has increased by 75%, but endoscopic treatment, which only became available part way through the study period, now accounts for 11% of surgical interventions for UTUC, mainly in stage I disease and in the elderly.

Conclusions

- Despite sharing its risk factors with bladder cancer, current incidence and mortality trends for UTUC contrast with those in bladder cancer. Increasing use of cross-sectional imaging may explain some of the identified increased incidence. Higher incidence specifically in people >80 years, together with stage migration to more advanced cancers, are likely to have caused at least some of the observed increased mortality.
- Further study is required to answer the questions of whether there are other hitherto unidentified aetiological or prognostic factors; whether less aggressive treatment of UTUCs in the elderly is always justified; and whether the rising frequency of minimally invasive treatment means suboptimum oncological management.

Keywords

cancer of the renal pelvis, cancer of the ureter, incidence, mortality, survival, upper tract urothelial cancer

Introduction

Upper tract urothelial cancer (UTUC) is rare, with about 900 cases diagnosed each year. It is frequently advanced at diagnosis and survival rates are poor. There are no previously published data on UTUC that can be used to analyse epidemiological trends in England, although some data is available from other countries, namely Denmark 1989–2003 [1], the Netherlands 1995–2005 [2], and the USA 1973–2005 [3]. Interestingly, epidemiological trends have been different in each of these countries. In Denmark the incidence of UTUC declined, in the Netherlands the incidence is static, there is stage migration to more advanced cancers and endoscopic treatment is increasingly used, and in the USA the overall incidence is increasing, there is no change in the proportion of metastatic disease at presentation, but the incidence of carcinoma *in situ* is increasing.

Like urothelial cancer of the bladder, UTUC is associated with occupational exposure to aromatic amines and current or past cigarette smoking. An up-to-date epidemiological scrutiny of this disease has been prompted by the changing

occupational profiles, reduced smoking rates, and newer endoscopic treatment options.

Patients and Methods

Incident cases in England were extracted from the National Cancer Data Repository (NCDR) for 1985–2009 and analysed by subgroups of stage at presentation (only available from 2000 onwards), age, gender and social deprivation. The NCDR is formed from extracts from all eight regional cancer registries in England and therefore forms a complete population-based database. Cancer diagnoses and treatments are reported to the registry from hospitals' patient record systems, pathology, post mortems and death certificates. A de-duplication process was undertaken, as some patients may be registered in more than one region. Cases were defined by the international classification of diseases (ICD 10) codes C65 (cancer of the renal pelvis) and C66 (cancer of the ureter), which excludes carcinoma *in situ* and non-invasive papillary carcinomas.

The BAUS audit database of new diagnoses is a voluntary database contributed to by members of BAUS. About half of new diagnoses each year are recorded on the BAUS database (as compared with the NCDR). In the present study, data on disease stage from the BAUS database were used to augment the staging data from the NCDR, as the BAUS database staging information is more complete for the cases recorded. Cases identified from the NCDR were linked to the BAUS audit database using their unique NHS number, date of diagnosis and postcode of residence. An NHS number is allocated to all English residents at birth, and immigrants are allocated an NHS number when they first register with a doctor in this country.

Survival data were taken from the UK cancer registries Cancer Information System (CIS). This is an online system available to registry staff, primary care trust staff and hospital staff, which allows easy access to high-level epidemiological statistics for cancer. Data for the system are extracted from the NCDR. Relative cohort survival was used as this takes into account the background mortality rate for different ages, gender and social deprivation, giving an excess mortality rate for the disease of interest. Survival data were available for earlier time periods than mortality data as the exact cause of death from the Office of National Statistics (ONS) was not required; only the date of death was needed, which is collected by cancer registries.

Mortality information is received annually from the ONS and was available for 1995–2010. Mortality data were analysed by age, gender and social deprivation. Stage is not recorded on death certificates and we were unable to link to diagnosis data because of a lack of personal identifiers. Mortality data were recorded from death certificates, and assigned an underlying cause. The underlying cause was defined as the condition which sets into motion the chain of events leading to death, but the ONS implements a set of rules which can result in a different cause being selected e.g. those recorded as dying from Kaposi's Sarcoma on their death certificate are recoded as dying from HIV; therefore, the cause of death is not always directly derived from the wording of the conditions on the death certificate. Those records with UTUC (ICD10 codes C65 and C66) assigned as the underlying cause of death were selected for analysis. For both incidence and mortality, the data used in the present study were the most recent data available.

Data on treatment method for 1998–2009 were obtained from the Hospital Episodes Statistics (HES) database, which was established in the 1997–1998 financial year. The first complete calendar year of data was therefore 1998. The HES database covers patients admitted to NHS hospitals in England, or treated in a private hospital at NHS expense. Each period of care under one consultant is termed an 'episode' and forms one record in the database. The data are entered by clinical coding teams at each trust and the full database is assembled by the NHS Information Centre. A number of treatment fields are recorded for each HES episode, and these are used to identify relevant treatments using the appropriate OPCS codes ("Office of Population Censuses and Surveys: Classification of Surgical Operations and Procedures" codes). The codes used are C65 and C66 (together coding for all UTUCs) in conjunction with any of the following: M02.2 (nephroureterectomy), M10.1 (endoscopic extirpation of lesion of kidney), M18.1 (total uretectomy), M18.2 (excision of segment of ureter), M29.1 (endoscopic extirpation of lesion of ureter), and M32.1 (endoscopic extirpation of lesion of ureteric orifice). This way, all operations for UTUC are captured, but operations for RCC, for example, are excluded.

Smoking prevalence data were obtained from the ONS for 1974–2010.

Statistics

Rates were calculated with standardisation for age and gender, standardising to the European Standard Population. Deprivation quintiles were assigned based on Lower Super Output Area (LSOA) of residence, where each LSOA in England was assigned a quintile based on the Income Deprivation score from the 2007 English Indices of Deprivation. LSOAs are grouped such that the total quintile population is as close to one-fifth of the England population as possible, rather than equal numbers of areas.

The statistical significance of a change in rate was tested using a two-sided z-test on the log of the rate ratio, and the associated standard error. The null hypothesis was that there was no change in rate (i.e. the rate ratio is 1), and a P value of ≤ 0.05 was taken as evidence to reject the null hypothesis.

Limitations

The limitations of this study are largely those of the databases used. Firstly, each of the databases is populated prospectively, but the data extraction was retrospective. Secondly, the focus of the NCDR is to provide a complete database of diagnoses, but staging data are extremely limited. The BAUS database is voluntary and hence incomplete in terms of cases. Despite the robust linkage of the NCDR and BAUS databases, staging information was only available for ~12% of cases of UTUC. Thirdly, robust survival data is available from the CIS, which is again a complete database, but no records are kept relating to the cause of death. Mortality data regarding cause of death from the ONS are complete, but lack personal identifiers, which makes linkage to other databases impossible. Lastly, each database was established in a different year, and processes such as de-duplication cause a delay in release of the data. Hence data are available for variable time periods for each of the databases.

Results

Overall Incidence and Mortality

The incidence of UTUC increased from 484 cases in 1985 to 969 cases in 2009. This increasing trend was more pronounced in women (age-standardised rate increased by 77%; $P < 0.001$) than in men (age-standardised rate increased by 38%; $P < 0.001$). The mortality rate for UTUC increased from 92 cases in 1995 to 175 cases in 2010. Age-standardised trends in incidence and mortality rates are shown in Fig. 1.

The 5-year relative survival rate for all patients with UTUC decreased from 60 to 48% (for diagnoses made in 2003–2005 compared with those in 1985–1987; $P < 0.05$) and the 1-year relative survival rate decreased from 76 to 71% (for diagnoses made in 2007–2009 compared with those in 1985–1987; $P < 0.05$ [Fig. 2]).

Gender and Age

Similarly to bladder cancer, the incidence of UTUC is higher in men than in women. The male : female ratio for age-standardised rates was 2.1:1, with the ratio being 1.7 per 100 000 in men and 0.8 per 100 000 in women.

The incidence of UTUC was highest in men and women aged ≥60 years (Fig. 3). Incidence increases with increasing age from 40 to 79 years and this fact has not changed over time. The mean age at diagnosis increased from 67.9 years in 1985–1987 to 72.9 years in 2007–2009. In 1985, incident cases of UTUC in those aged ≥80 years were lower than in those aged 70–79 years, but since 2005–2007 the numbers have overtaken this latter group, as diagnoses are

Fig. 1 Incidence and mortality rates for UTUC: age-standardised rate per 100 000 people.

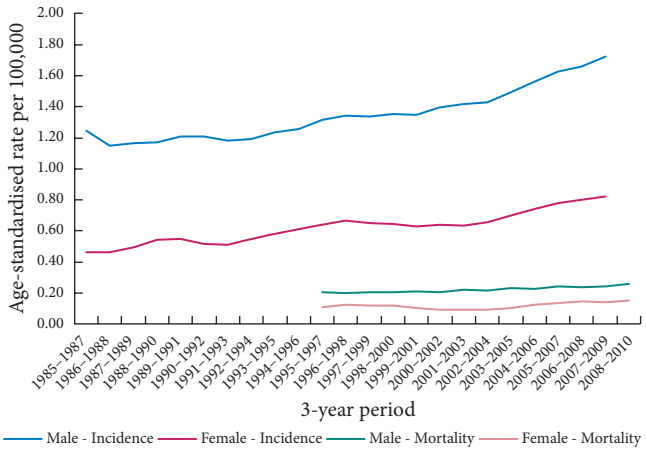


Fig. 2 The 1-year and 5-year relative survival rates for UTUC.

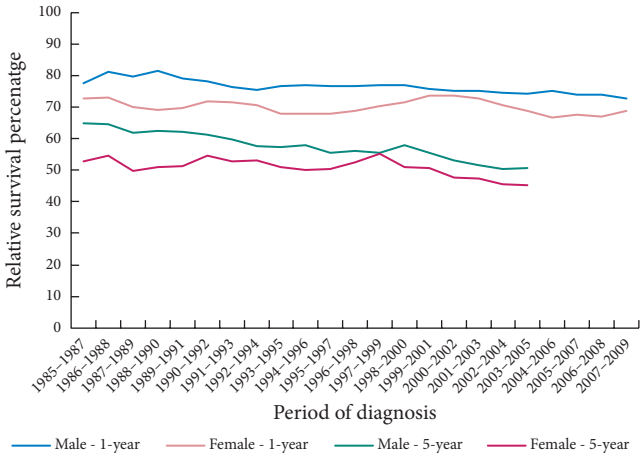


Fig. 3 Age-specific UTUC incidence rate, stratified by age at diagnosis.

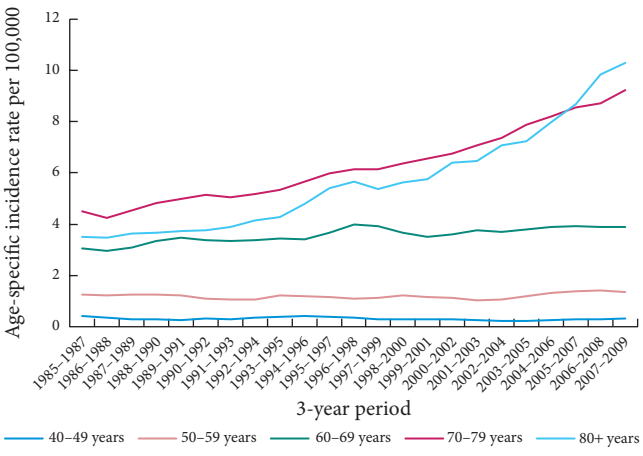


Fig. 4 Deaths from UTUC: age-specific rate per 100 000, stratified by age at death.

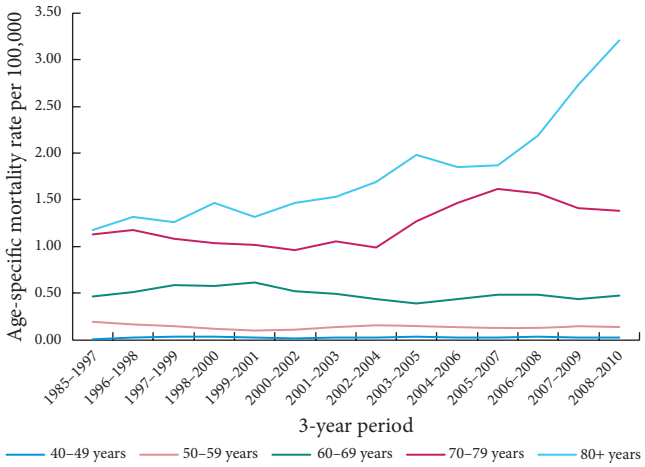
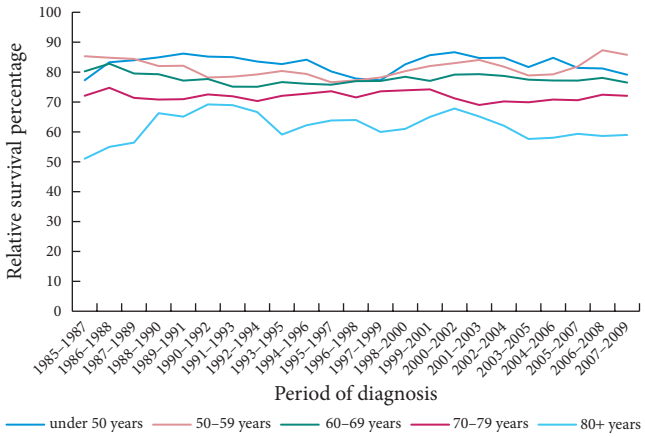


Fig. 5 The 1-year survival rates for UTUC, stratified by 10-year age groups.

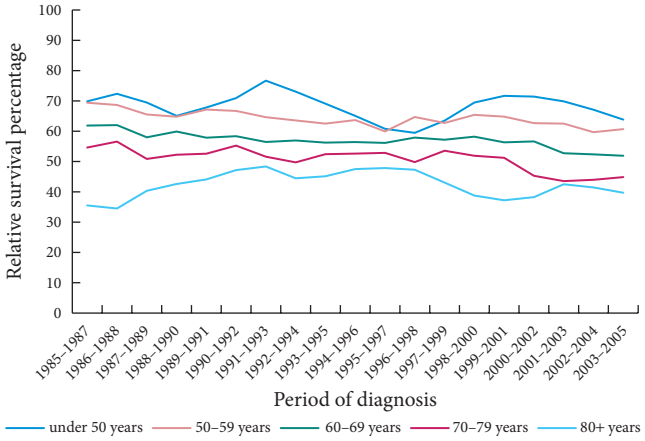


increasingly made in those aged ≥80 years. In 2007–2009, 27% of all new cases were diagnosed in those aged ≥80 years.

Mortality from UTUC increases with age (Fig. 4). Age-specific mortality rates from UTUC were largely static, except in those aged >80 years. Age-specific mortality rates in those aged ≥80 years increased by 174%, from 1.2 per 100 000 in 1 985–1 987 to 3.2 per 100 000 in 2007–2009 ($P < 0.001$). This is in keeping with the significant increase in incidence in this group.

The 1-year survival rates (Fig. 5) for those diagnosed in 1985–1987 were significantly better for those <80 years (72–85%) than for those >80 years (51%). There was no significant difference between each of the younger age groups. The 1-year survival rates for those diagnosed in 2007–2009 in those <50 years (79%) were equal to those in

Fig. 6 The 5-year survival rates for UTUC, stratified by 10-year age groups.



60–79-year-olds (72–76%); the rate in 50–59-year-olds (86%) was not different from those <50 years, but was better than in 60–79-year-olds. Survival in those >80 years (59%) remained worse than in all younger age groups. There were no significant time trends within any of the age groups.

The 5-year survival rates (Fig. 6) for those diagnosed in 1985–1987 were significantly better for those aged 50–59 years (69%) than for those aged 70–79 years (55%); no other differences were significant up to age 79 years. The 5-year survival rate was worst in those aged ≥80 years (36%). The 5-year survival rates for those diagnosed in 2003–2005 were worse for those aged 70–79 years (45%) than for those <60 years (61–64%). No other differences were significant up to age 79 years. The 5-year survival rates were worse in those aged ≥80 years (40%) than in those <70 years (52–64%). There were no significant time trends within any of the age groups.

Stage

Diagnoses of UTUC at advanced stage now account for ~80% of cases (of those that have a valid stage recorded) and this has increased dramatically over time (Table 1). At the same time the number of cases diagnosed when the tumour is localised has decreased. The overall recording of stage for UTUC is poor with consistently only 12% of cases having a valid stage at diagnosis in 2000–2009. It is possible that there is a bias towards recording of stage IV disease, as it does not require all of the T, N and M components to be recorded. If there are distant metastases (M = 1), spread to regional lymph nodes ($N = 1,2,3$) or the tumour has invaded adjacent organs or perinephric fat (T = 4) this is sufficient to record stage IV even if other data are missing. For stages I–III, all the T, N and M data are required; however, the fact that recorded stage IV diagnoses are

Table 1 Stage at diagnosis for UTUC, as a percentage of tumours with valid recorded stage.

Period of diagnosis	Recorded tumour stage, %			
	I	II	III	IV
2000–2002	23	18	14	45
2001–2003	21	15	17	47
2002–2004	16	14	19	51
2003–2005	13	14	14	59
2004–2006	13	11	13	63
2005–2007	11	8	10	71
2006–2008	10	5	11	73
2007–2009	7	5	9	80

Fig. 7 The 1-year survival rates for UTUC, stratified by stage at diagnosis.

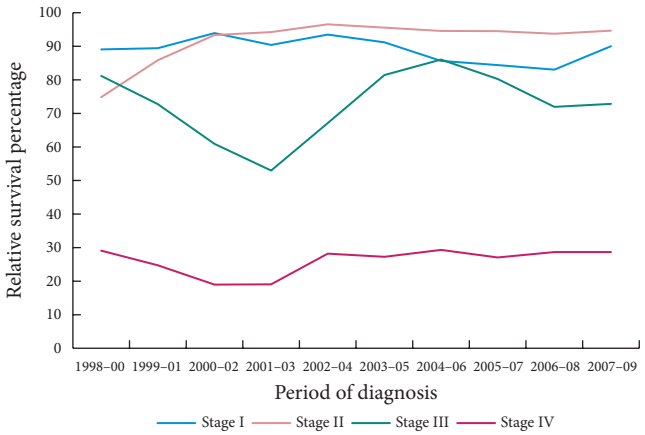


Fig. 8 The 5-year survival rates for UTUC, stratified by stage at diagnosis.

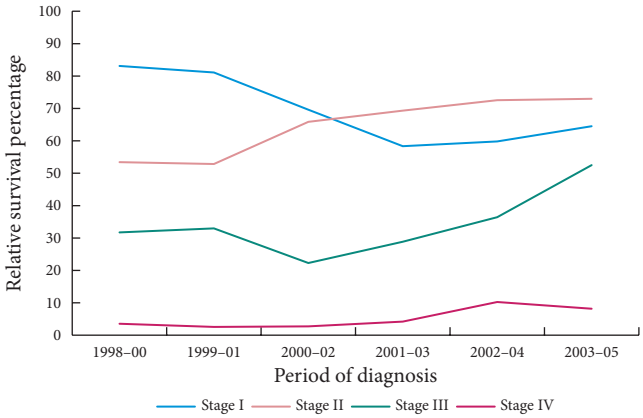


Table 2 Social deprivation and incidence of/mortality from UTUC, age-standardised rate per 100 000 people.

	Quintile of income deprivation				
	Least deprived	2	3	4	Most deprived
Incidence					
1985–1994	0.73	0.82	0.87	0.90	0.95
1995–2004	0.93	0.99	1.03	1.02	1.06
2005–2009	1.16	1.22	1.24	1.32	1.34
Mortality					
1995–2004	0.14	0.14	0.14	0.16	0.15
2005–2010	0.17	0.18	0.18	0.20	0.19

increasing with time, whilst overall stage completeness is unchanged, suggest there is a real effect of increased presentations at an advanced stage.

The 1-year survival rates (Fig. 7) for those diagnosed in 1998–2000 are statistically equal for those diagnosed with stage I and stage III disease (81–89%), and significantly better than those with stage IV (29%). The numbers with stage II are too small to make any meaningful statistical comparison. The 1-year survival rates for those diagnosed in 2007–2009 were significantly better for those diagnosed with stage I–III disease (73–95%), than for those with stage IV (29%). There were no significant time trends when grouped by stage.

The 5-year survival rates (Fig. 8) for those diagnosed in 1998–2000 were significantly better for those diagnosed with stage I disease (83%) than for those with stage IV (4%). There was no significant difference between stage II or III disease. The 5-year survival rates for those diagnosed in 2007–2009 were significantly better for those diagnosed with stage I–III disease (53–73%) than for those with stage IV (8%). From 1998 to 2009 there was a trend towards decreased 5-year survival in stage I, and increased 5-year survival in stage II and III, but none of these time trends were statistically significant.

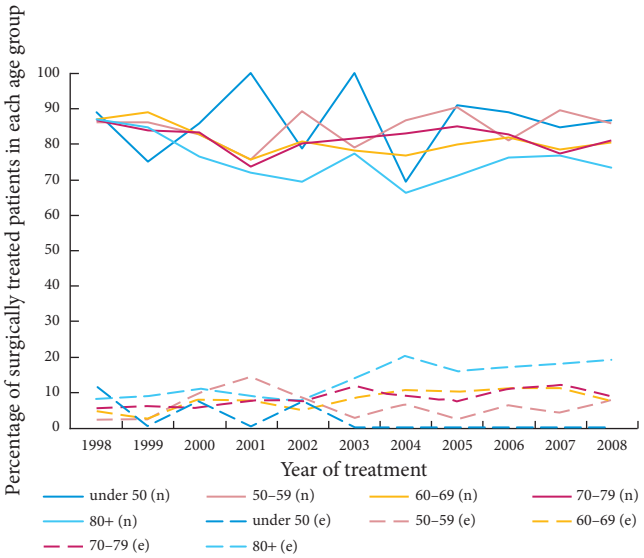
Social Deprivation

When examining 3-year incidence and mortality rates there is no evidence of any consistent correlation or clear trend between age-standardised incidence or mortality rates and social deprivation; however, when examining longer time periods (Table 2), there is evidence of higher incidence rates in the most deprived quintile of population. The rate in the most deprived quintile in 1985–1994 was 30% higher ($P < 0.001$) than in the least deprived, in 1995–2004 it was 15% higher ($P < 0.001$) and in 2005–2009 it was still 15% higher ($P = 0.005$). There was no difference in mortality rates with social deprivation, even over a longer time period.

Treatment

The treatment of UTUC largely depends on the fitness of the patient. The 'gold standard' treatment has long been nephroureterectomy, but newer endoscopic treatment options have become available over the last two decades. During the period from 1998 to 2009, overall numbers of

Fig. 9 Nephroureterectomy and endoscopic treatment by age group. n, nephroureterectomy; e, endoscopic treatment.

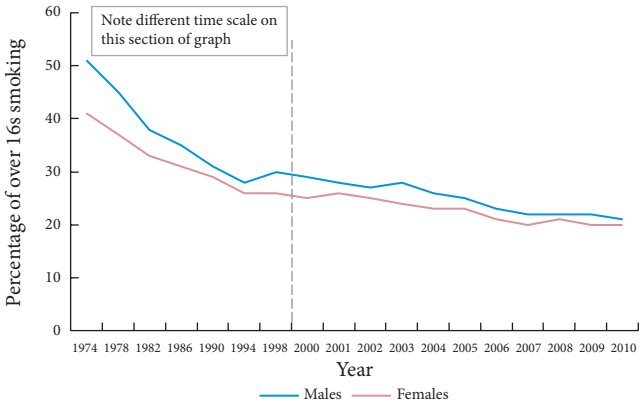


surgical treatments for UTUC increased as incidence rose; however, although the number of nephroureterectomies increased by 75%, endoscopic treatment has emerged as a new treatment option and in 2009 it accounted for 11% of all surgical interventions for UTUC.

Endoscopic treatment was significantly more commonly used for those aged ≥80 years (14.6% of this age group for 1998–2009 overall) than for those aged 50–79 years (6–9%) and for those under 50 years (2%). The use of nephroureterectomy increased in absolute terms in every age group, but as a percentage of surgical treatments for UTUC in each age group (Fig. 9), the use of nephroureterectomy decreased in patients aged ≥60 years (from 87 to 73–81%). The use of endoscopic treatment increased in patients aged 50–59 (from 2 to 8%) and particularly in those aged ≥80 years (from 8 to 19%); it has not been used in those <50 years since 2002. The remaining patients were treated by partial or complete ureterectomy (10% overall).

Bearing in mind the aforementioned limitations on stage data (which were only available for 12% of all diagnoses), endoscopic treatment was significantly more commonly used for stage I (9% of stage I) than stage IV (3%) disease; there was no statistical difference for stage II or III. Similarly, nephroureterectomy was more commonly used in stage I–III (74–87%) than stage IV (42%) disease. There was no statistical difference in the use of total ureterectomy (2–3%) or excision of segment of ureter (2–4%). There were no significant time trends in treatment when grouped by stage. Notably, owing to the poor stage recording and large percentage of stage IV tumours, there were only 332

Fig. 10 Prevalence of smoking in adults, from 1974 to 2010.



data sets with surgical treatment information for stage I–III in total.

Smoking

Smoking rates have been decreasing for several decades; the rates for 1974–2010 are shown in Fig. 10. The biggest decrease in smoking prevalence was during the 1970s and 1980s, with the number of men smoking falling by 40%, and the number of women smoking falling by 30%. Smoking rates continued to fall, albeit more slowly, during the 1990s and 2000s.

Discussion

We found a sharp increase in the incidence rates and a concerning reduction in 5-year survival rates for UTUC. Despite sharing its known risk factors with bladder cancer (occupational exposure and cigarette smoking), current incidence and mortality trends for UTUC contrast with those for bladder cancer. Smoking rates are decreasing, occupational exposure to known risk factors is decreasing, bladder and lung cancer incidence rates are decreasing, yet UTUC incidence continues to increase. The correlation of greater social deprivation with a greater incidence of UTUC is consistent with a disease where industrial exposure and smoking habits are aetiological factors, but a correlation between social deprivation and mortality from UTUC was not found. This may be explained by higher mortality from chronic conditions, which are also more prevalent in the more deprived populations, e. g. cardiovascular disease.

One might argue that the increasing use of cross-sectional imaging, in haematuria clinics and in general, will invariably lead to an increase in the number of diagnoses of UTUC. This is a probable explanation for the observed increasing incidence especially in those aged ≥80 years, and also for the increasing mortality in the elderly, as

deaths may now be attributed to UTUC, where previously it may have remained undiagnosed. One would, however, expect significant positive stage migration overall, as tumours should be picked up at an earlier stage, but in fact the observed shift in stage shows an increase in advanced disease, consistent with the only published study to observe stage migration [2].

The present data showed a clear shift towards more endoscopic treatment. The current European Association of Urology guidelines [4] still cite nephroureterectomy as the gold standard, with endoscopic treatment options reserved for those with a single kidney, bilateral tumours, significant comorbidities making nephroureterectomy unfeasible, or for highly selected small volume low grade UTUC. There is currently no evidence to support the use of endoscopic treatment more generally, as highlighted by a recent systematic review [5]. As expected, endoscopic treatment is most commonly used in stage I disease, when it may suffice as treatment, and in the elderly, when more radical treatment may be unfeasible. The lack of time trends when treatment is analysed by stage is influenced by very limited data, as only 12% of all diagnoses have a valid stage recorded and not all of these received surgical treatment. There are simply too few recorded data currently to reach any firm conclusion.

Looking at age and stage vs survival rate in more detail, the survival rate was consistently worse for those aged >80 years and those diagnosed with stage IV disease. There were no significant time trends within any of the age or stage groups, suggesting no major impact on survival of any change in treatment. This will of course be affected by the often less aggressively interventional treatment of UTUC in the elderly. The increased incidence in those aged >80 years, the increased percentage of stage IV disease and the unchanged survival rate when divided into age groups and stage groups explains at least part of the increased mortality. Deaths are increasingly attributed to UTUC (that was probably previously missed), without altering the survival rates of those diagnosed with UTUC. We must, therefore, focus further research on UTUC to answer the following questions: Are there other hitherto unidentified aetiological or prognostic factors causing increasingly advanced disease? Is UTUC in the elderly increasingly treated without curative intent and is this always justified? Does the rising frequency of minimally invasive treatment mean suboptimum oncological management?

Acknowledgements

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Conflict of Interest

None declared.

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Abbreviations: UTUC, upper tract urothelial cancer; NCDR, National Cancer Data Repository; ONS, Office for National Statistics; HES, Hospital Episodes Statistics; LSOA, Lower Super Output Area.