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Bladder Cancer Incidence and Survival in the South-eastern Part of the Netherlands, 1975–1989

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Trends in cancer occurrence and survival may reflect changing risks and prognosis, respectively, but may also be caused by changes in detection, classification and registration. Changed classification of low-stage papillary carcinomas may have a material effect on observed trends in the occurrence of bladder cancer. We studied the effect of the implementation of the WHO grading system and the third edition of the TNM staging system on bladder cancer incidence in the south-eastern part of the Netherlands. Data on superficial and invasive bladder cancer incidence between 1975 and 1989 were derived from the population-based Eindhoven cancer registry. Data on survival of patients with stages I–IV bladder cancer were derived from the municipal population registers. Age-adjusted bladder cancer incidence per 100 000 person-years rose from 25.9 to 40.7 in males and from 3.1 to 8.5 in females. This increasing trend was caused almost entirely by non-invasive pTa papillary carcinoma. A considerable shift was observed towards lower disease stages, which was less evident within the group of invasive tumours. The relative 5-year survival of patients with stages I–IV invasive bladder cancer was 59% in 1975–1977 and 70% in 1984–1986. After stratification by stage, however, no striking improvement was observed in the prognosis. We conclude that the increasing trend of bladder cancer occurrence in the Netherlands since 1975 has largely been caused by changed classifiation systems and reporting procedures for pTa tumours (formerly classified as papillomas).

Key words: bladder cancer, incidence, trend, diagnosis, stage distribution, classification, survival
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INTRODUCTION

ONE OF the major problems in cancer registration is the reporting and classification of low-grade non-invasive papillary-shaped bladder tumours [1]. This problem relates particularly to the distinction between papillary-shaped tumours with benign behaviour and those that will eventually manifest (progressive) malignancy if left untreated. As such, non-invasive carcinomas can form a substantial proportion of all bladder tumours, and treatment may prevent them from progressing to invasive disease. Then the incidence of malignant bladder cancer would probably relate to differences in urological care [2]. Furthermore, changes in the reporting and classification of these low-stage papillary tumours may result in biased trends in time of both bladder cancer incidence and survival [3]. In this study we explored trends in the incidence of bladder cancer from 1975 to 1989 in the south-eastern part of the Netherlands. Special emphasis is laid on changes in stage distribution and survival.

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DATA AND METHODS

Data source

Data on bladder cancer incidence were derived from the population-based cancer registry in the area of Eindhoven [4]. The registry is based on notifications of newly diagnosed malignancies from all the pathology laboratories and community hospitals (including one radiotherapy department) in the area. It is considered to be complete in a core area, with a population of approximately 850 000, since the early 1970s. We selected all new patients with bladder cancer (ICD-O code 188 [5]) diagnosed between January 1975 and January 1990. Diagnoses, which were originally classified according to ICD revisions 8 and 9, were converted into ICD-O codes. There is no routine reporting of benign and/or unspecified papilloma of the bladder (ICD-O behaviour codes 0 and 1, respectively) in the cancer registry, so these tumours were not included. The tumours were staged according to the TNM classification [6] (Table 1). The second edition of the TNM staging system was used until 1980, the third since that year. All new tumour occurrences in bladder cancer patients, whether or not in a higher stage category, were considered to be recurrences and were, therefore, not registered.

Analyses

Incidence rates per 100 000 person-years in males and females were calculated for 1975–1989 inclusive. To adjust for the pronounced ageing of the population, the incidence rates were age-adjusted to the European standard population [7]. Trends in rates were presented as 3-year moving averages. The incidence rates were calculated separately for superficial and invasive

Table 1. TNM stage grouping of urinary bladder cancer (UICC, 1987)

Stage	Primary tumour	Regional lymph nodes	Distant metastases
0	Tis	N0	M0
	Ta	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3a	N0	M0
	T3b	N0	M0
IV	T4	N0	M0
	Any T	N1, N2, N3	M0
	Any T	Any N	M1

tumours. Superficial tumours comprise tumours which do not involve the muscle layer of the bladder wall (TNM stages pTis, pTa and pT1, i.e. stage 0–I in the stage grouping in Table 1). Stage I bladder cancer is defined as superficial in urology even though it is an invasive tumour according to the TNM classification. The stage distribution was compared in five triennial calendar periods.

Except for patients with stage 0 disease, data on vital status until 1 July 1991 were collected from the municipal population registers. Less than 1% of all the patients were lost to follow-up. The actuarial relative survival rate was calculated as a measure of patient survival adjusted for the effect of (age-, sex- and calendar period-specific) mortality attributable to competing risks of death [8]. The standard errors of the relative survival estimates were obtained using Greenwood's formula [9]. Owing to the relatively small number of female patients, the relative survival in successive triennial periods was calculated for both sexes combined. For the calculations, we used a computer programme developed by the Finnish Cancer Registry [10].

RESULTS

Between 1975 and 1989, 1909 newly diagnosed patients with bladder cancer were registered, 1537 (80.5%) males and 372 (19.5%) females. Of all the tumours, 97.5% had been histologically verified (0.2% of which at autopsy), 1.6% had been verified with urine cytology only, and in 0.9% no microscopical verification had taken place. Of all the tumours, 95.4% were classified as transitional cell carcinoma (pure or mixed with another morphology), 2.2% as squamous cell carcinoma, 1.2% as adenocarcinoma and 1.2% had another or unknown morphology (including the cases without microscopical verification). These later 1.2% (n = 23) were excluded from further analyses.

Incidence

Age-adjusted urinary bladder cancer incidence in males rose steadily from 25.9 per 100 000 person-years in 1975 to 40.7 per 100 000 person-years in 1989. In females, these rates were 3.1 and 8.5, respectively. This increase in bladder cancer incidence can be attributed almost entirely to an increase in the number of superficial tumours reported. For males, the incidence of superficial (stages 0 and I) bladder cancer doubled in the first half of the 1980s (Figure 1). Invasive bladder cancer incidence (stages II–IV) increased only marginally from 10.6 per 100 000 person-years in 1975 to 12.8 in 1989. An increase in the incidence of superficial bladder cancer was also seen in females (Figure 2). However, in females there seems to have been a small increasing

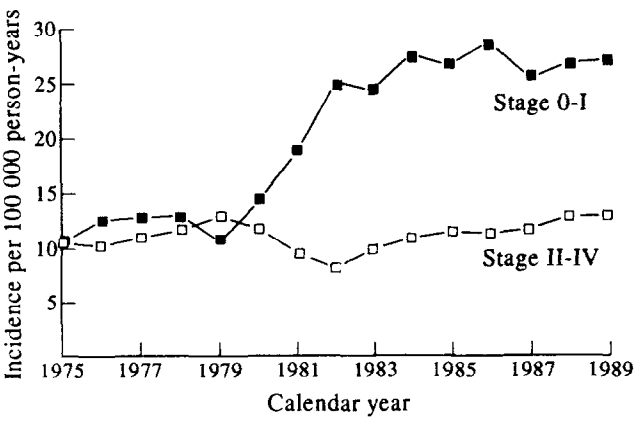

Figure 1. Superficial and invasive bladder cancer incidence per 100 000 person-years in males in the south-eastern part of the Netherlands between 1975 and 1989. Rates are presented as 3-year moving averages after age adjustment to the European standard population.

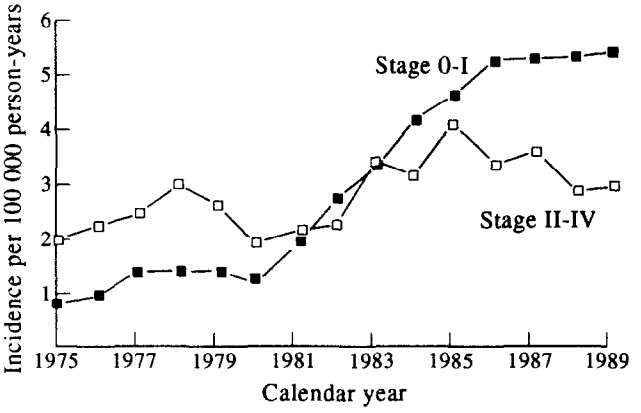

Figure 2. Superficial and invasive bladder cancer incidence per 100 000 person-years in females in the south-eastern part of the Netherlands between 1975 and 1989. Rates are presented as 3-year moving averages after age adjustment to the European standard population.

trend in invasive bladder cancer also (from 2 to 3 cases per 100 000 person-years).

Stage distribution

The increase in superficial bladder cancer was caused by an increase in non-invasive papillary pTa tumours (flat intraurothelial pTis tumours and pT1 tumours invading the lamina propria hardly increased). In 1975, not one pTa tumour was entered into the cancer registry. In 1989, the age-adjusted incidence of pTa tumours in males and females was 15.7 and 3.6, respectively. This resulted in a clear shift towards superficial tumours in the stage distribution of all bladder cancer (Figure 3). A shift towards lower disease stages was less evident when stage 0 tumours (pTis and pTa) were excluded (Figure 4), although it appeared that after 1980, relatively fewer tumours were diagnosed in stages III and IV.

Relative survival

The observed cumulative 5-year survival in male and female patients with stages I–IV in the total study period was 48%. The relative 5-year survival was calculated to be 64% [95% confidence interval (CI) 60–68%]. On average, the male patients were

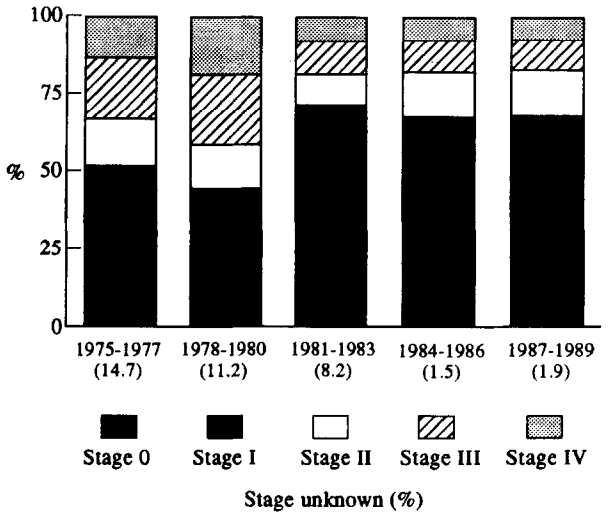

Figure 3. Stage distribution of (male plus female) bladder cancer in the south-eastern part of the Netherlands in five successive triennial calendar periods.

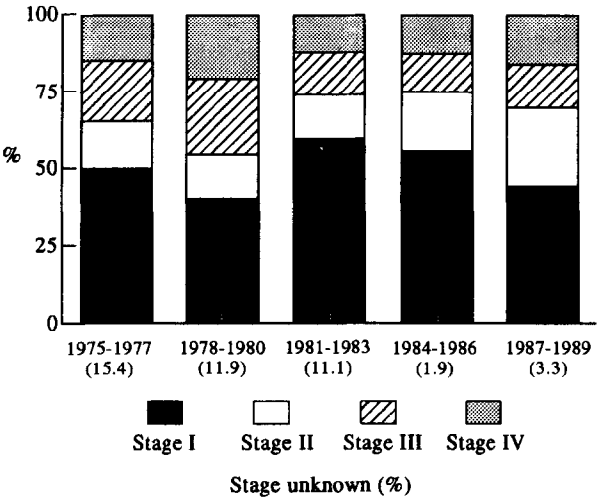

Figure 4. Stage distribution of (male plus female) invasive bladder cancer in the south-eastern part of the Netherlands in five successive triennial calendar periods.

diagnosed with lower staged disease than the female patients: 28% of the male patients with invasive disease had stage III or IV disease at diagnosis compared to 43% of the female patients. This favourable disease stage distribution resulted in a significantly higher 5-year relative survival for male patients: 69% (95% CI: 65–73%) versus 47% (95% CI: 38–56%) in female patients. The stage-specific relative survival of the patients diagnosed in the four successive triennial periods (for both sexes combined) is illustrated in Table 2.

DISCUSSION

Between 1975 and 1989, bladder cancer incidence in the south-eastern part of the Netherlands almost doubled in males and more than doubled in females. In both sexes, this increasing trend appeared to be caused almost entirely by an increase in the number of non-invasive papillocarcinomas (pTa) entered into the cancer registry, which resulted in a shift towards a more favourable disease stage distribution (Figure 3).

Until the WHO grading system was implemented in 1973 [11], all low-grade non-invasive papillary-shaped tumours were called papillomas. After 1973, pathologists and urologists started to define tumours with 'the least degree of cellular anaplasia compatible with a diagnosis of malignancy' as grade 1 papillocarcinomas [12,13]. It took a number of years, however, before these tumours were reported to and/or entered into the cancer registry. Until the third edition of the TNM classification became available (in 1978), which the Eindhoven registry started to use in 1980, there was no separate code for non-invasive papillocarcinoma. Classifying these tumours as pTis would have been wrong because flat carcinoma *in situ* is known to be a fairly aggressive lesion which is often widespread over the urothelium and (by definition) poorly differentiated. It was only after the implementation of the third TNM edition that all papillary non-invasive tumours with some degree of morphological atypia were classified as papillocarcinomas (pTa).

In theory, the increased incidence of pTa tumours could have also resulted from earlier diagnosis due to improved acuity and heightened public awareness. However, a substantial reduction in diagnostic delay is unlikely in the Netherlands where all the inhabitants have easy access to medical care and there are no long urological waiting lists (not even in 1975). The initial symptom in more than 80% of the male and more than 70% of the female patients with bladder cancer is macroscopical painless haematuria [14,15]. This symptom will probably be enough reason to seek medical care. It is possible that there may occasionally be some delay in the diagnosis of bladder cancer, e.g. in patients with cystitis as the presenting symptom instead of haematuria and in female patients in whom haematuria may be attributed to infection [14]. However, there is little reason to assume that this diagnosis delay has changed over the years. In recent years, more low-stage bladder tumours may have been diagnosed as a coincidental finding during transurethral resection of the prostate or with a routine medical examination (microscopical haematuria). Nevertheless, this cannot explain

Table 2. Five-year relative survival (S_5) of patients with invasive bladder cancer [95% confidence interval (CI)]

Calendar period	Stage I			Stage II–IV			Stage I–IV		
	n	S_5	95% CI	*n*	S_5	95% CI	*n*	S_5	95% CI
1975–1977	92	83%	(70–96%)	93	34%	(22–46%)	185	59%	(49–69%)
1978–1980	88	93%	(81–99%)	134	45%	(34–56%)	222	65%	(56–74%)
1981–1983	151	83%	(73–93%)	103	35%	(23–47%)	254	64%	(56–72%)
1984–1986	201	90%	(82–98%)	155	41%	(31–51%)	356	70%	(63–77%)

the pronounced increase in pTa bladder cancer in the first half of the 1980s. Neither can new diagnostic techniques, such as flow cytometry using monoclonal antibodies. As in 1975, a careful history, physical examination, cytology and cystoscopy are still the accepted diagnostic methods [16].

An alternative explanation for the increased incidence of pTa bladder cancer is a real increase in the risk of developing this disease. The major risk factor for bladder cancer in males and females is smoking [17]. The influence of smoking appears to be similar for low- and high-stage tumours, as well as for low- and high-grade tumours at diagnosis [18]. The prevalence of smoking among male adults in the Netherlands decreased from 90% in the 1950s to about 40% in the 1980s, whereas females exhibited an increase from 20 to 40%. Therefore, one would expect a decreasing trend in male bladder cancer incidence, if any, rather than an increasing one (it has already been shown that the risk of dying from bladder cancer in the Netherlands decreases in successive male birth cohorts [19]). In women, a slight increase in bladder cancer was expected, but one would not expect it to be confined to superficial tumours almost entirely (Figure 2). Thus, it is highly likely that most (if not all) of the increase in urinary bladder cancer incidence is the result of changing classification following the implementation of the WHO grading system and the third edition of the TNM staging system.

The actuarial relative 5-year survival in male and female patients with invasive bladder cancer was 70% in 1984–1986 compared to 59% in 1975–1977. After stratification by stage, it appeared that the trend towards a higher survival in recent years had almost disappeared (Table 2), although small numbers complicated the interpretation of the results. The absence of any trend in stage-specific survival rate since 1975 is not very surprising. Over the past 15 years, there have been no major changes in the treatment of stages II-IV invasive bladder cancer. The radiotherapy techniques (with simulation and linear accelerators) and cystectomy techniques (with the development of continent forms of urinary diversion and nerve-sparing approaches) have been improved but have not led to a significantly better prognosis [20]. Recently, some promising results from neoadjuvant chemotherapy regimens (such as methotrexate, vinblastine, doxorubicin and cisplatin, M-VAC) have been reported [21], but the ultimate benefit of these regimens remains to be proven [22].

Progress has been achieved in the management of stages 0–I bladder cancer. The past two decades of clinical experimentation have provided convincing evidence that the intravesical administration of adjuvant chemotherapy or Bacillus Calmette-Guérin (BCG) causes a significant reduction in the risk of recurrence [23, 24]. However, the ability of cytotoxic drugs and BCG to prevent progression to muscle invasion, metastatic bladder cancer and death from bladder cancer, is still a matter of debate [25]. Thus, although innovations in treatment management may have improved the quality of life of patients with invasive bladder cancer, as well as the recurrence-free interval of superficial bladder cancer, they may have had less merit with regard to the ultimate disease outcome.

We conclude that over the past 15 years, there has been no clear shift towards a more favourable disease stage distribution or a far better prognosis in patients with primary invasive bladder cancer. There has been a small increase in the occurrence of invasive bladder cancer in females. The increase in the occurrence of superficial bladder cancer can be explained by changes in classification and is, therefore, artificial.

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