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Increasing Survival of Patients with Urinary Bladder Cancer. A Nationwide Study in Sweden 1960–1986

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Survival rates were analysed in 29 055 patients with urinary bladder cancer diagnosed in Sweden from 1960 to 1986 and followed up until 1987. The 2-, 5- and 10-year relative survival rates were 79, 70 and 64% for men and 75, 68 and 63% for women, respectively. Patients with a history of bladder cancer for at least 15 years ran a negligible risk of dying from their disease. Prognosis was consistently better in younger than in older patients; below 50 years of age the 5-year relative survival rate was 90%, as compared with 60% in patients aged 70–79 years. Patients diagnosed between 1960 and 1964 had a 60% 5-year relative survival, as compared to 71% in those diagnosed between 1980 and 1984. Multivariate analyses further confirmed that age but not sex is an important prognostic factor in bladder cancer and, further, that a substantial improvement in survival rates took place during the 1960–1986 period. Compared with 1960–1964 the risk of dying of bladder cancer within 5 years in patients diagnosed between 1980 and 1984 was 51% lower in men [relative risk (RR) = 0.49; 95% confidence interval (C.I.) 0.42–0.57] and 44% lower in women (RR = 0.56; 95% C.I. 0.45–0.70).

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INTRODUCTION

PROGRESS in treatment of urinary bladder cancer has only been studied to a limited extent. Without treatment, the average survival time from the time of the first symptom has been estimated at 16.5 months [1]. A review of progress in the curability of bladder cancer in the U.S.A. during 1932–1971 revealed only modest improvements [2]. Few population-based analyses of trends in survival are available; and they have usually included relatively small numbers of patients [3–6].

We analysed survival rates with emphasis on temporal trends in nearly 30 000 patients with urinary bladder cancer, diagnosed during 1960–1986, in the total Swedish population. Advantage was taken of the almost complete registration and follow-up procedures available in this country. Relative survival rates were calculated to correct for deaths from causes other than bladder cancer. The possible confounding effect of changing distributions by gender, age at diagnosis and years of follow-up on trends in survival was adjusted for multivariate analyses.

PATIENTS AND METHODS

The Cancer Register

The Swedish National Cancer Register was founded in 1958. All clinicians, pathologists and cytologists must report to the register every patient with a newly diagnosed malignant disease [7]. The Register contains information on gender, date of birth, site or type of cancer, histological classification and date of

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diagnosis. The diagnoses are coded according to the International Classification of Diseases (ICD-7) [8]. The stage of the disease and the treatment are not recorded in the Register.

The files of the Cancer Register were linked—through the individually unique national registration number assigned to all Swedish citizens—to the nationwide Death Register, an updated register of living persons covering the total population of Sweden.

Patients

A total of 32 555 patients were reported to the Cancer Register as having urinary bladder cancer (including papillomas) between 1 January 1960 and 31 December 1986. We excluded 3050 patients whose bladder cancer was first diagnosed at autopsy and 337 patients who died during the calendar month when the diagnosis was made. Only 113 patients were lost to follow-up. Thus, the analyses of survival rates were based on a cohort of 29 055 patients with complete follow-up through to 1987. Distribution by gender, age and year of diagnosis is shown in Table 1. The mean and median ages at diagnosis increased by about 4 years in both sexes from 1960–1964 to 1985–1986.

Statistical methods

The observed survival rates for all causes of death were calculated by the actuarial method [9]. The bladder cancer-specific mortality was estimated from the relative survival rate, i.e. the ratio between the observed survival rate of the patients and the expected survival rate, obtained from Swedish population tables by age (5-year intervals), gender and calendar year [10, 11]. The annual bladder cancer-specific risk of death was calculated as the complement of the annual relative survival rate [12].

To adjust for possible confounding we fitted multivariate regression models and used gender, age at diagnosis, time period of diagnosis and follow-up year as explanatory variables. The multivariate analysis of relative survival was based on the first 5 years of follow-up and it was assumed that the total hazard $h(t)$ can be expressed as the sum of a general hazard $h^*(t)$ and a disease-specific hazard [13]. The disease-specific hazard was assumed to depend on the explanatory variables in a multiplicative way. On the basis of an assumption of binomial probabilities, maximum likelihood estimates were obtained by the GLIM system, using individual link functions [14].

RESULTS

Overall survival by sex and age

During the study period the incidence increased 100% in men and somewhat less among women (Table 1). Urothelial carcinoma was the dominating histopathological type both in men (85%) and in women (79%). Anaplastic carcinoma was less common and papillomas accounted for about 5% of the total number (Table 2).

Apart from a slightly better outlook in men than in women during the first year of follow-up, gender was not an important determinant of prognosis as shown in Fig. 1. The 2-, 5- and 10-year relative survival rates were 79, 70 and 64% in all men and 75, 68 and 63% in all women, respectively. The relative survival rate decreased in both sexes up to about 15 years after diagnosis and then remained almost constant (Fig. 1) indicating that surviving patients were cured. The relative hazard rates were significantly higher in women than in men during the first year of observation (Fig. 2). In both sexes the relative hazard decreased to about 1% after 8 to 10 years and remained at this level through at least 15 years of follow-up.

In both men and women, relative survival rates decreased

Table 2. Distribution of 29 055 patients (available for follow-up) with bladder cancer diagnosed in Sweden between 1960 and 1986 by sex and histopathology of tumours

	Men		Women	
	no.	(%)	no.	(%)
Adenocarcinoma	124	(0.6)	65	(0.9)
Papillomas	951	(4.4)	408	(5.4)
Urothelial carcinoma	18 361	(85.2)	5939	(79.2)
Squamous cell carcinoma	291	(1.4)	238	(3.2)
Anaplastic carcinoma	1136	(5.3)	494	(6.6)
Other histopathology	689	(3.2)	359	(4.8)
Total	21 552	(100.0)	7503	(100.0)

Table 1. Distribution of 29 055 patients (available for follow-up) with bladder cancer diagnosed in Sweden between 1960 and 1986 by gender, age and period of diagnosis

Age group (years)	1960–1964		1965–1969		1970–1974		1975–1979		1980–1984		1985–1986	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
< 50	187	63	227	83	259	82	279	79	282	102	127	37
50–59	452	178	584	171	599	199	698	194	670	191	275	70
60–69	793	267	1002	325	1274	416	1453	445	1639	459	734	215
70–79	626	302	927	384	1273	460	1614	524	2000	663	918	266
≥ 80	203	115	282	163	371	200	584	284	822	381	398	185
All ages	2261	925	3022	1126	3776	1357	4628	1526	5413	1796	2452	773
Mean age	65.06	66.67	65.69	67.46	66.64	67.92	67.55	69.21	68.81	70.15	69.26	70.76
Median age	66	68	67	69	68	69	69	70	70	72	70	72

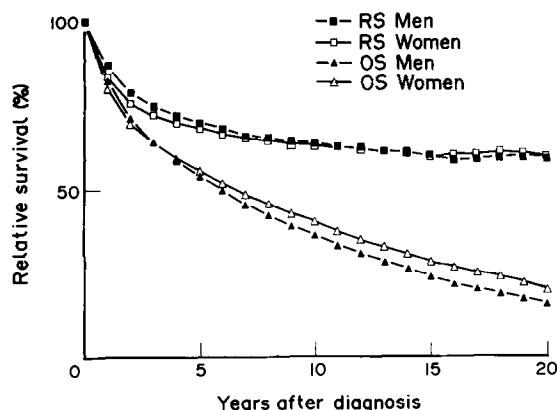


Fig. 1. Relative survival (RS) rates and observed survival (OS) rates in men and women with bladder cancer in Sweden between 1960 and 1986.

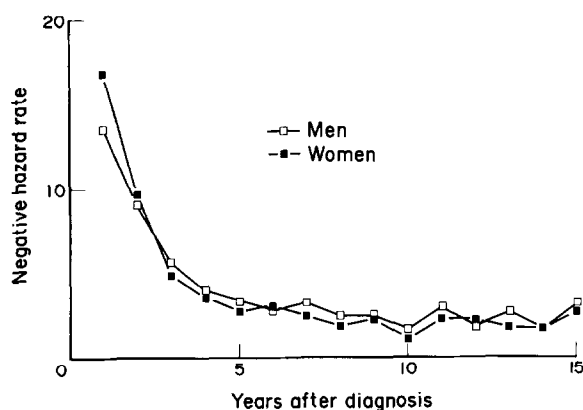


Fig. 2. Annual relative hazard rate in men and women with bladder cancer in Sweden between 1960 and 1986.

gradually with increasing age at diagnosis. Among men below 50 years of age, the 5-year survival rate was around 90%, whereas patients aged 70 to 79 years at diagnosis had a relative survival rate of 60% (Fig. 3a). A similar pattern was seen for women (Fig. 3b).

Trends in survival

In men, the 5-year relative survival rate increased gradually from 60% among subjects diagnosed during 1960–1964 to 73% among those diagnosed from 1975 and onwards (Fig. 4). The 5-year relative survival rate among women diagnosed during 1960–1964 was 60%, similar to that in men. However, the best prognosis was found among women diagnosed during 1970–1974—with a 5-year relative survival rate of 72%—whereas decreasing survival rates were found after this period (Fig. 4).

Multivariate analyses

When follow-up year, age at diagnosis and period of diagnosis were stepwise added to multivariate models, the deviance decreased markedly indicating strongly significant effects of these variables. Gender, however, reduced the deviance only marginally, suggesting a small effect on relative survival (Table 3). Addition of an interaction-term between period of diagnosis and gender improved the model, i.e. temporal trends in relative survival differed in men and women. There were also significant interaction-effects between follow-up year and gender and also

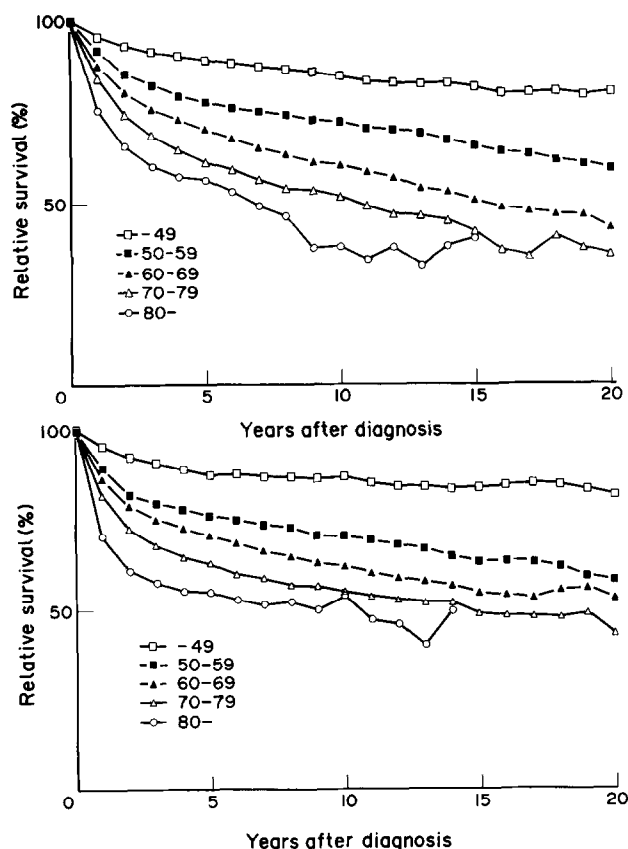


Fig. 3. (a) Relative survival rates in men with bladder cancer in Sweden between 1960 and 1986 by age at the time of diagnosis. (b) Relative survival rates in women with bladder cancer in Sweden between 1960 and 1986 by age at the time of diagnosis.

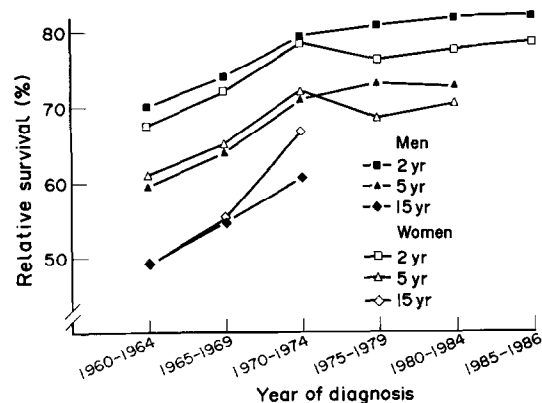


Fig. 4. Relative survival rates in men and women with bladder cancer in Sweden between 1960 and 1986 by period of diagnosis.

between follow-up year and age. The fit of the best models (models 4–8, Table 3) was acceptable, as shown by deviances only slightly larger than the degrees of freedom.

In a multivariate model for each gender (Table 4), the highly significant effects of follow-up year and age remained. The association between age at the time of diagnosis and prognosis was of similar magnitude in men and women; diagnosis at the age of 80 years or older compared with that below 50 years entailed an approximately six times higher relative risk of dying from bladder cancer (Table 4). The estimated improvement in prognosis over time was stronger in the multivariate analyses

Table 3. Multivariate regression models of the relative survival rates during the first 5 years of follow-up of bladder cancer diagnosed in Sweden between 1960 and 1986. Models expressed by their deviance and their degrees of freedom

	Deviance	Degrees of freedom	P-value
(1) Mean	3089	279	
(2) (1) + follow-up year	1476	275	<0.001
(3) (2) + age	648.7	271	<0.001
(4) (3) + period of diagnosis	338.4	266	<0.001
(5) (4) + sex	336.6	265	0.18
(6) (5) + period of diagnosis \times sex	321.7	260	0.011
(7) (6) + follow-up year \times sex	296.7	256	<0.001
(8) (7) + follow-up year \times age	252.1	240	<0.001

Table 4. Multivariate regression models of relative survival rates in men and women with bladder cancer, diagnosed in Sweden between 1960 and 1986. Relative hazards

		Model 4	
		Men	Women
Follow-up year	1	1.00 (reference)	1.00 (reference)
	2	0.68 (0.63–0.74)	0.58 (0.52–0.65)
	3	0.42 (0.38–0.47)	0.29 (0.24–0.35)
	4	0.31 (0.27–0.34)	0.21 (0.17–0.27)
	5	0.26 (0.22–0.31)	0.17 (0.13–0.23)
Age	< 50	1.00 (reference)	1.00 (reference)
	50–59	2.17 (1.75–2.69)	2.04 (1.48–2.80)
	60–69	3.18 (2.59–3.89)	2.67 (1.98–3.60)
	70–79	4.51 (3.68–5.52)	3.64 (2.71–4.89)
	≥ 80	6.49 (5.22–8.06)	5.68 (4.19–7.71)
Period	1960–1964	1.00 (reference)	1.00 (reference)
	1965–1969	0.83 (0.74–0.92)	0.82 (0.69–0.96)
	1970–1974	0.61 (0.54–0.68)	0.60 (0.50–0.71)
	1975–1979	0.54 (0.48–0.60)	0.67 (0.57–0.79)
	1980–1984	0.50 (0.45–0.56)	0.61 (0.52–0.72)
	1985–1986	0.49 (0.42–0.57)	0.56 (0.45–0.70)

which adjusted for confounding by increasing age at diagnosis. In both sexes the most marked improvement took place between 1960–1964 and 1970–1974; there was some evidence of a subsequent increase in survival among men, but not among women.

DISCUSSION

Population-based investigations of trends in survival from urinary bladder cancer have been few and the number of patients were usually smaller than in our study. Population-based studies like ours have been performed in Norway [3] and Finland [4]. In Norway, the 5-year relative survival rates improved only marginally from 1963 to 1975 and they were generally higher in men than in women. Indeed, a decrease during the last time period (1972–1975) in Norwegian women preceded a similar phenomenon in Sweden in 1975–1979 (Fig. 4). In Finland, the relative 5-year survival rate was about 40% in both sexes during the period 1953–1974 with a slight increase over time [4]. In the U.S.A., corresponding survival rates increased from 53% in 1960–1963 to 79% in 1981–1986 among white patients [15].

In Finland and Norway papillomas were not registered, but

they were included in our study and in that from the U.S.A. In Sweden, multiple tumours of the lower urinary tract are registered only according to the site of the first-reported tumour. In contrast, synchronous or metachronous tumours at these sites lead to multiple registrations of the same individual in Denmark [16]. Hence, differences in registration practices hamper direct comparisons between countries.

Like others [3, 4, 15], we found a decreasing relative survival with increasing age. It is not known whether this association is due mainly to a longer patient-delay and thus a more advanced tumour stage at the time of diagnosis in older people; or whether it is due to a more fundamental association between age and tumour biology [17]. In the Bristol Bladder Tumor Register [18] low-grade tumours were more common below the age of 50, but the reverse was true at older ages.

Tobacco smoking is probably the principal single risk factor for bladder cancer [19, 20]. Since smoking also is a risk factor for death due to many other diseases, smoking may account for at least part of the excess mortality in patients with bladder cancer and explain why the annual relative hazard seemingly

never reached zero. Conceivably the decreasing relative survival rates for women in the later periods may reflect an increasing proportion of smokers during the study period.

Changes in the definition of carcinoma-papilloma of the bladder may further influence trends in survival. During the early 1960s only tumours with unequivocal invasive growth were classified as carcinomas. The WHO panel of experts on bladder tumours proposed a strict definition in 1973; following this, the proportion of papillomas was estimated to be 3% in a large clinical material [21]. The change to a narrower definition of papillomas is evident in this study where their proportion was reduced from 18.5% to less than 2% after 1974 (data not shown). To obviate confounding effects on temporal trends due to changes in diagnostic criteria all papillomas were included in the analysis.

The increasing survival trend in Sweden cannot be readily explained. Changes in treatment policies may have contributed—for example, the shift from open resection to transurethral resection during the latter part of the 1960s, the introduction of intravesical instillations in the 1970s and the more extensive use of radical surgery during the latter part of the 1970s. Improved methods of radiotherapy and the development of urology as a separate surgical discipline throughout the country must also be considered. Postoperative mortality after cystectomy decreased from 10.9% in the 1960s [22] to less than 2% in the beginning of the 1980s [23]. Earlier diagnosis due to increased awareness in the general population and greater access to medical care are other explanations. However, the lack of improvement in survival during the later periods and an apparent difference in trends between men and women are hard to explain and require further study.

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