INVASIVE BLADDER CANCER - Aspects on staging and prognosis

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Diagnostic Delay and Prognosis in Invasive Bladder Cancer

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Objectives: To study diagnostic delay in invasive bladder cancer in a population-based material with long-term follow-up, and to evaluate whether delay in diagnosis affects the risk of bladder cancer death.
Material and Methods: In a previous study, 177 patients with invasive bladder cancer (T1–T4) diagnosed in 1988 were investigated with regard to diagnostic delay. A review of all available clinical records was performed. In the present study, causes of death for these patients were registered over a 12-year follow-up period, and the impact of diagnostic delay on bladder cancer death was studied by means of survival analysis.
Results: The median diagnostic delay in the material was 144 days. When the patients were stratified into groups with diagnostic delays of 0–3, 3–6, 6–12 and >12 months, those with T1 tumours in the two groups with a diagnostic delay of <6 months showed a trend towards a decreased risk of bladder cancer death. In contrast, in patients with muscle-invasive disease, a significantly increased risk of bladder cancer death was noted for those with a diagnostic delay of <6 months.
Conclusion: A trend towards better prognosis was found for patients with T1 tumours with a shorter diagnostic delay. The poor prognosis of patients with muscle-invasive disease and a short diagnostic delay suggests aggressive behaviour of the tumour and may explain the worse prognosis in these patients.

Key words: bladder cancer, diagnostic delay, prognosis.

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Delayed treatment of a disease occurs as a result of diagnostic and treatment delays. The diagnostic delay can be divided into the patient's delay, i.e. the time lag from the patient's first awareness of symptoms to the first medical consultation, and the doctor's delay, i.e. the time lag from that consultation to the establishment of a correct diagnosis (Fig. 1). Long waiting lists for referral departments and investigative procedures, with the consequent risk of a delay in diagnosis, make it clinically important to study both the prevalence and consequences of diagnostic delay. In an early study of bladder cancer, it was suggested that a delay in diagnosis and treatment might adversely affect patient survival (1). This general hypothesis has not been confirmed subsequently (2, 3), and in one study even a trend towards shorter survival was seen among patients with a short diagnostic delay (4). In a more recent study of diagnostic delay in invasive tumours (T1 and T2–T4), a short diagnostic delay was associated with better prognosis in T1 tumours but not in muscle-invasive tumours (5). In contrast, it has been reported that for patients with muscle-invasive bladder cancer, a delay in treatment, i.e. radical cystectomy, for >12 weeks was associated with a more advanced pathological stage and decreased 5-year actuarial survival (6). A recent prospective non-randomized study comparing patients with bladder cancer detected by means of home screening for haematuria and patients with standard clinical presentations showed a reduction in bladder cancer mortality, possibly due to a short diagnostic delay, in the screened group (7). The control population in this study was, however, a matched cohort of patients, and lead time bias cannot be excluded as a cause of increased disease-specific survival in the screened group. In other malignancies, such as colorectal cancer and breast cancer, in which screening has been investigated in a prospective randomized fashion,

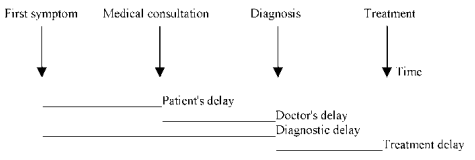

Fig. 1. Breakdown of the different parts of delay from first symptom until treatment.

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a reduction in disease-specific mortality has been found in some studies (8, 9).

The effectiveness of haematuria clinics has also been discussed in terms of diminishing both diagnostic and treatment delays (10, 11). A same-day diagnostic service for new cases of haematuria has successfully been introduced at some hospitals in the UK, resulting in a shorter hospital-based delay and an increase in the number of diagnostic cystoscopies performed within 4 weeks (12).

Screening has been discussed as a means to reduce bladder cancer mortality but as screening studies require a large amount of resources and take a long time to perform, we investigated an historical population-based bladder cancer material with regard to diagnostic delay and outcome. As a consequence of long waiting lists for investigative procedures, we are experiencing a variable diagnostic delay. The aim of this study was to correlate this delay and disease-specific survival with different tumour stages and, if possible, to evaluate whether earlier diagnosis influences survival.

MATERIAL AND METHODS

In a previous study (13), data derived from all 393 cases of bladder cancer in the Southern Swedish Health Care Region notified to the population-based Regional Tumour Register in 1988 were analysed. Fifty patients in whom clinical records revealed non-malignant disease, prostate cancer instead of bladder cancer, recurrent bladder cancer, missing data or a pathologist's report dated 1989 were excluded. As the present study included only invasive cases (T1–T4), 150 patients with non-invasive bladder cancer (Ta) were excluded. Relevant variables were extracted from all available records at every level of referral, and included onset date and specific pattern of symptoms, date of first medical consultation, details of investigations, cytologic and/or histologic findings and date of diagnosis, which was defined as the date of the first positive pathologic report on a transurethrally obtained tumour specimen. Of the 193 patients with invasive disease (T1–T4), information on delay was lacking in 16. Thus 177 patients constituted the study cohort.

For these patients, causes of death were retrieved from the Swedish Cause of Death Register for patients who had died and clinical records were again reviewed for patients who had malignancies other than bladder cancer listed as the cause of death in the Register. Such a review was performed in order to exclude the possibility that metastatic bladder cancer was registered as another primary tumour. The possibility that the impact of cancer based on the data in the Register was overestimated cannot be excluded. As the Register was available only until 1998, clinical records from January 1999 until June 2000 were reviewed to obtain causes of death for patients who had died during that time period. In nine patients in whom the diagnosis was established postmortem, survival was set to 1 day.

The relation between tumour stage and total delay in the 177 patients was analysed by means of box plots and a non-parametric trend test (14). The main endpoint was time from diagnosis of bladder cancer to bladder cancer death with follow-up censored at 30 June, 2000, or death due to other causes before that time. The relation between tumour stage and diagnostic delay was studied using Cox regression analysis. Diagnostic delay was split into four periods considered to be clinically relevant, as follows: 0–3 ($n = 62$); 3–6 ($n = 35$); 6–12 ($n = 34$); and >12 months ($n = 45$). As there are previous studies indicating a different effect of diagnostic delay in T1 and T2–T4 tumours, the interaction between tumour stage and diagnostic delay was tested, and separate analyses were performed in the T1 and T2–T4 groups. In the latter group the analysis was stratified by stage to adjust for differences in total delay in these groups. The cumulative incidence of bladder cancer death was used to illustrate the effect of stage and delay, as Kaplan–Meijer curves are not appropriate because of competing causes of death (15).

RESULTS

The distribution of tumour stage, age and sex among the 177 patients submitted to further analysis is shown in Table I. Twenty-one patients with T1 disease and 64 with T2–T4 disease died of bladder cancer and 27 and 30 patients, respectively died due to other causes. The median diagnostic delay for the whole cohort was 144 days (range 12–2866 days). A significantly longer diagnostic delay ($p = 0.02$) was detected for more

Table I. *Age and sex distributions of tumour stage*

Tumour stage	Number of patients	Median age (years)	No. of males	No. of females
T1	74	73	59	15
T2	66	75	47	19
T3	28	74	20	8
T4	9	80	7	2

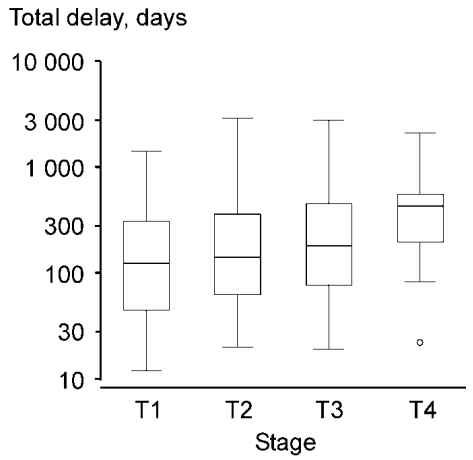

Fig. 2. Box plot showing diagnostic delay in relation to tumour stage (test for trend $p = 0.02$).

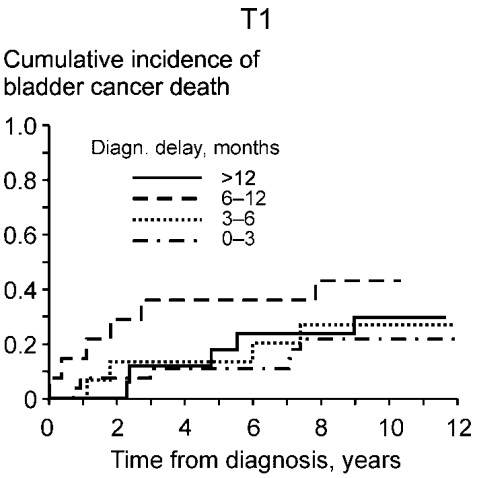

Fig. 4. Cumulative incidence of bladder cancer death by diagnostic delay for T1 tumours ($n = 74$).

advanced tumour stages (Fig. 2). In the T1 and T2–T4 tumour groups the median diagnostic delay was 124 and 157 days, respectively. Tumour stage correlated strongly ($p < 0.001$) with cumulative incidence of bladder cancer death (Fig. 3). There was a significant interaction ($p = 0.014$) between stage group and delay on the effect of bladder cancer mortality. Among patients with T1 tumours ($n = 73$), those with a diagnostic delay of >6 months showed a relative risk of bladder cancer death of 2.0 (95% CI 0.84–4.7; $p = 0.12$), compared to those with a shorter delay (Fig. 4). In the group with muscle-invasive tumours (T2–T4; $n = 103$), there was a relative risk of bladder cancer death of 0.39 (95% CI 0.23–0.69; $p = 0.001$) in the two groups with a longer diagnostic delay (>6 months) compared to the patients with a shorter diagnostic delay (Fig. 5). When stage-adjusted survival was analysed in terms of symptoms, comparing haematuria only with

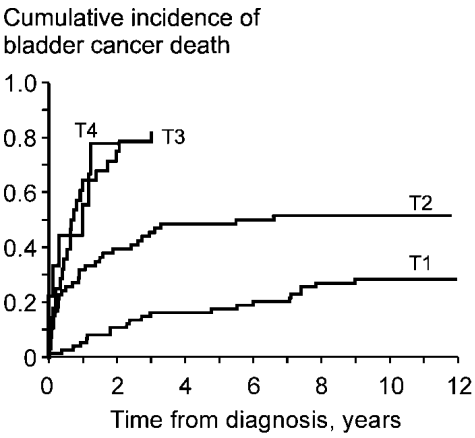

Fig. 3. Cumulative incidence of bladder cancer death by tumour stage.

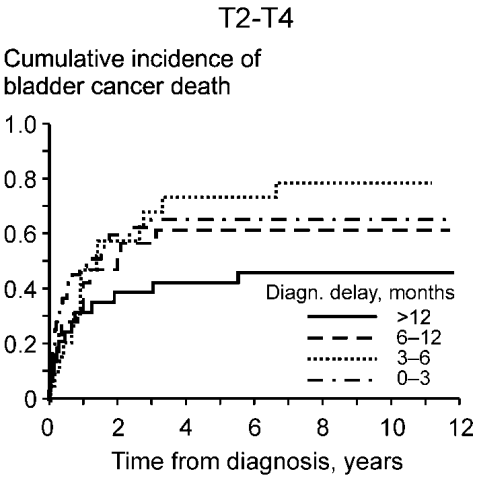

Fig. 5. Cumulative incidence of bladder cancer death by diagnostic delay for T2–T4 tumours ($n = 103$).

pain and/or urgency and/or haematuria, there were no differences in disease-specific survival (data not shown).

DISCUSSION

The median diagnostic delay of 144 days in this study is comparable to the median diagnostic delay of 15 weeks (105 days) described by Mommsen et al. (2) in a previous Scandinavian study. A similar delay was reported in a recent prospective study from the UK (5). For T1 tumours we found a trend towards a better disease-specific survival for patients with a shorter diagnostic delay. An inverse relation between diagnostic delay and bladder cancer death was found in muscle-invasive bladder cancer. The same survival figures were found when doctor's delay was analysed separately for both T1 and muscle-invasive disease (data not shown). A possible explanation for the inverse relation between delay and bladder cancer death in muscle-invasive disease may involve the selection of patients. Those with rapidly progressing tumours with a poor prognosis might have undergone early transurethral resection and diagnosis after cystoscopy and i.v. urography, as suggested by Gulliford et al. (4). Given that the tumour is invasive at diagnosis one might also argue that tumours with a shorter diagnostic delay are more aggressive and thus also have a worse prognosis.

The 5- and 10-year survival rates among patients in this material, especially those with T3 tumours, are much lower than those in modern series of muscle-invasive bladder cancers treated with cystectomy. In two recent studies, 10-year survival rates for pT3b tumours of 61% (16) and 40% (17) were reported. The low survival rates found in the present study probably reflect the fact that some patients in the present material never received curative treatment due to comorbidity or intercurrent diseases. This hypothesis is supported by a Swedish study in which only 40% of patients with muscle-invasive bladder cancer were considered fit for cystectomy (18). Our survival figures are similar to those reported for a large cohort of bladder cancer patients in the UK (5). It is possible that the influence of diagnostic delay on prognosis would have been different in a selected population scheduled for cystectomy.

The question of whether early active measures to establish diagnosis have an effect on prognosis in bladder cancer patients cannot be answered by this study due to its size and because there may have been confounding between delay and tumour aggressiveness. Intuitively, one would assume that a short delay improves survival, and a recent study supports this view (5). A study regarding diagnostic delay in lung cancer showed that tumour stage was favourably influenced by a short diagnostic delay (19), also supporting the general hypothesis that a short delay improves survival. Therefore it seems logical to expect that screening, with the consequent possibility of early diagnosis, is of importance, as has been found in patients with colorectal carcinoma (8). However, unselected population-based haematuria dipstick screening is likely to give a low yield of significant urologic disease, i.e. 1.2–2.6% (20, 21). More selective haematuria screening in men aged >50 years may be more relevant clinically (7), although a study of 2356 such men only detected superficial tumours causing only three bladder cancer deaths after 7 years of follow-up (22), arguing against this type of screening. It is also possible that aggressive bladder cancers emerge and become symptomatic between screening rounds, i.e. interval cancers, and that screening does not therefore lead to earlier diagnosis in these cases. The fact that T1 tumours with a short diagnostic delay had a better prognosis, while T2–T4 tumours with a short diagnostic delay had a worse outcome suggests heterogeneity among bladder tumours, making the outcome of screening uncertain. Potential recruitment of more health-conscious individuals and early detection of more indolent tumours by means of screening are factors to consider when evaluating screening programmes. Another approach to early bladder cancer detection is to perform screening in high-risk populations using specific biomarkers in large-scale randomized studies (23). The use of different biomarkers in that study increased sensitivity at least two-fold compared to haematuria testing only for detection of bladder cancer in benzidine-exposed workers.

In conclusion, a trend towards better prognosis was found for patients with T1 tumours with a shorter diagnostic delay. The poor prognosis of patients with muscle-invasive disease and a short diagnostic delay suggests aggressive behaviour and this could explain the worse prognosis in these patients. These results confirm that the relation between diagnostic delay and bladder cancer mortality is complex. The important issue of whether bladder cancer screening, either generally or for higher-risk individuals, can be of benefit for a population has to be addressed in large randomized studies.

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