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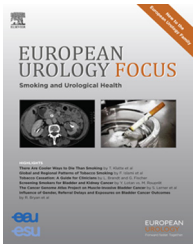

Bladder Cancer

A Comparative Analysis of the Influence of Gender, Pathway Delays, and Risk Factor Exposures on the Long-term Outcomes of Bladder Cancer

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Abstract

Background: The relationship between pathway delays and bladder cancer–specific survival is complex because of the influence of tumour- and patient-specific factors.
Objective: To investigate the influence of tumour factors, patient factors, carcinogen exposure, and pathway delays on the long-term outcome of urothelial bladder cancer (UBC).
Design, setting, and participants: A cohort of 1537 UBC patients were enrolled between January 1, 1991 and June 30, 1992 and followed up for 17.7 yr. The period from the onset of symptoms to first treatment (transurethral resection of bladder tumour, TURBT) was divided into three components of potential delay.
Outcome measurements and statistical analysis: Associations between patient factors, tumour factors, and delay times were analysed using the Pearson χ^2 test and the Mann-Whitney *U* test. Survival was calculated from date of TURBT to date of death or censor date (December 31, 2010). Competing risks of death were assessed with the cumulative incidence function (CIF); CIF comparisons were performed using the Gray test.
Results and limitations: At censor, reliable data were available for 1478 patients, of whom 75% had died. Females presented more commonly with muscle-invasive bladder cancer (MIBC; 30% vs 26%) and less frequently with pT1 disease (18% vs 24%; $p = 0.06$) and had a longer total delay time (median 120 d vs 106 d, $p = 0.02$), and those with MIBC had a significantly higher cumulative incidence of death due to UBC (80% vs 67% at 17 yr; $p < 0.02$). Cox regression identified age, smoking status, and tumour stage, grade, and size as the most significant determinants of poor outcome. We did not capture down-stream delays associated with cystectomy or radiotherapy.
Conclusions: Female UBC patients present later than males, and our data suggest that delay in referral may be contributory. The relationship between gender, outcomes, delays, and UBC aetiology is complex.
Patient summary: We followed a large group of bladder cancer patients for more than 17 yr. The relationship between pathway delays and survival is complex. However, female patients present later than male patients, and our data suggest that delay in referral from general practice may be contributory.

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1. Introduction

Urothelial bladder cancer (UBC) is the fifth most common cancer in Western societies, accounting for 10 000, 69 000, and 180 000 new cases per year in the UK, USA, and EU, respectively [1]. The global incidence of UBC is rising, reflecting patterns of cigarette smoking and occupational carcinogen exposure [2], the most common aetiological factors [1]. There has been little improvement in the outcome for UBC patients since the 1980s, reflecting complex diagnostic pathways and treatment regimens and a lack of therapeutic advances [3]. Given these constraints, much attention has been paid to reducing delays in presentation [4], diagnosis, and treatment [5].

For UBC the relationship between time to diagnosis and treatment, and disease-specific survival is complex [6–9]; many tumours are indolent, for which a delay in diagnosis does not alter survival [10], and outcomes for aggressive UBCs are multifactorial [6–9]. In addition to delays in health care pathways, disease biology (reflected by stage, grade, and tumour characteristics [11,12]) and patient-specific factors are important. The latter reflect aetiological exposure to agents (eg, smoking is more common in males) [9,13,14], gender-specific misdiagnoses (eg, females are more likely to be incorrectly diagnosed with infection [15]) [1,16,17], and potential differences in the molecular pathogenesis of male and female UBC [18].

To obtain a clearer understanding of factors affecting outcomes in UBC, we have followed a large cohort of prospectively recruited patients since 1991 [9]. This population represents 85% of new cases of UBC arising over an 18-mo period within the West Midlands region of the UK [9]. Here we report long-term outcomes and investigate the influence of gender, carcinogen exposure, and pathway delays for this cohort.

2. Patients and methods

2.1. Patients

Patients newly diagnosed with UBC within the West Midlands (UK) were prospectively recruited between January 1, 1991 and June 30, 1992 [9]. Data regarding exposures, date of symptom onset, first referral by general practitioner (GP), first hospital appointment, and first treatment (date of transurethral resection of bladder tumour [TURBT]) were collected at recruitment. Data were checked to ensure that TNM classification correlated with histopathology and bimanual examination findings. Discrepancies were resolved by the investigators and the operating consultant. All patients were notified to the West Midlands' cancer registry, who provided death information at the censor date of December 31, 2010. Ethics committee approval was received before the study was opened. Ex-smokers were defined as those who had abstained for >12 mo. Occupational exposure was identified by three assessors (>90% consensus) using International Agency for Research on Cancer contemporary evidence to assign no risk, possible risk, and definite risk of working in an occupation implicated in the pathogenesis of UBC (Supplementary Table 1) [19].

2.2. Pathway measures

Pathway times were defined as follows:

- Time 1: from date of onset of symptoms to date of first GP referral to secondary care.
- Time 2: from date of first GP referral to secondary care to date of first hospital attendance for urological assessment.
- Time 3: from date of first hospital attendance to date of first treatment by TURBT.

Hospital delay was calculated as the sum of times 2 and 3, and total delay as the sum of all three time periods.

2.3. Statistical methods

All statistical analyses were performed using Stata 11.2 (StataCorp LP, College Station, TX, USA) and R version 2.13.2 (The R Foundation for Statistical Computing, http://www.R-project.org). Associations between patient or tumour features and median delay times were analysed using the Pearson χ^2 test for categorical data and the Mann-Whitney *U* test for continuous data. Survival was calculated from the date of first TURBT to the date of death or the censor date of December 31, 2010, using all-cause mortality. Survival curves for each stage (Ta, T1, T2–4) were constructed using the Kaplan-Meier method, and outcomes were compared between groups using the log-rank test. We estimated relative survival to calculate the crude probability of death in the general population compared to patients diagnosed with pTa tumours according to the user-written Stata command *strs*, matched for age at diagnosis, sex, and year of diagnosis [20]. Probabilities were calculated according to the Ederer II method. Survival was compared in terms of demographic and tumour characteristics and delay times. A stratified survival analysis was used to test for differences within delay times adjusted for tumour stage and to test for smoking status adjusted for delay times. Cox proportional-hazards models using a complete case approach were applied to investigate the independent effect of age, sex, smoking status, haematuria, and tumour stage, grade, type, size, and number. We tested the proportional hazards assumption of the models by examining the Schoenfeld and scaled Schoenfeld residuals; in each test, the proportional hazards assumption was met. In addition, we evaluated the model fit using Cox-Snell residuals, which confirmed that the models fit the data well. This yielded a base model that was used to adjust the effects of each delay.

To assess competing risks of death, we first used a nonparametric test to assess the equality between groups by calculating the cumulative incidence function (CIF) as described by Scrucca et al [21]. Specific CIFs were compared using the Gray test [22] (Supplementary methods).

3. Results

3.1. Cohort description

In total, 1537 patients were enrolled into the study and reliable long-term survival data were available for 1478 participants (96.2%; Table 1). The cohort was typical for UBC, with a male/female ratio of 3:1 and a median age at diagnosis of 69 yr (interquartile range [IQR] 62–76 yr) for male and 71 yr (IQR 64–78 yr) for female patients. A large proportion of patients (973, 77%) were current or former cigarette smokers, and 330 (27%) patients were classified as having possible or definite exposure to occupational carcinogens. As detailed previously, patients were treated by contemporaneous standard practice (which did not