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Survival with bladder cancer, evaluation of delay in treatment, type of surgeon, and modality of treatment

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Abstract

Objective—To determine whether length of delay before treatment; specialty and grade of the surgeon; and use made of surgery, radiotherapy, and chemotherapy influenced the survival of patients with cancer of the bladder, after adjusting for case severity.

Design—Retrospective cohort study.

Setting—South East and South West Thames health regions.

Patients—609 men aged under 75 resident in the South Thames regions who had been registered as new cases of bladder cancer in 1982, 35 of whom were excluded, leaving 574 eligible patients. Analysis was based on 75% retrieval rate for case notes.

Main outcome measures—Duration of survival from date of diagnosis of the bladder tumour.

Results—10 prognostic variables were used to adjust for case severity. The median delay from referral to first treatment was 48 (interquartile range 27-84) days. Treatment after a short delay was associated with shorter survival because of the early treatment of more severe cases. Consultants treated 68% of patients, trainee surgeons treated less severe cases. Initial treatment was by a urologist in 67% of cases, but the specialty of the surgeon was not associated with prognosis. The associations of radiotherapy, cystectomy, and systemic chemotherapy with survival were interpreted in terms of selection bias as well as therapeutic effect.

Conclusions—Case severity was the most important influence on survival and influenced length of delay before treatment, grade and specialty of the surgeon, and main treatment allocation. After adjusting for case severity variations in these processes of care were not strongly associated with variations in survival.

Introduction

In England and Wales there are substantial variations in mortality from conditions which should be amenable to medical treatment^{1,2}; variations in survival with cancer have also been reported.^{3,4} Cancer of the bladder is one of the most common cancers,⁵ and health care is thought to influence the prognosis.⁶ An analysis

of cancer registry data for the South Thames regions showed systematic variation in the survival of patients with bladder cancer according to district health authority of residence (A Walker *et al*, unpublished data). One explanation for this observation could be that the quality of health care varied sufficiently to influence survival of these patients.⁷ The outcome of treatment for cancer of the bladder might be influenced by several characteristics of health care, including the length of delay before treatment⁸; the grade and specialty of the surgeon^{8,9}; and the use made of surgery, radiotherapy, and chemotherapy.¹⁰ These were relevant factors to investigate, given current problems with long waiting times,¹¹ staffing and surgical specialties,¹² and organisation of cancer treatment services.¹³ This study aimed at determining whether, after allowing for the severity of the underlying disease, survival of patients with cancer of the bladder in the South Thames regions was influenced by these processes of care.

Patients and methods

The patients in the study were men aged below 75, resident in the South Thames regions, and registered with cancer of the bladder at the Thames Cancer Registry in 1982. The registry supplied a list of 609 names believed to fulfil the entry criteria. We excluded 35 men after examining their hospital records: seven in whom a diagnosis of bladder cancer had not been confirmed, four who were not resident in the South Thames regions at the time of diagnosis, and 24 whose disease was not first diagnosed in 1982. Thus 574 patients were eligible for further investigation. After consultants' approval had been obtained we abstracted data from the patients' hospital notes and radiotherapy records at 71 hospitals and 11 radiotherapy centres with standard data collection forms.

The patient's age was calculated as 1982 minus the year of birth and was included as a continuous variable. The presence of associated disease was noted from the record of the first hospital admission. The categories none, cardiac, respiratory, renal, and other (specify) were reduced for analysis to "comorbidity present" and "comorbidity absent." The histological extent of tumour invasion was classed according to the Inter-

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national Union Against Cancer (UICC) categories¹⁴ as non-invasive (pTa), superficially invasive (pT1), and muscle infiltrating (pT2 or greater). It was not always clear, however, that an adequate biopsy specimen containing muscle had been obtained. The extent of invasion could not be classified for some patients because the histopathology report was not available or because the extent of invasion was not mentioned; a category was included for tumours whose extent of invasion was not classified or not known. The results of intravenous urography and blood urea and haemoglobin concentrations were reduced to the categories shown in table II. The results of other staging investigations performed at the initial assessment (including computed tomography, ultrasonography, radioisotope scans, and conventional radiography) were classified together as not done, normal, or not known, and abnormal. The total delay before treatment was calculated from the date of the initial referral letter to the date of first treatment. The outpatient delay was taken as the time from the referral letter to the date of the first hospital consultation. The hospital delay was calculated as the time from the first hospital consultation to the first treatment. The delay before radiotherapy was calculated from the date of the initial referral letter to the date of the first radiotherapy treatment.

TABLE I—Distribution of tumour by pT category and one, five, and seven year survival rates

pT grade	No (%)	Survival (%)		
		1 year	5 year	7 year
pTa	150 (35)	95	80	72
pT1	85 (20)	94	69	54
≥pT2	90 (21)	61	23	21
Unclassified	105 (24)	82	53	46

Overall $\chi^2 = 103.3$, $df = 3$, $p < 0.001$.

Trend across pT categories $\chi^2 = 88.5$, $df = 1$, $p < 0.001$.

TABLE II—Variables characterising case severity. Figures are hazard rates (95% confidence intervals) relative to first category of each variable, each adjusted for the other variables and significance of overall association of variable with survival (likelihood ratio test)

Variable	No of patients	Hazard rate (95% confidence interval)	p Value
Age (years)	430	1.04 (1.02 to 1.07)	<0.001
Comorbidity:			
Absent	310	1.00	0.012
Present	108	1.62 (1.16 to 2.25)	
Not known	12	0.67 (0.24 to 1.89)	
Symptoms at referral:			
Haematuria	289	1.00	0.032
Other, haematuria, or both	102	1.60 (1.12 to 2.30)	
Not known	39	1.43 (0.77 to 2.64)	
pT category:			
pTa	150	1.00	0.002
pT1	85	1.34 (0.79 to 2.28)	
≥pT2	90	2.52 (1.51 to 4.18)	
Unclassified and not known	105	1.78 (1.07 to 2.94)	
Tumour grade:			
Well differentiated	154	1.00	0.004
Moderately differentiated	116	1.44 (0.86 to 2.43)	
Poorly differentiated	105	2.42 (1.40 to 4.18)	
Not known	55	2.23 (1.21 to 4.13)	
Tumour appearance at cystoscopy:			
Papillary	223	1.00	0.010
Solid	108	1.75 (1.18 to 2.58)	
Other	22	2.36 (1.26 to 4.40)	
Not known	77	1.43 (0.93 to 2.19)	
Findings on intravenous urography:			
No abnormality	79	1.00	0.010
Filling defect	192	1.02 (0.64 to 1.64)	
Ureteric obstruction	59	1.67 (0.95 to 2.94)	
Other and not known	100	1.78 (1.09 to 2.91)	
Urea concentration (mmol/l):			
<5	120	1.00	0.037
≥5-8	163	0.84 (0.56 to 1.25)	
≥8	64	1.53 (0.96 to 2.43)	
Not known	83	0.72 (0.39 to 1.34)	
Haemoglobin concentration (g/l):			
≥140	230	1.00	0.003
≥120 <140	77	1.02 (0.67 to 1.54)	
<120	46	2.51 (1.55 to 4.07)	
Not known	77	1.27 (0.70 to 2.27)	
Other staging investigations:			
Not done, normal, not known	401	1.00	0.004
Abnormal	29	2.25 (1.33 to 3.81)	

Survival rates were estimated by the product limit method¹⁵; the log rank test was used to test the significance of differences between groups. For surviving patients the survival time was censored at the date of the last follow up or at 17 May 1989 (the date on which patient data were obtained from the registry), whichever was the sooner. The date of death was ascertained from hospital records and from the records of the registry (which also obtains information from the NHS central register). The proportional hazards model was used to estimate the associations of explanatory variables with survival.¹⁵ The associations with survival of prognostic variables intrinsic to the patient and tumour were first evaluated. A stepwise procedure with backwards elimination was used to select those variables which were independently associated with survival. The 10 prognostic variables selected by the stepwise procedure were used in subsequent analyses to adjust the associations of health care variables with survival for case severity. Thus case severity was defined by indentifying the characteristics of the patient which were independently associated with survival. Associations of health care variables with survival were estimated both in univariate (unadjusted) analyses and in multiple regression analyses in which adjustment was made for the 10 variables used to define case severity. Hazard rates relative to a baseline category were estimated for the categories of categorical variables. The values for hazard rates are associated with survival such that values greater than one indicate an increased risk of death and values less than one indicate a reduced risk of death. The overall significance of the association of the variable with survival was tested using the likelihood ratio. For clarity hazard rates for categories of variables recorded as "not known" were omitted from the data presented in table III and were not included in the likelihood ratio test.

Results

Case notes were retrieved for 466/574 (81%) patients. The retrieval rate was 246/281 (88%) for surviving patients and 220/293 (75%) for deceased patients. In 36 patients (31 who died and five who survived) the date of diagnosis was missing so the survival analysis was based on a 430/574 (75%) retrieval rate. The 466 patients whose data were available for analysis had a median age of 67 years (range 22-74 years), and at least one associated disease was recorded in 110 (24%) at the initial hospital assessment. The histological type of the cancer was transitional cell type in 408 (88%) patients. Table I shows survival rates by pT category. A stepwise procedure selected 10 characteristics of patient or tumour which were independently associated with survival (table II). These variables together were used to adjust for case severity in subsequent analyses. Three variables were associated with shorter survival in univariate but not in multiple regression analyses: non-transitional cell type, symptoms other than haematuria recorded at the first hospital consultation, and raised serum creatinine concentration.

There was a weak trend towards worsening prognosis with increasing duration of symptoms before referral, but the duration of symptoms was not mentioned in a third of cases and the association with survival was not significant (table III). Table IV shows the durations of delays before treatment. Patients with the shortest total or hospital delay had a worse prognosis than did those treated after longer delays (table III). Adjusting for case severity accounted for the associations of total delay and of hospital delay with survival. This suggested that patients with severe disease were given priority for treatment. Patients who were referred by general practitioners for admission to hospital (and

TABLE III—Associations of health care processes with survival, unadjusted and adjusted for case severity. Figures are hazard rates (95% confidence intervals) relative to first category* and overall significance of association of variable with survival

Variable	No of patients	Unadjusted survival		Survival adjusted for case severity	
		Hazard rate (95% confidence interval)	p Value	Hazard rate (95% confidence interval)	p Value
Duration of symptoms at referral (weeks):					
≤2 weeks	114	1.00		1.00	
>2 ≤8 weeks	82	1.34 (0.86 to 2.10)	0.249	1.27 (0.80 to 2.02)	0.062
>8 weeks	94	1.39 (0.91 to 2.14)		1.75 (1.10 to 2.79)	
Not known	140				
Type of referral:					
Outpatient	339	1.00	<0.001	1.00	0.586
Inpatient	57	2.07 (1.43 to 3.01)		1.13 (0.74 to 1.74)	
Not known	34				
Grade of doctor seen at initial hospital consultation:					
Consultant	260	1.00	0.176	1.00	0.878
Junior doctor	126	1.25 (0.91 to 1.73)		1.03 (0.73 to 1.45)	
Not known	44				
Type of follow up after initial hospital consultation:					
Outpatient	154	1.00	<0.001	1.00	0.165
Waiting list	195	1.19 (0.85 to 1.67)		1.18 (0.83 to 1.70)	
Inpatient	59	2.65 (1.75 to 4.01)		1.57 (0.99 to 2.50)	
Not known	22				
Total delay before treatment:					
<27 days	85	1.00	0.095	1.00	0.193
≥27- <48 days	89	0.59 (0.37 to 0.93)		0.62 (0.37 to 1.03)	
≥48- <84 days	90	0.65 (0.41 to 1.01)		0.85 (0.51 to 1.41)	
≥84 days	90	0.63 (0.40 to 1.00)		1.01 (0.60 to 1.70)	
Not known	76				
Hospital delay before treatment:					
<14 days	94	1.00	0.014	1.00	0.085
≥14- <26 days	92	0.51 (0.32 to 0.79)		0.60 (0.37 to 0.98)	
≥26- <51 days	95	0.60 (0.39 to 0.92)		0.68 (0.43 to 1.09)	
≥51	101	0.59 (0.39 to 0.91)		1.02 (0.63 to 1.65)	
Not known	48				
Grade of surgeon at initial cystoscopy:					
Consultant	313	1.00	0.018	1.00	0.872
Trainee surgeon	79	0.62 (0.40 to 0.94)		1.04 (0.65 to 1.65)	
Not known	38				
Specialty of surgeon:					
Urology	302	1.00	0.570	1.00	0.264
General surgery	93	1.20 (0.85 to 1.68)		1.27 (0.86 to 1.89)	
General surgery and urology	30	1.15 (0.65 to 2.03)		1.53 (0.83 to 2.81)	
Other and not known	5				
Type of operation:					
Transurethral resection	359	1.00	0.038	1.00	0.048
Total cystectomy	10	2.28 (1.06 to 4.86)		2.83 (1.17 to 6.83)	
Cystectomy after radiotherapy	14	1.76 (0.90 to 3.46)		1.27 (0.60 to 2.70)	
Other	39	1.58 (1.00 to 2.50)		1.70 (1.04 to 2.77)	
Not known	8				
Radiotherapy:					
None	255	1.00	<0.001	1.00	0.013
At initial assessment	122	5.50 (3.95 to 7.64)		1.62 (0.99 to 2.66)	
Later in first year	20	5.32 (3.09 to 9.16)		2.82 (1.52 to 5.22)	
After one year	33	2.56 (1.53 to 4.29)		1.35 (0.73 to 2.45)	
Chemotherapy:					
None	340	1.00	<0.001	1.00	0.041
Intravesical	67	0.50 (0.31 to 0.80)		0.66 (0.39 to 1.11)	
Systemic	18	2.79 (1.66 to 4.68)		1.86 (1.01 to 3.44)	
Not known	5				

*Hazard rates for variables recorded as not known are not shown and were not included in the likelihood ratio test.

who were therefore treated with a short delay) had a worse outcome than those referred for outpatient assessment (table III). Similarly, patients admitted to hospital after the first consultation had a worse prognosis than those placed on the waiting list. These associations were also accounted for by adjusting for case severity.

Patients were seen by a consultant at the initial hospital consultation on 263 (56%) occasions. The first cystoscopy was performed by a consultant on 318/466 (68%) occasions. The risk of death was less for patients in whom the initial cystoscopy was performed by a trainee surgeon (table III), but this was accounted for by adjusting for case severity; trainees were treating less severe cases. A urologist was responsible for the patient's initial management on 310/466 (67%) occasions.

TABLE IV—Delay times before treatment

Delay	No of observations (No eligible)	Median (interquartile range) delay (days)
Delay before initial treatment:		
Total delay	354 (466)	48 (27-84)
Outpatient delay	361 (466)	14 (4-26)
Hospital delay	382 (466)	26 (14-51)
Delay before radiotherapy:		
Referral at initial assessment	82 (146)	80 (50-115)
Referral later in first year of follow up	13 (22)	227 (187-341)

There was no association between specialty of surgeon and survival. After allowing for case severity the use of radiotherapy was not associated with survival, except in patients who were referred not at the initial assessment but after a subsequent cystoscopy in the first year of follow up. Cystectomy was employed infrequently and tended to be associated with a worse prognosis. Systemic chemotherapy was used in a few patients and was associated with a worse prognosis, after allowing for case severity. The use of intravesical chemotherapy was associated with longer survival overall because it was usually used in patients who developed frequent recurrences during prolonged follow up.

Discussion

In this study, variables characterising the severity of the condition¹⁶⁻¹⁹ were strongly associated with survival. Case severity was an important influence on treatment allocation but after adjusting for severity there was little evidence to suggest that processes of care contributed greatly to the variation in survival of patients with cancer of the bladder. In this observational study it is necessary to acknowledge potential biases, including the possibility that some confounding variables may not have been fully evaluated.

The patients were sampled from a population based registry. We excluded those aged over 75, in whom

health care was less likely to have had an important impact on the prognosis, and 24 patients whose first diagnosis was not in 1982, so that the investigation was confined to incident cases. We have shown that the non-retrieval of case notes was to some extent systematic²⁰; in particular, deceased patients and patients treated at teaching hospitals were under-represented because of the difficulty of finding their notes. Thus it may not be entirely justified to assume that the patients whose notes were obtained were representative of those whose notes were not. In addition, the retrieval rate for case notes varied systematically among health districts and hospitals and direct evaluation of the factors responsible for variation in survival among districts was therefore not possible.

Wallace and Harris⁶ reported that the three year survival with invasive cancer of the bladder was 60% when the duration of symptoms before treatment was less than four weeks but that it fell to 25% when the history was longer. This observation has not been confirmed subsequently.^{21,22} Our results suggest that patients with the worst prognosis were selected for early treatment, and there was little evidence to suggest that the prognosis deteriorated with increasing delay. Similarly, the results suggest that less severe cases in patients were selected for treatment by trainee surgeons: after allowing for severity there was no evidence that the grade or specialty of the surgeon had an effect on patient survival.

Patients received treatment over a varying period of follow up. The analysis presented here provides a crude summary of the use of different procedures and their associations with survival. The results must be interpreted cautiously, both in terms of the factors which influence selection for treatment and in terms of possible therapeutic effectiveness. Although adjustment was made for case severity, this may not entirely have accounted for confounding of disease severity with treatment allocation. The separate contributions of selection bias and therapeutic effectiveness to associations with survival therefore cannot be clearly quantified. Radiotherapy was used as the principal mode of treatment for invasive tumours. After adjusting for severity an adverse prognosis was associated with referral not at the first cystoscopy but later in the first year of follow up. The extent of tumour invasion could be classified for 15 patients in this group, 11 of these had tumours initially classed as pTa or pT1. These tumours might have been understaged at the initial operation, although we did not have data to show whether an adequate biopsy specimen containing muscle was obtained.²³ There was no evidence that the overall prognosis was worse for the patients referred later as the unadjusted hazard rate was similar to that for patients referred for radiotherapy at the initial assessment. The infrequent use of cystectomy is consistent with the uncertainty over its use,²⁴ but the results obtained suggest that further evaluation of the use of this operation would be justified. A few patients were treated with systemic chemotherapy, mainly in the context of a clinical trial whose negative results have been reported.²⁵ The results of our study suggest that selection for this form of treatment was an independent marker of case severity.

The release of hospital mortality statistics in the United States has provided a new stimulus to the investigation of health care characteristics associated with mortality.²⁶ In epidemiological studies case severity has been the most important influence on mortality.^{27,28} Our findings are consistent with this and provide some reassurance that the length of delay before treatment, the training and experience of surgeons, and the appropriateness of the use made of major treatment modalities were not factors which contributed substantially to the variation of survival of

patients treated for cancer of the bladder in these two regions. Evaluation by peer review might be more likely to identify departures from ideal practice which adversely affected prognosis.^{8,29} The strong dependence of mortality on case severity makes it a weak measure of the quality of health care.³⁰ Measures of outcome other than survival are therefore needed for monitoring and for use in clinical trials.³¹

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Correction

Physiotherapy for stress urinary incontinence: a national survey

An authors' error occurred in this paper by Jill Mantle and Eboo Versi (30 March, p 755). The last sentence in the results section "prognostic features" should read "On the optimistic side . . . 'young and premenopausal' (40) were the most common features" (not postmenopausal as printed).