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Original Paper

Factors Affecting Recurrence and Progression in Superficial Bladder Tumours

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Prognostic factors in superficial bladder tumours are highly correlated with each other. In this study, their relative importance is examined and grouping of patients in three different prognostic groups suggested. 576 patients (from EORTC protocols 30790 and 30782) were analysed. They have been followed from 3 months to 8.6 years with a median of 4 years. 76 patients developed an invasive tumour (≥T2); the shortest time to invasion was 12 weeks, the longest was 6.6 years. Time from invasion to death ranged from 3 weeks to 4.4 years with a median of 2 years. Prognostic factors contributing to recurrence, invasion and survival were investigated: age, sex, size of largest tumour, number of tumours, T-category, G-grade, time from diagnosis (years), prior recurrence rate/year, site of involvement. The relative importance of these factors was measured by performing a multivariate analysis based on Cox's proportional hazards regression model. Based on the most important prognostic factors and their association with invasion and death, an index was computed reflecting the risk of both invasion and death due to malignant disease, respectively. The index was used to assign patients to one of three prognostic groups. Three main factors determined patient's prognosis: tumour size, G-grade and prior recurrence rate/year. The model coefficients for invasion were 0.51 (recurrence rate <1/year, 1–3/year, >3/year), 0.84 (grade 1, 2, 3), 0.48 (size <1.5, 1.5–3, >3 cm) and for death due to malignant disease 0.89 (recurrence rate), 0.73 (grade) and 0.44 (size), respectively. Risk groups are suggested based on the index. Additional treatment in patients with superficial transitional cell carcinoma of the bladder may be decided depending on the risk group to which the patient belongs.

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INTRODUCTION

PROGNOSTIC variables as well as patient characteristics influence the outcome of all forms of cancer. In superficial transitional cell carcinoma of the bladder (STCC), category Ta/T1, prognostic factors may have a more important influence on further development of the disease treated by transurethral resection than the choice of adjuvant chemotherapy or immunotherapy. Furthermore, treatments may have different effects in patients with different prognostic characteristics.

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PATIENTS AND METHODS

In 1979, the EORTC-GU group started two superficial bladder cancer trials based on almost identical protocols (30790, 30782). Data from these two trials (excluding control arm of 30790) were pooled to facilitate analysis of prognostic factors. Patients without follow-up for recurrence were excluded. The results from 576 patients, all of whom received intravesical chemotherapy, were analysed. No association was found between the adjuvant treatment group assigned and either recurrence, invasion, or survival. Thus, the drugs selected were equally effective [1,2]. Patients received either doxorubicin 50 mg (Farmitalia, Milano, Italy), cisplatin 50 mg, or thiotepa 50 mg (Lederle Laboratories, Pearl River, New York, U.S.A.), all dissolved in 50 ml saline, or epodyl 1.13 g (Zeneca, Cambridge, U.K.) dissolved in 100 ml water, weekly for 1 month and monthly for 1 year. If recurrences occurred during the first year, the patients received a further course of four times weekly treatment after transurethral resection with the same drug, but the total length of treatment did not exceed 12 months. Cystoscopy was performed every 3 months during year 1 of follow-up, every 4 months during year 2 and every 6 months

Table 1. Patient characteristics

Coding	Patients		% of patients			
	Number	%	Recurrence	Invasion	Death	MD
Overall	576	100	54	13	22	10
Age						
(1) ≤60	154	27	57	9	8	5
(2) 61–79	379	66	52	15	26	12
(3) ≥80	43	7	53	9	44	19
Sex						
Female	97	17	52	9	15	4
Male	479	83	54	14	24	11
Size of largest tumour (cm)						
(1) <1.5	347	61	53	9	18	7
(2) 1.5–3	133	23	55	19	29	15
(3) ≥3	94	16	55	22	29	14
Number of tumours						
(1) ≤6	474	82	50	12	21	9
(2) ≥7	102	18	69	18	29	17
T-category						
(1) Ta	310	54	54	9	21	9
(2) T1	266	46	53	18	24	11
G-category						
(1) G1	236	44	47	6	16	4
(2) G2	247	46	59	17	26	14
(3) G3	56	10	61	30	25	16
Time from diagnosis (yrs)						
(1) primary	219	38	43	14	25	8
(2) 1 or less	99	17	61	12	22	14
(3) 2 or 3	109	19	64	16	25	16
(4) >3	147	25	56	11	18	7
Prior recurrence rate/year						
(1) primary	219	38	43	14	24	8
(2) <1	128	22	51	9	16	6
(3) 1–3	183	32	63	13	20	11
(4) >3	44	8	73	23	41	27
Trigone involvement						
(1) No	492	85	52	11	21	9
(2) Yes	84	15	65	24	30	18
Right or left ureteral orifice						
(1) No	422	73	56	13	23	11
(2) Yes	154	27	47	14	21	7
Right or left wall						
(1) No	235	41	46	10	20	8
(2) Yes	341	59	59	15	24	12
Anterior wall						
(1) No	504	87	53	13	21	10
(2) Yes	72	13	56	15	31	15
Posterior wall						
(1) No	353	61	48	14	20	9
(2) Yes	223	39	62	12	26	13
Dome						
(1) No	415	72	47	12	21	9
(2) Yes	161	28	70	15	25	14
Neck						
(1) No	124	78	51	9	20	8
(2) Yes	452	22	65	21	33	18
First cystoscopy after entry						
(1) Negative	480	83	44	10	21	8
(2) Positive	96	17	100	27	30	21
% positive cystoscopies after entry						
(1) 30 or less	435	76	—	6	18	6
(2) >30	141	24	—	37	37	25

MD, death due to malignant disease.

thereafter (provided there was no recurrence in the meantime). Patients were removed from the study when the first recurrence after 1 year of treatment or progression was observed.

Definition of end points

Time to first recurrence is defined as the time from randomisation to the time of first recurrence. Patients without recurrence were censored at the time they left the study (last cystoscopy).

The recurrence rate per year is defined as the number of follow-up cystoscopies at which a recurrence was seen, divided by the total number of months of follow-up. The result is then multiplied by 12. The recurrence rate takes into account the clinical course of patients during a longer interval and not only the time to first recurrence.

Time to invasion is defined as the time from randomisation until progression to stage T2 or worse. Patients without invasion were censored at the last available follow-up cystoscopy.

The duration of survival is defined as the time from entry into study until death. Patients still alive or lost to follow-up were censored at the last date they were known to be alive.

Statistical considerations

Curves estimating the time to first recurrence, invasion, and duration of survival among the various subgroups of patients were estimated using the Kaplan–Meier method [3] and compared using the log-rank test [4]. Whenever a factor had ordered categories, a log-rank test for trend was carried out. A comparison of recurrence rates in the different levels of a given factor was performed using a non-parametric permutation test [5,6]. Finally, multivariate analyses based on Cox's proportional hazards regression model and Cox's logistic regression model were used to measure the relative importance of the factors [7].

RESULTS

The 576 patients analysed were followed up from 3 months until 8.6 years, with a median of 4 years. Table 1 gives the distribution of patient characteristics for various factors.

At entry into the study, the patients were between 15 and 82 years of age and 73% were older than 60 years of age. Thirty-eight per cent of the patients were newly diagnosed before entering into the trial. The others were patients with recurrent Ta or T1 tumours. Their diagnoses date from 9 weeks to 9.6 years before entry, with a median of 2.4 years.

Table 2 shows how the patients' characteristics are correlated with each other. For example, primary patients tend to have more and smaller tumours and no neck or dome involvement. A positive first control cystoscopy is significantly correlated with the size of largest tumour and the number of tumours, but also with the G-grade and site involvement. Neck involvement is significantly associated with dome or posterior wall involvement. A percentage of >30 positive cystoscopies (frequent recurrences) is significantly correlated with the number of tumours, G-grade, prior RR, site involvement and the result of the first control cystoscopy.

Time to first recurrence

Tumours recurred in 54% of the 576 patients analysed (17% at first cystoscopy). Recurrence occurred at the earliest after 6 weeks of follow-up and at the latest after 5 years. The median time to first recurrence was 94 weeks.

The univariate analysis identified the factors listed in Table 3 as being associated with the time to first recurrence. These factors were highly correlated with each other (see Table 2). For instance, the number of tumours was positively correlated with the prior recurrence rate and site involvement and negatively correlated with tumour size. Also, neck and trigone involvement tended to be associated with either wall or dome involvement.

The association of these factors with the time to first recurrence was assessed by Cox's model as given in Table 4.

On reanalysing the data by ignoring sites of involvement, the number of tumours becomes a more important factor. The importance of involvement can be explained by the fact that the site brings a refinement to the number of tumours variable.

Recurrence rate per year

The endpoint recurrence rate per year was likewise analysed in a multivariate model using logistic regression. Again, the prior recurrence rate, G-grade, and number of tumours were the most important prognostic factors ($P < 0.0001$).

As a further endpoint, the recurrence rate starting after the first follow-up cystoscopy after 3 months (zero-point first follow-up cystoscopy) was used. Among the 576 patients analysed, 96

Table 2. Correlation between factors

	A‡	S	S	N	T	G	P	T	P	T	U	W	A	P	D	N	F	%
Age	*																	
Sex	0	*																
Size of largest tumour	0	0	*															
Number of tumours	0	0	0	*														
T-category	0	+	+	0	*													
G-grade	+	0	+	0	+	*												
Primary/recurrent*	0	0	−	+	0	0	*											
Time from diagnosis†	+	0	0	0	0	0	*	*										
Prior recurrence rate†	0	0	0	+	0	0	*	−	*									
Trigone	0	0	0	+	0	0	+	0	0	*								
Ureteral orifice	0	0	0	0	−	−	0	0	0	*								
Wall	0	−	+	+	0	0	0	0	0	0	−	*						
Anterior wall	+	0	0	+	0	0	+	0	0	+	0	0	*					
Posterior wall	0	0	−	+	0	0	+	0	0	+	−	0	+	*				
Dome	0	0	−	+	−	0	+	+	0	+	0	0	+	+	*			
Neck	0	0	+	+	0	+	+	0	0	+	0	0	0	+	+	*		
First cystoscopy	0	0	+	+	0	+	+	−	+	0	0	+	+	+	+	0	*	
% positive cystoscopies	0	0	0	+	0	+	+	−	+	+	0	+	0	+	+	+	+	*

+, significant positive correlation ($P < 0.05$); −, significant negative correlation ($P < 0.05$); 0, no correlation.
*Code: 1 = primary; 2 = recurrent; † In order to compute the correlations with these factors primary patients have been excluded; ‡ Letters correspond to initial letters of coding characteristics used in Table 1.

Table 3. Univariate analysis for time to first recurrence

Prognostic factor	*P* value
Number of tumours	<0.0001
G-grade	0.0016
Prior recurrence rate	<0.0001
Time from diagnosis	<0.0001
Involvement of	
trigone	0.0007
wall	0.0022
posterior wall	<0.0001
dome	<0.0001
neck	0.0001

Table 4. Multivariate analysis for time to first recurrence

Prognostic factors	Estimated coefficient	*P* value
Involvements included		
Prior recurrence rate	0.357	<0.0001
Tumour size	0.191	0.03
G-grade	0.297	0.001
Involvement of		
lateral wall	0.377	0.002
posterior wall	0.273	0.02
dome	0.406	0.001
Involvements excluded		
Prior recurrence rate	0.387	<0.0001
Tumour size	0.204	0.02
G-grade	0.282	0.002
Number of tumours	0.270	0.07

Variables are coded as in Table 1.

Table 5. Multivariate analysis of recurrence rate per year taking the first follow-up cystoscopy at 3 months as zero point

Prognostic factor	*P* value
Recurrence at 3 months (y/*n*)	<0.001
Prior recurrence rate	<0.001
Number of tumours at entry	<0.001
G-category	0.01
T-category*	NS

NS, not significant.
*Based on local pathology.

(17%) already had a recurrent tumour at the first cystoscopy. The most important prognostic factor for the long-term recurrence rate was by far the presence or absence of recurrence at 3 months (Table 5).

Whereas 53% of the patients without recurrence at 3 months remained free of further recurrences, only 17% with recurrence at 3 months experienced no further recurrences during follow-up (Table 6).

Time to invasion

Out of 576 patients, 76 progressed to T2 or worse, 43 (57%) did so while on treatment. The shortest time to muscle invasion was 12 weeks, and the longest was 6.6 years (Figure 1). Although muscle invasion was observed only in a few patients, one can expect to identify prognostic factors for this endpoint. In fact, the loss of power due to the small number of patients with invasion was balanced by the strong association between invasion and the prognostic factors. As for the time to first recurrence

Table 6. Recurrence in relation to presence of tumour at the first follow-up cystoscopy 3 months after entry into study

Recurrence at 3 months	Number of future recurrences 0	1	2	≥3	Total
No	235 (53%)	165 (37%)	42 (9%)	6 (1%)	448
Yes	12 (17%)	39 (55%)	14 (20%)	6 (8%)	71
Total	247	204	56	12	519

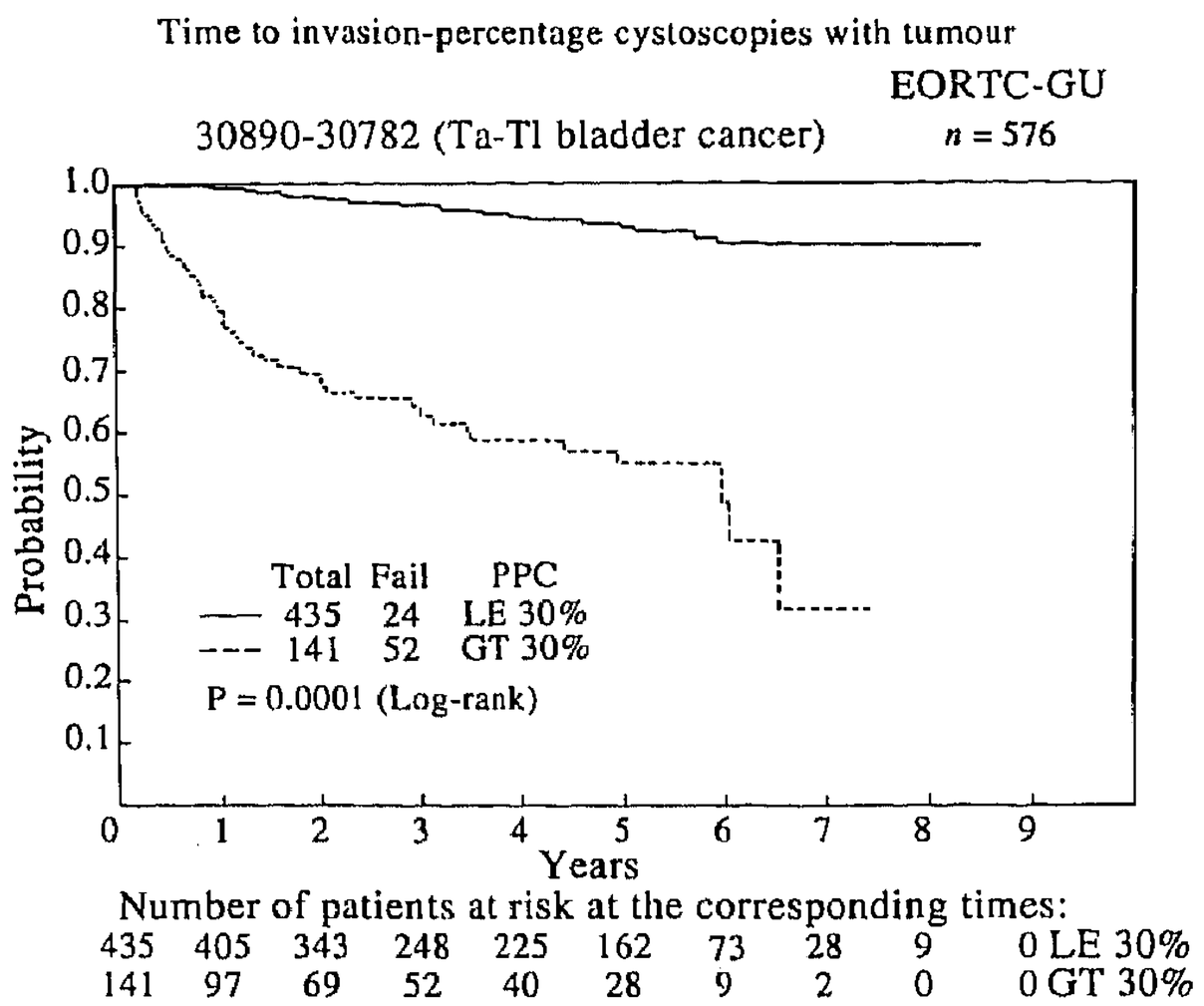

Figure 1. The risk of developing muscle invasive disease (≥T2) in patients with superficial bladder tumour, category Ta/T1. Taking more than 30% positive cystoscopies as cut-off point, the difference is highly significant ($P < 0.0001$).

and recurrence at 3 months, the univariate analysis identified tumour size, prior recurrence rate, G-grade, and involvement of trigone, wall or neck, as being important prognostic factors. The T-category and age were also factors related to invasion. Finally, recurrence at the first cystoscopy was highly correlated with invasion. Surprisingly, there was a negative association of posterior wall involvement with invasion and the number of tumours could not replace site involvement. The probability of developing muscle invasive disease was higher in patients with greater than 30% of positive cystoscopies (Figure 1).

The multivariate analysis confirmed that all these variables except T-category (correlated with tumour size and G-grade), and wall or neck involvement were associated with future invasion. The oldest patients had a risk of invasion similar to patients younger than 60 years of age. Results of the multivariate analysis are shown in Table 7.

Survival

Out of 576 patients, 129 (22%) died of various causes. Death occurred between 18 weeks and 8.2 years after entry into the study. The survival at 5 years was 75%. According to the univariate analysis, patients with the poorest prognosis tended to have a high recurrence rate at entry, numerous tumours, high G-grade, and involvement of the anterior wall, posterior wall or neck. Moreover, they were often old, male, and had already had

Table 7. Multivariate analysis for time to invasion (n = 535)

Factor	Estimated coefficient	*P* value
First cystoscopy	1.082	<0.0001
G-grade	0.867	<0.0001
Prior recurrence rate	0.517	0.005
Posterior wall involvement	−0.645	0.01
Trigone involvement	0.533	0.05
Tumour size	0.396	0.01
Sex	0.752	0.03

Coded as in Table 1.

Table 8. Multivariate analysis for survival: all causes of death (n = 535)

Factor	Estimated coefficient	*P* value
Involvement excluded		
Age	1.097	0.001
Sex	0.707	0.01
Prior recurrence rate	0.482	0.001
Tumour size	0.312	0.009

Table 9. Multivariate analysis of time to death due to malignant disease (n = 535)

Factor	Estimated coefficient	*P* value
Involvement excluded		
Age	1.061	<0.0001
Sex	1.423	0.006
Prior recurrence rate	1.053	<0.0001
G-grade	0.755	0.0005
Tumour size	0.414	0.02

a positive cystoscopy 3 months after entry. The multivariate analysis, which studies the possible correlation between these factors, identified (involvement excluded) age, sex, prior RR and tumour size and G-grade, as being associated with survival (Table 8).

An analysis of disease-related deaths was also carried out. 53 patients (10%) died of malignant disease. Their time to death ranged from 23 weeks to 7 years. The factors most associated with death of malignant disease were (site of involvement excluded) age, sex, prior recurrence rate, G-grade and tumour size (Table 9).

Figure 2 shows the survival curves for G-grade. For the 76 patients with invasion, the time from invasion to death ranged

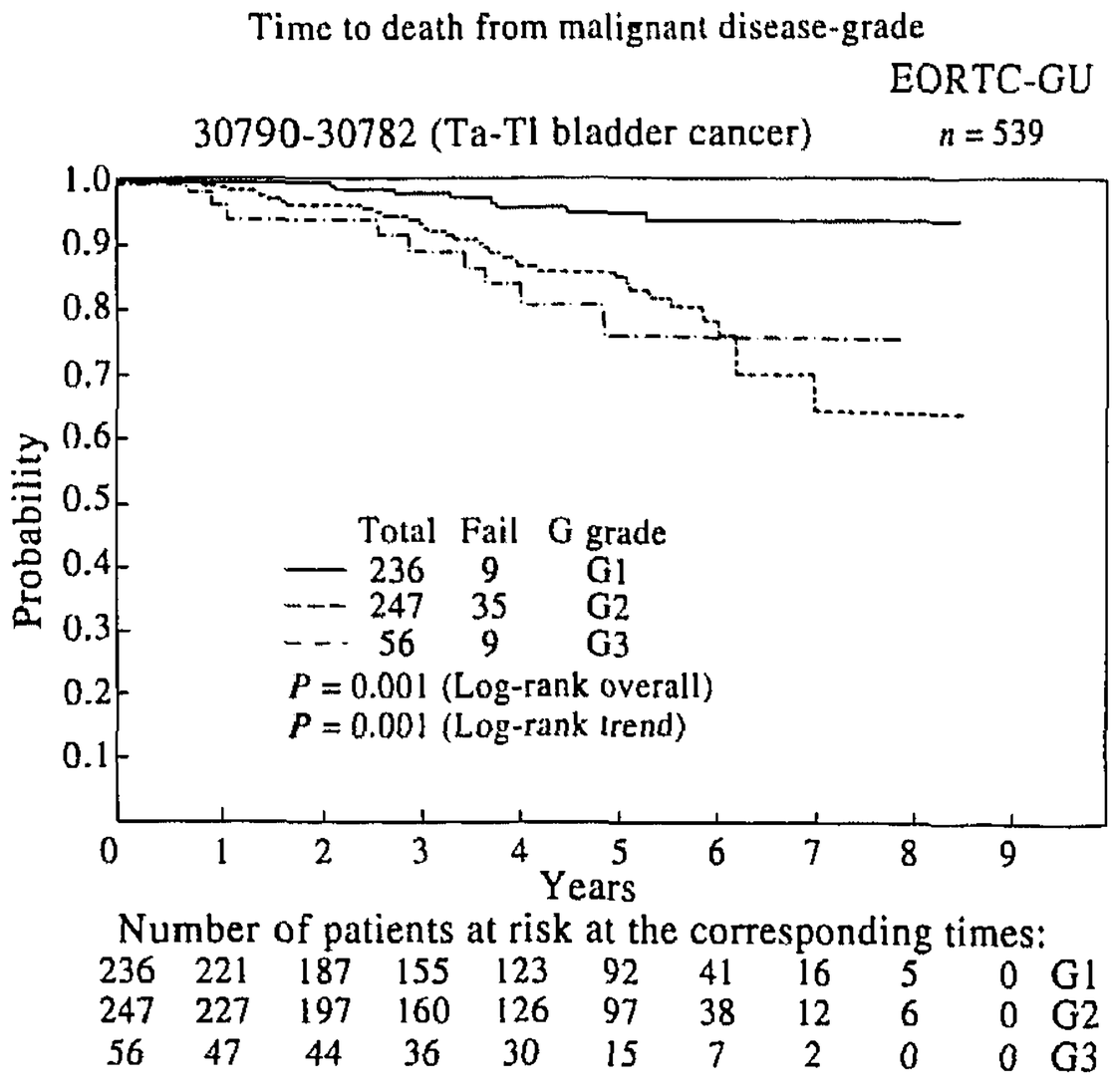

Figure 2. Time to death from malignant disease curves show an increased probability of death with an increased undifferentiation of the tumour ($P < 0.001$).

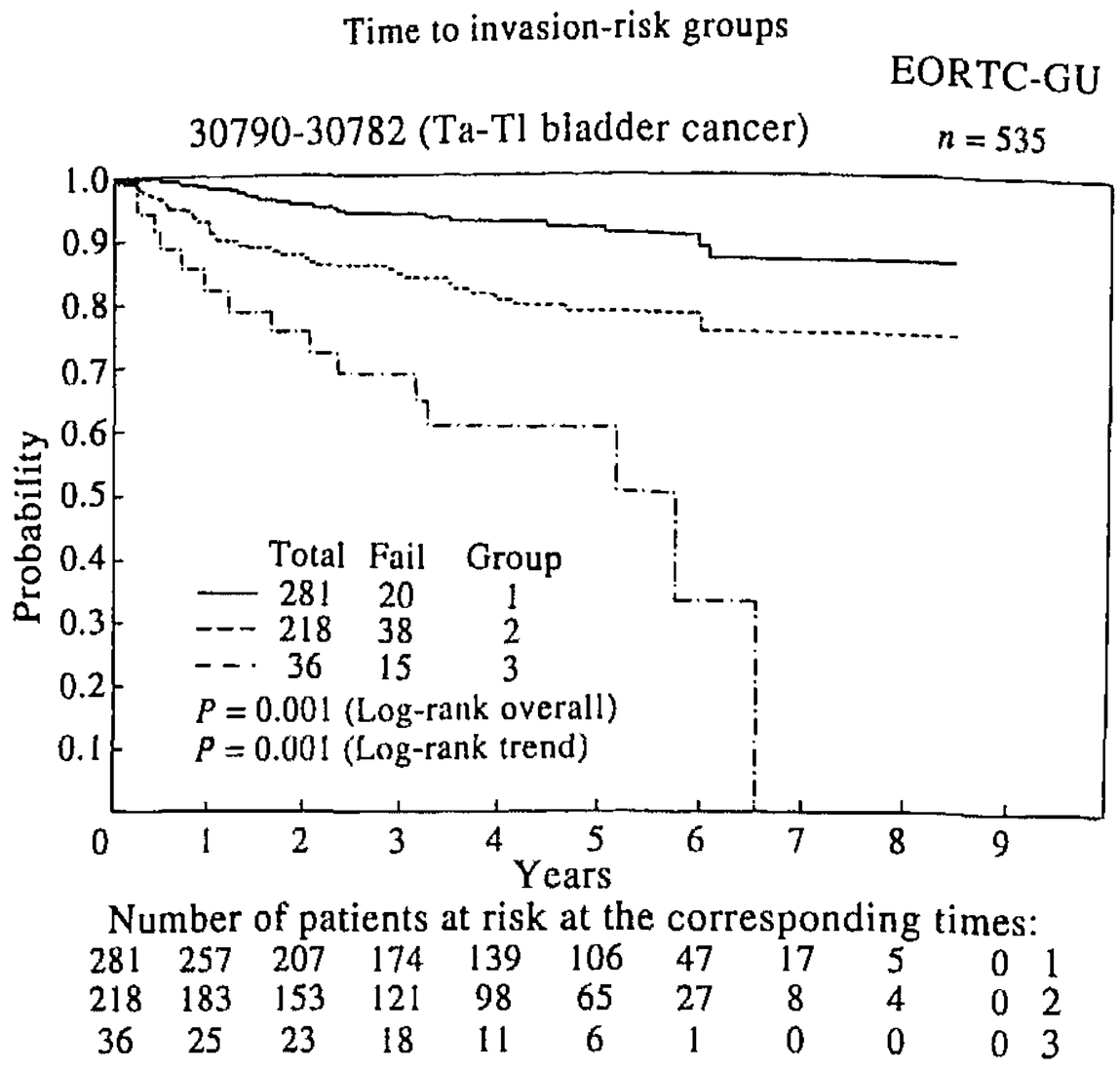

Figure 3. The distribution of (a) time to invasion and (b) time to death from malignant disease in each of the three risk groups.

from 3 weeks to 4.4 years, with a median of 2 years. To determine to what degree invasion was associated with survival, a variable representing invasion was included and updated at 1, 2 and 3 years using the best model for survival. Invasion then became, with age, the most significant factor ($P < 0.0001$).

Time to invasion and percentage of positive cystoscopies (less or more than 30%) were both clearly correlated with survival, and hence can be used as surrogate endpoints. It is advisable to use the recurrence rate, however. When comparing two treatments, the number of patients with invasion during adjuvant treatment is so small (7%) that one would need a large number of patients to detect improvement in the time to invasion.

Risk groups for progression ($\geq T2$) *and death due to malignant disease*

Three main factors determine the patient's prognosis: tumour size, G-grade and prior recurrence rate (grouping primary with a recurrence rate of less than one in a year). Based on these three

Table 10. *Risk index for patients in various subgroups*

Tumour size (G-grade)	Primary, RR <1			1–3			>3		
	<1.5	1.5–3	>3	<1.5	1.5–3	>3	<1.5	1.5–3	>3
G1	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**3**
	0	0.48	0.97	0.51	1.0	1.5	1.0	1.5	2.0
	0	0.44	0.87	0.89	1.3	1.8	1.8	2.2	2.7
	77	36	26	71	6	4	12	2	0
G2	**1**	**2**	**2**	**2**	**2**	**3**	**3**	**3**	**3**
	0.84	1.3	1.8	1.4	1.8	2.3	1.9	2.4	2.8
	0.73	1.2	1.6	1.6	2.1	2.5	2.5	3.0	3.4
	71	38	38	53	19	3	13	9	1
G3	**2**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**3**
	1.7	2.2	2.7	2.2	2.7	3.2	2.7	3.2	3.7
	1.5	1.9	2.3	2.4	2.8	3.3	3.3	3.7	4.1
	12	10	15	9	4	2	2	2	0

Each cell gives the risk group, the risk index pertaining to invasion and death from malignant disease as well as the number of patients.
RR, recurrence rate per year.
Risk index, odds ratio estimated from the Cox model including only three factors: Tumour Size (TS), G-grade (G) and RR.
The estimated Cox models are: for invasion: 0.51 RR + 0.84 G + 0.48 TS; for death: 0.89 RR + 0.73 G + 0.44 TS. The bold numbers in the table refer to the risk group: (1) 254 patients; (2) 218 patients; (3) 36 patients.

factors and their association with invasion and death due to malignant disease, an index was computed reflecting the risk of early invasion and death due to malignant disease (Table 10).

Table 11 shows the observed rate of tumour progression and death due to malignant disease according to the risk group as defined in Table 10. Figure 3a,b shows the distribution of time to invasion and death from malignant disease in each risk group.

DISCUSSION

Superficial bladder cancer comprises a spectrum of disease processes. Identification of prognostic variables predictive of recurrence and muscle invasion would identify which patients require adjuvant therapy after TUR (transurethral resection) or are candidates for additional surgery and, conversely, for which patients the potential toxic effects and cost of adjuvant chemotherapy could be spared.

In the present study, previous recurrence rate, tumour size and grade of the tumour when tested with other prognostic factors (as listed in Table 1) in a multivariate model were the most powerful predictors of either recurrence, muscle invasive disease or death due to malignant disease. Patients with a recurrent tumour at the first 3 month cystoscopy study did particularly poorly and had the highest chance of developing new recurrences and/or progressing to ≥T2. This confirms an earlier observation, reported by Parmar and colleagues for the British Medical Research Council subgroup on superficial bladder cancer [8]. Surprisingly the T-category (Ta/T1) did not add to the prognostic information and did not improve the separation between different groups. T-category in the present study was based on local pathology. Overestimation of the T-category may contribute to the lack of predictive value of this prognostic factor. Oosterlinck and associates reported that out of 96 patients with a T1-tumour as diagnosed by the local pathologist, only 41.6% were confirmed by the review pathologist, whereas 5.1% staged Ta were understaged and had a T1 lesion [9]. Similar observations were made by others [1, 8].

Thus, pathologists most likely upstage the pathological diagnosis. On the other hand, a higher percentage of pathologists seem to agree on the grade of the tumour. In the report by Oosterlinck and associates, agreement between local and review pathology is reported in 61.8%, a higher degree of undifferentiation by the review pathologist was seen in only 18% [9].

Size and previous recurrence rate are easy to calculate, and, therefore the three most powerful predictors of either recurrence or invasive disease are available in daily practice and allow assignment of a given patient to one of the three risk groups (Table 10). Obviously, more aggressive treatment (e.g. cystectomy and urinary diversion) should be considered only for those patients with superficial bladder tumour who failed conservative treatment (transurethral resection followed by either chemo- or immunotherapy) and who are assigned to risk group 3 (Table 10). This group is small in the present study (6.7%), but of a similar size (6 to 9%) as the poor risk group for recurrence and survival computed in a different way by Parmar and colleagues [8]. Patients possessing the criteria for the best profile might be spared adjuvant chemo- or immunotherapy until a worsening of one of these prognostic factors occurs.

Table 11. *Tumour progression and death due to malignant disease (DMD) by risk group*

Group	No. of patients	Progression (%)	DMD (%)
1	281	20 (7.1)	12 (4.3)
2	218	38 (17.4)	28 (12.8)
3	36	15 (41.6)	13 (36.1)
Total	535	73 (13.6)	53 (9.9)

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