J Cancer Res Clin Oncol (1993) 119:578–593

Journal of Cancer Research and Clinical Oncology

Guest editorial *

The value of tumour spread, grading and growth pattern as morphological predictive parameters in bladder carcinoma. A critical revision of the 1987 TNM classification

Javier C. Angulo[1], Jose I. Lopez[2], Nicolas Flores[1], Juan D. Toledo[2]

[1] Department of Urology, Santo Hospital Civil de Bilbao, Faculty of Medicine, Basque Country University, Bilbao, Spain
[2] Department of Pathology, Santo Hospital Civil de Bilbao, Faculty of Medicine, Basque Country University, Bilbao, Spain

Received: 23 September 1992/Accepted: 4 February 1993

Abstract. A group of 343 patients with bladder carcinomas was uniformly staged, both clinico-radiologically and pathologically. In accordance with pathological staging, they were treated from 1983 to 1990 and follow-up was closed on January 1992. No systemic chemotherapy regime was used. The present study was designed to assess the value of classical morphological parameters (tumour extension, histological subtype, grade and growth pattern) in the prediction of prognosis, and also to evaluate the adequacy of the current TNM classification (4th edition, 1987) of bladder cancer. The initial tumour stage appears the most useful criterion in the prediction of prognosis. Nevertheless, survival analysis confirms the necessity to modify the present TNM classification for routine clinical practice. In fact, stage III proves to be heterogeneous, and the difference in survival between categories pT3a and pT3b is even more statistically significant (log-rank $P<0.01$) than the difference between pT2 and pT3 as a whole (log-rank $P<0.02$). Consequently, invasion of the muscular layer should be reclassified into a common stage II, equivalent to the B category in the ABCD system. Moreover, stage IV is also heterogeneous in terms of survival. Despite the overall life-expectancy being rather poor for a patient with bladder carcinoma, three subsets with different prognosis (log-rank $P<0.001$) can be identified: pT4N0M0; pT*x*N1–3M0; pT*x*N*y*M1, where *x* and *y* represent any number. Therefore, we believe that various subgroups should be distinguished in a future edition of the TNM classification. Current treatment modalities, involving the role of systemic chemotherapy and aimed at bladder preservation, make such innovations even more convenient for a new edition of the TNM classification of bladder cancer. Apart from tumour staging, several microscopic morphological parameters are valuable in distinguishing patients with different prognosis. Pure transitional-cell histology, papillar growth, and low grade, are favourable data. In fact, tumour grade, although somewhat subjective, is a factor of major prognostic importance. Pauwels' distinction of intermedium grade 2 into 2A and 2B is also helpful in the assessment of a population of "intermediate" prognosis. Similarly, with regard to superficial tumours, the division of infiltration levels of subepithelial connective tissue into "superficial" or "deep into the muscularis mucosae", is also relevant, even after stratification by grade.

Key words: TNM classification – Bladder cancer – Tumour grade – Predictive parameters

Introduction

Several clinico-pathological parameters, such as stage, grade, growth pattern, tumour size, focality of the lesion, association of carcinoma in situ, and tumour response to radio- or chemotherapy, have been considered important in estimating the prognosis of patients with transitional-cell carcinoma (TCC) of the urinary bladder (Batata et al. 1981; Narayana et al. 1983; Shipley et al. 1985; Webb 1985; Friedell 1987; Raghavan 1988; Raghavan and Wallace 1990; Reuter 1990). No one disputes the fact that the most important of these is tumour stage at diagnosis (Kern 1984; Blomjous et al. 1989; Hendry et al. 1990; Greven et al. 1990; Lipponen et al.1990 a, 1991). On the other hand, histological grading does predict the outcome rather closely, and is not as limited in routine practice as are depth of invasion and growth pattern (Kern 1984; Jordan et al. 1987; Hendry et al. 1990; Carbin et al. 1991 b). What is more, tumour size and infiltration are determined by proliferative activity and therefore appear somehow secondary to tumour grading (Helpap 1992). There is no doubt, then, that the correlation between the grade of a

* The "Journal of Cancer Research and Clinical Oncology" publishes in loose succession "Editorials" and "Guest editorials" on current and/or controversial problems in experimental and clinical oncology. These contributions represent exclusively the personal opinion of the author
The Editors

This work has been supported by an institutional grant from the Health Department of the Basque Government, and is also part of the doctoral thesis of one of the authors (J. C. Angulo)

Abbreviations: TCC, transitional-cell carcinoma; TUR, transurethral resection; MM, muscularis mucosae

Correspondence to: J. D. Toledo, Servicio de Anatomía Patológica, Santo Hospital Civil de Bilbao, Adv. Montevideo 18, Bilbao 48013, Spain

bladder tumour and its clinical course is not a random one (Bergkvist et al. 1965; Gilbert et al. 1978; Collan et al. 1979; Sjolin et al. 1976; Jordan et al. 1987; Torti et al. 1987; Lipponen et al. 1990 a). However, besides being subjective (Ooms et al. 1983), the present histological grading systems do not satisfactorily predict the recurrence and progression of superficial tumours (Torti and Lum 1984; Lipponen et al. 1990 a). Histoquantitative techniques that are intended to replace or significantly improve histological grading, have been developed for that purpose (Blomjous et al. 1989; Lipponen et al. 1990 a, b, 1991). However, no clinically applicable morphometric grading system has been achieved to date (Lipponen et al. 1991), and the actual role of flow cytometry, which is evidently suboptimal for ploidy analysis, offers no particular advantage over stage or grade in predicting treatment outcome (Lipponen et al.1990 a; Walther 1992; Jacobsen et al. 1992). Both facts prompt us to consider classical histopathological criteria the most secure prognosticators in daily practice. Consequently, the decision on treatment of bladder malignancy is at present based on clinical stage and grade (Jacobi et al. 1985).

The relationship between depth of infiltration and both potential curability (Jewett and Strong 1946) and survival (Jewett 1952), demonstrated long ago, created the basis for the popular ABCD classification (Marshall 1952). The initial TNM classification of bladder tumours was published in 1968, but did not gain general acceptance until a second edition in 1974 (UICC 1974). The 1978/1982 version was widely recognized all over the world (UICC 1978, 1982; AJCC 1983) and used as a support for many clinical trials. Most of the changes introduced in the fourth 1987 edition were highly controversial (UICC 1987), even to the extent that both the EORTC Genitourinary Group and the MRC Working Party in Urological Cancer considered them unacceptable (Hall et al. 1968; Schröder et al. 1988; Chisholm 1988), and recommended stage grouping has been bitterly criticised. Similarly, the omission of the concept of minimal requirements has also been a matter of debate (Hall and Prout 1990). That is, whenever a biopsy is adequate to evaluate the highest pT category, pT determination from the transurethral resection (TUR) specimen is allowed (UICC 1987). Positive lymph-node involvement is known to have ominous significance (Fradet 1990). Pathological assessment is the only safe method to identify lymph-node metastases, but for several reasons biopsy or removal of lymph nodes is not performed in many cases of bladder carcinoma. Therefore, stage grouping in clinical practice is often determined by the assessment of N (and not pN), in the same way as happens with the M category.

It must be stressed that the objective of this paper is not the study of survival after any specific treatment. Nor is it, strictly speaking, to establish the accuracy, of the TNM classification in predicting prognosis, because treatment modalities differ according to stage. The present study intends to evaluate the adequacy of the actual 1987 edition of the TNM classification for routine practice. It is our opinion that, despite all criticism, the classification is valuable in predicting survival. Nevertheless, now that bladder preservation is increasingly the aim, and that systemic chemotherapy is somehow changing our attitude towards advanced bladder carcinoma, a critical review of this staging system appears mandatory.

Materials and methods

Between 1983 and 1990, 552 patients underwent clinical and pathological evaluation for bladder carcinoma. In accordance with the 1987 TNM classification of bladder cancer, a total of 343 cases (62.14%) could be reliably staged. Following actual criteria (Catalona 1991), thorough clinico-radiological staging was based on physical exploration, intravenous urography, sonographic studies, computed tomography (CT) scan examination, and bone scintigrams. Magnetic resonance imaging (MRI) was also occasionally used. Accurate pathological staging was achieved either from cystectomy specimens or from complete TUR (systematically including perivesical fat and prostate). Cases devoid of sufficient histopathological material (30.80%) to allow reliable pathological evaluation by 1987 TNM criteria were not considered in this study. Treatment modalities that could invalidate the initial histopathological staging (preoperative radiation, induction systemic chemotherapy, and salvage cystectomy after definitive radio- or chemotherapy) were also excluded (7.06% of cases). One pathologist had analysed all the material, and a counter-checking, performed by a second pathologist in a randomized group of 50 patients, did not reveal any differences of statistical significance.

The patients had been treated according to pathological stage (Table 3). In superficial tumours (59%) TUR was followed by intravesical instillation of chemotherapeutic agents (Adriamycin, mitomicin, thiotepa). Locally advanced tumours were treated radically: the patients consented to radical cystectomy (14%) or radical pelvic radiation (15%), according to their interest in preserving their bladder. Patient age was not an exclusion criterion for an operation. Openly disseminated disease was treated symptomatically (12%). Patients receiving systemic chemotherapy were not included in the study.

Lymphadenectomy was performed in 53 cases (15.51%) and in 48 it was followed by radical cystectomy. In the remaining patients the existence of lymph node metastases could only be evaluated clinico-radiologically. Superficial tumours are not to be treated radically, and lymph node dissection is not indicated in patients suffering openly disseminated bladder cancer or in patients opting for bladder preservation and refusing surgery. Therefore, in order to follow the 1987 recommendations for stage grouping, the pT category was combined not only with pN/pM but also with N/M categories whenever the former could not be stated. This limitation is daily observed in routine practice, e.g. when a TUR specimen shows infiltration of perivesical fat without invasion of the prostate (pT3b). Imaging studies rule out extension to neighbouring organs and discover massive lymph node invasion (N2). The fact that histopathological analysis of lymph node metastases is not performed does not exclude the possibility that the patient should be classified as stage IV. The adequacy of the ABCD (Jewett-Marshall-Strong) staging system in sorting patients with distinct prognosis was also investigated. Not only the validity, but also the reproducibility and limitations of that system were compared to those of the TNM classification.

Histological typing and tumour grading were performed following the classical criteria of the WHO classification (Mostofi et al. 1973; Koss 1975; Murphy 1983; Robbins et al. 1984). Greater precision was pursued and more recent adaptations of such criteria (Colpaert et al. 1987; Pauwels et al. 1988 a) were also observed. Following Pauwels' recommendations regarding the loss of cell polarity, grade 2 was divided into 2A and 2B (Pauwels et al. 1988 a). All histological sections from all blocks were reviewed. Additional sections were prepared if necessary for accurate classification. When the bladder neoplasms presented

Table 1. Inter- and intraobserver consistency at first observation and 1 month later (both in two sessions of 25 patients each)

Interobserver consistency	
Initial	39/50 (78%)
Repeated	42/50 (84%)
Intraobserver consistency	
A	45/50 (90%)
B	41/50 (82%)

Table 2. Clinical staging and grading

No. of patients	343					
Sex (male/female)	6.6 : 1					
Mean age (range) (years)	66 (44–88)					
Histological pattern						
Transitional cell carcinoma (TCC)	292 (85.1%)					
TCC plus squamous cell carcinoma	27 (7.9%)					
TCC plus adenocarcinoma	10 (3%)					
Pure squamous cell carcinoma	7 (2%)					
Pure adenocarcinoma	1 (0.3%)					
Small-cell carcinoma	6 (1.7%)					
Histological grading	G1 G2 G3					
	121 : 126 : 96					
T category	Tis	Ta	T1	T2	T3	T4
Clinical (T)	6	20	170	36	73	38
Pathological (pT)	6	26	170	27	75	39
N category	N0	N1	N2	N3	N*x*	
Clinical (N)	293	16	23	12	0	
Pathological (pN)	37	10	2	4	290	
M category				M0	M1	
Clinical (N)				308	36	
Stage grouping (UICC 1987)		0	I	II	III	IV
		32	170	25	51	65
Stage grouping		0	A	B	C	D
(Jewett/Strong/Marshall)		32	170	48	28	65

areas of more than one grade, the higher one was assigned. The grade was evaluated without attention being payed to stage classification.

Both inter- and intra-observer variability were studied in another group of 50 patients randomly chosen. Two experienced pathologists analysed them twice, and consistency, that is the extent to which diagnostic criteria are kept constant, was determined (Table 1).

The existence of a papillary architecture was also registered. Tumours were divided into papillary or non-papillary nodular types, and it was arbitrarily decided that, although a tumour may predominantly reveal a nodular pattern, a papillary growth pattern would be assigned if some papillar areas are detected on its surface. No disagreement arose between the two pathologists in the assessment of growth pattern and histological variant in a third group of 50 patients once more chosen at random.

A serious attempt to assess the real importance of muscularis mucosae (MM) in distinguishing two populations with different prognosis in superficial pT1 tumours, was also undertaken. Following Pryor's criteria, they were considered pT1A or pT1B tumours, depending on the depth of infiltration of subepithelial connective tissue (Pryor 1973). Whenever the MM could not be identified, arteries of relatively large calibre and wall thickness, oriented in parallel to the mucosal surface and closely associated with the fibres of MM, served as a distinctive morphological marker (Ro et al. 1987). Two pathologists analysed all pT1 cases under a multihead microscope and only those in which complete accordance was achieved (99 cases, 58.24% of pT1 patients) were assigned pT1A or pT1B. The prognostic value of such a distinction was analysed even after stratification by grade.

All patients were prospectively followed until death or the time when the study was closed, January 1992. Kaplan-Meier (Kaplan and Meier 1958) curves of survival were statistically constructed. Patients who died of other causes without evidence of bladder tumour or who were lost to follow-up, were included in the analysis of data by the Mantel-Haenszel life-table method (Mantel and Haenszel 1959).

Results

Table 2 shows data on the patients and the parameters of their tumours and Table 3 records the treatment they received.

Table 3. Type of treatment according to stage

Treatment [a]	No. cases in stage					Total (%)
	0	I	II	III	IV	
TUR+intravesical chemotherapy	32	170	–	–	–	202 (59)
TUR+radical cystectomy	–	–	12	25	11	48 (14)
TUR+radical radiotherapy	–	–	13	26	13	52 (15)
TUR alone	–	–	–	–	11	41 (12)
Total	32	170	25	51	65	343

[a] TUR, transurethral resection

Table 4. Staging error [a]

Clinical stage	No. pts.	Understaged no. (%)	Overstaged no. (%)	Agreement no. (%)
Ta	20	8 (40)	0 (0)	12 (60)
T1	170	27 (16)	11 (6)	132 (78)
T2	36	15 (42)	12 (33)	9 (25)
T3	73	7 (10)	24 (33)	42 (57)
T4	38	0 (0)	10 (26)	28 (74)
Total	337	57 (17)	57 (17)	223 (66)

[a] Clinical (T) versus pathological (pT stage: understaged, T < pT; overstaged, T > pT; agreement, T = pt

Table 4 records the discrepancies of T staging (clinical versus pathological) in the selected series in which accurate pathological staging was obtained. These patients also underwent a thorough clinico-radiological evaluation. Excluding the primary Tis category, the overall staging error was 34%. Agreement was present in 66% of cases (60% Ta, 78% T1, 25% T2, 57% T3, and 74% T4).

Invasion as a prognostic factor

According to Kaplan-Meier's actuarial method, the overall probability of survival was 57% at 5 years (Fig. 1 a) and 47% at 8 years. The pT category of the tumour proved to be predictive of survival (Fig. 1 b, Table 5). All patients pTa–pTis were alive at 5 years, and so were 74% of those with pT1 tumours. Higher T stages predicted a poorer survival: 40% of patients pT2, 18% of pT3, and none of those with pT4 disease survived 5 years. A log-rank test proved that the differences were statistically significant: pTa–pTis/pT1 ($P<0.02$), pT1/pT2 ($P<0.001$), pT2/pT3 ($P<0.01$), pT3/pT4 ($P<0.001$). Regarding T3 tumours, the difference between pT3a and pT3b was also significant (5-year survival 29% for pT3a and 13% for pT3b; log-rank test $P<0.01$) (Fig. 1 c, Table 5). Nevertheless, no difference was observed between pT2 or pT3a patients. That is, in the present series, the depth of muscle-infiltrating disease does not seem to be of prognostic importance in terms of survival (Fig. 1 c, Table 5). What is more, the distinct prognosis displayed by pT2 and pT3 lesions appears secondary to the difference between pT3a and pT3b (i.e. to the existence of fat invasion beyond the muscular layer).

A review of the clinico-pathological N staging errors established that 5/35 (14.29%) N0 patients were understaged, and 2/13 (15.38%) N1–3 patients were overstaged. Therefore, a sensitivity of 69%, a specificity of 94%, and an accuracy of 85% were obtained in the clinical investigation (CT scan and MRI) of lymph node metastases. In this context, the clinically staged N category proved to be a factor of major prognostic value (Table 6). Two-year survival was 89% for patients N0 and 4% for patients N1–3 (log-rank test $P<0.001$), regardless of pT category. χ^2 tests confirmed the presumed association between pT and N ($P<0.001$). So in order to assess the real predictive value of lymph node extension (N) apart from that of tumour spread (pT category), the survival of pT3bN0 and pT4N0 patients was compared to that of pT3bN1–3 and pT4N1–3 respectively. A Mantel-Haenszel test revealed the prognosis of those without lymph node involvement to be significantly better in both cases (log-rank $P<0.001$) (Fig. 1 d, Table 5). The size and number of affected lymph nodes also appeared prognostically relevant: 14% N1 patients lived beyond 2 years, but none of the N2 or N3 category did (Table 6). Mantel-Haenszel test revealed a difference in survival between the N1 and N2 categories ($P<0.05$), which vanished when the M category was taken into account. That is, no statistical difference could be maintained when comparing the survival of patients N1M0 and N2M0.

Although χ^2 tests proved the association between N and M categories ($P<0.001$), the existence of metastatic spread at diagnosis remained the most important factor in predicting prognosis: 85% M0 patients achieved a 2-year survival, while no M1 patient did (log-rank test $P<0.001$). Besides, the clinico-radiological evidence of macroscopic visceral dissemination at tumour presentation definitely enhanced the poor outlook of lymph node extension. While 65% of patients with affected nodes but without other metastases (N1–3M0) survived 1 year, only 17% of M1 patients did so. That is, despite the awesome prognosis of disseminated bladder cancer, a difference in survival of statistical value was demonstrated between N1–3M0 and N1–3M1 tumours (log-rank $P<0.001$) (Fig. 1 e, Table 6).

As postulated in the 1987 edition of the TNM classification, stage grouping proves to be of predictive value in terms of survival: all stage 0 patients outlived 5 years, and so did 74% stage I, 47% stage II, 26% stage III, and 8% stage IV (Fig. 1 f, Table 7) patients. Log-rank tests revealed that the difference in survival between them was statistically significant: stages 0/1 ($P<0.02$), I/II ($P<0.001$), II/III ($P<0.05$), III/IV ($P<0.001$). Nevertheless, the reported difference between pT3a and pT3b tumours reflects the heterogeneity of the stage III group. In fact, if all cases confined to the muscular wall (pT2N0M0, pT3aN0M0) were considered stage "II" (as in stage B of the Jewett classification), and only the tumours affecting perivesical fat (pT3bN0M0) were renamed stage "III" (Jewett stage C), the differences in survival would still be significant: stage I/"II") (log-rank $P<0.001$), "II"/"III" (log-rank $P<0.01$) and "III"/IV (log-rank $P<0.001$) (Fig. 1 g, Table 7).

Stage IV disease is equally heterogeneous. Three subsets (pT4N0M0, pT*x*N1–3M0, pT*x*N*y*M1) with different survival are distiguished in the present material: pT4N0M0/N1–3M0 ($P<0.05$), N1–3M0/M1 ($P<0.001$) (Fig. 1 e, Tables 5, 6). A significant difference cannot be recorded in our results when survival of pT3bN0 cases is compared to that of pT4N0 tumours. Prognosis of stage III patients seems to overlap with that of the most favourable subgroup in stage IV (Fig. 1 D, Table 5). Noticeably, although lymph node and metastatic spread are the factors of worst prognosis, they do not impair the predictive value of the pT category, for the survival of pT3bN1–3 is significantly better than that of pT4N1–3 ($P<0.01$) (Fig. 1 d, Table 5).

We could not demonstrate a difference in survival of pTis ($n=6$) and pTa ($n=26$) patients, maybe because of the limitation of the series. Regarding stage I tumours, the level of subepithelial connective tissue infiltration appeared prognostically relevant, as the 5-year survival of pT1A patients was 86% and that of pT1B 52%. The log-rank test proved that the difference was statistically significant ($P<0.02$) (Fig. 2 a, Table 5). Nevertheless the association between the level of subepithelial connective tissue invasion in stage I lesions and tumour grade was definitely proved (χ^2 test $P<0.01$). It must be noted that tumour invasion and grade were assigned at different sessions, and this fact reduces the risk of the observer's disposition to decide higher grades in more invasive tumours. Despite this association, the usefulness of MM in distinguishing two populations in stage I was proven after stratification by grade. The survival of pT1A G2 patients was significantly better than that of pT1B G2 ones (log-rank $P<0.05$). The first group achieved a 5-year survival of 75%, and the second of 41% (Fig. 2 b, Table 5).

When the patients were classified according to the American ABCD system, Kaplan-Meier analysis of survival revealed this staging system also to be valid in predicting the outcome. All stage 0 patients lived more than 5 years, like 74% of stage A, 36% of stage B, 14% of stage C, and 8% of stage D patients. Log-rank tests revealed the differences in survival between them to be statistically significant: stages 0/A ($P<0.02$), stages A/B ($P<0.001$), stages B/C ($P<0.01$), stages C/D ($P<0.001$) (Fig. 1 g, Table 7). Similarly, the prognosis of D1 and D2 lesions is clearly significantly distinct

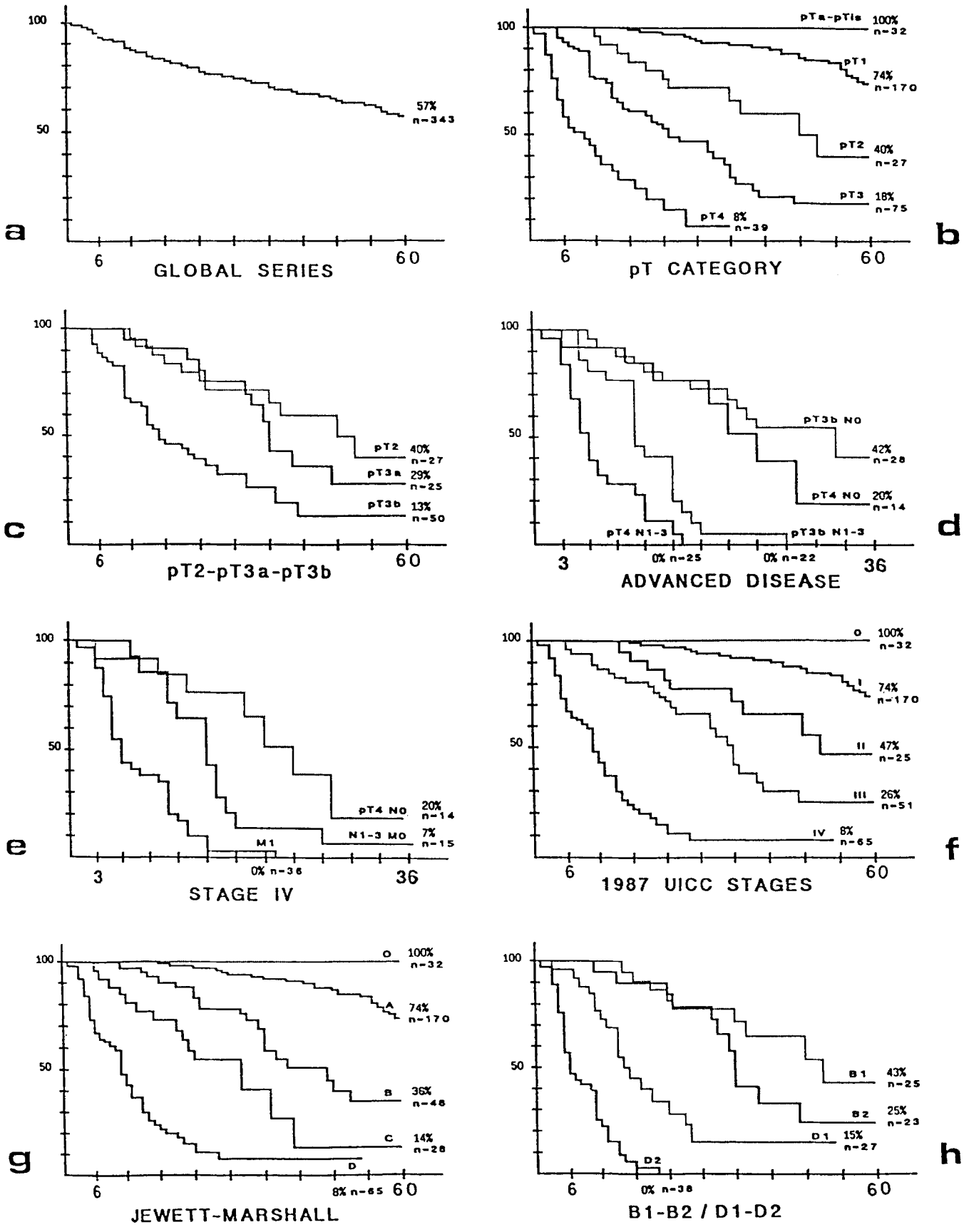


Fig. 1. a Global series, 5-year survival. **b–f** Tumour invasion (1987 UICC Classification) and survival. **g, h** Tumour invasion (ABCD classification) and survival

Table 5. pT and survival

Category	*n*	(%)	Survival (%)			95% C.I.
			1 year	3 years	5 years	
pTa–pTis [a]	32	9	100	100	100	5-yr (100–100)
pT1	170	50	100	92	74	5-yr (85– 64)
pT2	27	8	96	67	40	5-yr (76– 4)
pT3	75	22	76	31	18	5-yr (38– 0)
pT4	39	11	40	8	–	3-yr (10– 0)
pT3a [b]	25	7	96	43	29	5-yr (78– 0)
pT3b	50	15	66	26	13	5-yr (27– 0)
pT3bN0 [c]	28	8	81	42	14	2-yr (76– 35)
pT4N0	14	4	86	20	–	2-yr (70– 9)
pT3bN1–3	22	7	41	0	0	2-yr (12– 0)
pT4N1–3	25	7	12	0	0	2-yr (0– 0)
pT1a [d]	50	15	100	97	86	5-yr (100– 69)
pT1b	49	14	100	88	52	5-yr (74– 29)
pT1aG2	20	6	100	100	75	5-yr (100– 44)
pT1bG2	33	10	100	85	41	5-yr (66– 15)

[a] pTa–pTis/pT1, $P < 0.01$; pT1/pT2, $P<0.001$; pT2/pT3, $P < 0.01$; pT3/pT4, $P < 0.001$
[b] pT3a/pT3b, $P < 0.01$
[c] pT3bN0/pT3bN1–3, $P < 0.001$; pT4N0/pT4N1–3, $P < 0.001$; pT3bN1–3/pT4N1–3, $P < 0.01$
[d] pT1a/pT1b, $P < 0.02$; pT1aG2/pT1bG2, $P < 0.05$

Table 6. N, M and survival

Category	*n*	(%)	Survival (%)			95% C.I.
			1 year	2 years	3 years	
N0 [a]	293	85	98	89	79	1-yr (100–96)
N1	16	5	41	14	7	1-yr (63–30)
N2	23	7	22	0	0	1-yr (39– 5)
N3	12	3	25	0	0	1-yr (47– 3)
M0 [b]	308	90	96	85	78	1-yr (99–94)
M1	36	10	17	0	0	1-yr (30–11)
N1–3M0	15	4	65	14	7	1-yr (90–40)

[a] N0/N1–3, $P < 0.001$; N1/N2, $P < 0.05$
[b] M0/M1, $P < 0.001$; N1–3M0/M1, $P < 0.001$

Table 7. UICC/Jewett stages and survival

Stage	*n*	(%)	Survival (%)			95% C.I.
			1 year	3 years	5 years	
0 [a]	32	9	100	100	100	5-yr (100–100)
I	170	50	100	92	74	5-yr (85– 64)
II	25	7	100	73	47	5-yr (82– 13)
III	51	15	88	43	26	5-yr (51– 0)
IV	65	19	43	8	–	3-yr (25– 0)
O [b]	32	9	100	100	100	5-yr (100–100)
A	170	50	100	92	74	5-yr (85– 64)
B	48	124	98	59	36	5-yr (64– 7)
C	28	8	81	42	14	5-yr (32– 0)
D	65	19	43	8	–	3-yr (25– 0)
B1 [c]	25	7	100	72	43	5-yr (81– 6)
B2	23	7	95	42	25	5-yr (68– 0)
D1 [d]	27	8	73	15	–	3-yr (44– 0)
D2	38	11	22	0	0	3-yr (0– 0)

[a] 0/I, $P < 0.02$; I/II, $P < 0.001$; II/III, $P < 0.05$; III/IV, $P < 0.001$
[b] O/A, $P < 0.02$; A/B, $P < 0.001$; B/C, $P < 0.01$; C/D, $P < 0.001$
[c] B1/B2, not significant
[d] D1/D2, $P < 0.001$

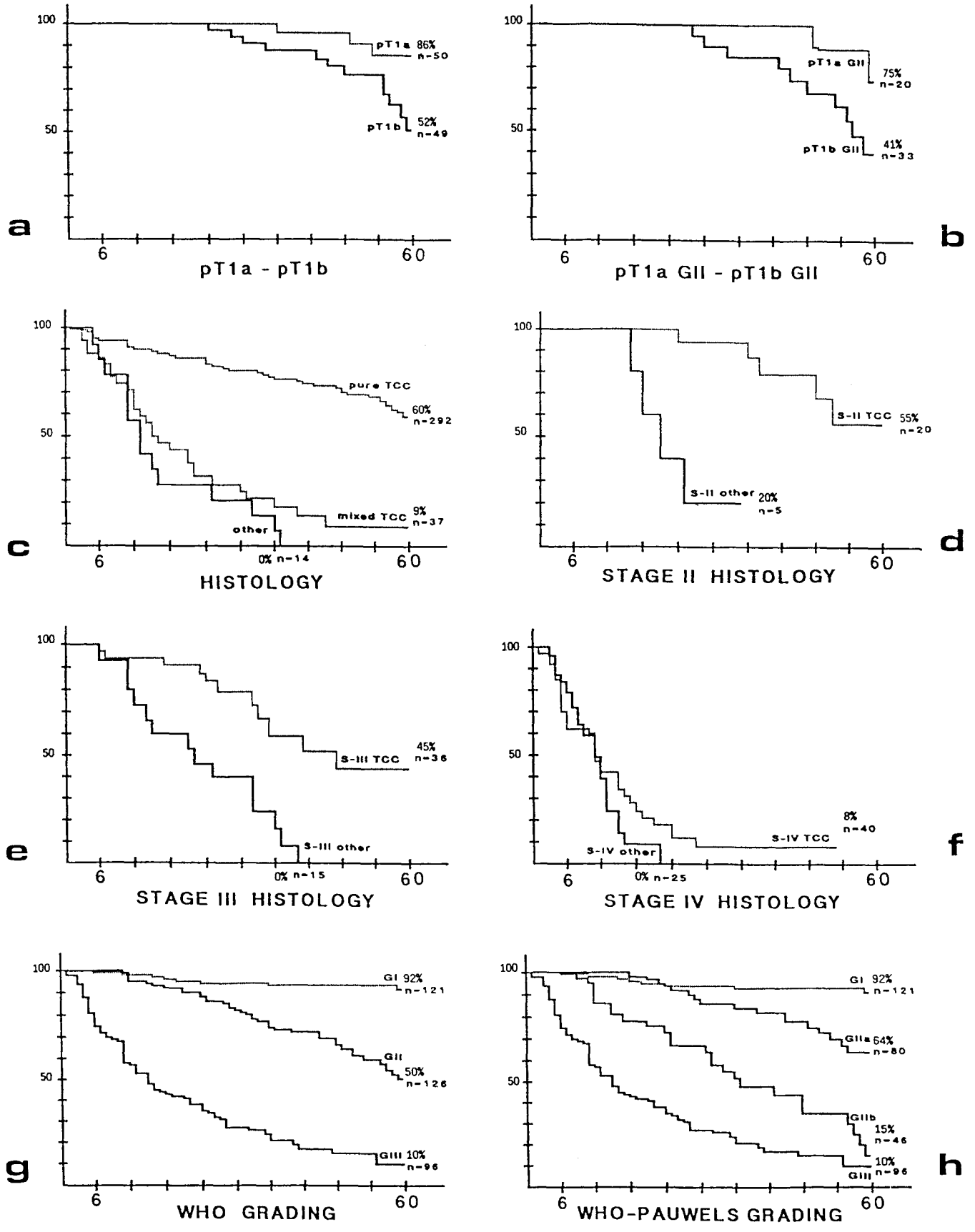


Fig. 2. a, b Survival as a function of the level of subepithelial connective tissue invasion. **c–f** Histology and survival. **g** Grading system (WHO and Pauwels' classifications) and survival

($P<0.001$), but in the present material no difference of statistical significance was recorded between B1 and B2 tumours (Fig. 1 h, Table 7).

Histology and grade as prognostic factors

Pure transitional-cell histology predominates (85%). Mixed transitional-cell carcinoma (TCC), that is TCC displaying additional areas of different histology (squamous cell or adenocarcinoma), represents a total of 11%. Sometimes TCC areas do not predominate in those tumours with mixed histology, but they should still be termed mixed TCC. Pure histology other than TCC is quite rare (4%), squamous cell carcinoma (SCC) being the most common in our material (Table 2). Pure TCC as a whole implied the best prognosis with 60% 5-year survival, compared to 9% for mixed TCC. No patient bearing a tumour of pure non-transitional-cell histology (squamous cell, small cell or adenocarcinoma), lived longer than 5 years. Mantel-Haenszel tests revealed no dif-

Table 8. Histology and survival

Histology	*n*	(%)	Survival (%)			95% C.I.
			1 year	3 years	5 years	
Pure TCC [a]	292	85	91	76	60	5-yr (70–49)
Mixed TCC [a]	37	11	63	19	9	5-yr (20– 0)
Other [a]	14	4	57	7	0	5-yr (0– 0)
Stage II [b]						
Pure TCC	20	6	100	88	57	3-yr (100–71)
Rest	5	1	80	20	–	3-yr (45– 0)
Stage III [c]						
Pure TCC	36	11	94	60	45	3-yr (85–47)
Rest	15	4	73	16	0	3-yr (33– 0)
Stage IV [d]						
Pure TCC	40	12	43	8	–	3-yr (24– 0)
Rest	25	7	40	0	0	3-yr (0– 0)

[a] Pure TCC/mixed TCC, $P < 0.001$; pure TCC/other, $P < 0.001$; mixed TCC/other, not significant
[b] Pure TCC/rest, $P < 0.001$
[c] Pure TCC/rest, $P < 0.001$
[d] Pure TCC/rest, not significant

Table 9. Grade and survival

Grade	*n*	(%)	Survival (%)			95% C.I.
			1 year	3 years	5 years	
G1 [a]	121	35	98	94	92	5-yr (99– 84)
G2	126	37	96	75	50	5-yr (65– 35)
G3	96	28	57	21	10	5-yr (29– 0)
G2a	80	23	100	85	64	5-yr (82– 47)
G2b	46	14	86	52	15	5-yr (30– 1)
Stage I [b]						
G1	83	24	100	96	96	5-yr (100– 88)
G2	78	23	100	87	60	5-yr (78– 42)
G2a	61	18	100	84	57	5-yr (78–3 7)
G2b	17	5	100	92	42	5-yr (71– 14)
Stage III [c]						
G2	22	6	95	56	42	3-yr (90– 23)
G3	27	8	81	29	12	3-yr (49– 9)
G2a	12	3	100	86	57	3-yr (100– 52)
G2b	10	3	89	52	–	3-yr (93– 10)
Stage IV [d]						
G2	15	4	77	25	–	3-yr (68– 0)
G3	48	14	35	0	0	3-yr (0– 0)
G2a	5	1	100	75	–	3-yr (100– 0)
G2b	10	3	63	0	0	3-yr (0– 0)

[a] G1/G2, $P < 0.001$; G2/G3, $P < 0.001$; G2a/G2b, $P < 0.001$; G1/G2a, $P < 0.001$; G1/G2a, $P < 0.001$
[b] G1/G2, $P < 0.001$; G2/G3, $P < 0.001$; G2a/G2b, $P < 0.001$
[c] G2/G3, $P < 0.02$; G2a/G2b, $P < 0.05$
[d] G2/G3, $P < 0.001$; G2a/G2b, $P < 0.05$

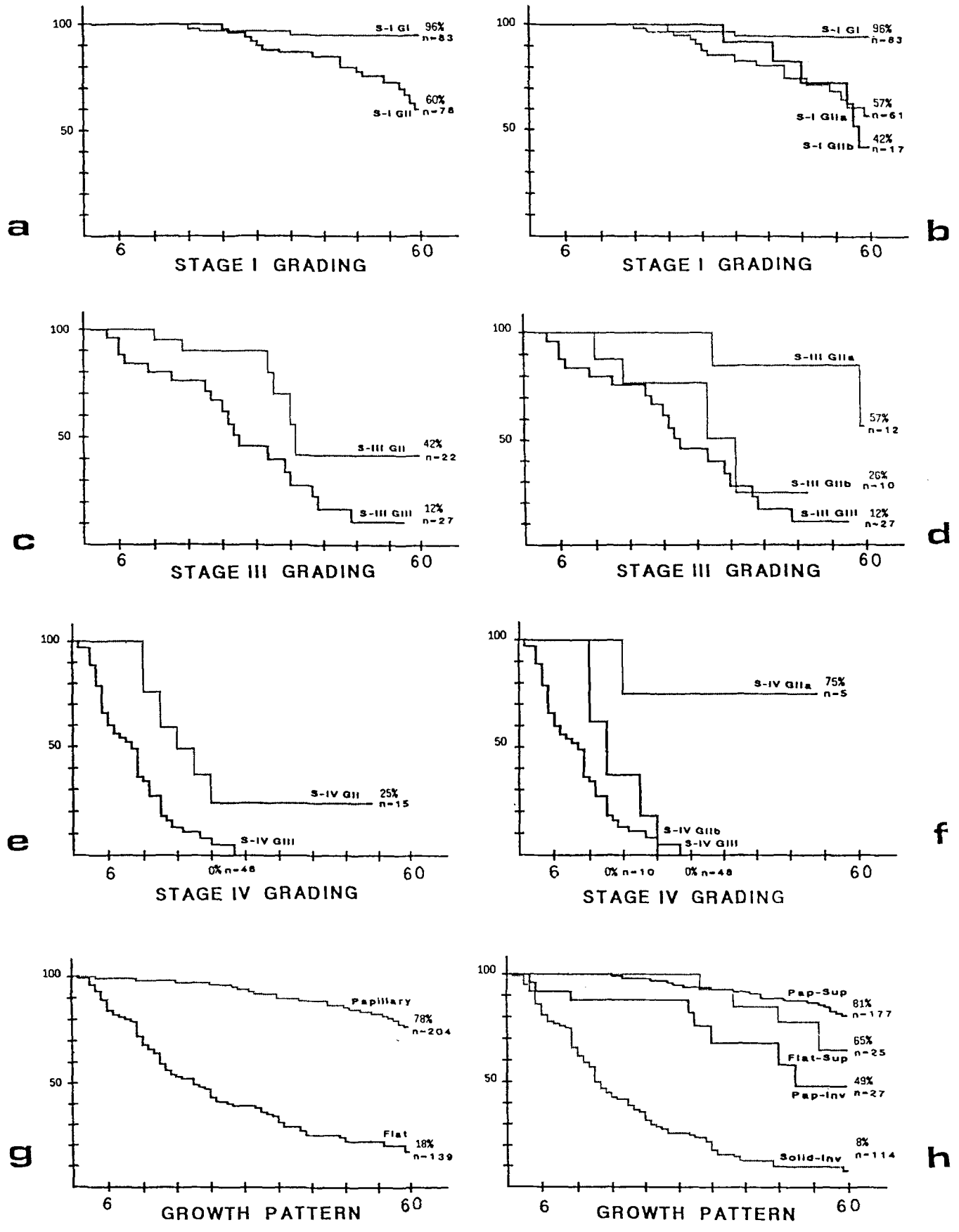


Fig. 3. a–f Grading and survival after stratification by stage. **g** Survival according to tumour surface. **h** Survival according to tumour growth pattern

ference in survival between mixed TCC and non-TCC, whereas pure TCC had a much better prognosis than the rest (log-rank, $P<0.001$) (Fig. 2 c, Table 8).

There is some association between tumour stage at diagnosis, and histology other than pure TCC (χ^2 test, $P<0.001$). These tumours present higher pT ($P<0.001$), positive N ($P<0.05$) and positive M ($P<0.05$). However, the poorer prognosis of urothelial carcinomas bearing foci of squamous cell or glandular differentiation was confirmed after stratification in stages II and III (log-rank $P<0.001$) (Fig. 2 d, e, Table 8), but not in stage IV (Fig. 2 f, Table 8). That is, the poor outlook of stage IV tumours is not worsened when their histological pattern is other than TCC.

Tumour grading following the WHO recommendations established three tumour populations with different prognosis: 92% of G1 tumours (n=121) survive 5 years, while 50% of G2 (n=126) and only 10% of G3 (n=96) lesions do so. Mantel-Haenszel tests revealed that differences in survival were statistically significant: G1/G2 ($P<0.001$), G2/G3 ($P<0.001$) (Fig. 2 g, Table 9). After the well-known association between grade and tumour infiltration (pT, N, M, and stage) had been demonstrated once more ($P<0.001$), the survival expectancies of each grade were restratified according to stage. Differences of statistical significance were detected in superficial tumours between G1 and G2 lesions, revealing a 5-year survival of 96% and 60% respectively ($P<0.001$) (Fig. 3 a, Table 9). On the other hand, a difference in prognosis of high-stage (stages III and IV) G2 and G3 lesions was also evident ($P<0.05$). Patients bearing stage III G2 tumours had a 42% 5-year survival rate, while that of patients with stage III G3 tumours was only 12% ($P<0.02$) (Fig. 3 c, Table 9). Similarly, 25% of stage IV G2 patients outlived 2 years, but only 6% of stage IV G3 patients did so ($P<0.001$) (Fig. 3 e, Table 9). These facts prove that tumour grade at diagnosis is, independent of tumour stage, quite useful in predicting survival.

Following Pauwels' criteria of histological grading, two populations of intermediate G2 urothelial carcinomas were distinguished, according to the persistence or loss of cell polarity. Consistency was investigated to establish the reproducibility of such a distinction, and proved to be satisfactorily high (Table 1). G2A patients had a more favourable prognosis than G2B, with 64% and 15% 5-year survival respectively ($P<0.001$) (Fig. 2 h, Table 9). Differences of statistical significance were also observed between G1 and G2A ($P<0.001$), and between G2B and G3 ($P<0.001$). These findings suggest that the controversial classification of histological grading into four categories, instead of three, might indeed be appropriate in terms of prediction of survival.

Nevertheless, the hypothetical advantage of using four categories for tumour grading is lost after restratification by stage. Although the prognosis of G2a infiltrating bladder cancer was significantly better than that of G2b, both in stages III and IV ($P<0.05$), no difference in survival could be registered between G2b and G3 in those stages (Fig. 3 d, f, Table 9). Besides, while stage I G1 behaves much better than stage I G2a ($P<0.001$), the difference between stage I G2a and G2b was not even significant (Fig. 3 b, Table 9).

Growth pattern as a prognostic factor

Papillary architecture is a readily distinguishable morphological parameter that can be assessed either endoscopically or by microscopic histological examination of the tumour specimen. The survival of neoplasms with a papillary surface in our series is significantly better than that of those with a solid or flat surface ($P<0.001$). While 78% of tumours with papillary histology (n=204) lived longer than 5 years, only 18% of the rest (n=139) did so (Fig. 3 g, Table 10). This favourable prognosis of papillary architecture is surely related to the fact that this pattern is associated with low stage (pT, N, M) and low histological grade ($P<0.001$). We have also confirmed the association between non-papillary tumours and the invasion of lymphatic vessels in the bladder wall ($P<0.001$).

Considering tumour surface and depth of infiltration (stages 0–I versus stages II–IV), four growth patterns can be distinguished: papillary superficial, flat superficial, papillary invasive and solid invasive. Although the 5-year survival of flat superficial tumours in our series (n=25) (65%) is worse than that of papillary superficial (n=177) (81%), the statistical significance of such difference could not be demonstrated. Nevertheless, a Mantel-Haenszel test revealed the difference between papillary invasive (n=27) (49%) and solid invasive (8%) (n=114) tumours to be significant ($P<0.001$) (Fig. 3 h, Table 10). After stratification by stage, a difference

Table 10. Growth pattern and survival

Pattern[a]	n	(%)	Survival (%)			95% C.I.
			1 year	3 years	5 years	
Papillary[b]	204	59	99	91	78	5-yr (87–69)
Flat	139	41	69	31	18	5-yr (29– 6)
Pap. Supf.[c]	177	52	100	94	81	5-yr (90–72)
Flat Supf.	25	7	100	94	65	5-yr (100–27)
Pap. Inv.	27	8	89	68	49	5-yr (89– 9)
Solid Inv.	114	33	62	18	8	5-yr (16– 0)

[a] Supf., superficial; Inv., invasive; Pap., papillary

[b] Papillary/flat, $P < 0.001$

[c] Papillary superficial/papillary invasive, $P < 0.001$; flat superficial/solid invasive, $P < 0.001$; papillary superficial/flat superficial, not significant; papillary invasive/solid invasive; $P < 0.001$

in survival of patients with stage III papillary versus flat tumours was demonstrated, although it did not reach statistical significance ($P<0.1$). It goes without saying that the prognosis of papillary and flat superficial tumours was much better than that of papillary and solid invasive tumours ($P<0.001$ in both cases) (Fig. 3 h, Table 10).

Discussion

The aim of the present study is to evaluate the predictive value of spread and invasion on the one hand, and grading and histological aspects of bladder cancer on the other. We do not strictly intend to analyse the survival of patients with bladder cancer, nor do we attempt to provide worthwhile information about therapy. The patients we present are managed according to different treatment modalities, always in accordance with the pathological stage at diagnosis. Homogeneous clinico-pathological evaluation allows us to define this series as being representative of daily medical practice in a tertiary hospital. Our institution covers a population of 450 000 inhabitants in an industrial area of Northern Spain (Basque Country, Bilbao).

If patients are properly managed, tumour stage at diagnosis is the most important factor in predicting survival (Kern 1984; Blomjous et al. 1989; Hendry et al. 1990; Greven et al. 1990; Lipponen et al. 1990 a, 1991). The present study is seriously concerned with the suspected inadequacy of the current TNM classification (Pagano et al. 1991), and aims at evaluating the reliability of the TNM staging system in routine practice for sorting the patients into groups with different prognosis. In reality a state of increasing confusion exists, where some are talking about stages, the critics still maintain that categories should be used, and yet others are dubious about which classification to employ. Detailed studies have been performed in patients undergoing cystectomy (Skinner 1977; Slack et al. 1977; Skinner and Lieskovsky 1984; Pagano et al. 1991). Nevertheless, the 1987 edition of the TNM classification allows for a definite evaluation of bladder cancer by TUR, provided that biopsy is "adequate to evaluate the highest pT category". For several reasons, fewer than half of the patients with invasive bladder cancer undergo radical cystectomy in our environment. Besides, induction therapies (formerly preoperative radiation and nowadays chemotherapy) will not always allow accurate staging at the time of cystectomy. Therefore, the necessity to classify patients after a thorough clinico-radiological evaluation and complete TUR of the lesion is now undeniable, in view of the new therapeutic attitudes trends towards bladder preservation and the increasing use of chemotherapy.

Depth of tumour at the time of diagnosis could be reliably determined in approximately 60% of the patients who were clinically evaluated. We must then be conscious of the serious limitations of TUR in assessing the local extent of the lesion. Nevertheless, if a biopsy proves valid in determining tumour infiltration, the clinico-pathological staging errors in T2, T3, and T4 tumours (Table 4) are quite similar to those obtained by cystectomy (Skinner 1977; Pagano et al. 1991). On the other hand, total agreement (66%) is somewhat higher than that reported in patients managed with radical surgery (44%) (Pagano et al. 1991). This is surely due to the fact that superficial cases (Ta, T1) in which radical cystectomy was performed were most often the consequence of a staging error.

Life expectancy is higher in patients with lower tumour extension. Regarding superficial lesions, the distinction between Tis, Ta and T1 tumours is made by the pathologist (Chisholm et al. 1980; Abel et al. 1988). In fact, their clinical differentiation is merely academic and this explains the high proportion of understaged Ta tumours (Table 4). The absence of infiltration of the muscular layer is the best guarantee for a favourable outcome (Cifuentes-Delatte et al. 1982). Nevertheless, we have demonstrated that the prognosis of superficial tumours invading subepithelial connective tissue below the MM (pT1a) is definitely worse than that of tumours not invading MM (pT1a), even after restratification by grade.

This prognostic importance of assessing invasion with respect to MM has already been claimed (Pryor 1973; Keep et al. 1989; Younes et al. 1990), but its independence from tumour grade has not been illustrated before. We see no reason to distinguish three levels of invasion pT1a (above MM), pT1b (to the level of MM), and pT1c (below MM) (Younes et al. 1990; Algaba 1991) for pT1b cannot be recognized in TUR specimens; instead we propose two categories, like those in the original description (Pryor 1973).

The depth of muscle infiltration cannot be assessed in TUR specimens when full-thickness resection is not performed or deep-biopsy material is absent (Barnes et al. 1977; Abel et al. 1988; Denis 1992). In this sense, the much-criticised omission in the 1987 TNM edition of the concept of palpable mass after TUR will be viewed with even more skepticism (Schröder et al. 1988; Hendry et al. 1990). In routine urological practice TUR means definite surgery in the majority of cases and forms the main source of pathological assessment (Denis 1992). Therefore, for practical purposes, a single T2–T3a clinical category was recommended and confirmed in cystectomy series (Chisholm et al. 1980). In the absence of lymph-node involvement, no difference in survival has been noted between pT2 and pT3a patients treated by cystectomy (Pagano et al. 1991). Similarly, the present study reveals that they form a homogeneous group in routine practice when treated radically (either surgery or radiotherapy).

In the present material, extension to perivesical fat implies a definitely worse prognosis. Similarly, the analysis of large series of invasive bladder tumours treated by radical cystectomy and pelvic lymphadenectomy (Skinner and Lieskovsky 1988; Pagano et al. 1991) also suggests that the critical depth of penetration is that into perivesical fat, since the 5-year survival of pT2 and pT3a patients without nodal involvement is rather similar, whereas a significant difference exists between pT3a and pT3b cases. This fact suggests that stage III, as adopted by the 1987 TNM edition, is artificial and represents a historical mistake. Initially, Jewett and Strong stated that the potential curability of a bladder tumour decreased when perivesical infiltration was present (stage C), compared to infiltration of muscular layer (stage B) (Jewett and Strong 1946). Two years later the division of stage B into B1 (superficial muscle) and B2 (deep muscle) was proposed upon a detailed analysis of the cystectomy specimen (Jewett and Lewis 1948). The TNM system adopted the distinction and classified both categories as T2 and T3a. This was later critizised (Skinner and Kaufman 1978; Chisholm et al. 1980; Denis 1992). Obviously such confu-

sion has favoured the widespread use of the ABCD classification.

Before the establishment of the 1987 TNM edition, it was proposed that categories T2 and T3 (N0M0) should equal stages B and C respectively (Cifuentes-Delatte et al. 1984). Nevertheless, it seems there was no time for such reclassification. In fact, categories (TNM) were compared to stages (ABCD) and at that time no stage grouping was recommended by the UICC. Finally, the 1987 edition accepted the use of stages, but did not incorporate changes, thus reflecting the old dilemma: "Two B's or not two B's" (Jewett 1978). Now, it is time to set forth a full revision of the problem. First of all, most often TUR offers the only pathological material available, specially today when bladder preservation is in vogue. Besides, the present study, reflecting daily urological practice and also the retrospective analysis of cystectomy specimens (Pagano et al. 1991), supports strong evidence in favour of changes in the controversial current UICC staging system.

Although both the UICC 1987 and the Jewett/Strong/Marshall systems prove valid in predicting outcome, several arguments in favour of the ABCD classification can be brought forward after critical comparison. To begin with, the distinction between superficial or deep muscular infiltration is secondary, and both lesions belong to the same group "B". Besides, perivesical disease, unrelated to deep muscular invasion, is classified as a distinct stage "C". What is more, although all patients suffering ganglionar or metastatic spread are classified as "D", two subsets of disseminated disease are defined. It would be desirable that the TNM classification, now that stage grouping is recognized, take into account these advantages of ABCD classification.

To this end, a new proposal for adaptation of TNM T category and stage grouping on bladder cancer is currently being studied in the National TNM Committees, forming the basis for a future edition of the TNM classification (Denis 1992). We hope that the redefinition of stage II proposed here (comprising the actual pT2N0M0 and pT3aN0M0) will be taken into account. In selected cases this group of patients could undergo bladder preservation after induction chemotherapy (Shipley et al. 1985; Herr 1987; Scher 1990; Kaufman et al. 1992).

Similarly, the establishment of different subgroups in the definition of stage IV should be considered. The present study supports the view that, although clinically staged, patients bearing N1–3M0 tumours have a different expectancy of survival than those with N1–3M1. Such a distinction could be of greater interest now that systemic chemotherapy offers new possibilities in the management of disseminated disease. This hypothetical benefit could also be of interest for inoperable T4 tumours (formerly T4b) which, if chemoresponsive, could be downstaged and then undergo a definitive therapeutic modality (Maffezzini et al. 1991).

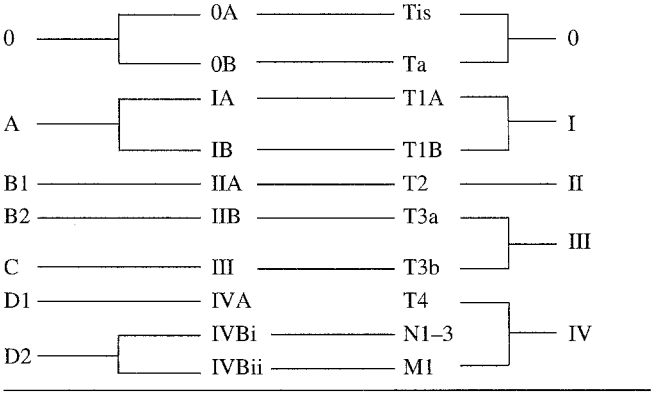
Future controlled studies should confirm our finding that in clinical practice the survival rate of patients judged to be pT3bN0M0 and pT4N0M0 is uniform. This has already been suggested (Pagano et al. 1991) and, if valid, both categories could be reclassified into stage III and considered amenable to radical surgery after induction chemotherapy. In fact, some tumours invading the prostate to a limited extent appear to have a better prognosis than large T3 tumours (Hall and Prout 1990). Therefore, the former distinction of T4a (single neighbouring organ invasion) and T4b (fixed tumour) could regain interest. According to the proposal for adapting the 1987 TNM classification. T4a could be considered stage III and T4b remain as stage IV (Denis 1992). We have not yet investigated much distinctions, as the material we present here was arranged strictly according to the 1987 classification, with its sole T4 category. Another matter of debate is whether or not non-invasive urothelial cancer of prostatic ducts should be classified as T4a (Hall and Prout 1990). At the present time, separate identification appears reasonable to enable future analysis.

We believe that the TNM 1987 stage grouping is far from definitive and should therefore be promptly revised. Since the present work on the adequacy of the TNM classification, we have used a practical modification of this staging system in our institution (Table 11). It must be clearly stated that we are conscious of these criteria being exclusively designed for internal use; they should not be proposed unless multicentre prospective analysis confirms them. Undeniably, however, bladder cancer staging is presently suffering some confusion, probably arising from greater knowledge of its natural history and our changing therapeutic attitudes.

Although the present study does not provide enough information to consider how much the long-term survival of pTa and pTis patients differs, there is sufficient evidence to separate both groups with respect to therapeutic attitudes, risk of progression, and prognosis (Melamed et al. 1964; Prout et al. 1983; Kakizoe et al. 1985). Hence, for practical purposes, we feel that stage 0A (pTa) and 0B (pTis) could be distinguished. Similarly, the identification of stage IA (pT1A) and IB (pT1B) subgroups would help in the assessment of prognosis of superficial tumours. Stage II should bring together all cases of muscular infiltration, and the historical distinction of pT2N0M0 (stage IIA) and pT3N0M0 (IIB) would only be of dubious significance. Stage III would define tumours effecting perivesical fat (pT3bN0M0). The distinction of micro- (pT3bi) and macroscopic (pT3bii) invasion could only be performed in tumours initially managed by cystectomy, and may be of little help today when neoadjuvant therapy is claimed and insistence on cystectomy as the "gold standard" for tumour staging is no longer appropri-

Table 11. Comparative chart of classifications

Jewett-Marshall	New proposal	UICC 1987: TNM, E
0	0A	Tis
	0B	Ta
A	IA	T1A
	IB	T1B
B1	IIA	T2
B2	IIB	T3a
C	III	T3b
D1	IVA	T4
D2	IVBi	N1–3
	IVBii	M1



ate (Hall and Prout 1990). Stage IV comprises locally advanced (pT4N0M0, stage IVA), and disseminated (ganglionar and metastatic, stage IVB) disease. Within the last category of worst prognosis, two different subgroups could also be distinguished: pT*x*N1–3M0 (stage IVBi) and pT*x*N*y* M1 (stage IVBii). Prospective trials with current and future treatment modalities in metastatic bladder cancer will have to confirm this observation.

The fact that unusual histological types of bladder carcinoma arise from the same urothelial cells that give rise to TCC is an example of the urothelium's pluripotential capacity (Mostofi 1954). In this sense, findings of focal areas of squamous or glandular differentiation are not uncommon in intermediate and high-grade TCC (Reuter 1990). Following actual criteria, these lesions should still be classified as TCC and, in the present paper, are termed mixed TCC. Nevertheless, sometimes the TCC component is but minor and we agree that these cases should be given the same term. This series confirms the classical fact that 95% of bladder tumours are TCC (Koss 1975), that is, 85% are pure TCC and 10% mixed TCC. Epithelial tumours of other cell types only account for 5%.

Most studies evaluating pathological prognostic factors in bladder cancer refer to pure TCC. Urothelial tumours with atypical histology are known to be less likely responders to chemotherapeutic regimens (Scher et al. 1988; Ayala and Ro 1989), but no conclusive evidence exists to show that, prior to the use of modern chemotherapy, patients with unusual histological types fared worse than stage-matched patients with TCC (Reuter 1990; Algaba 1991).

Their bad prognosis was assumed because unusual types of bladder cancer are found at diagnosis to be deeply invasive high-grade, or arising in a high-grade TCC (Algaba 1991). Apart from confirming the association between histology other than pure TCC and both high stage (depth of invasion and tendency to metastasize) and high grade, we could demonstrate its unfavourable prognosis even after restratification by stage, both in stages II and III. Nevertheless, in our experience, the bad prognosis of stage IV disease enhances the negative value of non-conventional histology. As far as we know, this is one of the first studies to address the importance of tumour heterogeneity regarding squamous or glandular differentiations in TCC. Their clinical aggressiveness seems to be independent of their response to chemotherapy.

Multiple grading schemes have been developed and used over the years in an attempt to predict a tumour's biological potential. Lesions cytologically resembling normal urothelium are low-grade and cytological anaplasia characterizes poorly differentiated high-grade neoplasms. Pathologists consistently distinguish low-grade from high-grade tumours, but it is the distinction of low-grade from intermediate and intermediate from high-grade that causes the problem (Reuter 1990). A more objective way to categorize intermediate-grade lesions is, therefore, needed in order to distinguish those that would lead to metastases from those to be controlled by a variety of bladder-preserving procedures. Added inter- and intraobserver variability among pathologists make this subject even more disappointing (Ooms et al. 1983). Nevertheless, it has been demonstrated that, once precise criteria are settled and the whole section is systematically examined, more reproducible results can be obtained (Colpaert et al. 1987).

The Bergkvist system, which proposes five categories, was used long ago in Scandinavia (Bergkvist et al. 1965), but the WHO classification into three grades is now used worldwide (Mostofi et al. 1973). The option of using G4 for anaplastic tumours is respected in the 1987 edition of the TNM classification (Schröder et al. 1988). Several modifications have been proposed in order to clarify the heterogeneous biological potential of grade 2 neoplasms. Malmström et al. distinguished 2a and 2b on the basis of cellular disorder, nuclear atypia and mitotic frequency (Malmström et al. 1987). Similarly, Lipponen thought it possible to divide WHO grade 2 into two groups, according to "nuclear area" (Lipponen et al. 1990 b). More recently Carbin proposed a modification of the Bergkvist system that would separate 2a and 2b on the basis of variations in nuclear size and mitotic frequency. (Carbin et al. 1991 a, b) DNA cytophotometry, and cell kinetic analyses also show that G2 carcinomas are a mixture of two different prognostic groups (Helpap et al. 1985; Helpap 1992). Regarding the persistence or loss of cell polarity, Pauwels recommended distinguishing 2a and 2b superficial papillary neoplasms, both on clinical (risk of progression) and cytogenetic grounds (Pauwels et al. 1988 a, b). The meaning of such a distinction in terms of survival has not been reported.

In our experience, an assessment of the "loss of cell polarity" in the group of intermediate prognosis (G2) may help to distinguish tumours with poorer outlook, and need not only be performed in superficial neoplasms. Nevertheless, independent of the association between grade and stage, we could not demonstrate a worse prognosis for G3 lesions compared to G2b. It does not seem strictly necessary to subdivide tumour grade into four categories, for the prognostic value of such a distinction somehow depends on tumour invasion at diagnosis. We therefore conclude that three grades are prognostic enough, but that tumours with intermediate anaplasia and devoid of cell polarity (G2b) should be separated from the rest and considered high-grade as G3 lesions.

A simpler grading system could then be achieved if only two categories were used: group A would collect WHO G1 (A1) and Pauwels' G2a (A2), and group B would comprise Pauwels' G2b (B1) and WHO G3 (B2). In this sense, multivariate analysis would surely benefit from this redefinition of low-grade and high-grade categories, thereby improving Carbin's recent redistribution of Bergkvist's grades (Bergkvist et al. 1965; Carbin et al. 1991 a, b). High-grade (B) tumours share the loss of cell polarity. In our experience this loss also implies the absence of papillary architecture.

"Tumour configuration" is another important prognostic variable. The less aggressive behaviour of papillary tumours is demonstrated by the fact that nodular configuration tends to present at a higher stage and grade (Kakizoe et al. 1988). Besides, tumours with solid architecture are likely to infiltrate bladder wall lymphatics and small vessels, and to be associated with lymph node involvement (Soto et al. 1977; Heney et al. 1983). It is not surprising that the biological behaviour of papillary invasive TCC is, regardless of the treatment received, more favourable than that of its solid invasive counterpart (Jewett et al. 1964; Soto et al. 1977; Heney et al. 1983; Van der Werf-Messing et al. 1983; Shipley et al. 1985;

Hendry et al. 1990). Is has also been suggested that papillary tumours may be more sensitive to full-dose radiation therapy (Slack and Prout 1980; Shipley et al. 1987). Nevertheless, the biological behaviour of papillary tumours is still controversial in the literature. Some authors do not confirm a significant difference in survival linked to tumour appearance (Quilty and Duncan 1986), and others even show a statistically worse outcome for patients with papillary histology (Greven et al. 1990). This last contradictory result can be explained by the fact that the patients were referred from several community urologists, and that different pathologists analysed the material. We have to stress the need for uniformity in pathological assessment.

It has recently been stated that tumour stage at diagnosis, the most important prognosticator in bladder cancer, is not followed by grade but by papillary status (Lipponen et al. 1991). What is more, histological grade proves to be a distinct prognostic factor within papillary tumours, and within grade 2 tumours too, papillary status has an independent prognostic value (Lipponen et al. 1991). This evidence confirms papillary status as a first-line prognosticator. We therefore wonder why tumour configuration is not systematically specified when bladder cancer is classified. Thus, "papillary pattern" could be detailed within "stage" in a future edition of the TNM system.

Acknowledgements. The authors are grateful to Dr. Juan Bilbao (Department of Biostatistics, Basque Country University) for supplying information and helping with the statistics.

References

Abel PB, Henderson D, Bennett MK, Hall RR, Williams G (1988) Differing interpretations by pathologists of the pT category and grade of transitional cell cancer of the bladder. Br J Urol 62:339–342

AJCC (American Joint Committee on Cancer) (1983) Beahrs OH, Myers MH (eds) Manual for staging of cancer, 2nd edn. Lippincott, Philadelphia

Algaba F (1991) Atlas de patología de los tumores urogenitales. Pulso Ediciones, Barcelona, pp 85–185

Ayala AG, Ro JY (1989) Premalignant lesions of the urothelium and transitional cell tumors. In: Young RH (ed) Pathology of the urinary bladder. Churchill Livingstone, New York, p 65

Batata MA, Chu FCH, Hilaris BS (1981) Factors of prognostic and therapeutic significance in patients with bladder cancer. Int J Radiat Oncol Biol Phys 7:575–579

Barnes RW, Dick AD, Hadley HL, Johnston OL (1977) Survival following transurethral resection of bladder carcinoma. Cancer Res 37:2895–2897

Bergkvist A, Ljungqvist A, Moberger G (1965) Classification of bladder tumours based on the cellular pattern. Acta Chir Scand 130:371–378

Blomjous ECM, Schipper NW, Baak JPA, Vos W, De Voogt HJ, Meijer CJLM (1989) The value of morphometry and DNA flow cytometry in addition to classic prognosticators in superficial urinary bladder carcinoma. Am J Clin Pathol 91:243–248

Carbin B, Ekman P, Gustafson H, Christensen NJ, Sandstedt B, Silfverswärd C (1991 a) Grading of human urothelial carcinoma based on nuclear atypia and mitotic frequency. I. Histological description. J Urol 145:968–971

Carbin B, Ekman P, Gustafson H, Christensen NJ, Silfverswärd C, Sandstedt B (1991 b) Grading of human urothelial carcinoma based on nuclear atypia and mitotic frequency. II. Prognostic importance. J Urol 145:972–976

Catalona WJ (1991) Bladder cancer. In: Gillenwater JY, Graghack J, Howard S (Eds) Adult and pediatric urology, 2nd edn. Mosby-Year Book, St. Louis, p 1141

Chisholm GD (1988) TNM classification of urological tumours in 1988. Br J Urol 62:501

Chisholm GD, Hindmarsh JR, Howatson AG, Webb JN, Busuttil A, Hargreave TB, Newsam JE (1980) TNM 1978 in bladder cancers: use and abuse. Br J Urol 52:500–505

Cifuentes-Delatte L, Garcia de la Peña E, Vela Navarrete R (1982) Survival rates of patients with bladder tumours. An experience of 1744 cases (1950–1978). Br J Urol 54:267–274

Cifuentes-Delatte L, Garcia de la Peña E, Vela Navarrete R (1984) Further comments on 1744 bladder tumors. In: Küss R, Khoury S, Denis LJ, Murphy GP, Karr JP (eds) Bladder cancer, part A: pathology, diagnosis and surgery. Liss, New York, pp 301–305

Collan Y, Mäkinen J, Heikkinen A (1979) Histological grading of transitional cell tumours of the bladder. Value of histological grading (WHO) in prognosis. Eur Urol 5:311–318

Colpaert C, Goovaerts G, Buyssens N (1987) Factors influencing the subjective grading of bladder cancer. Virchows Arch [A] 411:479–484

Cotran RS, Kumar V, Robbins SL (1989) The lower urinary tract. In: Pathologic Basis of Disease, 4th ed. Saunders, Philadelphia, pp 1083–1097

Denis LJ (1992) Clinical staging: its importance in therapeutic decisions and clinical trials. Hematol Oncol Clin North Am 6:41–58

Fradet Y (1990) Biological markers of prognosis in invasive bladder cancer. Semin Oncol 17:533–543

Friedell GH (1987) Urinary bladder cancer. Selecting initial therapy. Cancer 60:496–501

Gilbert HA, Logan JL, Kagan AR, Friedman HA, Cove JK, Fox M. Muldoon TM, Lonni YW, Rowe JH, Cooper JF, Nussbaum H, Chan P, Rao A, Starr A (1978) The natural history of papillary transitional cell carcinoma of the bladder and its treatment in an unselected population on the basis of histological grading. J Urol 119:488–492

Greven KM, Solin LJ, Hanks GE (1990) Prognostic factors in patients with bladder carcinoma treated with definitive irradiation. Cancer 65:908–912

Hall RR, Prout GR (1990) Staging of bladder cancer: is the tumor, node, metastasis adequate? Semin Oncol 17:517–523

Hall RR, Beynon LL, Horwich A, Kaye S, Tolley D (1988) Urology and the TNM classification. Lancet II:1145–1154

Helpap B (1992) Grading and prognostic significance of urologic carcinomas. Urol Int 48:245–257

Helpap B, Schwabe HW, Adolphs HD (1985) Proliferative pattern of urothelial bladder cancer and urothelial atypias. J Cancer Res Clin Oncol 109:46–54

Hendry WF, Rawson NSB, Turley L, Dunlop A, Whitfield HN (1990) Computerisation of urothelial carcinoma records: 16 years' experience with the TNM system. Br J Urol 65:583–588

Heney NM, Proppe K, Prout GR Jr, Griffin PP, Shipley WU (1983) Invasive bladder cancer: tumor configuration, lymphatic invasion and survival. J Urol 130:895–897

Herr HW (1987) Conservative management of muscle infiltrating bladder cancer: prospective experience. J Urol 138:1162–1163

Jacobi GH, Engelmann U, Hohenfellner R (1985) Classification of bladder tumours. In: Zingg EJ, Wallace DMA (eds) Bladder cancer. Springer, Berlin Heidelberg New York, pp 117–139

Jacobsen AB, Pettersen EO, Amellem O, Berber A, Ous S, Fossa SD (1992) The prognostic significance of deoxyribonucleic acid flow cytometry in muscle invasive bladder carcinoma treated with preoperative irradiation and cystectomy. J Urol 147:34–37

Jewett HJ (1952) Carcinoma of the bladder: influence of the depth of infiltration on the 5-year results following complete extirpation of the primary growth. J Urol 67:672–680

Jewett HJ (1978) Comments on staging of invasive bladder cancer. Two B's or not two B's: that is the question. J Urol 119:39–42

Jewett HJ, Lewis EL (1948) Infiltrating carcinoma of the bladder: curability by total cystectomy. J Urol 60:107

Jewett HJ, Strong GH (1946) Infiltrating carcinoma of the bladder: relation of depth of penetration of the bladder wall to incidence of local extension and metastases. J Urol 55:366

Jewett HJ, King LR, Shelley WJ (1964) A study of 365 cases of infiltrating bladder cancer: relation of certain pathological characteristics to prognosis after extirpation. J Urol 92:668–678

Jordan AM, Weingarten J, Murphy WM (1987) Transitional cell neoplasms of the urinary bladder. Can biologic potential be predicted from histologic grading? Cancer 60:2766–2774

Kakizoe T, Matumoto K, Nishio Y (1985) Significance of carcinoma in situ and dysplasia in association with bladder cancer. J Urol 133:395–398

Kakizoe K, Tobisu K, Takai K (1988) Relationship between papillary and nodular transitional cell carcinoma in the human urinary bladder. Cancer Res 48:2293–2303

Kaplan EL, Meier P (1958) Non-parametric estimations from incomplete observations. J Am Stat Assoc 53:457–481

Kaufman DS, Shipley WU, Althausen AF (1992) Radiotherapy and chemotherapy in invasive bladder cancer with potential bladder sparing. Hematol Oncol Clin North Am 6:179–194

Keep JC, Piehl M, Miller A, Oyasu R (1989) Invasive carcinoma of the urinary bladder. Evaluation of tunica muscularis mucosae involvement. Am J Clin Pathol 91:575–579

Kern WH (1984) The grade and pathologic stage of bladder cancer. 53:1185–1189

Koss LG (1975) Tumours of the urinary bladder. Atlas of tumor pathology, series 2, fascicle 11. Armed Forces Institute of Pathology, Washington DC

Lipponen PK, Collan Y, Eskelinen MJ, Personen E, Sotarauta M, Nordling S (1990 a) Comparison of morphometry and DNA flow cytometry with standard prognostic factors in bladder cancer. Br J Urol 65:589–597

Lipponen PK, Kosma VM, Collan Y, Kulju T, Kosunen O, Eskelinen M (1990 b) Potential of nuclear morphometry and volume-corrected mitotic index in grading transitional cell carcinoma of the urinary bladder. Eur Urol 17:333–337

Lipponen PK, Eskelinen MJ, Kiviranta J, Pesonen E (1991) Prognosis of transitional cell bladder cancer: a multivariate prognostic score for improved prediction. J Urol 146:1535–1540

Maffezzini M, Torelli T, Villa E, Corrada P, Bolognesi A, Leidi GL, Rigatti P, Campo B (1991) Systemic preoperative chemotherapy with cisplatin, methotrexate and vinblastine for locally advanced bladder cancer: local tumor response and early followup results. J Urol 145:741–743

Malmström PU, Busch C, Norlen BJ (1987) Recurrence, progression and survival in bladder cancer. A retrospective analysis of 323 patients with greater than or equal to 5-year follow-up. Scand J Urol Nephrol 21:185–195

Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. JNCI 22:719–748

Marshall VF (1952) The relation of the pre-operative estimate to the pathologic demonstration of the extent of vesical neoplasms. J Urol 68:714–723

Melamed MR, Vousta NG, Grabstaldt H (1964) Natural history and clinical behaviour of carcinoma in situ of the human urinary bladder. Cancer 17:1533–1545

Mostofi FK (1954) Potentialities of bladder epithelium. J Urol 71:705

Mostofi FK, Sorbin LH, Torloni H (1973) Histological typing of urinary bladder tumors. International classification of tumors, no. 10. World Health Organisation, Geneva

Murphy WM (1983) Current topics in the pathology of bladder cancer. Pathol Annu 18:1–25

Narayana AS, Loening SA, Slymen DJ (1983) Bladder cancer: factors affecting survival. J Urol 130:56–60

Ooms ECM, Anderson WAD, Alons CL, Boon ME, Veldhuizen RW (1983) Analysis of the preformance of pathologists in the grading of bladder tumors. Hum Pathol 14:140–143

Pagano F, Bassi P, Prayer Galetti T, Meneghini A, Milani C, Artibani W, Garbeglio A (1991) Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with emphasis on the inadequacy of the tumor, nodes and metastases classification. J Urol 145:45–50

Pauwels RPE, Schapers RFM, Smeets AWGB, Debruyne FMJ, Geraedts JPM (1988 a) Grading in superficial bladder cancer. 1. Morphological criteria. Br J Urol 61:129–134

Pauwels RPE, Smeets AWGB, Schapers RFM, Geraedts JPM, Debruyne FMJ (1988 b) Grading in superficial bladder cancer. 2. Cytogenetic classification. Br J Urol 61:135–139

Prout GR, Griffin PP, Daly JJ (1983) Carcinoma in situ of the urinary bladder with and without associated vesical neoplasms. Cancer 52:524–532

Pryor JP (1973) Factors influencing the survival of patients with transitional cell tumours of the urinary bladder. Br J Urol 45:586–592

Quilty PM, Duncan W (1986) Primary radical radiotherapy for T3 transitional cell cancer of the bladder: an analysis of survival and control. Int J Radiat Oncol Biol Phys 12:858–886

Raghavan D (1988) Preemptive (neo-adjuvant) intravenous chemotherapy for invasive bladder cancer. Br J Urol 61:1–8

Raghavan D, Wallace M (1990) Preemptive (neoadjuvant) chemotherapy: can analysis of eligibility criteria, prognostic factors, and tumor staging from different trials provide valid or useful comparisons? Semin Oncol 17:613–618

Reuter V (1990) Pathology of bladder cancer: assessment of prognostic variables and response to therapy. Semin Oncol 17:524–532

Ro JY, Ayala AG, El-Naggar A (1987) Muscularis mucosa of urinary bladder. Importance for staging and treatment. Am J Surg Pathol 11:668–673

Scher HI (1990) Chemotherapy for invasive bladder cancer: neoadjuvant versus adjuvant. Semin Oncol 17:555–565

Scher HI, Yagoda A, Herr H, Sternberg CN, Bosl G, Morse MJ, Sogani PC, Watson RD, Dershaw DD, Reuter V, Geller N, Hollander P, Vaughan ED, Whitmore WF, Fair W (1988) Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. J Urol 139:470–474

Schröder FH, Cooper EH, Debruyne FMJ, Denis L, Newling DWW, Pavone-Macaluso M, Smith PH, Sylvester R, and Members of the EORTC-GU Group (1988) TNM classification of genitourinary tumours 1987. Position of the EORTC Genitourinary Group. Br J Urol 62:502–510

Shipley WU, Rose MA, Perrone TL, Mannix CM, Heney NM, Prout GR Jr (1985) Full-dose irradiation for patients with invasive bladder carcinoma: clinical and histological factors prognostic of improved survival. J Urol 134:679–683

Shipley WU, Prout GR Jr, Kaufman D, Perrone TL (1987) Invasive bladder carcinoma. The importance of initial transurethral surgery and other significant prognostic factors for improved survival with full-dose irradiation. Cancer 60:514–520

Sjolin KE, Nyholm K, Trautner K (1976) Studies of transitional cell tumours of the bladder. Acta Pathol Microbiol Scand [A] 84:361–374

Skinner DG (1977) Current state of classification and staging of bladder cancer. Cancer Res 37:2838–2844

Skinner DG, Kaufman JJ (1978) Management of invasive and high grade bladder cancer. In: Skinner DG, DeKernion JB (eds) Genitourinary cancer. Saunders, Philadelphia, pp 269–283

Skinner DG, Lieskovsky G (1984) Contemporary cistectomy with pelvic node dissection compared to preoperative radiation therapy plus cystectomy in management of invasive bladder cancer. J Urol 131:1069–1072

Skinner DG, Lieskovsky G (1988) Management of invasive and high-grade bladder cancer. In: Skinner DG, Lieskovsky G (eds) Diagnosis and management of genitourinary cancer. Saunders, Philadelphia, pp 295–312

Slack NH, Prout GR Jr (1980) The heterogeneity of invasive bladder carcinoma and different responses to treatment. J Urol 123:644–652

Slack NH, Bross IDJ, Prout GR (1977) Five-year follow-up results of a collaborative study of therapies for carcinoma of the bladder. J Surg Oncol 9:393–405

Soto EA, Friedell GH, Tiltman AJ (1977) Bladder cancer as seen in giant histologic sections. Cancer 39:447–455

Torti FM, Lum BL (1984) The biology and treatment of superficial bladder cancer. J Clin Oncol 2:505

Torti FM, Lum BL, Aston D (1987) Superficial bladder cancer: the primary of grade in the development of invasive disease. J Clin Oncol 5:125–130

UICC (Union Internationale Contre le Cancer) (1974) TNM classification of malignant tumors. G. de Buren, Geneva

UICC (Union Internationale Contre le Cancer) (1978) Harmer MH (ed) TNM classification of malignant tumors, 3rd edn. International Union against Cancer, Geneva

UICC (Union Internationale Contre le Cancer) (1982) Spiessl B, Scheibe O, Wagner G (eds) TNM atlas: illustrated guide to the classification of malignant tumors. Springer, Berlin Heidelberg New York

UICC (Union Internationale Contre le Cancer) (1987) Hermanek P, Sobin LH (eds) Classification of malignant tumors, 4th edn. International Union against Cancer, Geneva

Van der Werf-Messing B, Menon RS, Hop WCJ (1983) Carcinoma of the urinary bladder T3NXM0 treated by the combination of radium implant and external irradiation: second report. Int J Radiat Oncol Biol Phys 9:177–180

Walther PJ (1992) The role of flow cytometry in the management of bladder cancer. Hematol Oncol Clin North Am 6:81–98

Webb JN (1985) The histopathology of bladder cancer. In: Zingg EJ, Wallace DMA (eds) Bladder cancer. Springer Berlin Heidelberg New York, pp 23–51

Younes M, Sussman J, True LD (1990) The usefulness of the level of the muscularis mucosae in the staging of invasive transitional cell carcinoma of the urinary bladder. Cancer 66:543–548