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Original Article

Histopathological aspects of transitional cell carcinoma of the bladder: Analysis of 20 years experience

ALESSANDRO SCIARRA,[1] ANNA DE MATTEIS,[2] GIANNA MARIOTTI,[1] GIUSEPPE VORIA,[1] ROSSANA LUCERA[1] AND FRANCO DI SILVERIO[1]

[1]*Department of Urology 'U Bracci' and* [2]*Institute of Pathology, University La Sapienza, Rome, Italy*

Abstract

Background: In this study we used histopathological examinations performed over a 20-year period to describe the characteristics of newly diagnosed transitional cell carcinoma (TCC) of the bladder in relation to patient age, and to verify changes in the TCC over different periods of observation or in relation to patient age.

Methods: We reviewed all histopathological examinations performed from January 1979 to December 1998 in patients undergoing surgery who were newly diagnosed with TCC of the bladder. All examinations were performed by the same pathologist and reviewed by two pathologists. In each case analyzed, we evaluated T classification of the tumor, histological grade, size, localization, growth type, multiplicity and carcinoma *in situ* (CIS).

Results: The study population included 3113 men and 620 women. The mean patient age was 66.31 ± 10.84 years. A high percentage of Ta (52.2%) and T1 (27.7%) tumors were found. The number of cases observed and, in particular, the percentage of Ta tumors increased significantly and progressively from the first (1979–1983 = 376 cases; Ta = 37.8%) to the last (1994–1998 = 1732 cases; Ta = 56.3%) period of observation ($P < 0.001$). A significant difference in the distribution of histological grade and T classification in the different age decades was apparent ($P < 0.001$); in particular, for G1 and Ta tumors there was a trend to decrease, whereas for G3, T1 and T2 tumors there was a tendency to increase with age decades.

Conclusion: In our analysis, age of patient and the period of examination significantly influenced different pathological characteristics of newly diagnosed TCC of the bladder.

Key words bladder cancer, grade, histopathology, stage, transitional cell carcinoma.

Introduction

The present study reports our experience with transitional cell carcinoma (TCC) of the bladder through 20 years of histopathological examinations performed by the same pathologist (ADM). In particular, we focused our attention on newly diagnosed TCC.

The aim of the study was: (i) to analyze the histopathological characteristics of newly diagnosed TCC of the bladder; (ii) to verify whether their histological presentation is influenced by patient gender and age; (iii) to analyze whether these characteristics have changed in 20 years of examination (from 1979 to 1998); and (iv) to verify correlations among the different variables considered.

We limited our analysis to aspects of TCC obtained from the histopathological examination and we did not compare these data with other clinical parameters and survival rates of patients.

Correspondence: Alessandro Sciarra MD, V Nomentana 233, 00161 Rome, Italy. Email: sciarrajr@hotmail.com

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Methods

This is a retrospective, single center study. We reviewed all histopathological examinations consecutively performed from 1979 to 1998 in patients undergoing

surgery at the Department of Urology, University la Sapienza, Rome, who were newly diagnosed with TCC of the bladder.

All histopathological examinations were performed by the same pathologist (ADM) and all slides were reviewed by two pathologists (ADM, GM). To obtain homogeneous results, in each case the final classification of the tumor (based on the different histopathological characteristics) was established through the agreement of both pathologists.

Inclusion in this study was based on the following criteria: (i) histopathological examinations were performed from January 1979 to December 1998; (ii) examinations were obtained from surgical procedures performed in our urology clinic (e.g. transurethral resection of the bladder or open surgery [partial or radical cystectomy]); (iii) tissue samples had to be adequate for a complete histopathological evaluation; and (iv) TCC of the bladder must have been only newly diagnosed, based on the results of the histopathological examinations. We restricted our analysis to the period from 1979 to 1998 because it corresponds to the activity of our pathologist (ADM) in our clinic.

A total of 3733 histopathological examinations fulfilled the criteria and were included in our analysis. Only 138 examinations were excluded from the review, because these involved inadequate histological specimens. Of the total 3733 examinations, 3101 (83.1%) were obtained from transurethral resection of the bladder (TURB) and 632 (16.9%) were obtained from open surgery.

Treatment of TCC of the bladder was completed according to uniform guidelines.[1] Newly diagnosed superficial tumors were primarily treated by transurethral resection without prophylactic intravesical chemotherapy. The primary treatment of newly diagnosed T2 to T4 tumors was cystectomy without neoadjuvant radiotherapy or chemotherapy.

Specimens were studied by routine histological procedures. In each case, we evaluated the following variables: localization, size (diameter), multiplicity, growth type (pattern), histological grade, T classification of the tumor based on pathological data, and associated carcinoma *in situ* (CIS). For tumor localization, we obtained data for only 2403 cases (missing values, 1330). For all other variables, we obtained data for each case.

In all cases, T classification of the tumor was assigned according to TNM, and during revision, all data were adjusted retrospectively according to the 1997 classification system (Ta = non-invasive papillary; CIS = carcinoma *in situ*; T1 = subepithelial connective tissue; T2 = muscularis propria: T2a = inner half, T2b = outer half; T3 = perivesical tissue: T3a = microscopical, T3b = extravesical mass; T4a = prostate, uterus, vagina; T4b = pelvic wall, abdominal wall).[2] In our analysis, we considered only T classification and did not include the evaluation of regional lymph nodes (N) because lymphadenectomy was not routinely performed in all open surgical procedures, especially during the first 10 years of examination.

Histological grade was assigned using the World Health Organization (WHO) histological classification, Geneva, 1973 (G1 = well differentiated; G2 = moderately differentiated; G3 = poorly differentiated).[3] If we compare specimen interpretation obtained by the same pathologist (ADM) in the first histopathological analysis and then after revision, no significant variability in results was found, according to WHO grading of the tumor. In particular, all TCC classified as G1 and G3 during the first examination were classified in the same WHO category after revision. Only 21 (all during the 1979–1983 period) out of the 1205 TCC classified as G2 during the first examination were classified as G1 after revision.

Growth pattern of the tumor also was recorded and tumors were divided into papillary or non-papillary type. Afterwards, the whole population of 3733 cases was divided into different groups on the basis of patient gender, age, and period of examination.

Based on their age, the patients were considered as being in one of four age decades: Group 1, 40–49 years; Group 2, 50–59 years; Group 3, 60–69 years; Group 4, 70–79 years. In this part of the analysis, to classify cases in the four age decades, we included only examinations conducted on patients aged from 40 to 79 years. Between 1979 and 1998, only 59 cases less than 40 years old and 142 more than 79 years old were evaluated in our clinic.

According to the period of observation we considered: Group 1, 1979–1983; Group 2, 1984–1988; Group 3, 1989–1993; Group 4, 1994–1998.

Statistical analysis

Descriptive statistics were used to characterize the age of patients (mean ± SD, median and range) as well as T classification of the tumor, grade, localization, size, growth type, multiplicity, and CIS. Age of patient and tumor size were used as continuous variables, whereas the other parameters were classified naturally and transformed into indicator variables.

Statistical evaluations were performed on either the whole population of 3733 cases, or on the different groups assigned on the basis of sex, age decades, and period of examination (described above). Variations in

the parameters for each of the different groups were reported.

Analyses performed on the data included χ^2 tests, to evaluate significant differences in the categorical distribution of the variables in the different groups, the Fisher's exact test, the Kruskal–Wallis test, Mantel trend tests and the Mantel–Haenszel test to adjust comparison for other categorical variables.[4,5] Linear regression models were also used. Spearman's correlation coefficients were calculated to measure the association among the different variables.

Considering the high number of cases in this study, we assumed as significant only those correlation coefficients (r) explaining more than 5% of the variance of one factor on the other ($r \geq 0.2236$; $R^2 \leq 0.05$).

Results

Our analysis included 3733 histopathological examinations for newly diagnosed TCC of the bladder. Table 1 summarizes data for the 3733 cases that satisfied the study criteria; age and size are reported as mean ± SD (median and range) whereas the other variables are described as number of cases (%).

The most frequent localizations for TCC were right lateral wall (1072 cases) and left lateral wall (992 cases) of the bladder.

According to histological grade, the 3733 cases showed a homogeneous distribution (G1: 30.9%; G2: 32.3%; G3: 36.8%). According to T classification of the tumor, a high percentage of Ta (52.2%) and T1 (27.7%) tumors were found. In all T1 cases, the muscularis propria was present in the specimen and free of tumor.

Carcinoma *in situ* (CIS) was present in 270 (7.2%) of our cases. According to Herr we distinguished between primary and concurrent CIS.[6] Thirty-one cases of the 270 CIS (11.5%) were primary and 239 (88.5%) were concurrent CIS.

Results of correlations among the different variables, showed a significant positive association between histological grade and T classification ($r = 0.58594$; $P < 0.0001$). In particular, 57.6% of Ta tumors were G1, 36.7% were G2, and 5.7% were G3; only 3.1% of T1 were G1, 39.1% were G2, and 57.8% were G3; 0% of T2 were G1, 15.2% were G2 and 84.8% were G3. No G1 cases were found in T3 and T4 tumors.

A significant positive association was also found between T classification and growth type ($r = 0.45558$; $P < 0.0001$), and between grade and growth type ($r = 0.38204$; $P < 0.0001$).

The association of CIS with histological grade ($r = 0.28311$; $P = 0.0001$) was somewhat stronger than that between CIS and T classification ($r = 0.17867$). CIS was found in only one G1 tumor, in 1.9% of G2 tumors and in 17.9% of G3 tumors.

The association of tumor size with T classification ($r = 0.41589$; $P < 0.0001$) was stronger than that between size and grade ($r = 0.27862$; $P < 0.0001$). Blad-

Table 1 3733 cases with newly diagnosed transitional cell carcinoma of the bladder†

Variable	No. cases	%
Period		
1979–1983	376	10.1
1984–1988	570	15.2
1989–1993	1055	28.3
1994–1998	1732	46.4
Gender		
Male	3113	83.4
Female	620	16.6
Surgery		
TURB	3101	83.1
Open	632	16.9
Grade		
G1	1155	30.9
G2	1205	32.3
G3	1373	36.8
T classification		
Ta	1950	52.2
T1	1033	27.7
T2	519	13.9
(a)	298	7.9
(b)	221	6.0
T3	156	4.2
(a)	103	2.8
(b)	53	1.4
T4	75	2.0
(a)	59	1.6
(b)	16	0.4
Growth type		
Papillary	3258	87.3
Non-papillary	475	12.7
CIS	270	7.2
Multiplicity		
Single	2548	68.3
Multiple	1185	31.7
Localization		
Bladder neck	691	28.7
Trigone	517	21.5
Superior wall	355	14.8
Right lateral wall	1072	44.5
Left lateral wall	992	41.3
Anterior wall	420	17.5
Posterior wall	606	25.2
Missing	1330	35.6

†Age of patients (mean ± SD), 66.31 ± 10.84 years (median 67; range 36–88); size of tumor (mean ± SD), 2.18 ± 1.65 cm (median 2.00; range 0.5–12).

der neck localization was significantly associated with multiple tumors ($r = 0.25844$; $P < 0.0001$). All other associations were very weak ($r < 0.20$) and not statistically significant.

Period of observation

The distribution of the different variables in the four observation period groups is described in Table 2; age and size are reported as median values whereas the other variables are described as percentages.

The number of cases examined significantly and progressively increased from the first (1979–1983 = 376 cases) to the last (1994–1998 = 1732 cases) group (Fig. 1). Mean and median age of patients did not significantly vary from Group 1 (66.06 ± 11.04; median 67 years) to Group 4 (65.83 ± 10.11; median 66 years) ($P = 0.426$) (Table 2).

The proportion of observations in the two different categories of gender (male, female) did not significantly vary from group to group ($P = 0.377$) (Table 2).

The categorical distribution of histological grade (G1, G2, G3) significantly varied in the four groups ($P < 0.001$) (Table 2), but it was not possible to predict a specific trend in data.

A significant difference in the categorical distribution of T classification of the tumor (Ta, T1, T2, T3, T4) in the different periods of examination was found ($P < 0.001$) (Table 2), and in particular, in regards to Ta tumors, there was a trend to increase from Group 1 to

Table 2 Distribution of the different variables according to the period of observation

Variable	Group 1 (1979–1983)	Group 2 (1984–1988)	Group 3 (1989–1993)	Group 4 (1994–1998)
No. cases ($P < 0.001$)	376	570	1055	1732
Age (years) ($P = 0.426$)	67	68	66	66
Size (cm) ($P < 0.05$)	3.5	3.5	2.5	2.0
Gender ($P = 0.377$)				
Male	84.6%	81.4%	82.7%	84.2%
Female	15.4%	18.6%	17.3%	15.8%
Surgery ($P < 0.001$)				
TURB	58.2%	73.5%	85.6%	90.1%
Open	41.8%	26.5%	14.4%	9.9%
Grade ($P < 0.001$)				
G1	33.0%	28.9%	29.3%	32.2%
G2	23.1%	36.8%	32.8%	32.4%
G3	43.9%	34.3%	37.9%	35.4%
T classification ($P < 0.001$)				
Ta	37.8%	46.6%	53.9%	56.3%
T1	37.8%	34.0%	20.8%	27.7%
T2	16.7%	12.1%	17.0%	11.9%
T3	5.6.%	5.6%	5.3%	2.7%
T4	2.1%	1.7%	3.0%	1.4%
Growth type ($P < 0.001$)				
Papillary	80.9%	87.3%	88.4%	87.9%
Non-papillary	19.1%	12.7%	11.6%	12.1%
CIS ($P = 0.041$)	6.1%	8.4%	8.7%	6.2%
Multiplicity ($P < 0.001$)				
Single	70.7%	79.6%	79.4%	57.2%
Multiple	29.3%	20.4%	20.6%	42.8%
Localization ($P < 0.001$)				
Bladder neck	10.6%	21.0%	21.6%	17.5%
Trigone	13.0%	13.8%	15.2%	13.2%
Superior wall	2.1%	11.2%	8.2%	11.3%
Right lateral wall	13.8%	28.9%	29.8%	31.2%
Left lateral wall	11.4%	28.1%	29.8%	27.4%
Anterior wall	8.7%	11.2%	12.8%	10.8%
Posterior wall	8.0%	22.1%	16.6%	15.9%
Missing	42.5%	36.1%	34.0%	34.9%

CIS, carcinoma *in situ*; TURB, transurethral resection of the bladder.

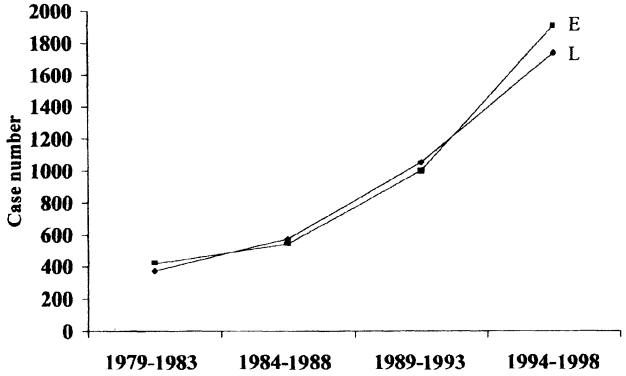

Fig. 1 New diagnosis of transitional cell carcinoma of the bladder examined from the first to the last period of observation. Cases number trend according to linear (L), and exponential (E) models. L: F(1,2) 35.23, $P = 0.027$; E: F(1,2) = 403.71; $P = 0.002$.

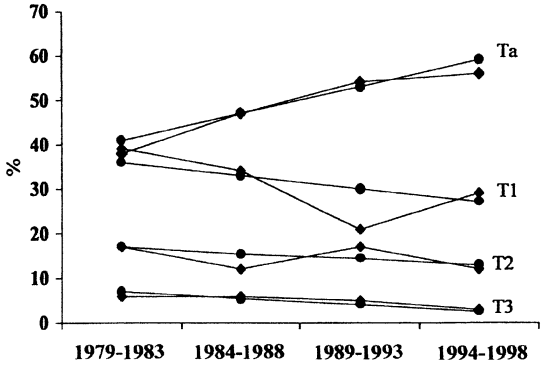

Fig. 2 Linear regression model (ANOVA): T classification trend according to the different periods of examination. Because of the limited number of cases we did not include the T4 category in this model. Ta: F(1,2) = 46.924, $P = 0.021$; T1: F(1,2) = 18.195, $P = 0.051$; T2: F(1,2) = 2.613, $P = 0.247$; T3: F(1,2) = 101.63, $P = 0.010$. ◆, trend; ●, normal distribution.

Group 4 (Fig. 2). Using Group 1 as the reference, cases in Groups 2, 3, and 4 were progressively more likely to have a TCC classified as Ta (Ta *vs* ≥ T1) (Group 2 *vs* Group 1: odds ratio 1.23, 95% confidence interval (CI) 1.03–2.15; Group 3 *vs* Group 1: odds ratio 1.42, 95% CI 1.07–2.26; Group 4 *vs* Group 1: odds ratio 1.49, 95% CI 1.08–2.31).

A significant difference in the distribution of the categories of surgery (TURB, open), growth pattern (papillary, non-papillary), multiplicity (single, multiple) and localization of the tumor in the different periods of examination was found (Table 2), and for TURB procedures only, there was a trend to increase from Group 1 to Group 4 ($F_{1,2} = 32.928$; $P = 0.029$). Localization on the lateral wall of the bladder remained the most frequent in each period.

By analyzing correlations among the variables in each group, the association between grade and growth pattern was seen to be progressively stronger from Group 1 to Group 4 (Group 1: $r = 0.33193$; Group 2: $r = 0.35539$; Group 3: $r = 0.37453$; Group 4: $r = 0.40495$; $P < 0.00001$), as was the association between T classification and growth pattern (Group 1: $r = 0.31191$; Group 2: $r = 0.43887$; Group 3: $r = 0.47663$; Group 4: $r = 0.50243$; $P < 0.00001$).

The association between T classification and grade remained strong in the different groups (Group 1: $r = 0.56041$; Group 2: $r = 0.59262$; Group 3: $r = 0.60355$; Group 4: $r = 0.58668$; $P < 0.0001$).

Patient age

Median age of patients with G1 TCC (63 years) was significantly lower than that of patients with G2 (67 years) and G3 TCC (68 years) ($P < 0.001$). Median age of patients with Ta TCC (64 years) was significantly lower than that of patients with T1 (68 years) and T2 or more (70 years) tumors ($P < 0.001$).

A significant difference in median age was found according to the multiplicity of the tumor (multiple: 67 years; single: 65 years; $P < 0.05$) but not according to the presence of CIS (CIS: 65 years; without CIS: 66 years; $P = 0.1377$).

The distribution of the different variables in the four groups is described in Table 3; age and size are reported as median values whereas the other variables are described as percentages. The number of cases examined significantly ($P < 0.001$) and progressively increased from the 4th (239 cases) to the 7th age decade (1381 cases).

The highest male to female ratio (7 : 1) was found in Group 2 (Fig. 3).

The categorical distribution of histological grade significantly varied from group to group ($P < 0.001$) (Table 3), and for G1 tumors there was a trend to decrease, whereas for G3 there was a trend to increase with decades of age (Fig. 4).

Using Group 1 (40–49 years) as the reference, patients in groups 2, 3, and 4 were progressively less likely to have a TCC of the bladder classified as G1 (G1 *vs* ≥ G2) (Group 2 *vs* Group 1: odds ratio 0.78, 95% CI 0.53–1.05; Group 3 *vs* Group 1: odds ratio 0.56, 95% CI 0.32–0.61; Group 4 *vs* Group 1: odds ratio 0.44, 95% CI 0.23–0.54); in contrast, patients in groups 2, 3, and 4 were progressively more likely to have a TCC classified as G3 (G3 *vs* ≥ G2) (Group 2 *vs* Group 1: odds ratio 1.69, 95% CI 1.05–2.28; Group 3 *vs* Group 1: odds ratio 1.92, 95% CI 1.33–2.77; Group 4 *vs* Group 1: odds ratio 2.11, 95% CI 1.46–3.04).

Table 3 Distribution of the different variables according to patient decades of age

Variable	Group 1 (40–49)	Group 2 (50–59)	Group 3 (60–69)	Group 4 (70–79)
No. cases ($P < 0.001$)	239	642	1270	1381
Age (years)	43	55	65	76
Size (cm) ($P = 0.845$)	3.0	3.0	2.5	2.0
Gender ($P < 0.001$)				
Male	79.5%	87.5%	85.7%	79.4%
Female	20.5%	12.5%	14.3%	20.6%
Surgery ($P < 0.001$)				
TURB	82.2%	78.1%	81.9%	86.9%
Open	17.8%	21.9%	18.1%	13.1%
Grade ($P < 0.001$)				
G1	54.3%	42.3%	30.5%	24.0%
G2	26.7%	25.6%	33.0%	35.8%
G3	19.0%	32.1%	36.5%	40.2%
T classification ($P < 0.001$)				
Ta	71.0%	58.5%	54.1%	47.4%
T1	18.3%	23.1%	26.1%	32.5%
T2	7.7%	12.2%	12.8%	15.5%
T3	1.7%	5.3%	4.9%	2.9%
T4	1.3%	0.9%	2.1%	1.7%
Growth type ($P = 0.050$)				
Papillary	95.6%	91.4%	89.9%	90.5%
Non-papillary	4.4%	8.6%	10.1%	9.5%
CIS ($P = 0.090$)	5.1%	6.5%	8.5%	4.9%
Multiplicity ($P = 0.003$)				
Single	73.2%	74.0%	69.5%	66.1%
Multiple	26.8%	26.0%	30.5%	33.9%
Localization ($P = 0.120$)				
Bladder neck	13.4%	17.9%	19.4%	21.5%
Trigone	12.1%	16.7%	14.0%	14.7%
Superior wall	5.4%	9.2%	9.4%	11.9%
Right lateral wall	26.3%	31.1%	31.2%	29.9%
Left lateral wall	29.2%	26.5%	28.4%	28.3%
Anterior wall	7.9%	9.8%	11.5%	13.9%
Posterior wall	15.9%	17.0%	15.7%	18.8%
Missing	40.2%	36.9%	37.5%	37.8%

CIS, carcinoma *in situ*; TURB, transurethral resection of the bladder.

Fig. 3 Male to female ratio according to the different decades of age.

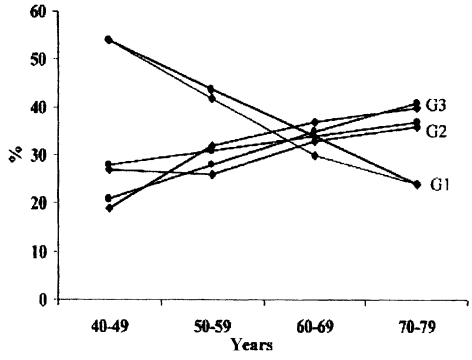

Fig. 4 Linear regression model (ANOVA): histological grade trend according to the different decades of age. G1: $F(1,2) = 131.91$, $P = 0.007$; G2: $F(1,2) = 7.972$, $P = 0.106$; G3: $F(1,2) = 24.805$, $P = 0.038$. ◆, trend; ●, normal distribution.

A significant difference was shown in the categorical distribution of the T classification of the tumor in the different age decades ($P < 0.001$) (Table 3). In particular, for Ta tumors there was a trend to decrease, whereas for T1 and T2 there was a trend to increase with age decades (Fig. 5).

Using Group 1 as the reference, patients in groups 2, 3, and 4 were progressively less likely to have a TCC classified as Ta (Ta *vs* ≥ T1) (Group 2 *vs* Group 1: odds ratio 0.82, 95% CI 0.51–1.02; Group 3 *vs* Group 1: odds ratio 0.76, 95% CI 0.44–0.85; Group 4 *vs* Group 1: odds ratio 0.66, 95% CI 0.36–0.79); in contrast, patients were more likely to have a TCC classified as T1 or more (≥T1 *vs* Ta) (Group 2 *vs* Group 1: odds ratio 1.43, 95% CI 0.97–1.96; Group 3 *vs* Group 1: odds ratio 1.58, 95% CI 1.07–2.37; Group 4 *vs* Group 1: odds ratio 1.81, 95% CI 1.15–2.61).

Localization on the lateral wall of the bladder remained the most frequent in each age decade.

Results of correlations among the variables in each group showed that the association between CIS and grade decreased progressively with increasing age (Group 1: $r = 0.43054$; Group 2: $r = 0.32944$; Group 3: $r = 0.31028$; Group 4: $r = 0.22766$; $P < 0.00001$).

The association between grade and stage (Group 1: $r = 0.61023$; Group 2: $r = 0.66768$; Group 3: $r = 0.57810$; Group 4: $r = 0.54412$; $P < 0.00001$), grade and growth pattern (Group 1: $r = 0.39208$; Group 2: $r = 0.40758$; Group 3: $r = 0.40930$; Group 4: $r = 0.34428$; $P < 0.0001$)) and T classification and growth pattern of the tumor (Group 1: $r = 0.35608$; Group 2: $r = 0.51440$; Group 3: $r = 0.46912$; Group 4: $r = 0.42358$; $P < 0.0001$) remained strong in the different age groups.

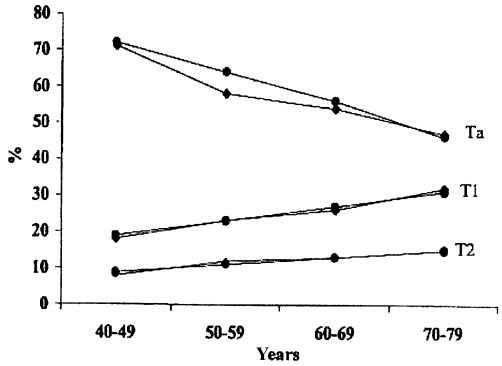

Fig. 5 Linear regression model (ANOVA): T classification trend according to the different decades of age. Because of the limited number of cases we did not include the T3 and T4 categories in this model. Ta: $F(1,2) = 234.48$, $P = 0.004$; T1: $F(1,2) = 90.993$, $P = 0.011$; T2: $F(1,2) = 20.107$, $P = 0.034$. ◆, trend; ●, normal distribution.

Discussion

In the present study we used histopathological examinations performed by the same pathologist over a 20-year period to describe the characteristics of newly diagnosed TCC of the bladder in relation to patient age and different periods of observation. The strengths of our study were the relatively large sample size and the standardized review of pathological materials.

As in other studies, a higher percentage of examinations derived from patients submitted to TURB (83.1%) than from those undergoing open surgery (16.9%).[7] The treatment of TCC of the bladder was completed according to uniform guidelines.[1] In each case, we evaluated widely accepted histopathological variables that can also be prognostic markers for TCC of the bladder.[8]

So that our results were comparable with other works in the literature, primary tumor stage was assigned according to the 1997 TNM system, and histological grade was assigned using the WHO histological classification, Geneva, 1973.[2,3] WHO grading is widely used and correlates well to survival of patients.[7,9–12] Furthermore, Lipponen *et al*. emphasized the importance of the growth pattern as a prognostic factor in bladder cancer.[7] Therefore, as described by other authors in connection with grading, in the present analysis we registered the growth pattern of the tumor.[7]

The incidence of TCC of the bladder is rising in western countries. The epidemiology of TCC cancer is rather complex. Our study population was represented only by white European people. Notably, mean and median ages of our cases, and male to female ratios, are similar to those reported in epidemiological studies on TCC of the bladder.[12–14]

In line with data reported in the literature, in the majority of cases in the present study, newly diagnosed TCC of the bladder presented as a low grade, Ta (52.2%) or T1 (27.7%), papillary (87%) tumor, whereas 37% of all newly diagnosed TCCs had a high histological grade and approximately 30% of all TCCs were multiple.[14–16] In contrast, carcinoma *in situ* was found in a low percentage of our cases (7%), whereas higher percentages (20%) have been reported by other authors.[17] We found a higher percentage of CIS in male cases (7.7%) when compared with female cases (4.8%) ($P = 0.015$). Herr defined different types of CIS: primary CIS (isolated, without previous or concurrent bladder tumor) and concurrent CIS (coexisting with exophytic tumor).[6] The real incidence of primary CIS is not well known, being approximately 2–3% of all bladder tumors and 10% of all CIS with a similar prognosis to other types of CIS.[18] Similar percentages were found in the present study population. There is no complete agreement with

respect to a different prognosis of CIS, depending on the bladder extension affected, and this is hindered by definitions of 'diffuse' and 'focal' CIS, which are not always in complete agreement.[19] In our cases, CIS was significantly associated with high-grade tumors ($r = 0.28311$). In particular, only one G1 tumor, compared with 17.9% of G3 tumors, presented a concurrent CIS.

Contrary to other experiences, in the present study, multiple tumors were similarly associated with low or high histological grade ($r = 0.09330$).[11]

Some authors consider the localization of TCC, in particular bladder neck involvement, a significant predictor of tumor progression.[20,21] There are known anatomic differences in the bladder neck from other subsites.[20] For example, lymphatic drainage from the bladder neck proceeds to the sacral nodes and median common iliac nodes, whereas lymphatic drainage from the remainder of the bladder goes to the external and internal iliac nodes entering the common iliac chain. In the present study, TCCs were predominantly localized in the lateral wall of the bladder, followed by the bladder neck (28.7%). Unfortunately, we only obtained data on localization of the tumor in 2403 cases (1330 missing values), which has reduced the statistical significance of our results. Localization of the tumor was not significantly associated with tumor grade, T classification or growth pattern, but bladder neck involvement was frequently associated with multiple tumors ($r = 0.25844$).

The first variable analyzed in the present study was the period of examination; we verified whether, in our experience, the histopathological characteristics of newly diagnosed TCC of the bladder have changed significantly in 20 years of evaluation. Dividing the period of examination into intervals of 5 years each, the number of cases with newly diagnosed, histologically proved TCC of the bladder significantly and progressively increased from 1979 to 1998. The number of diagnoses of TCC is also progressively increasing in the USA and several European countries.[9] Interestingly, in the present study, particularly for the proportion of Ta tumors, there was a trend to progressively increase from the first period (Ta = 37.8%) to the last period of our evaluation (Ta = 56.3%). In contrast, over these 20 years of evaluation, the male to female ratio and the mean and median age did not change significantly and, in regard to tumor histological grade, a specific trend in data could not be found.

The progressive increase over time in the number of new histopathologically diagnosed TCCs of the bladder, and the increase in the proportion of tumors diagnosed at an initial stage (Ta classification), might indirectly suggest that early diagnosis for this tumor has progressively improved, at least in the 20 years of our experience. However, it is not possible to confirm this suggestion using data obtained from the histological examination only. From a first analysis of the clinical characteristics of our population, in a representative sample of 2187 cases (data not shown), we found that the percentage of new diagnosis of TCC suspected by ultrasonography increased from the first to the last period of examination (1979–1983, 68%; 1984–1988, 74%; 1989–1993, 85%; 1994–1998, 88%). In particular, the percentage of incidental diagnosis of TCC (pelvic ultrasonography performed for other diseases) increased from the first to the last period of examination (1979–1993, 7%; 1984–1988, 8%; 1989–1993, 15%; 1994–1998, 18%). A modification in smoking habits, occupation, or other socioeconomic factors (risk factors for bladder cancer) in the population might also contribute to this increase in TCC cases.[4] Prout *et al*. showed that smoking history is a significant predictor of invasive disease (T1 *vs* Ta) among white patients.[12] In the sample of 2187 cases that we started to analyze, a smoking history (more than 10 cigarettes per day for at least 10 years) was present in a high percentage of these cases (67%, 1458 cases). This percentage was higher in men (76%, 1385 cases) than in women (20%, 73 cases), and in men only the percentage of smokers showed a slight increase from the first to the last period of examination (1979–1983, 72% of males, 131 cases; 1984–1988, 73% of males, 196 cases; 1989–1993, 75% of males, 386 cases; 1994–1998, 78% of males, 672 cases).

In short, in addition to increases in the sensitivity of our histopathological techniques over time, there is probably a variety of different factors, related to changes in the behaviour of the population, that have led to our observation that early diagnosis of TCC of the bladder has increased over the past 20 years. (Note: We did not include these clinical data in our results for two reasons: (i) the initial aim of this study was to analyze the histological characteristics of newly diagnosed TCC of the bladder; and (ii) the sample from which we obtained these clinical data, represents only a subgroup for each period of examination.)

In the third part of our study, we tried to analyze differences in the expression of the histopathological characteristics of newly diagnosed TCC of the bladder, by grouping patients according to age. In this analysis we chose to exclude a limited number of cases, aged less than 40 years or more than 79 years, so as to classify our cases according to four age decades, rather than considering the first decade as 'less than 50 years' and the last one as '70 years or more'. Because the number of cases and data analyzed are very large, some

differences are statistically significant, but they do not reveal a clinically significant change in the characteristics of TCC with age. For example, the difference in median age among G1, G2 and G3 TCC was statistically significant; however, we cannot ascribe any clinical significance to this result. Nevertheless, other significant trends can be described.

Most of our cases (71%) were in the 6th or 7th decade of age. Epidemiologic studies showed that the risk of developing bladder cancer increases with age.[14] In the present study, a significant difference in the distribution of the categories of T classification, grade of the tumor and multiplicity in the different decades of age, was shown. A patient in the 7th decade of age is more likely to have a newly diagnosed TCC of the bladder classified as T1-T2 and G3, than patients in earlier age decades; on the contrary, a patient in the 4th decade of age is more likely to have a TCC classified as Ta and G1 than patients in the later decades.

The percentage of papillary pattern remained high in the different age decades, and it was not possible to find a specific and progressive trend for CIS. The association between CIS and grade was stronger ($r = 0.43054$) in the 4th decade and progressively decreased in the other decades (7th: $r = 0.22766$). Therefore, in patients aged 40–49 years, the presence of CIS is strongly associated with a high-grade tumor; after 50 years this association progressively decreases.

Much research has been done on bladder cancer and the value of different histopathological characteristics of TCC has been well defined. In a future analysis, we will try to transform this retrospective study into a longitudinal study, comparing the 20 years of histopathological experience with clinical outcomes, recurrence, progression and survival rates in patients with TCC of the bladder.

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