

Gender-Related Differences in Clinical and Pathological Characteristics and Therapy of Bladder Cancer

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Abstract

Objective: To confirm the very high male:female ratios previously observed among Spanish bladder cancer patients and to assess gender differences in tumoral characteristics, diagnostic procedures, and treatment in a large series of consecutive bladder cancer patients.

Patients and Methods: All newly diagnosed bladder cancer patients ($n = 615$) in 17 Spanish hospitals, between 1997–2000, were included. Information was collected both through personal interviews to patients and from medical records using a structured form.

Results: Seventy-six percent of tumours were superficial. The male:female ratio was 6.7 and it was similar for superficial and infiltrating tumours. Women were older than men at the diagnosis of bladder cancer (68.2 ± 9.4 years versus 65.7 ± 9.7 years, $p = 0.01$). Ten percent of superficial tumours in women, versus 3% in men, were classified as “other histological types” ($p = 0.008$). T1GIII tumours were more frequent among men (17% versus 7%, $p = 0.047$). On the other hand, women were more likely to present with 0a-stage tumours (48.6% versus 35.5%, $p = 0.04$), multiple tumours (50% versus 29%, trend test: 0.005), multi-centric tumours (54% versus 38%, $p = 0.019$), and larger infiltrating masses (5.2 cm versus 3.8 cm, $p = 0.03$) than men. Among 0a-stage tumours, only 23% of women compared to 54% of men received transurethral resection (TUR) alone ($p = 0.002$). Women were almost five-fold more likely to receive additional therapies to TUR ($p = 0.004$) after adjusting for age, geographical area, stage, tumoral size, nuclear grade, and multiplicity.

Conclusion: The study confirms the very high male:female ratio of bladder cancer in Spain. We found substantial differences in the pathological characteristics of tumours from men and women. There was a tendency for women to receive more frequently non-standard, more aggressive, therapy than men.

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Keywords: Bladder cancer; Sex ratio; Women; Treatment; Stage; Pathological characteristics

Abbreviations: TUR, transurethral resection; BCG, Bacille Calmette-Guerin; TNM, tumour, lymph node, and metastases system; OR, odds ratio; 95% CI, 95% confidence interval

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1. Introduction

Bladder cancer is the fourth most common malignancy in men from developed countries. It is less frequent in women, especially in Southern European countries, where it ranks at the 10th position [1]. The excess risk of bladder cancer in men compared to



women occurs in all areas of the world regardless of age [2]. However, the sex ratio appears to vary widely, ranging from 3:1 in the US to 7:1 in Spain and other Southern European countries [3,4]. Several authors have studied the causes of this difference pointing at factors such as gender differences in smoking habits or occupational exposures as well as anatomic features, urination habits, urinary tract infection, and hormonal factors between sexes [1,2,5–7]. However, this issue has not yet been solved.

Less work has been performed comparing gender differences related to clinical and pathological characteristics of bladder tumours. Several studies have reported differences in histological type [8,9], tumoral stage [7,8,10–12], and grade [13,14]. To what extent tumour characteristics reflect diverse environmental exposure patterns has not been extensively studied [15–17]. However, it has been suggested that tumour characteristics could partly explain gender-related differences in bladder cancer prognosis (i.e. survival) [18,19].

In this work, we have taken advantage of a large prospective series of consecutive bladder cancer patients to begin to study in greater detail the gender-associated differences previously observed among Spanish bladder cancer patients and to assess whether there are differences between genders regarding tumour characteristics, diagnostic procedures, and clinical management. The study is part of a larger project (EPICURO Study) aiming at: (1) analysing bladder cancer risk in relation with genetic susceptibility factors (i.e. polymorphisms of genes coding for metabolic and DNA repair enzymes) of tobacco, occupation, environmental exposures, diet, drugs, and past medical history; and (2) identifying molecular prognostic markers for bladder cancer. This report concentrates on the evaluation of gender-differences in bladder cancer risk in a large patient series and a detailed clinical description of gender-related differences in patient management at first diagnosis and clinical–pathological characteristics of patients. This work is the basis to study in greater detail the causes of such differences.

2. Patients and methods

2.1. Study population

Between May 1997 and December 2000, all bladder cancer patients newly diagnosed in 17 hospitals from five regions of Spain (two in Catalunya and one each in Alicante, Tenerife, and Asturias) were included in the study. Cases with histologically confirmed bladder cancer (International Classification of Diseases, 9th revision, code 188 [20]), between 20 and 80 years of age, whose

residence was in the catchment's area of each hospital, were selected. Patients with a previous diagnosis of lower urinary tract cancer, including bladder, renal pelvis, ureter and urethra were not eligible for inclusion in the study. Two cases with HIV infection were also excluded to avoid risk of contamination during biological sample handling. The study made no attempt to impose a common diagnostic or therapeutic strategy in the participating hospitals and reflects clinical practice at these centers.

All patients were approached by a study investigator during the first hospital admission, most of them because of a transurethral resection (TUR) procedure in Urology Departments. Written informed consent for study participation was requested from all patients. Only 7.8% of men and 8.2% of women refused to participate in the study.

2.2. Data collection

Information on sociodemographics and symptoms at presentation was collected through personal computer-assisted questionnaires conducted by trained interviewers during the first hospital admission. Macroscopic haematuria, vesical irritation, incontinence, and dysuria were recorded as symptoms at presentation. Time lag to diagnosis, expressed in months, was computed as the time between the patient's first awareness of symptoms to the TUR. Age was also computed to the TUR date.

Clinical information related to diagnostic procedures, first treatment, stage, and tumoral characteristics were collected from medical records through reviews conducted by physicians using a structured questionnaire. These data were sent to the coordinating centre where they were edited and coded. Use of diagnostic procedures such as abdominal ultrasonography, cystoscopy, intravenous pyelogram, computed tomography scan of the abdomen and pelvis, chest X-ray, and radioisotope bone scan were recorded, and the main findings registered. Since TUR also provided diagnostic data, information obtained from cystoscopy and TUR procedures was pooled under "endoscopy".

Detailed macro- and microscopical tumoral features were recorded including, number and location of masses, size, gross tumour appearance, mucosal appearance, tumour growth pattern, stage, grade, and histology of the largest mass. Tumour, lymph node, and metastases (TNM) system was used for pathologic staging [21]. On the basis of the pT-stage, patients were subsequently classified as suffering from a superficial (Ta, T1, Tis) or an infiltrating tumour (T2–4). Grade of nuclear atypia was recorded as low (I), medium (II), and high (III) [22]. A small fraction of tumours was graded in four categories according to Ash's classification [23]. For this analysis, the first category (grade I) was compared to all others regardless of the classification scheme used. Histology was categorised as "pure" transitional or "other", the latter including squamous, adenocarcinoma, mixed, and non-specific tumoral histology.

Tumour location was recorded as lateral right wall, lateral left wall, anterior wall, posterior wall, trigone, dome, and neck; when more than one area was affected, it was appropriately registered. Subsequently, tumour location was grouped as one versus ≥ 2 areas (multicentricity) and as trigone versus non-trigone areas. Number of tumours and size of the largest mass were determined by three methods: abdominal ultrasonography, CT scan, and endoscopy. The largest tumour was classified as sessile or pediculated; gross tumour appearance was classified as papillary, solid, or mixed; and mucosal appearance was considered as a two-category factor, normal versus abnormal.

Treatment management was categorised according to conventional criteria [24,25] and stratified by stage. In summary, standard

treatments were considered to be the following: TUR for all superficial tumours; additional intravesical therapy, either chemotherapy or Bacille Calmette-Guerin (BCG), for patients with T1 or Ta depending on tumour grade, size and multiplicity; radical cystectomy, radiotherapy, and systemic chemotherapy, for patients with infiltrating tumours. Treatment strategies different from those specified above were grouped under the “other” category.

2.3. Data analysis

The distribution of patient and tumoral characteristics among men and women was assessed. Analyses were conducted separately for superficial and infiltrating tumours. Data were managed using ACCESS databases (Microsoft Corporation, 1997) and statistical analysis was performed using version 9.0 SPSS statistical package (SPSS Inc., Chicago, IL, 1999).

To assess the independence of two categorical variables, the chi-square test and the chi-square test for trend were applied. When 20% of cells had expected counts of less than five, Fisher’s exact test was used. To determine the relationship between a categorical variable with two levels and normally or non-normally distributed quantitative variables, Student’s *t*-test and Mann–Whitney *U* tests were applied, respectively. Correlation coefficients were computed to compare ultrasonography and CT scan with endoscopy measurements of tumoral size and number of masses. Outliers were removed from these analyses. Number of masses measured by ultrasonography and CT scan was compared to those obtained by endoscopy and agreement between procedures was assessed by estimating kappa indexes. Logistic regression models were fit to achieve adjusted odds ratios (OR) of “having received only TUR” versus “having received TUR plus other treatments”. The models were adjusted for potential confounding factors such as age, geographical area, stage, grade, number of masses, and size of the largest mass measured by endoscopy. Results were considered significant at the two-sided *p* of 0.05 level.

3. Results

A total of 615 patients were considered for this analysis, 87% were men and 13% were women, yielding a sex ratio of 6.7 (Table 1). Women were significantly older and more illiterate than men. Four hundred and seventy patients (76%) had a superficial tumour and 145 (24%) had an infiltrating tumour. Both groups of patients were highly similar according to sex and age. Women with superficial tumours had a higher frequency of 0a-stage tumours than men (*p* = 0.04).

3.1. Tumour symptoms and diagnostic procedures

Macroscopic haematuria was the commonest first symptom in patients with superficial or infiltrating tumours, occurring in 80 and 92% of patients, respectively (Table 2). Vesical irritation was the presenting symptom in 34 and 61% of patients with superficial and infiltrating tumours, respectively. Similarly, dysuria was more commonly referred by patients with infiltrating tumours. These symptoms did not show any association with gender. Incontinence was the only first symptom that women described more frequently, mainly when the tumour was superficial (40% of women versus 27% of men, *p* = 0.05). Time from occurrence of first symptom to diagnosis was similar in men and women with superficial tumours. By contrast, 41% of women with infiltrating tumours, compared to 13% of men, were diagnosed in

Table 1

Description of the study population by gender

	Total <i>n</i> (%)	Men <i>n</i> (%)	Women <i>n</i> (%)	<i>p</i>
Total	615	535 (87)	80 (13)	
Age ^a				
Mean ± S.D.	66.1 ± 9.7	65.7 ± 9.7	68.2 ± 9.4	0.01
Level of education				
Illiterate	31 (5.3)	19 (3.8)	12 (15.4)	
Primary school incomplete	246 (42.1)	213 (42.0)	33 (42.3)	
Primary school finished	196 (33.5)	171 (33.7)	25 (32.1)	
High school	76 (13)	73 (14.4)	3 (3.8)	
University	30 (5.1)	25 (4.9)	5 (6.4)	
Others	6 (1)	6 (1.2)	0	<0.001
Missing information	30	28	2	
Stage ^b				
0a	207 (37.1)	173 (35.5)	34 (48.6)	
I	259 (46.4)	233 (47.7)	26 (37.1)	
II	39 (7)	35 (7.2)	4 (5.7)	
III	30 (5.4)	25 (5.1)	5 (7.1)	
IV	23 (4.1)	22 (4.5)	1 (1.5)	0.186
Missing information	55	45	10	

^a One man with missing data.

^b Two superficial cases with stage IV: TaN1 and T1N2 (ring cells).

Table 2

Symptoms at presentation and time-interval to diagnosis according to sex and tumour invasiveness

	Superficial tumours ^a			<i>p</i>	Infiltrating tumours ^a			<i>p</i>
	Total <i>n</i> (%)	Men <i>n</i> (%)	Women <i>n</i> (%)		Total <i>n</i> (%)	Men <i>n</i> (%)	Women <i>n</i> (%)	
Macroscopic haematuria								
No	75 (20.4)	64 (20.4)	11 (20.8)	0.950	9 (7.9)	8 (8.2)	1 (5.9)	1.000
Yes	292 (79.6)	250 (79.6)	42 (79.2)		105 (92.1)	89 (91.7)	16 (94.1)	
Missing information	103	95	8		31	29	2	
Vesical irritation								
No	243 (66.4)	204 (65.2)	39 (73.6)	0.230	44 (38.9)	38 (39.6)	6 (35.3)	0.738
Yes	123 (33.6)	109 (34.8)	14 (26.4)		69 (61.1)	58 (60.4)	11 (64.7)	
Missing information	104	96	8		32	30	2	
Incontinence								
No	261 (71.5)	229 (73.4)	32 (60.4)	0.052	55 (48.2)	50 (51.5)	5 (29.4)	0.092
Yes	104 (28.5)	83 (26.6)	21 (39.6)		59 (51.8)	47 (48.5)	12 (70.6)	
Missing information	105	97	8		31	29	2	
Dysuria								
No	291 (79.5)	246 (78.6)	45 (84.9)	0.292	58 (51.3)	52 (54.2)	6 (35.3)	0.151
Yes	75 (20.5)	67 (21.4)	8 (15.1)		55 (48.7)	44 (45.8)	11 (64.7)	
Missing information	104	96	8		32	30	2	
Symptom-TUR interval								
≤1 month	75 (23.5)	65 (24)	10 (20.8)	0.893	19 (17.4)	12 (13.1)	7 (41.2)	0.018
1–3 months	71 (22.3)	60 (22.1)	11 (22.9)		23 (21.1)	21 (22.8)	2 (11.7)	
>3 months	173 (54.2)	146 (53.9)	27 (56.3)		67 (61.5)	59 (64.1)	8 (47.1)	
Missing information	151	138	13		36	34	2	

^a Superficial tumours, Tis, Ta, T1 (TNM); infiltrating tumours, T2, T3, T4 (TNM).

the course of the first month since the first symptom occurred ($p = 0.02$), although the number of cases was small.

Diagnostic procedures were similarly used in women and men (Fig. 1). Ultrasonography was conducted in

81% of superficial and 83% of infiltrating tumours, endoscopy in 99 and 98%, intravenous pyelogram in 44 and 41%, CT scan in 8 and 86%, radioisotope bone scan in 4 and 57%, and chest X-ray in 97 and 99%, respectively.

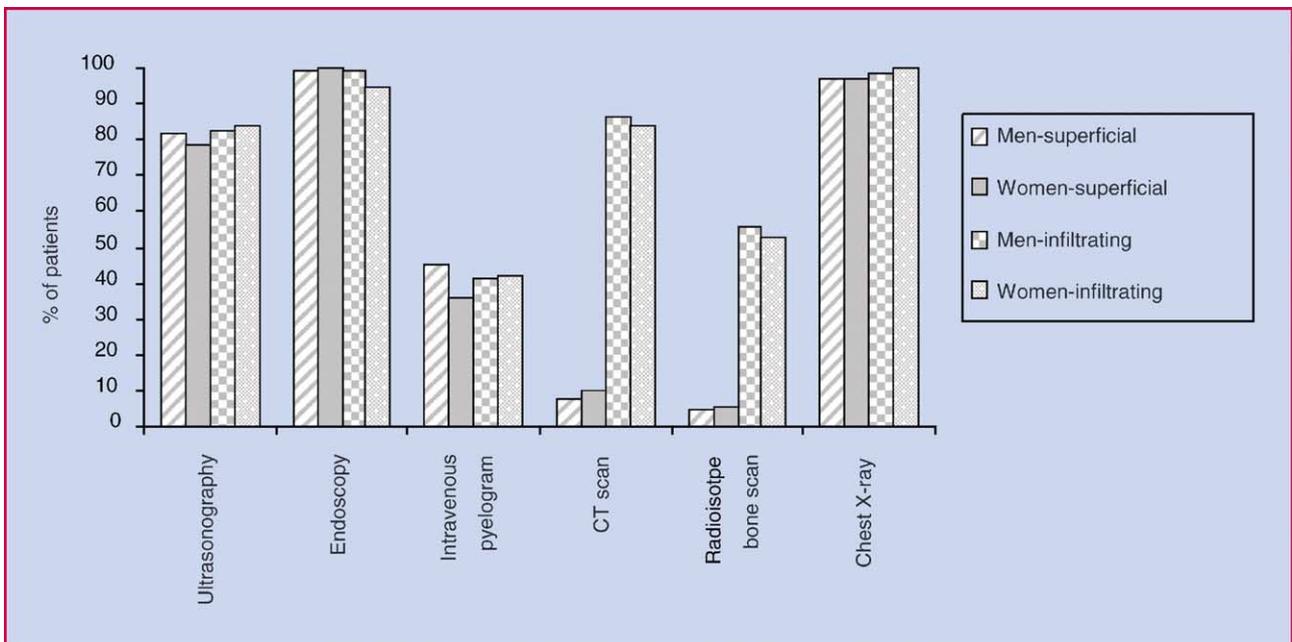


Fig. 1. Diagnostic tests applied according to gender and invasiveness.

Table 3

Pathological characteristics of tumours according to sex and tumour invasiveness

	Superficial tumour			<i>p</i>	Infiltrating tumour			<i>p</i>		
	Total <i>n</i> (%)	Men <i>n</i> (%)	Women <i>n</i> (%)		Total <i>n</i> (%)	Men <i>n</i> (%)	Women <i>n</i> (%)			
Histology										
Transitional	446 (96.5)	394 (97.5)	52 (89.7)	0.008	115 (80.4)	98 (79)	17 (89.5)	0.367		
Others	16 (3.5)	10 (2.5)	6 (10.3)		28 (19.6)	26 (21)	2 (10.5)			
Missing information	7	5	2		2	2	0			
Grade										
GI	94 (20.2)	84 (20.7)	10 (16.9)	0.503	0	0	0			
GII + GIII	371 (79.8)	322 (79.3)	49 (83.1)		133 (100)	115 (100)	18 (100)			
Missing information	4	3	1		12	11	1			
Tumour location										
>1 localization	182 (40.2)	151 (38.1)	31 (54.4)	0.019 ^a	72 (52.6)	65 (54.2)	7 (41.2)	0.315 ^a		
Trigone	43 (9.5)	41 (10.4)	2 (3.5)		14 (10.2)	12 (10)	2 (11.7)			
Others	228 (50.3)	204 (51.5)	24 (42.1)		0.394 ^b	51 (37.2)	43 (35.8)		8 (47.1)	1.000 ^b
Missing information	11	8	3		7	5	2			
Tumour growth										
Papillary	351 (87.3)	302 (86.5)	49 (92.5)	0.231	29 (23.2)	25 (23.1)	4 (23.5)	0.991		
Solid	31 (7.7)	30 (8.6)	1 (1.9)		80 (64)	69 (63.9)	11 (64.7)			
Mixed	20 (5)	17 (4.9)	3 (5.6)		16 (12.8)	14 (13)	2 (11.8)			
Missing information	62	55	7		17	16	1			
Tumour gross appearance										
Sessile	182 (52.5)	163 (53.8)	19 (43.2)	0.188	93 (93)	82 (93.2)	11 (91.7)	0.847		
Pedunculated	165 (47.5)	140 (46.2)	25 (56.8)		7 (7)	6 (6.8)	1 (8.3)			
Missing information	117	101	16		43	37	6			
Mucosal appearance										
Normal	240 (72.5)	207 (72.6)	33 (71.7)	0.899	58 (61)	52 (61.9)	6 (54.5)	0.745		
Others	91 (27.5)	78 (27.4)	13 (28.3)		37 (39)	32 (38.1)	5 (45.5)			
Missing information	139	124	15		48	41	7			

^a >1 Localization vs. trigone.^b Trigone vs. others.

3.2. Tumoral characteristics

Most tumours were “pure” transitional carcinomas. Nevertheless, 10% of superficial tumours in women, compared to 3% in men, were classified as “other” histologies ($p = 0.008$; Table 3). Two subjects were diagnosed of Tis. There were 32 additional superficial carcinomas in which in situ tumour was present together with Ta or T1 masses. Only 21% of superficial tumours in men and 17% in women were grade I. Although rare, TaGIII tumours were found to be more frequent among women (7% versus 2% in men, $p = 0.052$). In contrast, T1GIII tumours were more frequent among men (17% versus 7% in women, $p = 0.047$).

Women were also more likely to present multiple superficial tumours (50% versus 29% of men, trend test: 0.005) and larger infiltrating masses than men regardless of the method used to estimate tumoral size: ultrasonography (5.5 cm versus 3.5 cm in men, $p = 0.003$), CT scan (5.3 cm versus 3.6 cm in men, $p = 0.025$), and endoscopy (5.2 cm versus 3.8 cm in men, $p = 0.03$; Fig. 2). In addition, women with superficial tumours

were more commonly affected of multicentricity (54% versus 38% of men, $p = 0.019$; Table 3). However, the latter finding lost significance when the number of tumours was considered in the model. Tumoral size measurements by ultrasonography and endoscopy were highly correlated, showing coefficients of 0.542 for superficial and 0.533 for infiltrating tumours. A comparison of CT scan and endoscopy yielded correlation coefficients lower than 0.1 in both superficial and infiltrating tumours. The agreement on the number of masses estimated by ultrasonography and CT scan, compared with those obtained by endoscopy, showed Kappa indexes of 0.391 and 0.097, and 0.328 and 0.185 for superficial and infiltrating tumours, respectively.

3.3. Treatment

Treatment administered to patients with superficial tumours is displayed as shown in Table 4. Men were more likely to undergo a TUR alone than women (39.7% versus 19.3%, crude OR = 2.45, 95% CI 1.22–4.93, $p = 0.012$). This finding was mainly observed among 0a-stage tumours: 54% of men, compared to 23% of

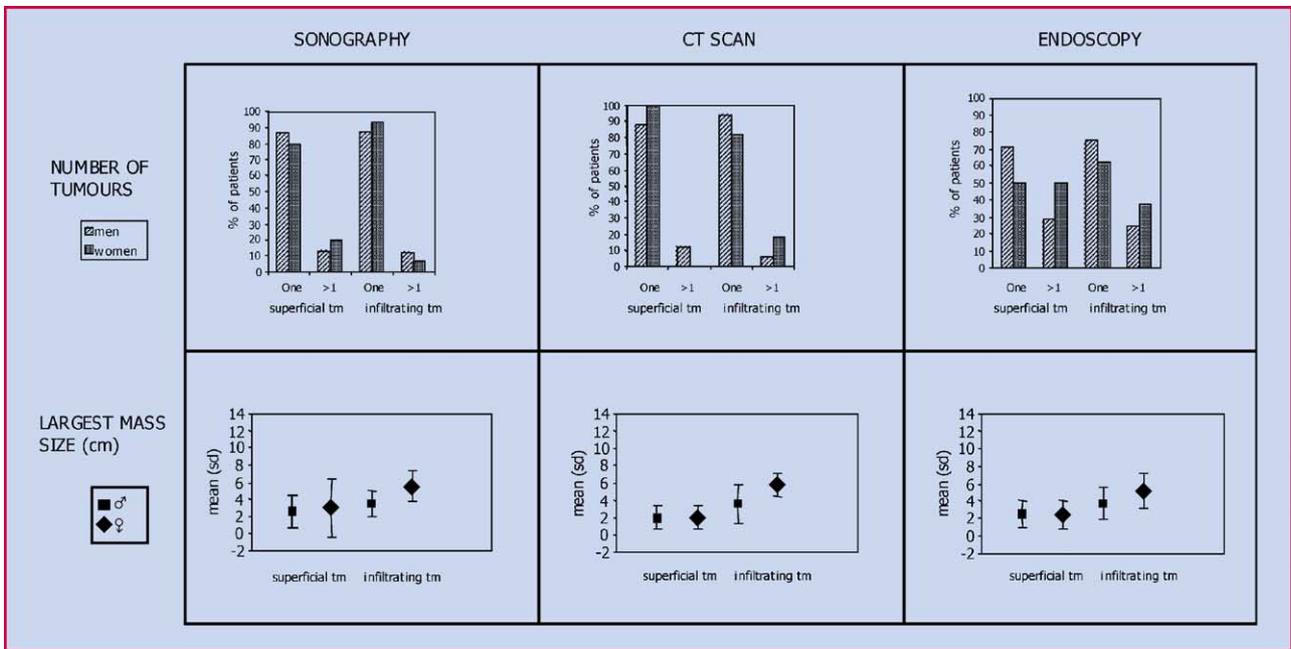


Fig. 2. Differences between genders on the number of tumours and size of the largest mass according to diagnostic test used.

Table 4

Treatment of patients with superficial tumours according to gender

	Total <i>n</i> (%) ^a	Men <i>n</i> (%)	Women <i>n</i> (%)	<i>p</i> ^b
Ta				
TUR 'alone'	93 (49.5)	86 (54.4)	7 (23.3)	0.002
TUR + BCG	18 (9.6)	11 (7.0)	7 (23.3)	
TUR + CT endovesical	45 (23.9)	37 (23.4)	8 (26.7)	
TUR + BCG + CT endovesical	30 (16)	23 (14.6)	7 (23.3)	
Others	2 (1)	1 (0.6)	1 (3.4)	
Missing	19	15	4	
T1				
TUR 'alone'	59 (26.9)	55 (27.9)	4 (18.2)	0.770
TUR + BCG	87 (39.7)	78 (39.6)	9 (40.9)	
TUR + CT endovesical	53 (24.2)	46 (23.4)	7 (31.8)	
TUR + BCG + CT endovesical	17 (7.8)	15 (7.6)	2 (9.1)	
Others	3 (1.4)	3 (1.5)	0	
Missing	40	36	4	

^a Two cases with superficial tumours with stage IV: TaN1 and T1N2 (ring cells) have been excluded from the analysis.

^b The *p*-value without stratifying by stage was 0.067.

women, underwent TUR alone ($p = 0.002$). Women received BCG as an additional treatment more often than men: 47% versus 22% ($p = 0.004$). Among patients with stage-I tumours, gender-associated differences in treatment were also observed though they did not reach statistical significance. The risk of being treated with "TUR alone" was adjusted for co-factors that could explain a different treatment strategy among women: age, geographical area, stage, endoscopy-measured tumoral size, nuclear grade, and multiplicity. The OR became even more significant after adjustment, men

being five times more likely than women to undergo only TUR (OR = 5.19, 95% CI 1.69–15.91).

4. Discussion

The main goal of this study was to assess differences in clinical–pathological characteristics and management among men and women recruited at a large prospective series of bladder cancer patients from Spain. While we did not find major gender-associated

differences concerning diagnostic procedures, there were differences in the pathological characteristics of tumours and in the treatment given to patients.

This case series comprised 76% of superficial and 24% of infiltrating tumours. These data are in agreement with other authors [11,26] who have reported that superficial tumours represent 60–80% of all bladder cancers [27]. The men:women ratio observed in our study was almost 7 and it was similar for both superficial and infiltrating cancers. Such similarity between the two groups of tumours has also been reported by other Spanish authors [28]. Nevertheless, other authors described higher men:women ratios among superficial tumours [8,12,18]. Our findings confirm in a very large series that the highest men:women bladder cancer ratio are found in Spain, the ratio being almost twice of that reported in Northern European countries and North America, where it ranges from 3 to 4 [10,12,28–30]. Our study also confirms that women were consistently older than men at the time of diagnosis [11,31]. While this finding may be due to differences in exposure patterns or to the presence of genetic and endogenous protective factors in women, more work is necessary to rule out the effect of a higher life expectancy among women. In the near future, the study should be able to provide some clues to better understand the high men:women ratio observed in Spain.

We have searched for sex-related differences in superficial and infiltrating tumours, independently, since it has been proposed these two neoplasms may be different molecular entities [32]. Overall, transitional cell carcinoma is the predominant bladder cancer histology in industrialised countries [9,33]. Our results are in agreement with the above statement. The proportion of “pure” transitional cell carcinomas was significantly higher among superficial tumours, a finding that is consistent with other reports [8] and could be explained by the fact that invasive tumours tend to be composed of mixed histologies. When the analysis was stratified by sex, we observed that the “mixed histology” diagnosis was more common in women than in men and that only three cases with squamous cell carcinoma, one superficial and two infiltrating tumours, were diagnosed in men. This represents a lower percentage than that described in the literature whose etiological significance is presently unknown [34].

Depth of infiltration and grade of differentiation are important prognostic parameters in bladder cancer. Several authors have described that women are diagnosed at advanced stages more frequently than men [7,8,10–12] and have suggested that, because bladder cancer is less common in women, medical doctors may

be less prone to consider this diagnosis at the woman’s first visit [35]. In addition, the higher frequency of urinary tract infections among women may lead to less extensive investigation of haematuria [8]. Nevertheless, several observations from our study do not provide support to this hypothesis and suggest that the differences in stage at presentation are not due to diagnostic delay: (1) the proportion of Ta tumours was significantly higher in women than in men; (2) the proportion of Ta tumours in men is in fact lower than that reported in other series (42% versus approximately 70%) [28,36]; (3) the first symptom to diagnosis interval was shorter for women than for men, especially for infiltrating tumours.

Multiplicity, tumour location, and tumour size, among others, have also been proposed as independent prognostic factors of recurrence and progression of bladder tumours [37,38]. Unlike other studies, we have observed differences regarding these variables related to gender. Although, women had tumours in more than one location more commonly than men, this difference disappeared when multiplicity was taken into account. This is probably due to the fact that urologists report the presence of tumour in more than one location either in the case of large masses that occupy more than one bladder area, or when several tumours are located in different areas.

It has been described that treatment of superficial bladder cancer is similar for men and women [7]. In the present study, we found that women with Ta tumours were more likely to receive TUR plus adjuvant immunotherapy than men with the same T-stage tumours. The association persisted even after adjusting for age, geographical area, stage, size, grade, and multiplicity in a multivariate model. There are no known reasons to account for this finding. Whether urologists are more aggressive when treating women with bladder cancer because the disease is less common and has worse prognosis in women deserves further investigation. Mulders et al. observed that treatment may alter the biological behaviour of the tumour and, thus influence prognosis [37]. Many studies have demonstrated the benefit of adjuvant treatment, such as BCG, in decreasing the recurrence rate or in prolonging the disease-free interval of patients with superficial tumours [34]. Thus, treating women with Ta tumours more aggressively might result in an increased recurrence-free interval. We are only aware of one study evaluating differences in treatment according to gender and bladder cancer prognosis: women with infiltrating bladder tumours were treated more aggressively but there was no effect on survival [11]. Further analyses of the reasons and consequences of differential therapeutic strategies

between genders as related to bladder cancer prognosis are planned.

In this study, clinical data were collected retrospectively, while lack of detailed information is a major problem when using medical records as a source, the fact that all physicians used the same structured questionnaire minimises the possibility of misclassification and the large size of the study allows for stratification of results according to tumour subgroups.

This study, including 615 patients, is one of the largest series in which gender-associated differences in bladder cancer characteristics have been analysed. The fact that only 7.8% of men and 8.2% of women refused to participate excludes the possibility that factors such as motivation and attitudes towards health could impair the study's external validity. Furthermore, since all newly diagnosed bladder cancer patients in the participating hospitals were prospectively identified and consecutively included in the study, selection bias is very unlikely and the study population should be considered as fully representative of bladder cancer patients in the five areas examined.

In addition to confirming the very high men:women ratio among patients with bladder cancer in Spain compared to Northern Europe and the US, the study shows that bladder tumours in women presents different pathological characteristics than those in men. Although we cannot yet assess the association of such differences with tumour recurrence, we observed that standard treatment was less commonly applied to women than to men, women being treated more aggressively. This finding should be taken into account when analysing gender-related differences in bladder cancer prognosis.

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Appendix A. Centers and members of the EPICURO Study Group

Center	Member
Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra (coordinating center)	M. Kogevinas ^a , N. Malats ^a , F.X. Real ^a , M. Sala ^b , G. Castaño ^b , M. Torà, D. Puente, C. Villanueva ^c , F. Fernández, R. Boixeda, M. Velasco, J. Deu, A. Alfaro ^c , C. Pipó ^c , H. López, M. Bautista ^d , F. Sánchez-Aguilera ^d , D. DeLamo ^d , C. del Mayo ^d , M. Juan ^d , N. Peiró ^d , A. Amoros, G. Carretero.
Hospital del Mar (Barcelona)	S. Serrano ^e , J. Lloreta ^e , L. Ferrer ^e , A. Gelabert, J. Carles, O. Bielsa, K. Villadiego.
Hospital Germans Tries i Pujol (Badalona, Barcelona) Hospital de Sant Boi (Sant Boi, Barcelona)	L. Cecchini, J.M. Saladié, L. Ibarz, M. Nadal. M. Céspedes.
Centre Hospitalari Parc Taulí (Sabadell, Barcelona)	C. Serra ^b , D. García, Y. Vélez ^c , J. Montés ^c , T. Pujol, J. Pujadas, R. Hernando, E. Martínez, A. Cabezuelo, M. Nogué.
Centre Hospitalari i Cardiològic (Manresa, Barcelona)	M. Domènech, C. Lao, J. Badal.
Hospital Universitario (La Laguna, Tenerife)	R. García-Closas ^b , A. Perez ^c , P. Hernández, C. Benito ^c , J. Rodríguez de Vera, A.I. Martín.
Hospital La Candelaria (Santa Cruz, Tenerife)	F. Taño, Galbis, F. Cáceres.
Hospital General de Elche (Elche, Alicante)	A. Carrato ^b , F. García-López, M. Ull, A. Teruel, E. Andrada, A. Bustos, A. Castillejo ^c , E. Jover ^c .
Universidad de Oviedo (Oviedo, Asturias)	A. Tardón ^b , A. Menéndez, A. Menéndez ^c , C. Arias ^c , N. Blanco ^c .
Hospital San Agustín (Aviles, Asturias) Hospital Central Covadonga (Oviedo, Asturias) Hospital Central General (Oviedo, Asturias)	J.L. Guate, J.M. Lanzas, J. Velasco. J.M. Fernández, J.J. Rodríguez, A. Herrero. R. Abascal, C. Manzano, T. Miralles.

Appendix A. (Continued)

Center	Member
Hospital de Cabueñes (Gijón, Asturias)	M. Rivas, M. Arguelles.
Hospital de Jove (Gijón, Asturias)	M. Díaz, J. Sánchez, O. Diaz.
Hospital de Cruz Roja (Gijón, Asturias)	A. Mateos, V. Frade.
Hospital Alvarez-Buylla (Mieres, Asturias)	P. Muntañola, C. Pravia.
Hospital Jario (Coaña, Asturias)	A.M. Huescar, F. Huergo.
Hospital Carmen y Severo Ochoa (Cangas, Asturias)	J. Mosquera.

^a Principal investigator.

^b Area coordinator.

^c Interviewer.

^d Laboratory technician.

^e Study reference pathologist.

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