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The Difference Between Women and Men in Muscle-Invasive Bladder Tumors: A Retrospective Analytical Study of a French Regional Population

Poli C[1], Trétarre B[2,3], Trouche-Sabatier S[2], Foucan AS[2], Abdo N[4], Poinas G[5], Azria D[6], Rébillard X[5], Iborra F[2,4]

[1]Department of Urology, Carémeau University Hospital, Nîmes, France

[2]Hérault cancer registry, Montpellier, France

[3]Center for Epidemiology and Research in Population Health (CERPOP), Toulouse, France

[4]Department of Urology, Lapeyronie University Hospital, Montpellier, France

[5]Department of Urology, Clinique Beau Soleil, Montpellier, France

[6]National Institute of Health and Medical Research U 1194, institute of cancer, University of Montpellier, France

*Corresponding author:

Brigitte Trétarre,
Center for Epidemiology and Research in Population Health (CERPOP), Hérault cancer registry, Montpellier, 208 rue des Apothicaires, 34298 Montpellier Cedex 5, France

Micro Abstract

Our study is a population-based, analytic study on muscle-invasive bladder cancers using data from a cancer registry in a French department. We show that women with bladder cancer are less often treated by cystectomy and have worse prognosis than men, all other variables being equal. A better knowledge of the factors involved could improve prognosis in women.

1. Abstract

1.1. Introduction: According to literature data regarding muscle-invasive bladder cancers (MIBC), women have a more advanced stage at diagnosis and worse prognosis than men. We performed a retrospective, population-based, analytic study on MIBC using data from a cancer registry in a French department, to compare patients, tumors, treatments, and overall and specific survival data in women versus men.

1.2. Patients and Methods: We included all patients living in the department of Hérault (France) and diagnosed with MIBC between 01/01/2017 and 31/12/2019. Univariable and multivariable analyses were performed on all variables of interest. For the survival study, the cut-off point was 31/12/2020.

1.3. Results: We included 124 women and 432 men. There were no significant gender differences in age or stage at diagnosis. Cystectomy was more frequent in man than in women (50.7% vs 35.4%) (p=0.0039). By multivariable analysis, the independent factors for being treated by cystectomy were gender (p=0.004), age (p<0.001) and stage (p<0.001). At the end of follow-up, overall mortality was 79% in women and 63% in men (p<0.001), and the median specific survival was 10.8 months in women and 32.7 months in men (p<0.0001). By multivariable analysis, the independent risk factors for mortality were: female gender (p=0.047), cT4 stage (p=0.005) and no cystectomy (p<0.001).

1.4. Conclusions: Our study shows that women are less often treated with cystectomy and have worse prognosis than men. The reasons for this gender difference are multifactorial, and elucidating them could help improve the prognosis of MIBC in women.

2. Introduction

In France, in 2018, 13,074 urothelial carcinoma of the bladder (UCB) and 5,335 deaths from bladder cancer were recorded. This pathology is the fourth most common cancer in terms of incidence, and seventh in terms of deaths from all cancers, with a male/female ratio of 4:1 [1]. Between 1990 and 2018, the incidence decreased by 7% per year in men, but remained stable in women. Over this same period, mortality decreased in both sexes (-1.4% per year in men and -1.2% per year in women). According to data from the literature, women have a more advanced disease stage at dia-

gnosis and a worse outcome compared to their male counterparts [2]. The reasons for this disparity are multifactorial and involve clinical, genetic, biological, anatomical factors, and variability in exposure or response to carcinogens [3]. Elucidating these factors could help to enhance oncologic treatment in both genders. The objective of this study was to compare the clinical, therapeutic and survival data of women with muscle-invasive bladder cancers (MIBC) compared to men over the same period in the department of Hérault (France).

3. Patients and Methods

3.1. Study Design

This report is a retrospective analytical study of population-based registry data. The data were extracted from the database of the Hérault Registry Specialized in Onco-Urology (RHESOU) [4]. This registry continuously and exhaustively records all the variables of interest in incident urological (both sexes) and male genital tumors. diagnosed since January 1, 2017 in patients who were residing in the Hérault department at the time of diagnosis. Hérault is a department in the south of France with a population of 1.2 million, and a single payer national health insurance system. We compared by gender, sociodemographic data, comorbidities, medical history, circumstances of diagnosis, tumor characteristics, primary treatments and overall and specific survival. We also analyzed by gender the overall survival of patients who had primary cystectomy. Mortality data was obtained from the medical records and the national death registry (https://deces.matchid.io). Cancer stages are presented according to the TNM 8th edition nomenclature [5].

3.2. Inclusion Criteria

We included MIBC of stage ≥cT2 diagnosed between January 1, 2017 and December 31, 2019 in adult patients (≥ 18 years old) residing in the Hérault Department at the time of diagnosis, and patients with a history of non-muscle invasive bladder tumor (NMIBT) that secondarily progressed into MIBC. These cases were confirmed by histological sampling on the bladder tumor or on metastases.

3.3. Exclusion Criteria

Patients not residing in Hérault at the time of diagnosis, those with recurrence of bladder cancer diagnosed before 2017, and tumors without histological diagnosis were excluded.

3.4. Statistical Analyses

Qualitative variables are presented as number and percentage, and quantitative variables as mean and standard deviation (SD) or median with interquartiles. The alpha risk was set at 5%. The Chi2 test was used to compare patient, tumor and treatment characteristics. Fisher's exact test was used for small expected frequencies, and the student test was used to compare quantitative variables.

Logistic regression analysis was performed, with death or cystectomy as the outcome variables, and including sex, age at diagnosis, cTNM stage, treatments, and metastatic or locoregional progression. Overall and specific survival was plotted using the Kaplan-Meier method and curves were compared with the log rank test. The study cut-off date was 12/31/2020. Statistical analyses were performed using R software version 3.6.3.

4. Results

Between January 1, 2017 and December 31, 2019, we identified 556 MIBC (124 women and 432 men).

4.1. Study Population

By univariable analysis, there was no significant difference between men and women in age at diagnosis or history of pelvic radiotherapy. Men more frequently had a history of NMIBT (p < 0.001). Hydronephrosis was more common in women (p < 0.0001). Hematuria revealed the disease more often in men whereas in women, the diagnosis was more frequently fortuitous (p<0.001) (Table 1).

The details of the histological characteristics and stage are given in (Table 2). Urothelial carcinomas represented 93.5% of cases in men and 79.8% in women. Squamous cell carcinomas were more common in women (p<0.001).

4.2. cTNM Stage at Diagnosis

At diagnosis, there was no difference between men and women in cTNM stage (p=0.6590). The metastatic stages (stage IV) concerned 21% of women and 18.3% of men (Table 2).

4.3. Primary Treatment

The treatment characteristics are detailed in (Table 2). The primary treatment varied significantly according to gender (p<0.0001). Men were more often treated with cystectomy than women (50.7% vs 35.4%, p=0.0039) and also with neoadjuvant chemotherapy (19.2% vs 12.9%). More women than men had no primary curative treatment (chemotherapy, palliative treatment or no treatment) (56.5% vs 38.6%).

The time between diagnosis of MIBC and cystectomy was similar in both sexes (p=0.1540), and the surgical approaches were also similar (p=0.2742). Robotic assistance was used in 14 men (6.4%) but was not used in any women in this study population. There was no difference between sexes in the type of urinary diversion (p=0.2788) and bladder replacement (p =0.1236), pelvic lymph node dissection (p=0.7814), number of lymph nodes removed (p=0.2513) and surgical margins (p=0.1739). There was no difference between women and men in pT (p=0.0739) and number of metastasized node lymph (p=0.0944) (Table 3). By multivariable analysis, the independent factors for no treatment by cystectomy were female gender (p=0.004), age ≥ 75 years (p≤0.004) and stage IV (p<0.001) (Table 4).

Table 1: Univariable analysis of population characteristics by sex. Histological analysis of tumors

Age at diagnosis, Mean (SD)	Women (N = 124) N (%)	Men (N = 432) N (%)	p
	75.4 (±11.9)	75.3 (±10.6)	0.9134*
History of Pelvic radiotherapy			
No	119 (96.0)	405 (93.7)	0.4740**
Yes	5 (4.0)	27 (6.3)	
History of NMIBT1			
No	113 (91.1)	319 (74.0)	<0.001**
Yes	11 (8.9)	112 (26.0)	
Hydronephrosis			
No	60 (53.6)	307 (76.9)	<0.0001**
Unilateral	36 (32.1)	79 (19.8)	
Bilateral	16 (14.3)	13 (3.3)	
Mode of Detection			
Hematuria	70 (60.9)	288 (68.4)	<0.001**
Fortuitous	38 (33.0)	77 (18.3)	
Other	7 (6.1)	56 (13.3)	

* Student test, ** Chi2; (N) Number of patients, (%) Percentage of patients, (SD) Standard Deviation 1 NMIBT: non muscle invasive bladder tumor

Table 2: Univariable analysis of tumor characteristics and primary treatment by sex

	Women (N = 124) N (%)	Men (N = 432) N (%)	p
Histological type			
Urothelial carcinoma	99 (79.8)	404 (93.5)	<0.001**
Squamous cell carcinoma	16 (12.9)	13 (3.0)	
Neuroendocrine carcinoma	3 (2.4)	11 (2.5)	
Other	6 (4.9)	4 (0.9)	
cTNM*			
Stage II	77(62.1)	288 (66.7)	0.6590**
Stage III	17 (13.7)	47 (10.9)	
Stage IV	26 (21.0)	79 (18.3)	
Unknown stage	4 (3.2)	18 (4.2)	
Primary treatment			
Cystectomy alone	22 (17.7)	117 (27.1)	<0.0001***
Cystectomy+CT neoadjuvant chemotherapy	16 (12.9)	83 (19.2)	
Cystectomy + CT adjuvant chemotherapy	6 (4.8)	19 (4.4)	
Radiothérapy (+/- chemotherapy)	10 (8.1)	46 (10.6)	
Chemotherapy alone	12(9.7)	52 (12.0)	
palliative treatment, no treatment	58 (46.8)	115 (26.6)	

* cTNM : Stage II : cT2N0M0 ; Stage III : cT3N0M0- T2-3N+M0 ; Stage IV : M+; ** Fisher, *** Chi2 test
(N) Number of patients, (%) Percentage of patients , CT: chemotherapy

Table 3: Univariable analysis of surgical characteristics by sex

Time from diagnosis to cystectomy (months), mean(±SD)	Women (N= 44) N (%)	Men (N= 219) N (%)	p
	3.06 (±1.95)	3.56 (±2.59)	0.1540*
Surgical approach			
Laparotomy	36 (90.0)	184 (84.8)	0.2742**
Laparoscopy	4 (10.0)	19 (8.8)	
Robot-assisted	0 (0.0)	14 (6.4)	
Urinary diversion			
External incontinent or continent	34 (80.9)	156 (74.3)	0.2788**
Others	1 (2.4)	2 (0.9)	
Bladder replacement	7 (16.7)	52 (24.8)	0.1236***
Lymph node dissection			
Yes	39 (88.6)	198 (90.4)	0.7814***
No	5 (11.4)	21 (9.6)	
Number of lymph nodes removed			
<5	9 (23.7)	39 (20.1)	0.2513***
5≤NG<10	12 (31.6)	71 (36.6)	
10≤NG<20	11 (28.9)	70 (36.1)	
NG≥20	6 (15.8)	14 (7.2)	
Number of metastasized lymph nodes			
0	27 (71.1)	140 (72.2)	0.0944**
LN<5	7 (18.4)	49 (25.2)	
5≤LN<10	3 (7.9)	4 (2.1)	
LN≥10	1 (2.6)	1 (0.5)	
Surgical margins			
R0	39 (88.6)	201 (91.8)	0.1739**
R1	3 (6.8)	15 (6.8)	
R2	0 (0.0)	2 (0.9)	
Rx	2 (4.6)	1 (0.5)	
pT			
pT0	3 (6.8)	32 (14.8)	0.0739**
pTis	1 (2.3)	6 (2.8)	
pTa	0 (0.0)	1 (0.5)	
pT1	1 (2.3)	2 (0.9)	
pT2	11 (25.0)	65 (30.1)	
pT3	16 (36.4)	88 (40.7)	
pT4	12 (27.2)	22 (10.2)	

* Student test, ** Fischer, *** Chi2, (N) Number of patients, (%) Percentage of patients, (SD) Standard Deviation, (LN) Lymph Nodes

Table 4: Multivariable analysis of the factors associated with cystectomy by logistic regression (N=534).

	N	Cystectomy	OR	95% CI	P
Sex					
Men	414	309	1		
Women	120	66	0.48	[0.29-0.78]	0.004
Age group (years)					
[30 ; 75[	265	233	1		
[75 ; 80[	82	62	0.44	[0.25-0.76]	0.004

[80 ; 85[	80	51	0.25	[0.14-0.44]	<0.001
≥ 85	107	29	0.06	[0.03-0.11]	<0.001
cTNM*					
Stage II	365	263	1		
Stage III	64	52	1.27	[0.68-2.43]	0.457
Stage IV	105	60	0.09	[0.05-0.17]	<0.001

*cTNM : Stage II : cT2N0M0 ; Stage III : cT3N0M0- cT2-3N+M0 ; Stage IV : M+ (OR) Odds Ratio, (95% CI) 95% confidence interval, (p) p-value

4.4. Patient Follow-up

At the end of the follow-up period, overall mortality was 79% in women and 63.2% in men (p<0.001) (Table 5). Cancer-related death was observed in 60.2% of women and 53.8% of men, with a high rate of missing data regarding the cause of death. At the study cut-off date, 17.7% of women and 29.9% of men were alive without recurrence. By multivariable analysis, the independent factors associated with mortality were female gender (p=0.047), cT4 stage (p=0.005), metastatic stage (p<0.001) and absence of cystectomy (p<0.001) (Table 6).

Two hundred and sixty-three patients underwent cystectomy (44 women and 219 men; 47% of the overall population). In patients who underwent cystectomy, there was no difference in metastatic progression between women and men (p=0.8705), with progression at a mean of 7.8 ±6.2 months after surgery in women, versus 10.1 ±10.1 months in men (p=0.2951). There was locoregional recurrence in 11.4% of women and 9.1% of men (p=0.5825). At the end of the follow-up, overall mortality among operated patients was 56.8% in women and 47.5% in men. At the cut-off date, 46.1% of men were alive without recurrence vs 36.4% of women (p=0.1813) (Table 7).

Table 5: Univariable analysis of the follow-up of the overall population according to sex

	Women (N= 124) N (%)	Men (N = 432) N (%)	p
Metastatic progression			
Yes	27 (21.8)	109 (25.2)	0.5022*
No	97 (78.2)	323 (74.8)	
Time diagnosis to metastatic progression (months), mean (SD)	9.55 (±7.08)	12.25 (±8.39)	0.0946**
Status at last news			
Deceased	98 (79.0)	273 (63.2)	<0.001***
Living without recurrence	22 (17.7)	129 (29.9)	
Living with recurrence	0 (0.0)	19 (4.4)	
Unknown	4 (3.2)	11 (2.5)	
Cause of death			
Died of cancer	59 (60.2)	147 (53.8)	0.1889*
Unknown cause	31 (31.6)	84 (30.8)	
Died of other cause	8 (8.2)	42 (15.4)	

* Chi2, **Student test, *** Fisher, (N) Number of patients, (%) Percentage of patients

Table 6: Multivariable analysis of the factors associated with death, by logistic regression analysis.Patients who underwent surgery

	N	Deceased	OR	95% CI	p
Sex					
Women	118	93	1	-	0.047
Men	422	248	0.57	[0.32-0.98]	
Age group (years)					
[30;70[	164	83	1	-	
[70;80[	174	103	1.35	[0.80-2.27]	0.257
≥ 80	202	155	1.35	[0.74-2.47]	0.322
cT:					
cT2	445	267	1	-	

cT3	36	25	1.77	[0.77-4.25]	0.186
cT4	40	36	4.98	[1.77-16.73]	0.005
cTx	19	13	0.98	[0.33-3.14]	0.973
Cystectomy					
No	285	230	1	-	
Yes	255	111	0.22	[0.14-0.35]	<0.001
Metastatic progression					
No	404	240	1	-	
Yes	136	101	3.21	[1.95-5.41]	<0.001
Local recurrence					
No	494	307	1	-	
Yes	46	34	2.08	[0.95-4.85]	0.076

(OR) Odds Ratio, (95% CI) 95% confidence interval, (p) p-value

Table 7: Univariable analysis of the outcome of patients who underwent cystectomy, by sex

	Women (N = 44) N (%)	Men (N = 219) N (%)	p
Metastatic progression			0.8705*
Yes	14 (31.8)	64 (29.2)	
No	30 (68.2)	155 (70.8)	
Time from cystectomy to metastatic progression (months), mean (±SD)	7.8 (±6.2)	10.1 (±10.1)	0.2951**
Local recurrence			0.5825***
Yes	5 (11.4)	20 (9.1)	
No	39 (88.6)	199 (90.9)	
Time from cystectomy to local recurrence (months), mean (±SD)	9.5 (±5.4)	14.1 (±9.9)	0.1800**
Status at last news			0.1813***
Deceased	25 (56.8)	104 (47.5)	
Living without recurrence	16 (36.4)	101 (46.1)	
Living with recurrence	0 (0.0)	8 (3.7)	
Unknown	3 (6.8)	6 (2.7)	

* Chi2, ** Student test, *** Fisher; (N) Number of patients, (%) Percentage of patients, SD Standard Deviation

4.5. Survival Analysis

The median overall survival was 9.4 months in women and 20.5 months in men (p<0.0001). For specific survival, the median was 10.8 months in women and 32.7 months in men (p < 0.0001). There was no difference between the overall survival of operated women and men (p=0.17) (Figure 1). Comparisons of locoregional and metastatic progression-free survival showed no difference between sexes.
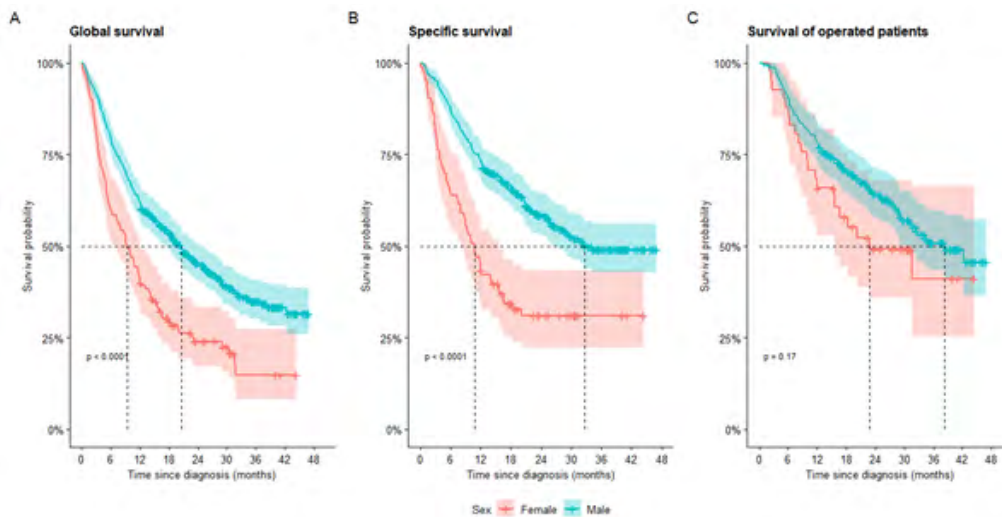

Figure 1: Overall survival (A), specific survival (B) and overall survival of operated patients (C) by sex (P-values from the log rank test)

5. Discussion

In the literature, women with MIBC have a more advanced stage at diagnosis and poorer prognosis than men [3]. Our study shows that there was no significant difference in age or stage between the sexes, but at similar age and stage, women less frequently had cystectomy, and had lower overall and specific survival than men. The factors that could explain this difference between the sexes are multiple and understanding them could help to improve the prognosis in women with bladder cancer. The excess mortality of MIBC in women could be explained by late diagnosis. Cohn et al. showed that the time between initial hematuria and the diagnosis of bladder cancers (BCs) was longer in women than in men (85.4 vs 73.6 days; p < 0.0001) [6]. Henning et al. reported that symptomatic treatment without exploration was prescribed in 19% of men versus 47% of women in the year preceding the diagnosis of MIBC [7]. The frequency of urinary tract infections and colonization in women could lead to misinterpretation of symptoms and thereby delay diagnosis [8].

Regarding the tumor stage, in the study by Thorstenson et al, women had a more advanced tumor stage at diagnosis [9]. Mungan and coworkers analyzed data from the German cancer registry between 1989 and 1994 on 20,541 BCs (16,415 men and 4,126 women). They found that the stage at diagnosis was more advanced in women, and 5-year survival was worse, regardless of the stage [10]. Our study did not show any difference between the sexes in cTNM stage. When examining the histological types, MIBC are pure urothelial carcinomas (UC) in 90% of cases [11]. There are non-urothelial carcinoma and histological variants that have a poorer prognosis [12]. In our series, there were more histological variants in women than in men (15.3% vs. 5.5%). The difference in survival between women and men could be linked to anatomical and embryological particularities. At the age of onset of MIBC, men have a thickened detrusor due to the prevalence of benign prostatic hyperplasia, and deep tumor invasion may be delayed. Bladder perforation during bladder resection is more common in women due to the thin detrusor, which could increase the risk of extra-vesical tumor dissemination [13]. The trigone and the posterior surface of the bladder neck have a common embryological origin with the upper third of the vagina. This embryological particularity could contribute to more rapid extra-vesical invasion in women. Tumor spread to the female urethra is facilitated by the lymphatics of the lateral vaginal walls, draining the lymph from the bladder neck to the internal iliac lymph node areas [14]. Bree et al. showed that patients with stage cT3/4 or with hydronephrosis treated with neoadjuvant chemotherapy had a rate of gynecological invasion similar to women without neoadjuvant chemotherapy [15]. This suggests that neoadjuvant chemotherapy in these at-risk patients would allow the preservation of gynecological organs.

The cornerstone of treatment for localized or locally advanced MIBC (T2-T4a) is surgery, preceded by chemotherapy with platinum salts. The recommended time between diagnosis and cystectomy is 8 to 12 weeks [11]. In our series, the time between diagnosis and surgery was a little longer than 3 months in both sexes. Elsewhere, Patafio et al found no difference in the number of cystectomies performed by gender [16]. In our series, 50.7% of men had a cystectomy versus only 35.4% of women (p=0.0039), despite comparable age and stage at diagnosis. Thorstenson et al reported, in more than 30,000 MIBC, that there was a higher proportion of operated men (38% versus 33% of women, p < 0.0001) [9]. In a series of 2,567 patients (414 women) treated by cystectomy without neoadjuvant chemotherapy, Mitra et al reported no difference between the sexes in specific and overall survival, but for stage pT4 patients, after cystectomy, the prognosis remained unfavorable in women [17]. In our series, we did not find any difference between the sexes in terms of specific or overall survival of the pT4 stage. There are likely more surgical difficulties in women, with reports of longer operative and hospitalization times and higher mortality within 90 postoperative days than in men [18]. Regarding lymph node dissection, some authors have found no difference, while others have reported less extensive lymphadenectomy in women [19]. In a study of 1,142 cystectomies, women had less frequent pelvic lymphadenectomy than men (90 vs. 96%); p<0.001) [18]. In our series, there was no difference between men and women in the number of pelvic dissections or lymph nodes removed. There was also no difference in surgical margins or the type of urinary diversion performed. Women had less neobladders than men, after adjusting for disease stage and patient factors. The disparities observed between the sexes could be linked to a higher incidence of voiding or continence disorders in women [20]. In metastatic patients, Haines has analyzed data from 8 phase II and III metastatic urothelial carcinomas (bladder and upper urinary tract) comparing chemotherapy in women versus men. Of 543 patients included there were 100 (18%) women. There were no gender differences in the number of cycles or toxicity of chemotherapy, but the protocols varied widely between studies. There was no gender difference in survival [21]. In our serie, the number of women with metastatic MIBC at diagnosis is too low to realize an analysis (N=26).

Other risk factors: Smoking is an etiological factor of BT. Freeman et al. showed that the risk of developing a bladder tumor (BT) was 3.7 times higher in male smokers than in female smokers, [22]. Many occupational risk factors for BT have also been investigated (paints, dyes, petroleum products, etc.), but the association between BT and professional status according to gender remains to be determined. The presence of androgen receptors (AR) and estrogen receptors (ER) in the bladder and in BCs in women has previously been studied [23], but their involvement in tumor development is still poorly explained. Abufaraj et al. studied the impact of hormones on the development of bladder tumors in women and showed that postmenopausal women had a higher risk of BT

than others, even after adjusting for smoking status. Young age of onset of menopause (≤ 45 years) has also been shown to be associated with an increased risk of BT [24]. Xu et al noted that nulliparous women had a higher risk of BC compared to women who have had pregnancies [25]. This is the first French population-based study to investigate the difference between women and men in muscle-invasive bladder tumors using high-quality data from one cancer registry, avoiding the introduction of selection bias. Other strengths include the reviewing of each individual case health record to confirm medical history, circumstances of diagnosis, tumor characteristics at diagnosis and treatment. This study has some limitations. Although the number of women is lower than in other series, gender differences could be described.

6. Conclusion

We evaluated the characteristics, management and outcomes of MIBC in women compared to men using data from a French departmental cancer registry. For a similar stage and age, women were less frequently treated with cystectomy and had poorer survival than men. Elucidating the reasons for the differences in treatment and survival between women and men could help to improve management and outcomes in both sexes.

7. Acknowledgment

We thank all those involved in onco-urology in Hérault who made this work possible.

8. Clinical Practice Points

Data in the literature show that the clinical stage and prognosis of muscle-infiltrating bladder tumors (MIBCTs) are worse in women than in men.

We performed a study of our specialized Onco-Urology database (RHESOU) without selection bias to analyze the difference between women and men in MIBCTs .

For a similar stage and age, women were less frequently treated with cystectomy and had poorer survival than men. Elucidating the reasons for the differences in treatment and survival between women and men could help to improve management and outcomes in both sexes.

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