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Gender and cystectomy for bladder cancer: A high-volume tertiary urologic care center experience

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A R T I C L E I N F O

Keywords:
Bladder cancer
Gender
Outcome
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Surgical offer

A B S T R A C T

Background: Differences have often been reported in the outcomes of bladder cancer (BC) patients according to gender.
Objective: This study aims to provide data on patients undergoing radical cystectomy (RC) in a high-volume tertiary urologic center and to assess whether gender discrepancies do exist in terms of surgical options and clinical outcomes.
Materials and methods: Consecutive BC patients treated between 2016 and 2020 at a single center (Careggi University Hospital, Florence, Italy) were included in the study. The impact of gender on disease stage at diagnosis, overall survival (OS), and type of surgery was analyzed.
Results: The study series comprised 447 patients (85 females and 362 males). At a median follow-up of 28.3 months (IQR: 33.5), OS was 52.6% and cancer-specific survival was 67.6%. Significant differences in OS emerged for age, acute myocardial infarction (AMI), Charlson Comorbidity Index (CCI), pT, and pN. OS rates were higher in patients undergoing robot-assisted surgery and in those receiving open orthotopic neobladder (ONB) ($p = 0.0001$). No statistically significant differences were found between male and female patients regarding surgical offer in any age group, surgical time, early postoperative complications, pathologic stage, and OS.
Conclusions: After adjustment for pathologic tumor stage and treatment modalities, female and male patients showed similar oncologic outcomes. Further studies should be undertaken to evaluate functional results in women subjected to RC.

1. Introduction

Bladder cancer (BC) is the most common malignancy of the urinary tract [1,2], with over 440,000 new cases diagnosed in men and 130,000 in women worldwide [3–5]. According to the latest European Association of Urology (EAU) guidelines, radical cystectomy (RC) with lymph node dissection is the standard of care for localized muscle-invasive bladder cancer (MIBC) and non-responsive non-muscle-invasive bladder cancer (NMIBC) [6].

Although male patients have a fourfold higher risk of developing urothelial bladder cancer (UBC), available data indicate an earlier diagnosis in both MIBC and NMBIC settings [7,8] as well as a lower cancer-specific mortality in men than women [9,10]. Several studies have also reported a reduced risk of recurrence and progression of NMIBC in males [11–14].

The reasons for this gender disparity in both diagnosis and prognosis remain mostly unknown. Various causes have been hypothesized, including exposure to environmental carcinogens, smoking, delayed diagnosis as well as genetic, hormonal, and anatomical factors [9,10, 15–18]. Investigations into the lower survival rates of UBC female patients have shown that, at diagnosis, women present with more advanced disease, larger lesions and histologic subtypes of urothelial

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carcinoma [19,20].

However, gender as an independent predictor of prognosis in UBC is still a matter of debate. Evidence of its role in cancer presentation and mortality is limited and international guidelines lacking, unlike for other tumor types such as head and neck, colorectal and lung cancer. In addition, clinical trials are more often targeted towards men, with findings only subsequently extended to women, resulting in gender imbalance.

The aim of this study is to provide an overview of patients undergoing RC in a high-volume tertiary urologic center, focusing on clinicopathologic presentation, surgical offer and midterm oncologic outcome, and to evaluate whether gender-related factors can affect tumor aggressiveness as well as response to therapies.

2. Materials and Methods

2.1. Setting and participants

After Institutional Ethical Committee and review board approval (*BladderBLOGrif CEAVC 18094),* data from BC patients receiving RC between January 2016 and April 2020 at our center were retrospectively collected. Inclusion criteria for RC were T2–T4a N0–Nx M0 disease or recurrent high-risk non-muscle-invasive tumors, as well as extensive papillary disease uncontrolled by transurethral resection of the bladder (TURB) and intravesical therapy alone. Exclusion criteria were presence of non-UBC histology in >80% of the primary tumor and RC performed for non-oncologic reasons.

Preoperative data comprised sex, age, Body Mass Index (BMI), smoking habits, previous abdominal surgery, presence of CIS at last TURB and type of UBC (if recurrent/progressive or de novo). Comorbidities diagnosed before surgery (e.g. cardiovascular diseases, diabetes, chronic kidney insufficiency, and chronic obstructive pulmonary disease) were classified according to the American Society of Anesthesiologists (ASA) score. Following EAU guidelines, neoadjuvant chemotherapy was offered to MIBC (T2-4a, cN0M0) patients, who were eligible for cisplatin-based combination chemotherapy.

2.2. Surgical techniques

All patients underwent RC with lymph node dissection according to the latest EAU guidelines [6]. Open orthotopic neobladder (ONB) was offered to patients under 80 years of age with no locally advanced disease (including absence of hydronephrosis) or bladder neck involvement, with normal renal and bowel function, capability to manage urinary diversion (UD), and no mental disorders. Patients who did not meet these criteria were given non-orthotopic UD, i.e. cutaneous ureterostomy (CU) or ileo-cutaneous ureterostomy.

Inclusion criteria for robot-assisted radical cystectomy (RARC) and urinary reconstruction were: 1) good patient performance status (ASA ≤2); 2) organ-confined disease (MIBC with no progression at re-staging CT scan after neoadjuvant chemotherapy); 3) no pelvic lymphadenopathies and/or distant metastases (cN0M0 stage), and no significant preoperative score (grade 0–2).

Surgical techniques for open reconstruction followed the principles of Vescica Ileale Padovana (VIP) neobladder, while robotic surgical approach consisted of both VIP and Florence Robotic Intracorporeal Neobladder (FloRIN) according to the surgeon's preference [21–23].

2.3. Follow-up

According to the EAU Guidelines, follow-up was scheduled every four months during the first year, six months in the second year and annually thereafter. Pathologic staging was defined as organ-confined non-muscle-invasive (T0/Ta/TIS/T1, N0), organ-confined muscle-invasive (T2, N0), extravesical (T3/T4, N0), and node-positive (any T, N1-3) disease. Intra- and postoperative outcomes were also recorded.

2.4. Statistical analysis

Descriptive statistics were obtained reporting mean and standard deviation (SD), median and interquartile range (IQR) values for continuous variables, as well as frequencies and proportions for categorical variables, as appropriate. Association between gender and selected individual characteristics was evaluated by appropriate test statistics (chi-square or Mann-Whitney test). Survival analysis was carried out using the Kaplan-Meier method. Overall survival (OS) was defined as the time from surgery to time of death or last follow-up (February 2022). We also assessed bladder cancer specific survival referring to the medical certificate of cause of death and performed a survival analysis by using a formal competing risk approach. Surviving patients were censored at the last follow-up. Differences between groups of patients were calculated with the log-rank test. Univariate Cox proportional regression analysis was done to obtain hazard ratios (HR) and corresponding 95% confidence interval (CI) for death. A multivariate Cox proportional regression model, including parameters significant at univariate analysis, was employed to identify independent factors of death. The cut-off to define the input of significant parameters into Cox regression model is $p < 0.05$. All two-sided p-values <0.05 were considered significant. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS"), version 22 (SPSS Inc., IBM Corp., Armonk, NY, USA).

3. Results

3.1. Study population

Of the 447 patients subjected to RC, 85 (19%) were females and 362 (81%) males. Overall, 272 (60.9%) patients were treated with open Bricker/CU, of whom 48 (56.5%) were females and 224 (61.9%) males. ONB was performed on 175 (37.6%) patients (37 females and 138 males), 40 (8.9%) receiving open VIP reconstruction (15 females and 25 males) and 135 (30.2%, 22 females and 113 males) robotic intracorporeal neobladder (51 FloRIN and 84 VIP cases). Surgical option, type of UD and technical approach are shown in Fig. 1.

Median age was 72 years (IQR: 14) and median BMI 25.42 kg/m^2 (IQR: 4.84). Significant gender differences emerged for BMI ($p = 0.0001$) and smoking habit ($p = 0.001$) with 25.4% of females and 18.1% of males being current smokers. No gender differences in workplace exposure, cardiovascular diseases, diabetes, chronic obstructive pulmonary disease (COPD), carcinoma in situ (CIS), ASA score, type of UBC (if progressive/recurrent or de novo) and neoadjuvant chemotherapy offered were found. Charlson Comorbidity Index (CCI) was >2 in 37% of patients (28.2% of females and 39.1% of males). Preoperative patient characteristics are detailed in Table 1.

3.2. Intra- and postoperative patient characteristics

Median overall operating time was 244 min (IQR: 189.3), while median operating time by type of surgery was 360 min (IQR: 179) for ONB and 187.5 min (IQR: 95) for Bricker/CU. No significant differences between genders emerged for type of surgery, operating time (Table 2) or postoperative patient characteristics (Table 3).

Due to adhesive intestinal obstruction, conversion from robotic to open surgery was required in 5 cases. Intraoperative complications were recorded in 14 patients, with no significant difference between males (9, 2.4%) and females (5, 5.8%) ($p = 0.593$). These involved blood transfusion (3 cases), bowel perforation (6 cases), bilateral ureter ligation (2 cases), obturator nerve injury (1 case), external iliac artery injury (1 case) and asystole (1 case) (Table 4).

We subdivided surgical options (neobladder vs. partial cystectomy vs. Bricker/CU) into four age groups (<60, 61–70, 71–80, and >80 years) to explore whether gender could have influenced the type of surgery proposed; no difference was found in any group (Supplementary

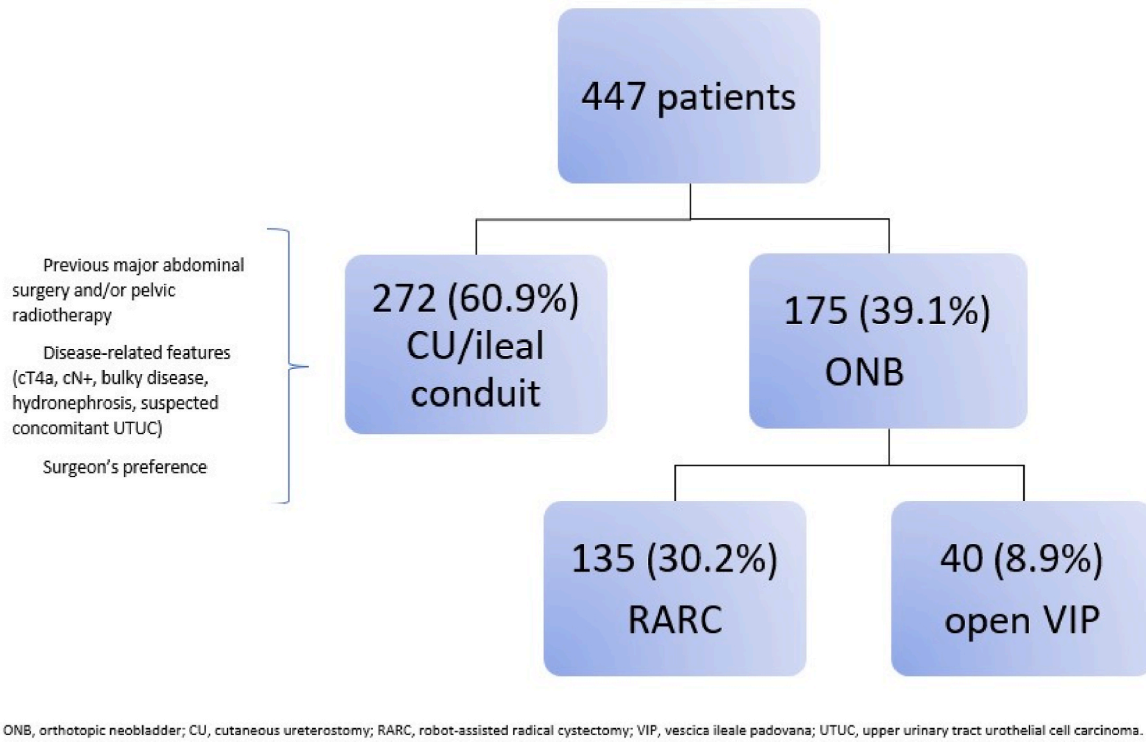

Fig. 1. Distribution of surgical options and types of urinary diversion.

Table 1). As regards the type of UD, incontinent UD was performed in 60.9% of cases and primarily offered to older patients (97.7% aged >80 years and 76.2% in the range of 71–80 years) with significant co-morbidities. Continent UD was performed in 37.6% of cases and was predominant among younger patients (80.6% aged <60 years and 63.8% in the range of 61–70 years) with good performance status (ASA ≤2) (Supplementary Table 1).

3.3. Postoperative complications

Overall, 27 (5.8%) patients (21 males and 6 females) experienced major early postoperative complications (≤90 days), including hydronephrosis and ureteral stenosis requiring nephrostomy placement (3 cases), symptomatic pelvic lymphocele (3 cases), ileo-neobladder fistula (5 cases), bowel occlusion necessitating open surgical revision (3 cases), bowel perforation (3 cases), acute myocardial infarction (AMI, 1 case), electrical cardioversion (2 cases), pace-maker implantation (1 case) and sepsis (5 cases). Death owing to septic shock occurred in 1 case. There was no significant gender difference in early postoperative complications ($p = 0.62$, Table 4).

Major late postoperative complications (>90 days) were recorded in 35 patients (29 males and 6 females). These comprised ureteral stenosis calling for nephrostomy placement (12 cases), sepsis (9 cases), ureteral reimplantation due to stenosis of uretero-ileal anastomosis (4 cases), bowel occlusion (4 cases), post-surgical abdominal hernia (2 cases), symptomatic pelvic lymphocele requiring drainage (1 case), ileo-neobladder fistula (2 cases) and severe incontinence requiring Urethral bulking injection (1 case). No significant difference in late postoperative complications was seen between males and females ($p = 1.0$, Table 4).

3.4. Histologic findings

Pathologic features are shown in Table 3. A total of 128 (33.9%) patients had lymph node involvement (pN), and 30 (6.7%) patients presented positive surgical margins. No significant gender-related differences in tumor stage (pT) and pN were recorded. Similar results were observed for positive surgical margins, vascular invasion, number of positive lymph nodes, and associated upper urinary tract neoplasms.

3.5. Oncologic outcomes

At a median follow-up of 28.3 months (IQR: 33.5), OS was 52.6%, with 50.8% for men and 60.4% for women ($p = 0.21$, Table 5, Fig. 2). Prognosis was poorer for patients over 73 years of age ($p = 0.0001$). Significant differences in OS also emerged for ASA score, AMI, CCI, pT, and pN. Furthermore, OS rates were higher in patients undergoing robot-assisted surgery and in those receiving ONB ($p = 0.0001$, Table 5).

Of the 191 deaths, 117 were due to BC, with a cancer-specific survival (CSS) at 67.6%. No gender discrepancy emerged in CSS (66.5% for men and 71.9% for women, $p = 0.47$). A distribution of CSS in male and female gender over time of follow up is represented in Fig. 3. Regarding OS, univariate Cox proportional regression analysis was used to calculate HR and its 95% CI for parameters statistically significant at survival analysis (i.e., age, AMI, ASA score, CCI, type of surgery, pT, and pN). Although all these parameters were positively associated with mortality risk ($p < 0.05$), only CCI, pT and pN persisted as statistically significant at multivariate Cox regression analysis (Supplementary Table 2). At the survival analysis performed by using a formal competing risk approach, women did not show a significant different death risk compared to men ($p = 0.49$) (Fig. 4).

4. Discussion

Current literature reports conflicting results concerning gender specific outcomes in patients affected by bladder cancer. Indeed, bladder carcinoma is three to four times more common in men than in women [18,24–27], but available data indicate an earlier diagnosis in both MIBC and NMBIC settings [7,8] as well as a lower cancer-specific mortality, in men than women [9,10]. Moreover, Eurocare-4 data show that overall and cancer-specific survival rates are significantly higher in women for many tumors [28], however in BC the female gender is

Table 1
Preoperative characteristics of 447 patients.

Variables	Females n (%) 85 (19.0)	Males n (%) 362 (81.0)	Overall n (%) 447 (100.0)	P value*
Age at diagnosis, yrs median (IQR)	71 (16)	73 (13)	72 (14)	0.27
BMI, kg/m^2, median (IQR)	22.91 (5.24)	25.83 (4.37)	25.42 (4.84)	0.0001
BMI groups, kg/m^2, n (%) ^ 18.5–24.9	46 (65.7)	121 (41.9)	167 (46.5)	0.002
25–29.9	18 (25.7)	131 (45.3)	149 (41.5)	
≥30.0	6 (8.6)	37 (12.8)	43 (12.0)	
Tobacco smoking, n (%)^				
Current smoker	18 (25.4)	57 (18.1)	75 (19.4)	0.001
Ex-smoker	28 (39.4)	197 (62.3)	225 (58.4)	
Never-smoker	25 (35.2)	62 (19.6)	87 (22.2)	
Workplace exposure, n (%)	10 (11.8)	37 (10.2)	47 (10.5)	0.40
Cardiovascular diseases, n (%)	10 (11.8)	82 (22.7)	92 (20.6)	0.025
Diabetes mellitus, n (%)	11 (12.9)	56 (15.5	67 (15.0)	0.62
COPD, n (%)	5 (5.9)	37 (10.2)	42 (9.4)	0.30
CKI (>2°), n (%)	3 (3.5)	7 (1.9)	10 (2.2)	0.41
CCI, n (%)^				0.056
≤2	51 (71.8)	184 (60.9)	235 (63.0)	
>2	20 (28.2)	118 (39.1)	138 (37.0)	
ASA score^				0.33
1	10 (11.9)	44 (12.1)	54 (12.1)	
2	49 (58.3)	180 (49.9)	229 (51.5)	
3	25 (29.8)	137 (38.0)	162 (36.4)	
Type of urothelial carcinoma^ recurrent/progressive	28 (39.4)	152 (47.1)	180 (45.7)	0.29
de novo	43 (60.6)	171 (52.9)	214 (54.3)	
Presence of CIS at last TURB no	81 (95.3)	322 (89.0)	403 (90.2)	0.10
yes	4 (4.7)	40 (11.0)	44 (9.8)	
Neoadjuvant chemotherapy^ no	75 (89.3)	329 (92.4)	404 (91.8	0.38
yes	9 (10.7)	27 (7.6)	36 (8.2)	

IQR: interquartile range; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CKI, chronic kidney insufficiency; CCI, Charlson comorbidity index; *P value from Chi-square or Mann-Whitney test, as appropriate; ^some data are missing.

Table 2
Intraoperative patient characteristics.

Variables	Females n (%)	Males n (%)	Overall n (%)	P value*
Robot-assisted surgery, n (%)	22 (25.9)	112 (30.9	134 (30.0)	0.43
Type of surgery, n (%)				0.39
Neobladder	37 (43.5)	138 (36.4)	175 (37.6)	
Bricker/CU	48 (56.5)	224 (61.9)	272 (60.9)	
Surgical time (min) median (IQR)				
Overall	270 (175)	235 (190)	244 (189.3)	0.49
By type of surgery Neobladder	365.0 (192.5)	360.0 (166.3)	360.0 (179.0)	0.50
Bricker/CU	200.0 (139.0)	185.0 (85.0)	187.5 (95.0)	0.56

CU, cutaneous ureterostomy; IQR: interquartile range; *P value from Chi-square or Mann-Whitney test, as appropriate.

Table 3
Postoperative patient characteristics.

Variables	Females n (%)	Males n (%)	Overall n (%)	P value*
Histology, n (%)				0.79
Conventional UC	58 (68.2)	254 (70.2)	312 (69.8)	
UC subtypes	27 (31.8)	108 (29.8)	135 (30.2)	
pT, n (%)				0.81
pTa/T1-2	35 (41.2)	142 (39.2)	177 (39.6)	
pT3-4	50 (58.8)	220 (60.8)	270 (60.4)	
pN, n (%)^				0.56
0	47 (68.1)	203 (65.7)	250 (66.1)	
1	9 (13.0)	40 (12.9)	49 (13.0)	
2	13 (18.9)	57 (18.5)	70 (18.5)	
3	0 (0)	9 (2.9)	9 (2.4)	
CIS, n (%)				0.41
CIS alone	7 (36.8)	32 (25.8)	39 (27.3)	
CIS + invasive UC	12 (63.2)	92 (74.2)	104 (72.7)	
Positive surgical margins, n (%)	8 (9.4	22 (6.1)	30 (6.7)	0.33
Vascular invasion, n (%)	16 (20.3)	103 (30.3)	119 (28.4)	0.10
Number of examined lymph nodes, mean (SD)	13.9 (11.2)	15.4 (12.2)	15.1 (12.0)	0.37
Positive lymph nodes, mean (SD)	1.1 (2.7)	1.5 (4.1)	1.4 (3.9	0.63
Upper urinary tract neoplasm, n (%)	10 (11.9	53 (14.7)	63 (14.2)	0.60

CIS, carcinoma in situ; SD, standard deviation; UC, urothelial carcinoma; *P value from Chi-square or Mann-Whitney test, as appropriate; ^some data are missing.

generally associated with greater risks of recurrence, progression and death [11–14]. The reasons for this gender disparity in both diagnosis and prognosis remain mostly unknown. Gender as an independent predictor of prognosis in UBC is still a matter of debate, evidence of its role in cancer presentation and mortality is limited and international guidelines lacking. The aim of this study is to provide an overview of patients undergoing RC in a high-volume tertiary urologic center, focusing on clinico-pathologic presentation, surgical offer and midterm oncologic outcome, providing key findings on prognosis and post-operative outcomes.

Firstly, since the primarily surgical nature of our case history, the only etiopathogenetic factor we considered is smoking habits. In our case history the majority of patients were smokers, with the percentage of active smokers significantly higher in females than males. However, no significant difference related to smoking habits emerged for OS. Tobacco smoking is widely accepted as the most common risk factor for BC [13,34]. Historically, the gender difference in the incidence of urothelial carcinoma hinged on smoking habits. While smoking rates have generally declined over the last two decades, tobacco use among women has increased and is predicted to double between 2005 and 2025 [35]. Our data support this trend, with the percentage of active smokers that resulted significantly higher in females than males, as probable result of social and life-style changings. To be noted, the fact that no significant difference related to smoking habits emerged for OS is in contrast with what reported in literature. Indeed, some authors claim that smoking status and high cumulative smoking exposure are associated with advanced tumor stage, nodal metastasis, disease recurrence and cancer-specific mortality in patients undergoing RC for MIBC or non-responsive NMIBC [34,36,37].

Secondly, speaking of oncologic outcomes, in our study no

Table 4
Intra- and postoperative complications.

Variables	Females n (%)	Males n (%)	Overall n (%)	P value*
Intraoperative, n (%)	5 (5.8)	9 (2.4)	14 (3.1)	0.59
Intraoperative (n)				
Obturator nerve injury (1)				
External iliac artery injury (1)				
Bowel perforation (6)				
Blood transfusion (3)				
Bilateral ureter ligation (2)				
Asystole (1)				
Major early postoperative, n (%)	6 (7.1)	21 (5.8)	27 (6.0)	0.62
Major early postoperative (n)				
Grade 3a				
Percutaneous drainage of symptomatic pelvic lymphocele (3)				
Nephrostomy for hydronephrosis (3)				
Electrical cardioversion (2)				
Pace-maker implantation (1)				
Grade 3b				
Ileo-neobladder fistula requiring open surgery (5)				
Bowel occlusion requiring open surgery (3)				
Bowel perforation (3)				
Grade 4a: AMI (1)				
Grade 4b: Sepsis (5)				
Grade 5: Death due to septic shock (1)				
Major late postoperative, n (%)	6 (7.0)	29 (8.0)	35 (7.8)	1.0
Major late postoperative (n)				
Grade 3a				
Percutaneous drainage of symptomatic pelvic lymphocele (1)				
Nephrostomy for hydronephrosis (12)				
Grade 3b				
Ileo-neobladder fistula requiring open surgery (2)				
Bowel occlusion requiring open surgery (4)				
Laparocele (2)				
Stenosis of uretero-ileal anastomosis treated with ureteral reimplantation (4)				
Severe incontinence requiring Urethral bulking injection (1)				
Grade 4b: Sepsis (9)				

ONB, orthotopic neobladder; AMI, acute myocardial infarction; *P value from Chi-square test.

Table 5
Kaplan-Meier survival analysis of 447 patients.

Variable	Patients (n)	Deaths (n)	OS° (%)	P value*
Sex				
Male	362	160	50.8	0.21
Female	85	31	60.4	
Age (median)				
≤73	238	81	63.6	0.0001
>73	209	110	38.0	
AMI				
no	393	158	55.1	0.0001
yes	54	33	34.7	
CCI^				
≤4	174	55	65.5	0.0001
>4	199	110	35.5	
Type of surgery				
ONB	175	51	68.0	0.0001
Bricker/CU	272	140	41.6	
pT				
1–2	177	35	76.2	0.0001
3–4	270	156	36.6	
pN^				
0	250	70	67.5	0.0001
1	49	27	40.4	
2	70	43	32.9	
3	9	9	0	
ASA score^	54	18	63.4	0.0001
1	229	84	60.1	
2	162	88	34.5	
3				
Type of urothelial ca.^ recurrent/	180	67	55.9	0.09
progressive	214	95	52.4	
de novo				
CIS at last TURB no	403	177	51.5	0.09
yes	44	14	62.3	
Neoadjuvant chem.^ no	404	174	52.3	0.29
yes	36	12	65.1	
Total	447	191	52.6	

AMI, acute myocardial infarction; ONB, orthotopic neobladder; CCI, Charlson comorbidity index; CU, cutaneous ureterostomy.
° data related to the end of follow-up study; *from log-rank test; ^some data are missing.

significant differences in OS was seen between males and females at a median follow-up of 28.3 months (IQR: 33.5), with similar oncologic outcomes after RC. Moreover, we found no statistically significant differences in tumor stage and grade at diagnosis between the genders. These findings are in contrast to what often reported in literature. Indeed, in BC the female gender is generally associated with greater risks of recurrence, progression and death [12–14]. Furthermore, in a recent systematic review and meta-analysis of patients undergoing cystectomy for BC, Uhlig et al. demonstrated that OS, recurrence-free and cancer-specific survival were significantly worse in females [26]. Similarly, Donsky et al. reported increased disease-specific mortality in women than in men as a common phenomenon worldwide [11].

Thirdly, neither surgical approach (open vs robot-assisted) nor type of UD was gender-related in any age group of our series, and no gender difference in intra- and postoperative complication rates was observed. These findings are in contrast to the trend presented in the literature. Indeed, despite strong indications for ONB [45–47], incontinent UD remains the preferred option for female patients [45,48,49]. ONB has been proposed more recently for women than for men, due to the presumed higher risk of incontinence and urethral neoplastic involvement [50,51]. Although data on differences in surgical procedures between the genders are still limited, incontinent UD noticeably implies worse quality of life (QoL) compared with ONB, mainly on account of the poor physical and emotional perception of body image [50]. We do think that having the surgical expertise to offer similar type of surgery (continent vs incontinent urinary diversion) and surgical approach (open vs robot-assisted) is a key point to bridge the gender gap by offering a surgical treatment that does not differ between males and females per age group.

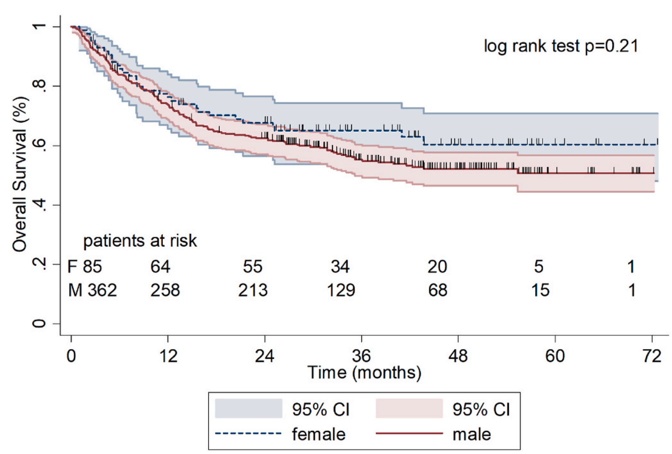

Fig. 2. Overall survival in male and female population at 72 months of follow up.

The relationship between gender and BC is complex, and the mechanisms pointed out as to contributing to this gender gap are multifactorial, including environmental, genomic, hormonal, social and medical factors.

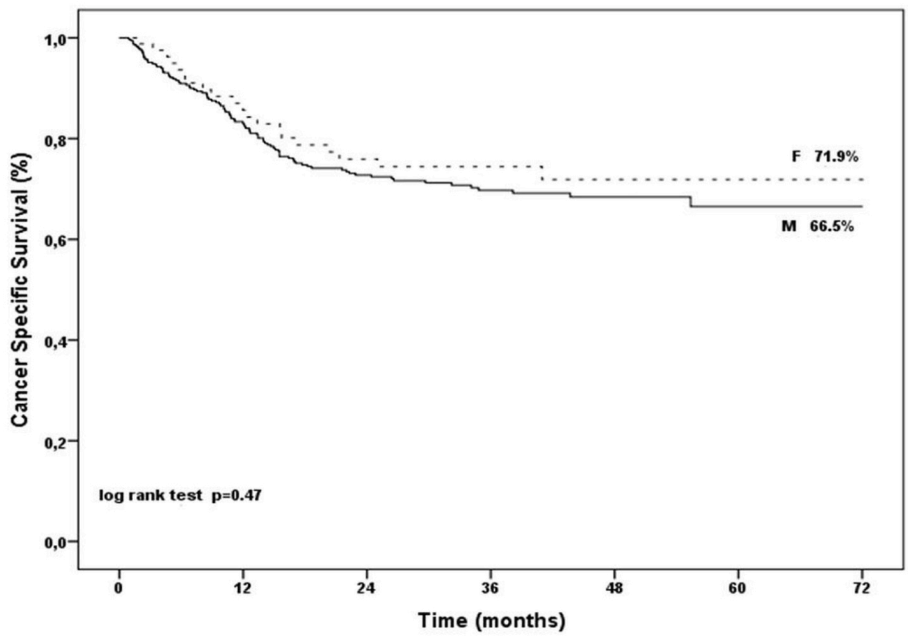

Fig. 3. Cancer specific survival in male and female population at 72 months of follow up.

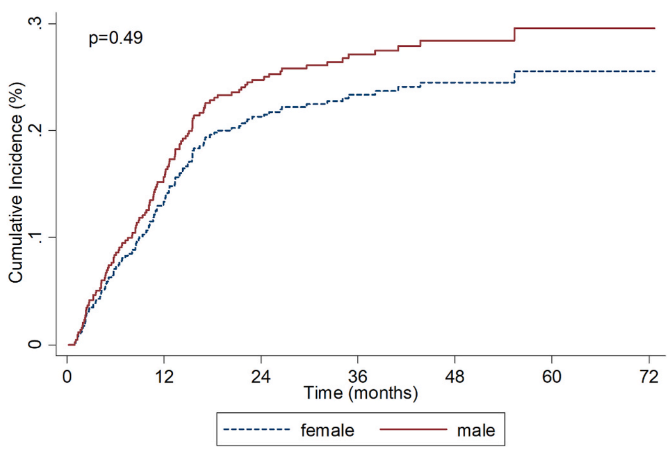

Fig. 4. Competing-risks regression in male and female population at 72 months of follow up.

Recent years have witnessed analysis of mutations and genomic subtypes in NMIBC, elucidating alterations in DNA repair pathways that lead to metabolic vulnerability and enhanced apoptosis with genetic instability [29,30].

As regards sex hormones, both androgen and estrogen receptors are normally expressed in the urothelium. Epidemiological studies have disclosed a lower BC risk for women who are older at menarche, multiparous or receive combined estrogen and progesterone replacement therapy [31–33]. However, the protective role of estrogens in BC is still a matter of debate, and literature data are often contradictory.

Anatomical differences can also contribute to gender disparities. The thicker detrusor muscle in men may influence blood perfusion and the possibility of metastatic spread. Moreover, the middle circular muscle layer at the bladder neck appears to be less robust in females, which may affect lymphatic drainage patterns of this portion of the urinary bladder. It has also been suggested that the prostatic pseudocapsule and the intimate envelopment of the prostatic urethra by glandular prostatic tissue may hinder vascular invasion [38].

Although males have a higher BC incidence than females, numerous studies have established that women generally present with more advanced disease. A possible explanation to that could be the fact that women tend to be treated for other disorders, such as urinary tract infections or postmenopausal bleeding, before being referred to a urologist. Time from initial hematuria claim to hematuria evaluation (e.g. cystoscopy, upper urinary tract imaging, and urine cytology) is therefore longer than for men, and BC diagnosis can be delayed by at least 30 days [15,39–41], potentially causing gender-specific differences in OS [42–44].

So, as just described, literature is rich in works that report how women have worse prognosis than men due to multiple factors, such as delayed examination, ignored or misrecognized symptoms, and involvement of physiological and anatomical factors. However, in our case history we have observed results that differ from what just stated. To be considered, though, is that the nature of our case history is primarily surgical. Hence, our oncological outcomes concern a selected slice of the population affected by MIBC, that is the population fit for complex demolitive surgery. This aspect differentiates our study from population ones, since it does not claim to have epidemiological significance. Furthermore, we did not focus our interest on the study of etiopathogenetic reasons upstream of a diagnosis of MIBC that may determine a gender difference even in terms of OS (such as hormones, genes, occupational exposure). The only element we have analyzed is exposure to smoking, which in our case history did not affect OS. In addition, being a high-volume tertiary urologic care center, patients often come to our attention only after having already been diagnosed with MIBC disease. Therefore, some clinical data regarding the history preceding the onset of MIBC disease, and therefore OS, are missing. For those patients firstly coming to our attention, as to guidelines recommendation, we try to pay particular attention to focus on those specific symptoms that are often misrecognized, especially in female patients, in order to define accurate therapeutic pathway with no-avoidable delay. However, thanks to its high-level surgical expertise, our center tries to bridge the gender gap by offering a surgical treatment that does not differ between males and females per age group both in type of surgery offered (incontinent vs continent urinary diversion) and in surgical approach (open vs robot-assisted).

Despite its strength, this study presents some limitations. Indeed, it lacks evaluation of functional outcomes after ONB. This aspect is crucial to in-progress investigations, since health-related QoL is often lacking in studies on RC and UD, and consequently gender-specific questionnaires would serve to better assess urinary and sexual dysfunction [10,50,52]. Moreover, another limitation to be considered is its retrospective nature and the heterogeneity of surgeons and surgical approach. In addition, as many patients have already undergone previous TURB or received a diagnosis of MIBC at other hospital centers, we could not retrieve many clinical and perioperative data (such as number/size of lesions, any previous BCG/MMC cycles, clinical stage) that could be helpful in better identify preoperative risk categories.

5. Conclusions

We report a large series of UBC cases from a high-volume referral center with experienced open and robot-assisted surgery teams, focusing on preoperative aspects such as surgical offer and diagnostic algorithms. The relationship between gender and BC is complex and treatment of female patients may be a hard task for urologists on account of diagnostic issues, technical challenges, and functional outcomes. Our findings show similar surgical options with comparable oncologic results in both genders. Well-designed multicentric studies, with a majority of women in the analytic cohort and with improved patients' selection including accurate clinical information, are mandatory to confirm these data in order to limit gender-related discrepancies in BC diagnosis and management, guiding surgeons towards evidence-based decisions.

Availability of data and materials

The datasets generated during the current study will be available upon reasonable request.

CRediT authorship contribution statement

A. Mariotti: Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Visualization. **P. Spatafora:** Conceptualization, Writing – original draft, Writing – review & editing. **F. Sessa:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **C. Saieva:** Formal analysis, Writing – review & editing. **I.C. Galli:** Resources. **G. Roviello:** Resources. **L. Doni:** Resources. **C. Zaccaro:** Data curation. **C. Bisegna:** Data curation. **F.L. Conte:** Data curation. **R. Mariottini:** Data curation. **A. Marzocco:** Data curation. **L. Masieri:** Supervision. **G. Vignolini:** Supervision. **A. Minervini:** Project administration. **S. Serni:** Project administration. **M. Carini:** Project administration. **G. Nesi:** Conceptualization, Writing – original draft, Writing – review & editing. **D. Villari:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization.

Declaration of competing interest

All authors declare that there's no financial/personal interest or belief that could affect their objectivity. They also declare that there's no potential competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.107034.

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