



Treatment Pathway and Clinical Outcomes of the Population with Muscle-invasive Bladder Cancer in Italy: A Real-world Analysis with Administrative Databases

Paolo Luraghi · Valentina Perrone · Daniela Castelletti · Serena Losi · Matteo Risi · Stefania Mazzoni · Luca Degli Esposti · Lorenzo Antonuzzo

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ABSTRACT

Introduction: In Italy, real-world data on muscle-invasive bladder cancer (MIBC) are scanty. This analysis exploited administrative databases to describe the clinical characteristics and treatment outcomes of patients with MIBC.

Methods: Adults hospitalized for non-metastatic bladder cancer who underwent cystectomy in 2018 were proxied for MIBC. The following variables were examined: demographic and clinical characteristics, number of transurethral resections of the

bladder tumor (TURBs) and time to cystectomy to discriminate de novo diagnoses from progressions; chemotherapy \pm 6 months before/after cystectomy to distinguish neoadjuvant or adjuvant regimens; creatinine clearance (CrCl) as an indicator of renal function for cisplatin eligibility; disease-free survival (DFS) and overall survival (OS) using Kaplan-Meier method.

Results: Among 394 patients included, 79.4% were men; mean age was 72.5 years and Charlson comorbidity index (CCI) 0.6. Three hundred thirty-nine (86%) had ≥ 1 TURBs pre-cystectomy:

Paolo Luraghi and Valentina Perrone have contributed equally.

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P. Luraghi · D. Castelletti · S. Losi · M. Risi
Department of Medical Oncology, AstraZeneca,
Milan, Italy

V. Perrone (✉) · S. Mazzoni · L. D. Esposti
CliCon S.R.L. Società Benefit, Health, Economics &
Outcomes Research, Via Murri 9, 40137 Bologna,
Italia
e-mail: valentina.perrone@clicon.it

L. Antonuzzo
Department of Experimental and Clinical Medicine,
University of Florence, Florence, Italy

L. Antonuzzo
Clinical Oncology, Azienda Ospedaliera
Universitaria Careggi, Florence, Italy

222 (56%) were de novo diagnoses and 117 (30%) progressions from non-muscle-invasive disease. After stratification by CrCl (<40, 40–60, and ≥60 ml/min), patients with lower renal function showed older age (76.8, 77.0, and 69.1 years), worse comorbidity profile (CCI: 1.5, 0.7, and 0.6), and markedly higher mortality rates (95.0%, 92.9%, and 42.3%). One hundred ninety-five patients (49.5%) underwent surgery-only, 199 (50.5%) received chemotherapy: 47 (12%) as neoadjuvant, 132 (33.5%) as adjuvant, and 20 (5%) as perioperative treatment. Median DFS was 0.9 years with a time to progression of 2.1 years; median OS was 2.1 years with a 5-year OS rate of 43%.

Conclusions: From this real-world analysis, Italian patients with MIBC emerged as a population of elderly subjects (>75 years) burdened by comorbidities. Treatment choice was influenced by other factors rather than cisplatin eligibility since only 11% of patients with CrCl ≥60 ml/min in 2018 and 20% in 2022 were treated before cystectomy, highlighting a scenario of low adherence to guidelines with underutilization of neoadjuvant chemotherapy.

Keywords: Chemotherapy; Cisplatin eligibility; Cystectomy; Disease progression; Muscle-invasive bladder cancer; Overall survival; Transurethral bladder resection

Key Summary Points

Why Carry out this Study?

Muscle-invasive bladder cancer (MIBC) is an aggressive disease with high mortality, and Italian real-world data on its management and outcomes are scarce.

Understanding patients' characteristics, treatment patterns, and outcomes can help to identify gaps between guideline recommendations and clinical practice.

This study aimed to describe the demographic and clinical profile, treatment patterns, and survival outcomes of Italian patients with MIBC undergoing radical cystectomy, using administrative healthcare databases.

What was Learned from the Study?

Among 394 patients with MIBC in 2018, the mean age was 72.5 years, 49% were ≥75 years old, and comorbidities were common. Only 11% of cisplatin-eligible patients (CrCl ≥60 ml/min) received neoadjuvant chemotherapy in 2018, increasing slightly to 20% in 2022, despite guideline recommendations. The 5-year overall survival rate was 43%, with poorer outcomes in patients with impaired renal function.

Treatment choice appeared to be influenced by factors beyond cisplatin eligibility, such as age, comorbidities, and disease status, indicating low adherence to guidelines and underutilization of neoadjuvant chemotherapy.

These findings highlight a persistent gap between evidence-based recommendations and real-world practice in Italy, underscoring the need for strategies to improve perioperative treatment uptake and potentially enhance survival outcomes.

INTRODUCTION

Bladder cancer is the ninth most frequently diagnosed type of cancer globally, with approximately 614,000 new cases and 220,000 deaths reported in 2022 [1]. While non-muscle invasive bladder cancer (NMIBC) represents most bladder neoplasms [2], in up to 30% of the cases, the tumor progresses to muscle invasive bladder cancer (MIBC), characterized by the invasion of cancer cells into the muscular layer of the bladder wall [3]. MIBC has a high risk of progressing towards the metastatic phase within 2 to 3 years after diagnosis (50% of risk), thus constituting an immediate threat to life [4]. At diagnosis, roughly 70% of bladder tumors are superficial (non-muscle-invasive), whereas the remaining 30% already exhibit muscle infiltration, with 10–15% of these cases being metastatic [5]. Among patients undergoing radical cystectomy, about 57% have muscle-invasive disease from the onset, whereas 43% initially present with non-muscle-invasive tumors that later progress despite bladder-preserving treatments [6]. Moreover, one-quarter of cystectomy-treated patients have lymph node metastases at the time of surgery, while nearly one-third with carcinoma infiltrating the muscle layer are believed to have metastases not visible at the start of the primary tumor treatment [6, 7].

Given that lymph node involvement markedly reduces the chance of cure and worsens patients' prognosis, therapeutic interventions in patients with MIBC are targeted at both the cancer itself and preventing the spread to lymph nodes. The treatment options considered for patients with MIBC are radical cystectomy, neoadjuvant chemotherapy, adjuvant chemotherapy, and radical radiotherapy. Radical cystectomy, consisting of the surgical removal of the bladder with the surrounding fatty tissue and possibly nearby lymph nodes, is currently considered the standard treatment for MIBC [8]. However, other bladder-sparing strategies have been developed, including trimodal therapy, which is a maximal transurethral resection of the bladder tumor (TURB) followed by radiochemotherapy [9, 10]. Neoadjuvant chemotherapy, applied to reduce the tumor size before

surgery and possibly eradicate micro-metastatic disease, was shown to significantly improve survival in MIBC [11] and is recommended in national [12] and international guidelines [4, 13] as standard of care for cisplatin-eligible patients [14]. The main eligibility criteria for cisplatin-based chemotherapy are adequate renal function, with a creatinine clearance (CrCl) > 60 ml/min [15–18], and good performance status (ECOG 0–1) [19, 20]. Post-surgery adjuvant chemotherapy is also considered for patients who did not receive neoadjuvant chemotherapy or for patients whose pathology findings after radical cystectomy show invasion into deep muscle layers or beyond, lymph node involvement, lymphovascular invasion, or variant pathology [21, 22].

In Italy, bladder cancer is among the top ten most common malignancies. According to the latest updates of cancer registries, 29,700 new diagnoses were made in 2023 (around 23,700 in men and 6000 in women), with an estimated prevalence of 313,600 alive individuals after a diagnosis of bladder cancer (255,000 men and 58,600 women), and 8300 deaths (6400 men and 1900 women) [23]. MIBC accounts for a substantial proportion of these cases, representing a significant public health issue in Italy, in line with other countries [24]. Understanding its prevalence, management strategies, and treatment approaches within the Italian healthcare system is essential for providing effective care and improving patients' outcomes. In Italy, real-world data on MIBC are currently very limited [24, 25].

The present analysis exploited administrative databases of Italian healthcare entities, aiming to describe the demographic and clinical characteristics of patients with MIBC and investigate treatments and disease progression in terms of disease-free survival (DFS) and overall survival (OS).

METHODS

Study Design and Data Source

An observational retrospective analysis was conducted using data extracted from the administrative databases of a pool of Italian healthcare entities, covering around 6 million health-assisted citizens and with data available from January 2009 to December 2023. For the purposes of the analysis, the following databases were browsed: beneficiaries' database, for patients' demographic data, such as age, sex, and date of death (if applicable); pharmaceutical database, for information on drug prescriptions, including the anatomical therapeutic code (ATC), prescription date, number of packages; hospitalization database, for data related to hospital admissions, like the date of hospitalization, primary and secondary diagnosis identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Diagnosis Related Group (DRG); outpatient specialist service database for information on laboratory test, diagnostic procedures and specialist visits with type and date of provision; exemption database, for information on payment waiver codes that allow patients to be uncharged from medical expenses in the presence of a certain diseases.

The dataset used consists solely of anonymized data. All analysis results were produced and presented as aggregated summaries. Approval was obtained from the following ethics committees of the participating healthcare entities: authorization of the Ethics Committee "BAT (Barletta-Andria-Trani) Comitato etico interprovinciale Area I" (protocol no. 68/CE/20, approval date 3/12/2020); authorization of the Ethics Committee of Bergamo (protocol no. 330, approval date 6/4/2023); authorization of the Ethics Committee "Berica Comitato Etico per le Sperimentazioni Cliniche (CESC) della Provincia di Vicenza" (protocol no. 1627, approval date 28/10/2020); authorization of the Ethics Committee "Foggia Comitato etico interprovinciale Area I" (protocol no. 63/CE/20, approval date 3/12/2020); authorization of the Ethics Committee "Frosinone Comitato Etico Lazio 2" (protocol no. 0179046/2020,

approval date 28/10/2020); authorization of the Ethics Committee "Roma 3 Comitato Etico Lazio 2" (protocol no. 0031200/2021, approval date 10/02/2021); authorization of the Ethics Committee "Roma 6 Comitato Etico Lazio 2" (protocol no. 0216084/2020, approval date 16/12/2020); authorization of the Ethics Committee "Serenissima Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS S. Camillo" (28/07/2020); authorization of the Ethics Committee "Umbria 2 Comitato Etico Regionale Umbria" (protocol no. 19414/20/ON, approval date 16/09/2020); authorization of the Ethics Committee "Vercelli Comitato Etico Interaziendale A.O. SS. Antonio e Biagio e Cesare Arrigo—Alessandria" (protocol no. 0008668, approval date 20/04/2021).

Study Population

From January 2018 to December 2018, adult patients with a hospitalization discharge diagnosis for bladder cancer (ICD-9-CM code: 188) were screened. Among them, those who had undergone a cystectomy (partial cystectomy, procedure code: 57.6; total cystectomy, procedure code: 57.7, used as proxy of MIBC diagnosis) and without metastases (identified as patients without previous discharge diagnosis for metastasis, ICD-9-CM codes: 196–198) were included in the analysis.

The date of the first cystectomy was considered the index date, and the patients were investigated for all the available period before and after the index date, at least 12 months (characterization period and follow-up, respectively).

Patients younger than 18 years, with previous cystectomies, with previous metastasis, or with < 12 months of available data within the databases were excluded.

Study Variables: Patients' Demographic and Clinical Characteristics, Procedures, and Treatments

Age at index date was reported in years as mean and standard deviation (SD) and by age classes (< 60 years, 60–74 years, ≥ 75 years). Sex

distribution was presented as number and percentage of males and females.

The comorbidity profile of the included patients was evaluated by the Charlson Comorbidity Index (CCI), which assigns a score to each concomitant disease, assessed in the 12 months prior to the index date, based on drug treatment and hospitalizations [26]. For this analysis, a modified adaptation of CCI, excluding the cancer score, was applied.

Among the previous conditions, the proportion of patients with diabetes and cardiovascular disease was also assessed. Diabetes was identified by the presence of at least one hospitalization with a discharge diagnosis with ICD-9-CM code

250 or at least one prescription of ATC code A10 (drugs used in diabetes) or an active exemption code 013.

Cardiovascular disease was defined as follows: ischemic heart disease (at least one hospitalization with a discharge diagnosis with ICD-9-CM codes 410, 411, 413, 414); stroke (at least one hospitalization with a discharge diagnosis with ICD-9-CM codes 430–438); heart failure (at least one hospitalization with a discharge diagnosis with ICD-9-CM code 428 or an active exemption code 021); cardiac dysrhythmias (at least one hospitalization with a discharge diagnosis with ICD-9-CM code 427); atherosclerosis and aneurysm (at least one hospitalization

Table 1 Demographic and clinical characteristics of patients with MIBC

	Patients with MIBC
No. of patients	394
Males, <i>N</i> (%)	313 (79.4%)
Females, <i>N</i> (%)	81 (20.6%)
Age, years, mean ± SD	72.5 ± 9.6
< 60 years, <i>N</i> (%)	40 (10.2%)
60–74 years, <i>N</i> (%)	161 (40.9%)
≥ 75 years, <i>N</i> (%)	193 (49.0%)
CCI, mean ± SD	0.6 ± 0.8
0, <i>N</i> (%)	236 (59.9%)
1, <i>N</i> (%)	114 (28.9%)
≥ 2, <i>N</i> (%)	44 (11.2%)
Diabetes, <i>N</i> (%)	81 (20.6%)
Cardiovascular disease, <i>N</i> (%)	72 (18.3%)
Creatinine clearance	
≥ 60 ml/min, <i>N</i> (%)	246 (62.4%)
40–60 ml/min, <i>N</i> (%)	88 (22.3%)
< 40 ml/min, <i>N</i> (%)	60 (15.2%)
Concomitant lymph node dissection, <i>N</i> (%)	235 (59.6%)
Follow-up time in years, mean ± SD	4.8 ± 0.5
Characterization period, years, mean ± SD	4.8 ± 3.0

CCI Charlson comorbidity index, SD standard deviation

Table 2 Number of patients with MIBC with 1, 2, and ≥ 3 TURBs and months from TURB to cystectomy

	No. of patients	Time interval from TURB to cystectomy, months			
		Mean \pm SD	Median (IQR)	Min	Max
1 TURB	210	3.6 \pm 5.7	2.3 (1.4–3.4)	0.3	49.5
2 close* TURBs	12	3.6 \pm 3.2	2.6 (1.3–3.5)	1.2	12.0
2 distant** TURBs	46	13.9 \pm 11.4	11.0 (7.6–15.5)	3.5	68.3
≥ 3 TURBs	71	37.6 \pm 30.2	26.2 (14.7–51.3)	4.5	113.3

* < 2 months between each other; ** > 2 months between each other

IQR interquartile range, SD standard deviation, TURB(s) transurethral bladder resection(s)

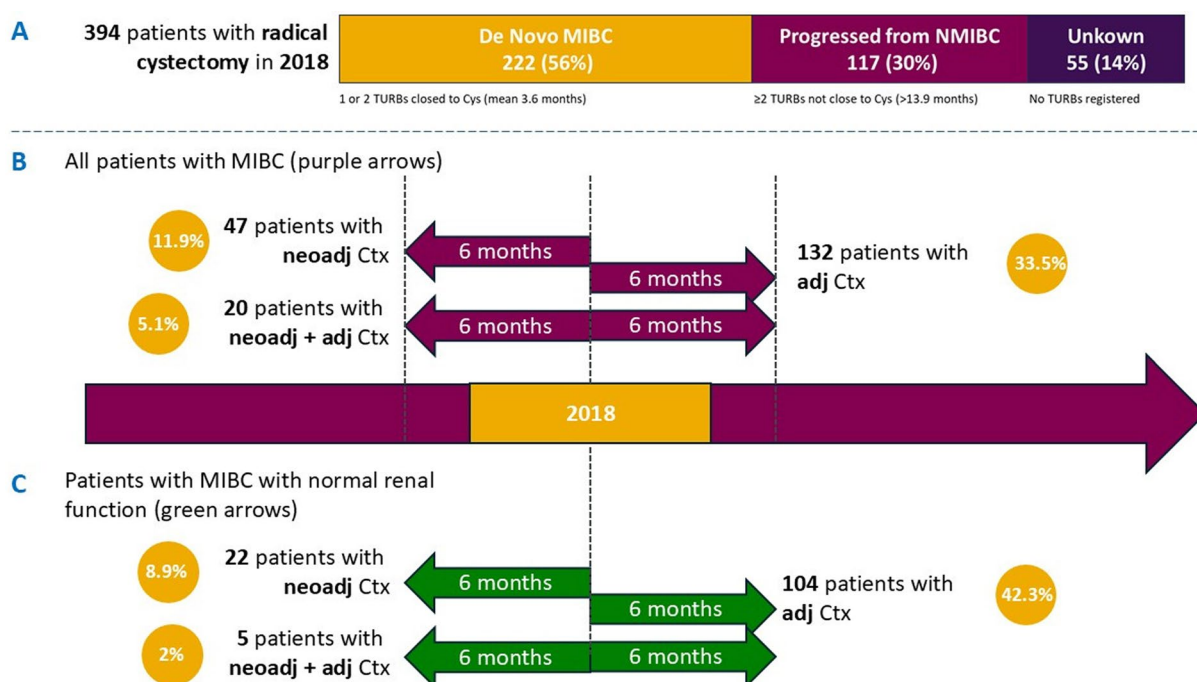


Fig. 1 Overview of patients with MIBC with radical cystectomy in 2018, distributed by: **A** type of diagnosis and chemotherapy in the ± 6 months interval before/after cystectomy **B** in all MIBC population (purple arrows) and

C in patients with normal renal function (green arrows). Ctx chemotherapy, MIBC muscle-invasive bladder cancer, NMIBC non-muscle invasive bladder cancer, TURB(s) transurethral bladder resection(s)

with a discharge diagnosis with ICD-9-CM code 440–442); other peripheral vascular disease (at least one hospitalization with a discharge diagnosis with ICD-9-CM code 443).

CrCl was detected in the 12 months before index date, and patients were stratified into three groups according to their renal function:

CrCl < 40 ml/min, CrCl 40–60 ml/min, and CrCl ≥ 60 ml/min. If CrCl was not available, the value was estimated from serum creatinine using the Cockcroft-Gault equation [15]. Since the patient's weight is not available in the administrative databases, it was estimated using charts on average weight by age range and sex.

Table 3 Pattern of chemotherapy in overall patients with MIBC (A) and in patients with MIBC with normal renal function (B)

A. Total patients with MIBC	394
Chemotherapy treatment, <i>N</i> (%)	199 (50.5%)
In the previous 6 months from cystectomy only, <i>N</i> (%)	47 (11.9%)
In the 6 months after cystectomy only, <i>N</i> (%)	132 (33.5%)
In the 6 months both before and after cystectomy, <i>N</i> (%)	20 (5.1%)
Patients without chemotherapy*, <i>N</i> (%)	195 (49.5%)
B. Patients with creatinine clearance \geq 60 ml/min	246
Chemotherapy treatment, <i>N</i> (%)	131 (53.3%)
In the 6 months before cystectomy only, <i>N</i> (%)	22 (8.9%)
In the 6 months after cystectomy only, <i>N</i> (%)	104 (42.3%)
In both the 6 months before and after cystectomy, <i>N</i> (%)	5 (2.0%)
Patients without chemotherapy*, <i>N</i> (%)	115 (46.7%)

*Including patients without chemotherapy tracked in the database

Lymph node dissection concurrent with cystectomy was identified through the procedure codes 40.3 and 40.5.

Previous TURBs (procedure code: 57.4) were analyzed in terms of the number of procedures and percentage of patients with TURBs during the characterization period. Specifically, the MIBC population stratified into (1) patients without TURB; (2) patients with one TURB, reporting the time interval (months) between TURB and cystectomy; (3) patients with two distant TURBs (>2 months between each other), reporting the time interval (months) between the first TURB and cystectomy; (4) patients with two close TURBs together (\leq 2 months between each other), reporting the time interval

(months) between the last TURB and cystectomy; (5) patients with three or more TURBs reporting the time interval (months) between the first TURB and cystectomy.

Length of hospital stay was presented as average time of hospitalization (in days) for cystectomy and urinary reconstruction/diversion.

Chemotherapy was assessed in terms of number of treatments administered and percentage of patients receiving systemic chemotherapy (ATC codes: L01XA01, L01XA02, L01BC05, L01BA01, L01CA01, L01DB01, L03AX03; procedure codes: 59.8, 96.49, 86.07, 99.25, 99.28, 99.29). Based on therapies, the MIBC population was then stratified as follows: (1) patients with chemotherapy in the previous 6 months from cystectomy only; (2) patients with only chemotherapy in the 6 months after cystectomy; (3) patients with chemotherapy both 6

months before and after from cystectomy; (4) patients without chemotherapy.

Survival Analysis

OS was defined as time (in years) from the date of first cystectomy to death for any cause. For alive patients, OS was censored at the date of database availability.

DFS was defined as time (in years) from the date of first cystectomy to death for any cause, relapse, or progression of disease, identified by the presence of chemotherapy after 6 months from cystectomy. In the absence of a record for death, relapse, or progression, DFS was censored at the date of database availability. Time to progression (TTP) was defined as the time from therapy initiation until first evidence of disease progression. Survival analysis was performed using Kaplan-Meier curves.

Statistical Analysis

All the statistical analyses are descriptive. Continuous variables are given as mean \pm SD, or median with interquartile range, minimum and maximum value, as appropriate. Categorical variables are reported as numbers and percentages. OS, DFS, and TTP were investigated using Kaplan-Meier survival analysis. A p value < 0.05 was considered statistically significant, and all the analyses were performed using STATA SE version 17.0.

RESULTS

Demographic and Clinical Characteristics of Patients with MIBC

From a catchment of 6,336,495 health-assisted residents, 394 patients with MIBC diagnosis in 2018 were identified. This population was characterized by a large predominance of male subjects (79.4%), with a mean age of 72.5 years and nearly half ≥ 75 years. Although the average CCI (excluding cancer) was low (0.6), indicating a mild comorbidity profile, 11.2% of patients fell into the cluster with $CCI \geq 2$. The pattern of

comorbidities revealed that 20.6% of patients had diabetes and 18.3% had cardiovascular disease. Normal renal function (proxied by the detection of a $CrCl \geq 60$ ml/min) was observed in 62.4% of the patients, while 22.3% and 15.2% of patients showed respectively borderline ($CrCl$ 40–60 ml/min) or impaired renal function (< 40 ml/min) (Table 1).

Treatment Patterns

The number and timing of TURBs before cystectomy were analyzed to distinguish de novo from recurrent MIBC. Overall, 86% of patients had at least one TURB before surgery. Based on TURB frequency and interval to cystectomy, 56% were classified as de novo cases, 30% as progressions from NMIBC, and 14% of uncertain origin (Table 2, Fig. 1A).

Among all patients, 50.5% received chemotherapy (12% neoadjuvant, 33% adjuvant, and 5% perioperative). Similar proportions were observed among those with normal renal function (Table 3, Figs. 1B, C).

Survival Analysis of Patients with MIBC

Kaplan-Meier survival analysis showed that 61.4% of patients died during follow-up, with a median OS of 2.1 years and a 5-year OS rate of 43% (Fig. 2A). When stratified by renal function, patients with lower $CrCl$ values were older and had higher comorbidity scores (mean age: 76.9, 77.0, and 69.1 years; mean CCI: 1.5, 0.7, and 0.6 for $CrCl < 40$, 40–60, and ≥ 60 ml/min, respectively). Mortality rates followed the same trend (95.0%, 92.0%, and 42.3%; Fig. 2B).

The median DFS was 0.9 years with 74.6% of patients who died or experienced recurrence/progression of the disease (Fig. 3A). In the analysis of TTP with deaths censored, the median TTP increased to 2.1 years (Fig. 3B).

When clinical outcomes (OS, DFS and TTP) were assessed by treatment patterns, chemotherapy patients had the poorest prognosis, while those without chemotherapy showed the most favorable outcomes, likely reflecting less advanced disease (Figure S1 of the Supplementary materials).

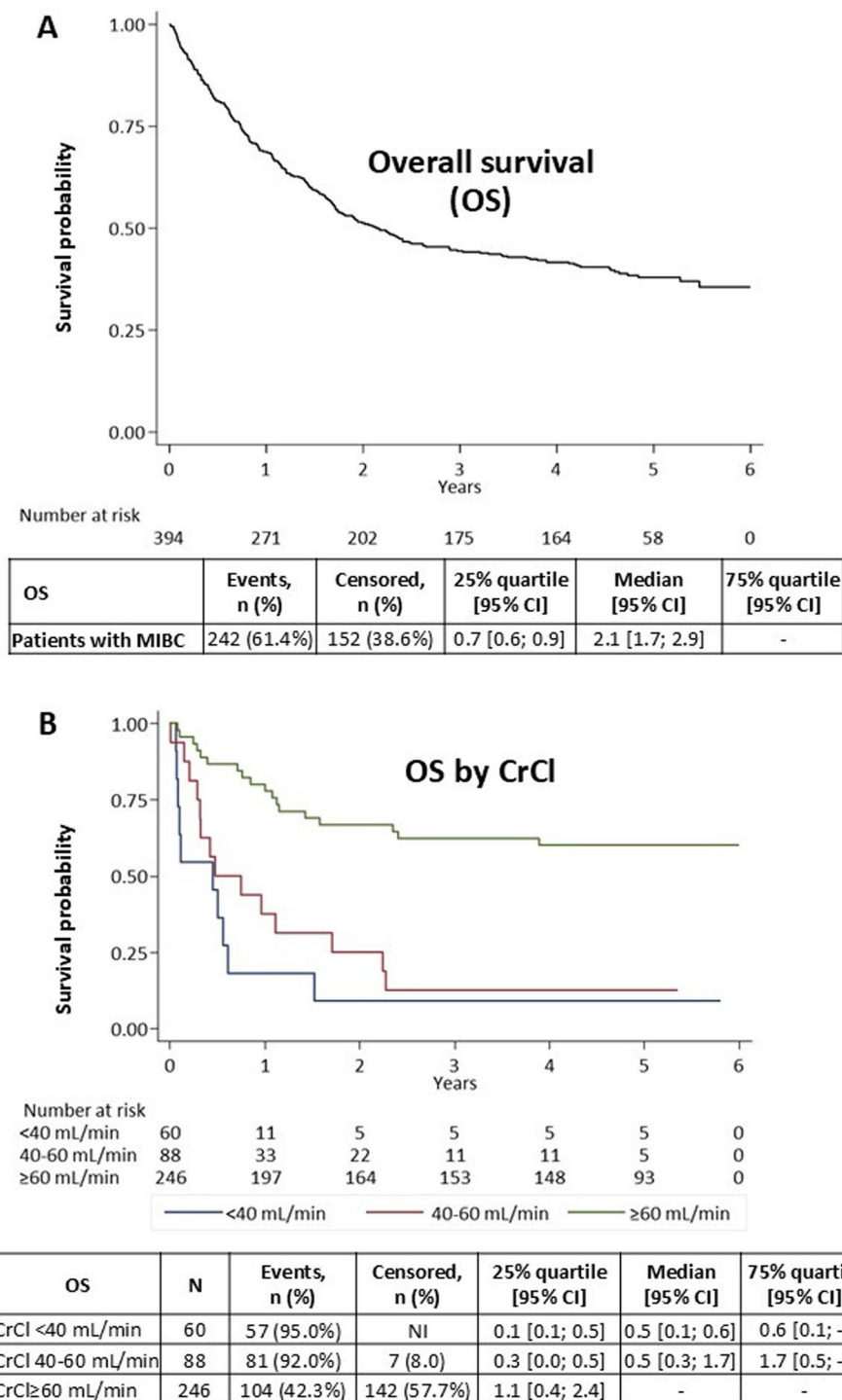


Fig. 2 Overall survival in **A** all patients with MIBC and **B** patients with MIBC stratified according to CrCl values. *CI* confidence interval, *CrCl* creatinine clearance, *MIBC* muscle-invasive bladder cancer, *OS* overall survival

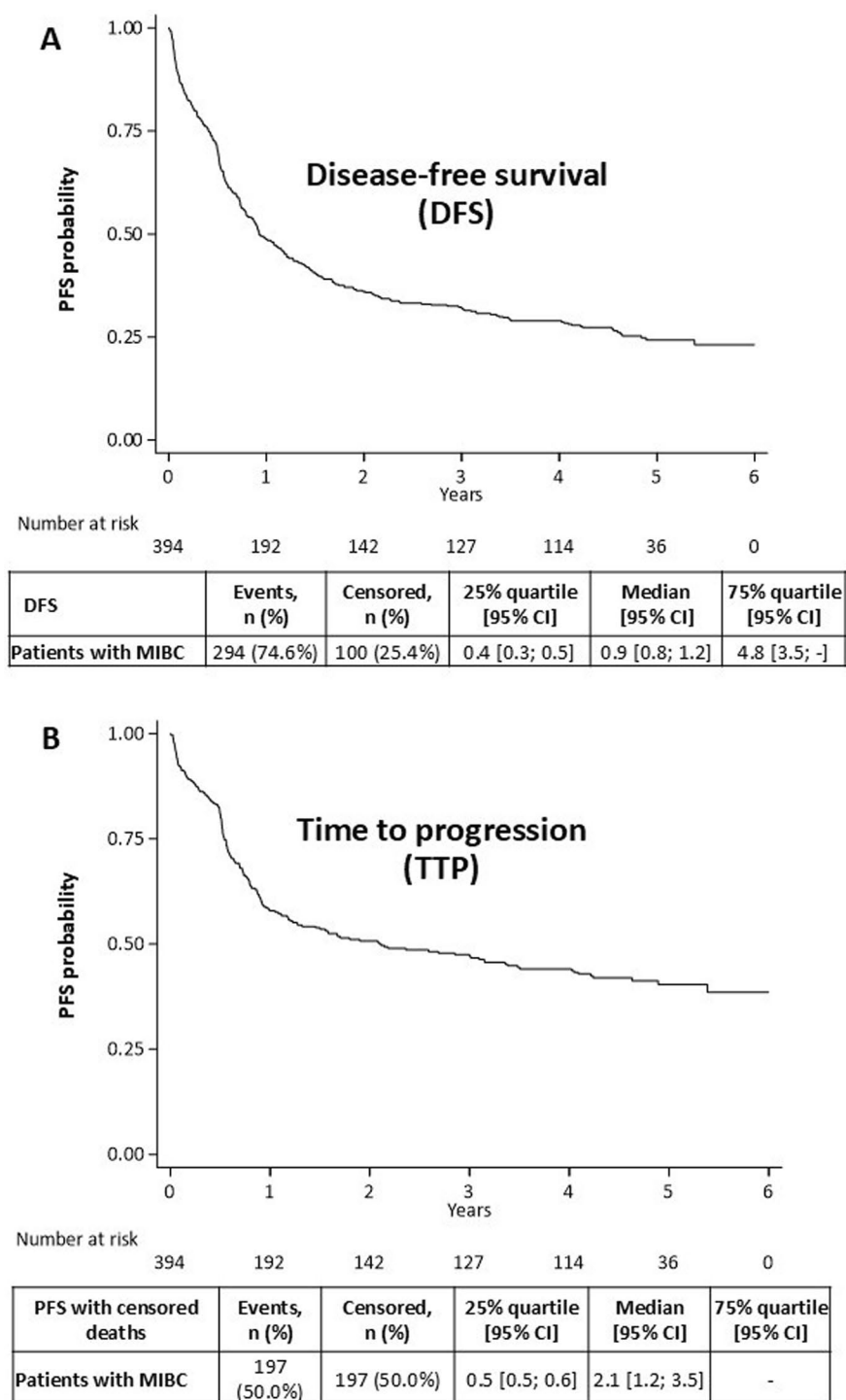


Fig. 3 A Disease-free survival and B time to progression in patients with MIBC. *CI* confidence interval, *CrCl* creatinine clearance, *MIBC* muscle-invasive bladder cancer, *DFS* disease-free survival

Minimal differences were instead observed among patients receiving chemotherapy either before or after cystectomy, making interpretation difficult.

Treatment Patterns in 2022 MIBC Cases

According to administrative data of MIBC patients who underwent radical cystectomies in 2018, eligibility for cisplatin did not emerge as a primary factor in the choice of neoadjuvant treatment, with only 11% of patients with normal renal function being treated pre-cystectomy (Fig. 1B). To verify whether this observation was related to a still inadequate adoption of guidelines in 2018, the analysis of treatment patterns was replicated in 2022 (Fig. 4). Among 313 patients identified, the distribution between de novo and progressed MIBC cases mirrored that of 2018 cases: 51.0% were estimated to be new diagnoses, 36.0% progressions from NMIBC, and 13.0% of unknown origin (Fig. 4A). Treatment patterns between 2022 and 2018 cohorts were also preserved, with only a slight increase of cases receiving CHT before cystectomy. Specifically, in all MIBC population, 12.5% of patients received CHT in the neoadjuvant, 31.3% in the adjuvant, and 9.5% in a perioperative setting (Fig. 4B). In patients with normal renal function, 13.0% received CHT in the neoadjuvant, 43.5% in the adjuvant, and 7.3% in a perioperative setting (Fig. 4C). Collectively, among potentially cisplatin-eligible patients, the use of neoadjuvant chemotherapy showed only a modest rise from 2018 to 2022.

DISCUSSION

The present analysis was undertaken to provide a real-world picture of clinical practice in Italy for patients with MIBC for which very few data are available.

Despite the limitations of administrative data that impose the use of proxies to identify MIBC and to describe their characteristics, the population selected displayed demographic

and comorbidity profiles that are consistent with findings reported by the literature worldwide: several studies have indeed reported male predominance, advanced age and significant comorbidities in these patients [27–33]. Notably, the CrCl analysis corroborated these observations, indicating that patients with mild or severe renal function impairment were on average older and exhibited a worse comorbidity profile (documented by a higher CCI).

To discriminate between de novo MIBC diagnoses and tumors progressed from NMIBC, the number of TURBs and time to cystectomy were used as a proxy: 56.3% of patients were deemed as new MIBC diagnoses; 29.7% of patients were considered progressions from NMIBC; 14.0% had no TURB registered and were considered of unknown origin. Similarly, a single-center German study of 1100 patients with MIBC treated with a cystectomy-only approach reported a distribution of 72% de novo MIBC and 28% progressions from NMIBC. The mean number of TURBs was 1.9 and the distance from cystectomy was 2.4 months for de novo tumors and 48.7 months for recurrent disease, thus confirming the reliability of the proxy used here [34].

The analyses of treatment patterns revealed that almost half of the patients underwent a cystectomy-only approach, consistent with one real-world evidence (RWE) analysis conducted in The Netherlands from medical records [35]. Among the other half of patients with a registered chemotherapy administration, the fraction of those who received it in a neoadjuvant setting was only 12%. Surprisingly, after the stratification of patients by CrCl thresholds, only 11% of patients with normal renal function were treated pre-cystectomy in 2018, suggesting that platinum eligibility as defined by CrCl was not the main driver for choosing a neoadjuvant treatment approach. By analyzing data coming from patients who underwent cystectomy in 2022, only a slight increase up to 20% of neoadjuvant usage was observed in cisplatin-eligible patients, showing an underutilization. The 2024 AIOM guidelines for urothelial cancers reaffirm that cisplatin-based neoadjuvant chemotherapy provides a survival benefit, increasing 5-year overall survival by approximately 5–8%, and is still recommended for cisplatin-eligible patients

with muscle-invasive disease, regardless of the definitive treatment. It is not recommended for patients ineligible for cisplatin because of impaired renal function [12]. The above-mentioned RWE Dutch study reached similar results, with only 9% of patients with MIBC enrolled between 2008 and 2016 receiving a neoadjuvant chemotherapy: despite an increasing trend in the use of cisplatin-based chemotherapy regimens, a significant proportion of patients did not receive guideline-recommended chemotherapy, potentially because of factors such as age, comorbidities, and performance status [20, 35]. Reasonably, a similar explanation may be given for our analysis: treatment choices might have been driven mainly by disease status and patient's individual features rather than by cisplatin eligibility criteria.

The survival analysis of the included population with MIBC showed a mortality rate of 61.4% during follow-up, with a 5-year OS rate of 43% and a median survival time of 2.1 years, suggestive of worse outcomes than those reported in the literature. The National Cancer Institute in the USA reported a 5-year relative survival rate of 71% for localized bladder cancer [36]. Similarly, an analysis conducted on data from the Mallorca Cancer Registry in 2021 described a 5-year cancer-specific survival rate of 76% for bladder cancer patients [37]. However, these studies included both NMIBC and MIBC. Cancer Research UK provides survival statistics for bladder cancer by stage: in stage 2 and stage 3 bladder cancers, which encompass MIBC, the reported 5-year survival rate was 45% and 40%, respectively, in agreement with the present analysis [38]. The older age and associated comorbidities prevalent in our cohort might have influenced the poor survival rate observed. Indeed, by stratifying patients with MIBC according to renal function, we observed a strikingly worse outcome in those with $\text{CrCl} < 60$ ml/min, with 92–95% of deaths observed during follow-up, against only 42.3% of those with normal renal function. The worse overall clinical status of patients with impaired renal function might be partly attributable to their older age and higher comorbidity burden, which together could have markedly worsened their survival outcomes. Although we do not have tumor stage information in our administrative dataset, the influence of an intrinsically more aggressive

tumor cannot be entirely ruled out. Notably, a similar trend was reported in the German cohort of 1100 MIBC patients treated with cystectomy alone, where a significant difference was found between OS and disease-specific survival, suggesting that factors beyond tumor biology, such as comorbidities or competing causes of death, may influence OS outcomes [34].

The high rate of deaths in the first 2 years of follow-up also strongly influenced DFS: indeed, 74.6% of patients died or presented a relapse/progression of disease during follow-up with a median DFS time of 0.9 years, a result significantly shorter than in the reported data [39]. To estimate a disease-specific prediction of recurrence/progression, a TTP analysis was performed by censoring deaths: the proportion of patients with disease relapse/progression during follow-up dropped to 50% and median TTP rose up to 2.1 years, consistent with published reports [39].

The stratification of survival outcomes (OS, DFS, and TTP) according to treatment patterns suggests that the choice of treatment administration might be mainly driven by disease status. Patients with no registered chemotherapy had better outcomes, indicating that these were probably patients with a less aggressive disease (i.e., T2N0 tumors) in which chemotherapy was not added despite guideline recommendations. Although we cannot formally confirm this hypothesis without information from anatomy pathology records, the same result was reported in the mentioned Dutch RWE study, where 89% of patients treated with a cystectomy-only approach had T2N0 tumors [35]. Conversely, patients with chemotherapy administered both before and after cystectomy were those with the worst outcomes, which may be explained by the fact that these were the most aggressive tumors and were subjected to a pragmatic perioperative approach to shrink tumor size before surgery. Besides, patients administered chemotherapy either before or after cystectomy had intermediate survival outcomes, which are difficult to interpret and compare, making it hard to draw firm conclusions. These groups, comprising nearly half of treated patients, are those most likely to benefit from an intensified perioperative strategy aiming at improving DFS and OS outcomes. This is underscored by recent evidence from the NIAGARA trial (ClinicalTrials.gov number NCT03732677;

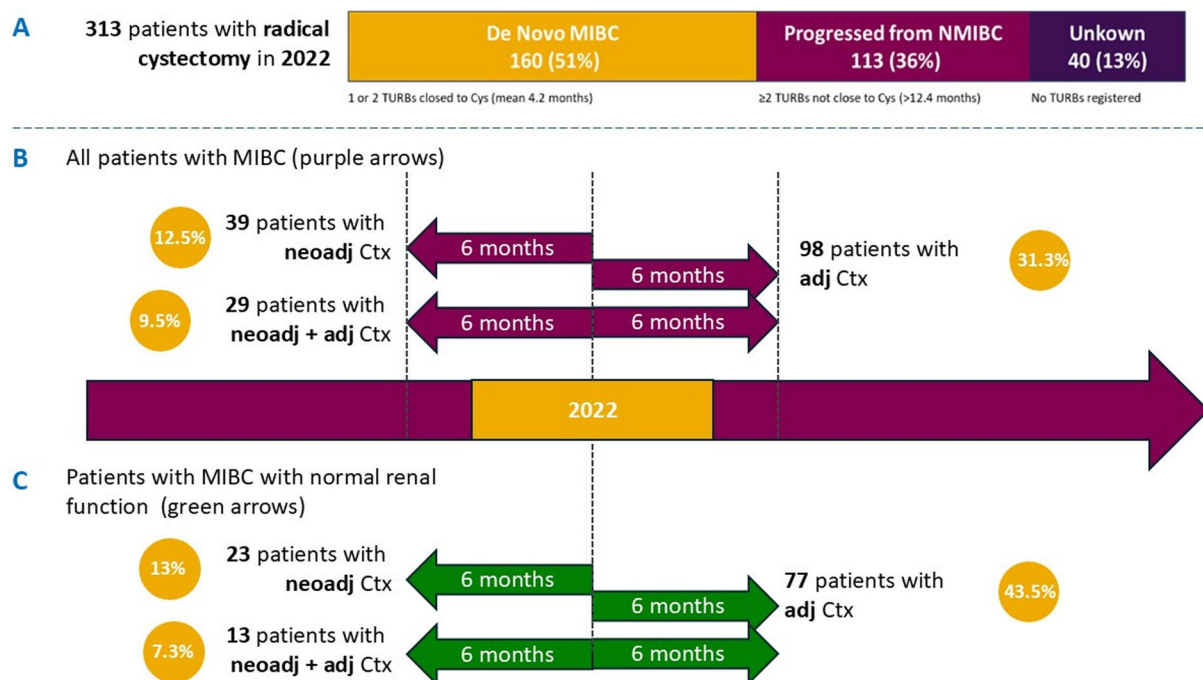


Fig. 4 Overview of patients with MIBC with radical cystectomy in 2022, distributed by: **A** type of diagnosis; **B** chemotherapy in the ± 6 months interval before/after cystectomy in all MIBC population and in patients with nor-

mal renal function. *Ctx* chemotherapy, *MIBC* muscle-invasive bladder cancer, *NIMBC* non-muscle invasive bladder cancer, *TURB(s)* transurethral bladder resection(s)

EudraCT no. 2018-001811-59) [40], where the combination of chemotherapy and the immune checkpoint inhibitor durvalumab demonstrated efficacy and marked the first of several upcoming studies exploring perioperative and alternative approaches [41]. Although cT2 patients inherently have a better prognosis—as also confirmed in the Dutch RWE study [35]—the NIAGARA trial showed meaningful benefits in this subgroup as well [40].

Collectively, our analysis represents a novelty in a scenario where real-world data on the characteristics, treatment patterns, and clinical outcomes of patients with MIBC are particularly scanty in Italy. The use of administrative data to proxy also clinical outcomes is indeed a novelty, and in addition to the formal limitations acknowledged below, the results obtained are consistent with those generated by studies using medical records in other countries. Data obtained by real-world retrospective studies may provide missing evidence about older and ‘unfit’ patients who are commonly

excluded from randomized clinical trials, providing a more realistic scenario. These findings highlight a mismatch between guideline recommendations and what is observed in daily practice. Despite robust evidence supporting cisplatin-based neoadjuvant chemotherapy, its use remains limited even among patients who meet eligibility criteria. This underuse likely reflects several barriers, including advanced age, comorbidities, delayed or absent multidisciplinary evaluation, and uncertainty about renal function assessment in routine care. Improving adherence to perioperative treatment guidelines will require early multidisciplinary discussion, consistent evaluation of cisplatin eligibility (including renal function and performance status), and the use of geriatric assessment tools to guide therapy in older adults. A more structured assessment of patient fitness and timely referral to oncology teams could help ensure that suitable candidates are considered for neoadjuvant therapy.

One of the main limitations of using administrative flows is that this approach might suffer from the incompleteness or limited accuracy of some variables, since only reimbursed medical services and drugs can be extrapolated. Another important limitation of this analysis lies in the identification of patients with MIBC through cystectomy as a diagnostic proxy, since many MIBC patients do not undergo cystectomy (because of clinical reasons, bladder-sparing approaches, or patient choice), resulting in their exclusion from our dataset. Furthermore, according to current guidelines, also some high-risk NMIBC patients may be considered for cystectomy. Therefore, we cannot fully rule out that a subset of the cases identified as progressed MIBC using the interval between TURB and cystectomy may actually have been in a NMIBC phase. However, considering that the analysis was conducted in 2018 and that in a recent Italian multicenter study only 1–2% of all NMIBC (5–10% of high-risk NMIBC) patients had undergone cystectomy [42], the potential impact on our cohort is likely limited. Finally, these results were generated from a sample corresponding to almost 10% of the Italian population, limiting their generalizability.

CONCLUSIONS

This study provides valuable insights into the characteristics, treatment patterns, and outcomes of patients with MIBC undergoing cystectomy in Italy. The analysis confirms that MIBC primarily affects elderly individuals, with a substantial portion > 75 years old, often presenting with comorbidities such as diabetes and cardiovascular disease, which may influence treatment choices and prognosis.

A major finding of the analysis is that, although national and international guidelines support the use of neoadjuvant chemotherapy in cisplatin-eligible patients, our real-world data suggest that treatment choice was influenced also by additional factors. Only 11% of those with CrCl \geq 60 ml/min in 2018 and 20% in 2022 were treated before cystectomy.

These findings describe a scenario of low-adherence to guidelines with underutilization of neoadjuvant chemotherapy and poor real-world outcome with still unmet clinical needs, which may represent a potential barrier to the optimal implementation of NIAGARA and other forthcoming perioperative indications.

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Declarations

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