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RESEARCH

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# Characteristics, management and survival outcomes in patients with muscle-invasive bladder cancer at high risk of recurrence in France: a subgroup analysis from the coblance cohort

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## Abstract

**Purpose** To describe characteristics, management, disease-free survival and overall survival of patients with muscle-invasive bladder cancer (MIBC) at high risk of recurrence (MIBC-HR) undergoing radical cystectomy in France and a subgroup of these patients who did not receive adjuvant chemotherapy after RC and were managed with active surveillance only (MIBC-HR-ASO).

**Methods** Patients aged  $\geq 18$  years with MIBC who had radical cystectomy from October 2012 to June 2018 were identified in the prospective COBLAnCE bladder cancer cohort. Patients with metastatic disease were excluded. Patients were classified as MIBC-HR based on TNM staging. Disease-free and overall survival were estimated using the Kaplan-Meier method with their 95% confidence intervals (95%CI).

**Results** 256 patients with MIBC-HR were enrolled. The median age at diagnosis was 68.5 years and 204 patients were men (79.7%). 201 patients (78.5%) were current or former smokers. For staging, 226 patients were (y)pT3a or higher (88.3%) and 132 were N- (51.6%). Forty-six patients received neoadjuvant chemotherapy (18.0%), and 69 received adjuvant chemotherapy (27.0%). Of the patients receiving adjuvant chemotherapy only, 59 received cisplatin-based therapy (86.8%). 182 patients (71.1%) constituted the ASO subgroup. 175 patients (68.3%) experienced an event up to the end of follow-up. Median follow-up was 5.0 years. Median disease-free survival was 1.30 years [95%CI: 1.01–1.60] in the MIBC-HR cohort and 1.21 years [95%CI: 0.70–1.53] in the MIBC-HR-ASO subgroup. Median overall survival was 2.31 years [95%CI: 1.85–3.10] in the MIBC-HR cohort and 2.11 years [95%CI: 1.61–2.65] in the MIBC-HR-ASO subgroup. At 5 years, DFS was 27.4% [21.7;33.9%] in the MIBC-HR population and 23.7% [17.4;31.4] in the MIBC-HR-ASO population. OS at five years was 33.2% [27.1;40.0] for the MIBC-HR population and 29.6% [22.7;37.7] for the MIBC-HR-ASO population.

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**Conclusion** Using real-world data, this study underscores the challenging prognosis of patients with MIBC-HR managed with RC, regardless of whether they receive adjuvant chemotherapy. New treatment protocols, such as the use of immunotherapies, may improve OS in this type of cancer, especially in the current therapeutic landscape where no highly effective treatment exists.

**Keywords** Bladder cancer, Muscle-invasive urothelial carcinoma, Radical cystectomy, Adjuvant chemotherapy, Survival, Prospective cohort

## Background

Bladder cancer (BC) accounts for 3% of cancer diagnoses worldwide, with 573,000 people having been diagnosed with BC in 2018 [1–3].

In BC, the tumour is initially restricted to the epithelial or sub-epithelial connective tissue layer, and around 70% of cases are diagnosed and treated at this stage (non-muscle-invasive BC) [4, 5]. As the tumour develops, it may infiltrate the muscle tissue layer of the bladder wall. Muscle-invasive BC (MIBC), has a poorer prognosis and carries a high risk of recurrence, either locally or through metastatic spread and, for this reason, requires more aggressive treatment [4, 5].

The gold standard treatment for MIBC is radical cystectomy (RC). The European Association of Urology (EAU) guidelines, published in 2020 and updated in 2023, recommend neoadjuvant chemotherapy with cisplatin for all eligible patients [6, 7]. These guidelines also strongly advocate the use of adjuvant chemotherapy in patients with ‘high-risk of recurrence’ who did not receive neoadjuvant treatment, despite the absence of a consensus definition for ‘high risk of recurrence’ [5]. In France, current use of neoadjuvant and adjuvant chemotherapy is poorly characterised and has been disputed [8].

COBLAnCE is a multicentre (14 centres), observational prospective cohort of newly diagnosed patients with BC initiated in 2012, designed to investigate the impact of environmental and genetic factors on prognosis and to generate real-world data on treatment patterns in BC in the French setting [9]. By 2018, 1,800 patients had been enrolled and prospectively followed over a 6-year period, making it the largest prospective cohort in this disease in Europe. The COBLAnCE cohort represents an extremely rich source of real-world data which are increasingly required by health authorities to assess innovative treatments. Here, we report results for a subgroup of the cohort, focusing on patients with MIBC at high risk of recurrence (MIBC-HR) who had undergone RC. Our study describes patient characteristics, treatment, disease-free survival (DFS) and overall survival (OS) in MIBC-HR patients and a subgroup of these patients who did not receive adjuvant chemotherapy after RC and were managed with active surveillance only (MIBC-HR-ASO).

## Methods

### Study population

This study was performed using the prospective COBLAnCE cohort, which has been described in detail elsewhere [9, 10]. Patients were included in the COBLAnCE cohort from October 2012 until June 2018, with a 6-year planned follow-up. The COBLAnCE cohort included patients with newly diagnosed BC and aged 18 years or older. For the current study, only patients with MIBC-HR who had undergone RC were selected. High-risk of recurrence was defined by pathological stage of pT3-pT4a, ypT2-ypT4a, or (y)pN+ according to the TNM classification [5]. Patients with metastatic disease at radical resection were excluded, as were patients receiving an experimental immunotherapy treatment in the adjuvant setting. A subgroup of patients not receiving adjuvant chemotherapy and followed with active surveillance only (MIBC-HR-ASO) was also evaluated.

### Patient characteristics

The COBLAnCE data collection has been detailed previously [10]. We considered sociodemographic and lifestyle characteristics at inclusion, such as age, gender, body mass index (calculated from height and weight) and smoking status (Never/Former/Current). Comorbidities such as hypertension, diabetes, heart failure, and angina pectoris were assessed by interview at enrolment and renal function was described by serum creatinine ( $\mu\text{mol/L}$ ) and glomerular filtration rate ( $\text{mL/min/1.72 m}^2$ ) reported in the medical records at inclusion, as described previously [9].

We also documented tumour characteristics at the time of surgery, such as tumour stage (pT0/pT1/pT2/pT3a/pT3b/pT4a), nodal status (N+/N-/Nx) and histological type of initial tumour (urothelial carcinoma/other) and the histological variant (conventional/micropapillary/multiple variants/squamous/other).

### Survival outcomes

During the follow-up period, we considered any observed disease recurrence or any death as an event. Recurrence was defined as either loco-regional or distant. The considered endpoints were OS, defined as the time between RC and death from any cause and DFS, defined as the time between RC and the first disease recurrence or death from any cause, whichever occurred first. All

patients were followed for a maximum of six years and the administrative censoring date was set at 24<sup>th</sup> January 2022. Patients for whom no events had been observed were censored at their last follow-up visit or at the end of follow-up (administrative censoring due to the 6-year maximum follow-up).

### Statistical analysis

Data presentation is purely descriptive and no statistical hypotheses were tested. Descriptive statistics are presented with mean values and standard deviations (SD) for continuous variables and as frequency counts and percentages for categorical variables, with a separate category for missing data. Median follow-up time was assessed using the reverse Kaplan-Meier method. Survival outcomes were evaluated using the Kaplan-Meier method, and median survival durations were determined with their 95% confidence intervals (95% CI). OS was described as median and 5-year OS, while DFS was described as median, 2-year and 5-year DFS. Statistical analyses were performed using SAS<sup>®</sup> software Version 9.4 (SAS Institute Inc. Cary, NC, USA).

## Results

### Study population

The COBLAnCE cohort enrolled 1,800 patients with BC aged  $\geq 18$  years between 2012 and 2018. Of these, 431 non-metastatic patients with MIBC undergoing RC were identified, of whom 256 were at high risk of recurrence. These 256 patients constituted the study population. Of these patients, 182 (71.0%) received no adjuvant chemotherapy (ASO subgroup). A flowchart illustrating the selection of patients is provided in Fig. 1.

Patient characteristics are presented in Table 1. MIBC-HR patients were principally men (79.7%), with a mean age of  $68.5 \pm 10.6$  years and the majority were current (28.8%,  $n=72$ ) or formersmokers (51.6%,  $n=129$ ). Most patients (78.3%) had impaired renal function (glomerular filtration rate  $\leq 90$  ml/min) and 42.5% had a history of hypertension. No major differences were observed between the MIBC-HR and the MIBC-HR-ASO patients, although the latter group was older and certain comorbidities were slightly more frequent.

Almost all RC interventions were performed by laparotomy (96.5%). Of the 204 men, 202 underwent total cystoprostatectomy (99.0%) and 46 of the 52 women (88.5%) underwent front pelvicectomy. Lymph node dissection was performed in 89.8% of the patients. More information on surgical techniques is provided in Table 2.

Tumour characteristics at the time of RC are presented in Table 1. The principal tumour type was urothelial carcinoma, accounting for more than 90% of cases, and the histological variant was conventional for more than half of the patients. Regarding tumour staging, the majority

were pT3a+ (88.3%), and 37.9% had nodal involvement. The tumour characteristics of MIBC-HR-ASO patients were similar to those of MIBC-HR patients, except for the proportion with nodal involvement, which was lower than nodal involvement in MIBC-HR patients (29.1% vs. 37.9%).

### Chemotherapy

The use of neoadjuvant and adjuvant chemotherapy is described in Fig. 1. Overall, over half of the 256 patients did not receive either neoadjuvant or adjuvant chemotherapy ( $n=140$ ; 54.7%), 41 patients (16.0%) received neoadjuvant chemotherapy only, and 69 patients (27.0%) received adjuvant chemotherapy only. MIBC-HR-ASO patients accounted for 71.1% of MIBC-HR patients ( $n=186$ ). Of the patients receiving adjuvant chemotherapy only, 86.8% received cisplatin-based therapy ( $n=59$ ). The other adjuvant chemotherapies were carboplatin-based protocols (4 patients, 10.0%) or other unspecified therapies (5 patients, 12.5%).

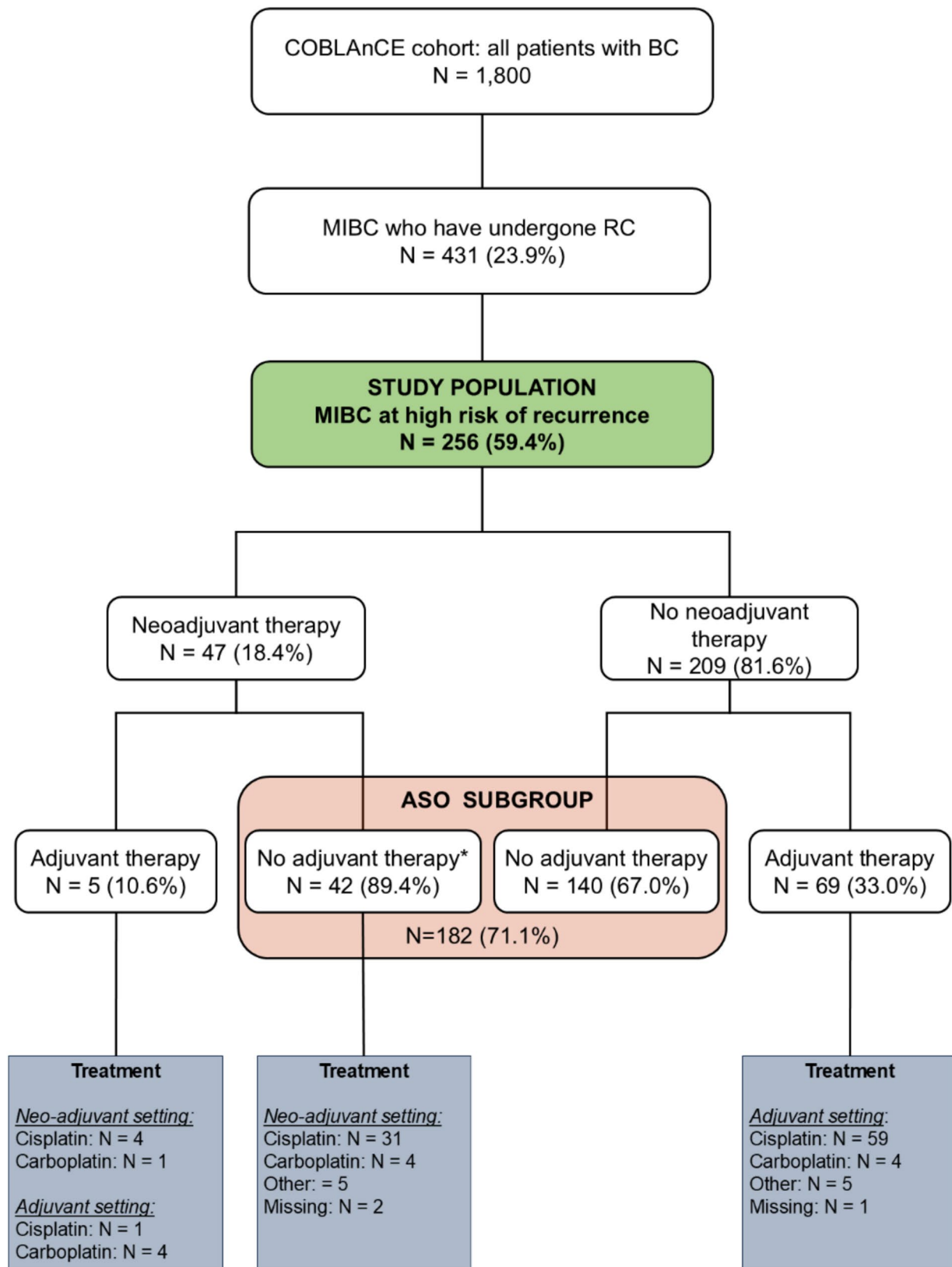
### Survival outcomes

The median follow-up was 5.0 years. Median OS was 2.31 years [95% CI: 1.85;3.10] in the MIBC-HR population and 2.11 years [95% CI: 1.61;2.65] in the MIBC-HR-ASO population (Fig. 2A, C). At 5 years, OS was 33.2% [27.1;40.0] and 29.6% [22.7;37.7] in the MIBC-HR and in the MIBC-HR-ASO populations. Median DFS was 1.30 years [95% CI: 1.01;1.60] in the MIBC-HR population and 1.21 years [95% CI: 0.70;1.53] in the subgroup of MIBC-HR-ASO population (Fig. 2B, D). At 2 and 5 years respectively, DFS was 39.9% [33.9;46.2] and 27.4% [21.7;33.9%] in the MIBC-HR population and was 37.9% [31.0;45.4] and 23.7% [17.4;31.4] in the MIBC-HR-ASO population.

## Discussion

This study focused on 256 patients with MIBC-HR undergoing RC who participated in the COBLAnCE cohort. The majority were aged  $>70$  years, had a history of smoking and presented with a histology of urothelial carcinoma. Their prognosis was poor, with 61.7% of included patients dying within six years of undergoing RC (median survival duration: 2.31 years). These characteristics are typical of patients with BC [4].

Current EAU guidelines recommend offering neoadjuvant cisplatin-based combination therapy for patients with T2-T4a cN0M0 BC and adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 or pN+ disease, if no neoadjuvant chemotherapy had been given previously [7]. Based on real-world data from the COBLAnCE cohort, adherence to these recommendations in France appears to be poor, since only 18% of patients received neoadjuvant chemotherapy, and only up to 30% (69/209) of patients received adjuvant



**Fig. 1** Patient flow and use of chemotherapy in patients with muscle invasive urothelial carcinoma

\*one patient received adjuvant radiotherapy

ASO: active surveillance alone; BC: bladder cancer, MIBC: muscle invasive bladder cancer, RC: radical cystectomy

The percentages are calculated with respect to the number in the box above

**Table 1** Patient and tumour characteristics

	<b>MIBC-HR (all patients) N= 256</b>	<b>MIBC-HR (ASO) N= 182</b>	<b>MIBC-HR (Adj. Chemo.) N= 74</b>
Gender (n; %)			
Male	204 (79.7%)	148 (81.3%)	56 (75.7%)
Female	52 (20.3%)	34 (18.7%)	18 (24.3%)
Age at diagnosis (years; mean ± SD)	68.5 ± 10.6	70.2 ± 10.7	64.2 ± 8.9
< 50	15 (5.9%)	11 (6.0%)	4 (5.4%)
51–60	44 (17.2%)	24 (13.1%)	20 (27.1%)
61–70	88 (34.4%)	55 (30.2%)	33 (44.6%)
71–80	71 (27.7%)	57 (31.3%)	14 (19.0%)
> 80	38 (14.8%)	35 (29.2%)	3 (4.1%)
BMI at inclusion (kg/m <sup>2</sup> ; mean ± SD)	25.9 ± 4.9	26.0 ± 5.2	25.5 ± 4.1
Missing	7	6	1
Smoking status at inclusion	N= 250	N= 176	N= 74
Never smoked	49 (19.6%)	31 (17.6%)	18 (24.3%)
Former smoker	129 (51.6%)	93 (52.8%)	36 (48.6%)
Current smoker	72 (28.8%)	52 (29.5%)	20 (27.0%)
Missing	6	6	0
Serum creatinine (µmol/L; mean ± SD)	110 ± 48	112 ± 50	106 ± 45
Missing	62	46	46
Estimated glomerular filtration rate (mL/min/1.72 m <sup>2</sup> )	N= 189	N= 131	N= 58
< 30	11 (5.8%)	9 (6.9%)	2 (3.4%)
30–59	68 (36.0%)	50 (38.1%)	18 (31.0%)
60–89	69 (36.5%)	44 (33.6%)	25 (43.1%)
> 90	41 (21.7%)	28 (21.4%)	13 (22.4%)
Missing	67	51	16
Comorbidities			
Hypertension	105 (42.5%)	73 (41.7%)	32 (44.4%)
Missing	9	7	2
Diabetes	39 (15.9%)	31 (17.8%)	8 (11.1%)
Missing	10	8	2
Heart failure	23 (9.3%)	18 (10.3%)	5 (6.9%)
Missing	10	8	2
Angina pectoris	28 (11.4%)	23 (13.2%)	5 (6.9%)
Missing	10	8	2
Histological type of initial tumour			
Urothelial carcinoma	239 (94.5%)	168 (93.9%)	71 (95.9%)
Other	14 (5.5%)	11 (6.1%)	3 (4.1%)
Adenocarcinoma (primary urinary bladder or urachal)	3 (1.2%)	2 (1.1%)	1 (1.4%)
Neuroendocrine carcinoma (admixed with urothelial carcinoma)	5 (2.0%)	4 (2.2%)	1 (1.4%)
Neuroendocrine carcinoma (pure)	1 (0.4%)	1 (0.6%)	
Squamous carcinoma (pure)	5 (2.0%)	4 (2.2%)	1 (1.4%)
Missing	3	3	0
Histological variant (urothelial carcinoma or admixed with urothelial carcinoma)			
Conventional	124 (50.8%)	93 (54.1%)	31 (43.1%)
Micropapillary	17 (7.0%)	12 (7.0%)	5 (6.9%)
Multiple variants	25 (10.2%)	13 (7.6%)	12 (16.7%)
Squamous	46 (18.9%)	33 (19.2%)	13 (18.1%)
Other	32 (13.1%)	21 (12.2%)	11 (15.2%)
Missing	12	10	2
Tumour stage at radical resection			
pT0	1 (0.4%)	1 (0.5%)	0 (0%)
pT1	3 (1.2%)	3 (1.6%)	0 (0%)
pT2	26 (10.2%)	20 (11.0%)	6 (8.1%)

**Table 1** (continued)

	<b>MIBC-HR (all patients) N=256</b>	<b>MIBC-HR (ASO) N=182</b>	<b>MIBC-HR (Adj. Chemo.) N=74</b>
pT3a	78 (30.5%)	58 (31.9%)	20 (27.0%)
pT3b	88 (34.4%)	59 (32.4%)	29 (39.2%)
pT4a	60 (23.4%)	41 (22.5%)	19 (25.7%)
Nodal status			
N+	97 (37.9%)	53 (29.1%)	44 (59.5%)
N-	132 (51.6%)	105 (57.7%)	27 (36.5%)
Nx	27 (10.5%)	24 (13.2%)	3 (4.1%)

ASO: active surveillance only; MIBC-HR: muscle invasive bladder cancer at high risk of recurrence; SD: standard deviation; Adj. Chemo.: adjuvant chemotherapy

**Table 2** Description of radical cystectomy interventions

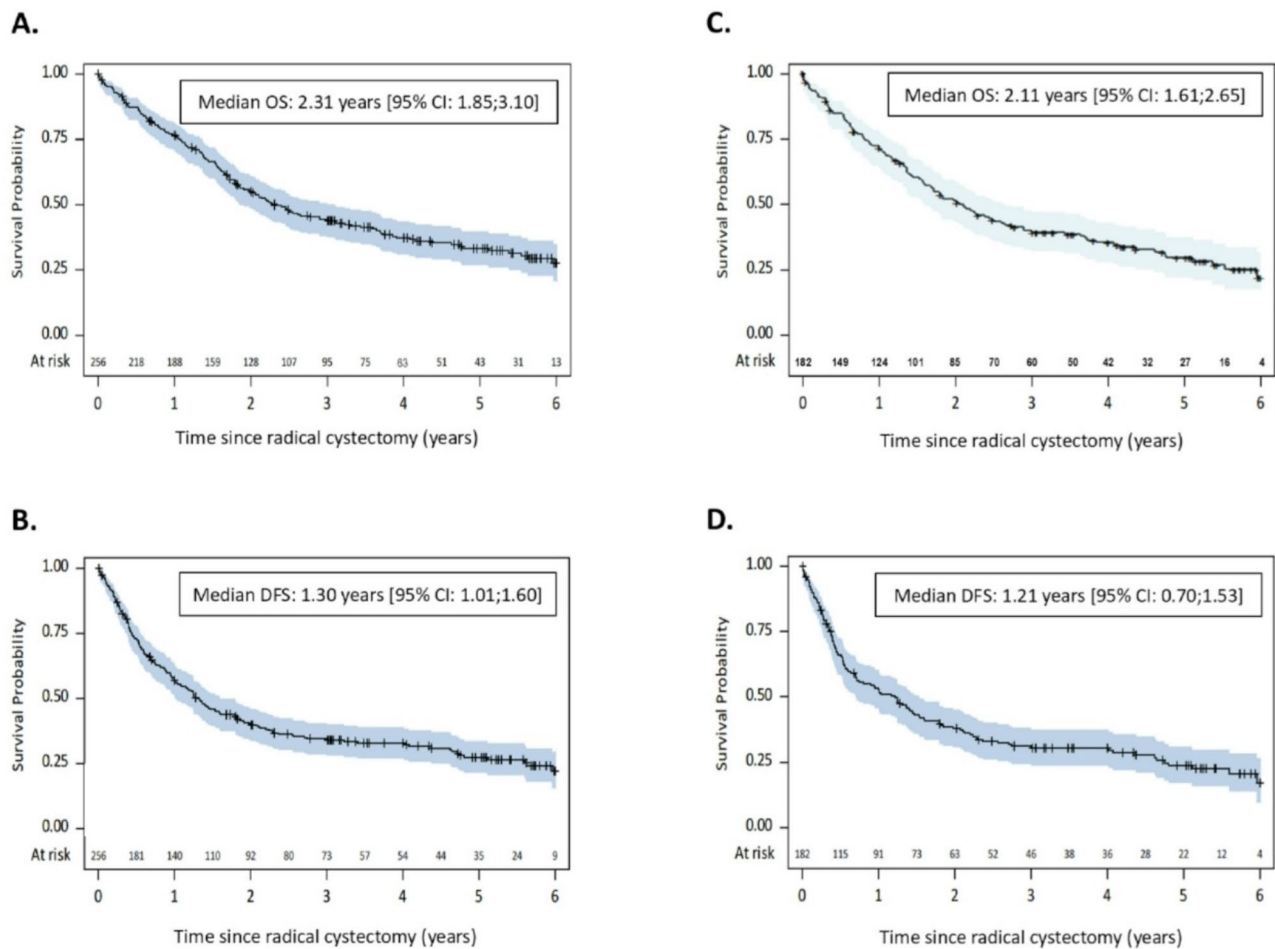
	<b>MIBC-HR N=256</b>
<b>Surgical access</b>	N=228
Laparotomy	220 (96.5%)
Coelioscopy	6 (2.6%)
Robot	2 (0.9%)
<b>Type of surgery in radical cystectomy</b>	N=256
Cystectomy with conservation of pelvic system (women)	6 (2.3%)
Cystectomy without prostatectomy (men)	2 (0.8%)
Front pelvicotomy (women)	46 (18.0%)
Total cystoprostatectomy (men)	202 (78.9%)
<b>Lymph node dissection</b>	N=256
No	26 (10.2%)
Yes	230 (89.8%)
<b>Type of dissection</b>	N=245
No dissection	26 (10.6%)
Local	124 (50.6%)
Extended	92 (37.6%)
Supraextended	3 (1.2%)
<b>Urinary bypass</b>	N=254
Bricker	157 (61.8%)
Orthotopic Neobladder	72 (28.3%)
Skin continent bypass	3 (1.2%)
Ureterostomy	22 (8.7%)

chemotherapy without neoadjuvant chemotherapy. Our study suggests that the decision to provide adjuvant chemotherapy did not seem to have been influenced by the tumour stage. However, for the patients who did receive adjuvant chemotherapy, 86.8% received a cisplatin-based treatment as recommended in the guidelines, and the recommended number of cycles were administered in most cases (see Supplementary – Table A). The prescription of the sequence neoadjuvant chemotherapy followed by adjuvant chemotherapy was very low, as per guidelines.

In terms of survival outcomes, comparison of DFS or OS for patients with MIBC-HR or MIBC-HR-ASO with findings from other studies is limited by the scarcity of available data and the lack of a common consensus definition of “high risk” of recurrence. Although our study did not show worse survival rates for the subgroup

of patients not receiving adjuvant chemotherapy, it is important to note that the study was not designed to detect such a difference. In particular, patients from this subgroup were older and might not have been fit for adjuvant chemotherapy. Other features, including glomerular filtration rates and comorbidities did not differ substantially. In the literature, evidence for the benefit of adjuvant chemotherapy in MIBC is not particularly robust and is at high risk of bias [11, 12]. A large randomised clinical trial (EORTC 30994) comparing immediate adjuvant chemotherapy after RC to delayed chemotherapy at the time of recurrence in 284 patients with MIBC failed to show a significant improvement in OS in patients receiving adjuvant chemotherapy [13]. In this clinical trial, the median OS was significantly higher than in our study (median OS: 6.74 years vs. 27.7 months), probably due to the enrolment of a significant number of patients aged over 80 years (14.8%) in the COBLAnCE cohort. On the other hand, two large studies using the US National Cancer Database found that the benefit is restricted to certain histological tumour types [14, 15].

This study has important strengths, notably its use of the only prospective BC cohort in France that documents detailed clinical characteristics for patients, with a follow-up duration of up to six years. The use of an established cohort has many advantages, notably the wealth of clinical information available on participants documented in a standardised way. However, the study also presents limitations: for example, only 14 hospitals enrolled patients, which limited the number of patients who could be enrolled and may have led to selection bias. Alternative study designs, such as extracting data on patients with MIBC from health insurance databases, would allow recruitment of a larger and more exhaustive population but can only provide limited clinical information. A study of MIBC based on the French national hospital database (*Programme de Médicalisation des Systèmes d'Information*; PMSI), which enrolled more than 2,500 patients with MIBC who had undergone RC in 2015, provided similar findings on demographics and overall survival to the present study [16]. However,



**Fig. 2** Overall survival and disease-free survival of patients with muscle invasive urothelial carcinoma (overall and restricted to those treated with active surveillance only). **A:** overall survival, MIBC-HR patients; **B:** disease-free survival, MIBC-HR patients; **C:** overall survival, MIBC-HR-ASO patients; **D:** disease-free survival, MIBC-HR-ASO patients  
95% CI: 95% confidence interval; DFS: disease-free survival; MIBC-HR: muscle-invasive bladder cancer at high risk of recurrence; MIBC-HR-ASO: muscle-invasive bladder cancer at high risk of recurrence treated with active surveillance only; OS: overall survival

it was not possible to stratify patients by risk of recurrence in this PMSI study due to the absence of relevant clinical data in the PMSI database [16]. Another limitation of the present study is that patients with a history of treatment for non-muscle invasive BC were not enrolled. According to a recent meta-analysis, such patients could have a worse prognosis than those without such a history (hazard ratio for cancer-specific survival: 1.29, 95% CI: [1.07–1.56]) [17]. A final limitation relates to the period of inclusion in the COBLAnCE cohort. Between 2012 and 2018, immunotherapies for BC were still under development, and for this reason, patients receiving immunotherapies in the context of a clinical trial were excluded from the study population. Treatments shown to improve survival recently became available after the end of the enrolment period of the COBLAnCE cohort [18, 19], which may thus not be fully representative of the current French therapeutic landscape. Nonetheless,

the COBLAnCE cohort remains a highly valuable source for documenting the current landscape of patients with MIBC and MIBC-HR in France.

**Conclusions**

Using real-world data, this study underscores the challenging prognosis of patients with MIBC-HR managed with RC, regardless of whether they receive adjuvant chemotherapy. New treatment protocols, such as the use of immunotherapies, may improve OS in this type of cancer, especially in the current therapeutic landscape where no highly effective treatment exists.

**Abbreviations**

ASO	Active surveillance only
BC	Bladder cancer
BMI	Body mass index
CI	Confidence intervals
DFS	Disease-free survival
EAU	European Association of Urology

MIBC	Muscle-invasive bladder cancer
MIBC/HR	Muscle-invasive bladder cancer at high risk of recurrence
OS	Overall survival
PMSI	Programme de Médicalisation des Systèmes d'Information (French national hospital database)
RC	Radical cystectomy
SD	Standard deviations
TNM	Tumour Node Metastasis System

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12894-025-01792-w>.

Supplementary Material 1

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Writing and editorial assistance was provided by SARL Foxymed.

## Author contributions

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published. AF, FC, JB, KG, ST, AP, SBr, SBe, YA and TL designed the study. MK, JB, KG, SBe and TL acquired the data. AF, FC, MK, JB, SBr, FR, YA and TL analysed the data. AF, FC, JB, ST, AP, SBr, FR, SBe, YA and TL interpreted the data.

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## Data availability

Anonymized data and biological samples collected during the study can be obtained for conducting scientific projects. Requests will be evaluated by the Scientific Committee of the COBLAnCE cohort.

## Declarations

### Ethics approval and consent to participate

The study was conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements. The COBLAnCE study was approved by the relevant French ethics committee (*Comité de Protection des Personnes Ile de France VII*; approval n° CO-12-001), the French data protection authority (Commission Nationale de l'Informatique et des Libertés; approval n° DR-2012-441) and the French biological tissue collection authority (approval n° DR-2012-1486). Each patient enrolled provided written informed consent. The current study did not require additional approval.

### Consent for publication

Not applicable.

### Competing interests

Julia Bonastre reports consulting fees for scientific advisory board from Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Janssen and Roche. Yves Allory reports fees to Institut Curie from Bristol Myers Squibb and Merck Sharp & Dome. Thierry Lebret reports personal fees from Bristol Myers Squibb and Ferring. Simone Benhamou reports personal fees from AstraZeneca. Florian Colrat, Siguroli Teitsson, Alexis Prudent and Sébastien Branchoux are employees of Bristol Myers Squibb. Aldéric Fraslin, Maryam Karimi, Karine Groussard and François Radvanyi declare no conflicts of interest.

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