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# BMJ Open Cohort profile: COBLAnCE: a French prospective cohort to study prognostic and predictive factors in bladder cancer and to generate real-world data on treatment patterns, resource use and quality of life

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## ABSTRACT

**Purpose** Bladder cancer is a complex disease with a wide range of outcomes. Clinicopathological factors only partially explain the variability between patients in prognosis and treatment response. There is a need for large cohorts collecting extensive data and biological samples to: (1) investigate gene-environment interactions, pathological/molecular classification and biomarker discovery; and (2) describe treatment patterns, outcomes, resource use and quality of life in a real-world setting.

**Participants** COBLAnCE (COhort to study BLadder CancEr) is a French national prospective cohort of patients with bladder cancer recruited between 2012 and 2018 and followed for 6 years. Data on patient and tumour characteristics, treatments, outcomes and biological samples are collected at enrolment and during the follow-up.

**Findings to date** We describe the cohort at enrolment according to baseline surgery and tumour type. In total, 1800 patients were included: 1114 patients with non-muscle-invasive bladder cancer (NMIBC) and 76 patients with muscle-invasive bladder cancer (MIBC) had transurethral resection of a bladder tumour without cystectomy, and 610 patients with NMIBC or MIBC underwent cystectomy. Most patients had a solitary lesion (56.3%) without basement membrane invasion (71.7% of Ta and/or Tis). Half of the patients with cystectomy were stage ≤T2 and 60% had non-continent diversion. Surgery included local (n=298) or super-extended lymph node dissections (n=11) and prostate removal (n=492). Among women, 16.5% underwent cystectomy and 81.4% anterior pelvicotomy.

**Future plans** COBLAnCE will be used for long-term studies of bladder cancer with focus on clinicopathological factors and molecular markers. It will lead to a much-

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The COBLAnCE cohort includes 1800 patients with extensive data recorded for the primary tumour and for all subsequent recurrences.
- ⇒ A central pathological review is conducted to overcome the variability in pathological data between centres and provide standardised annotations.
- ⇒ High-quality blood, tumour and urine samples were collected at baseline for over 80% of patients.
- ⇒ Date linkage of the COBLAnCE cohort with the French National Health Data system will enable comprehensive analysis of resource use, costs and long-term survival.
- ⇒ Centres participating in COBLAnCE may not be fully representative of routine care in France.

needed improvement in the understanding of the disease. The cohort provides valuable real-world data, enabling researchers to study various research questions, assess routine medical practices and guide medical decision-making.

## INTRODUCTION

Bladder cancer was the 10th most common cancer worldwide in 2018, with about 549 000 new cases and 200 000 deaths annually.<sup>1</sup> About 50% of bladder cancer cases in men are attributable to tobacco smoking.<sup>2</sup> Much remains unknown about bladder cancer, a complex disease characterised by a wide range of outcomes. At one end of the spectrum, low-grade non-muscle-invasive bladder cancers

(NMIBC) rarely progress to muscle-invasive bladder cancers (MIBC) or metastatic tumours, but as many as half will recur. At the other extreme, MIBC are prone to distant metastasis and cancer death, despite radical cystectomy.<sup>3</sup> Variability between patients in prognosis and treatment response is partially explained by usual clinical and pathological factors. Therefore, research that fuels mechanistic insight into urothelial carcinogenesis and progression, as well as identification of new prognostic and predictive biomarkers of bladder cancer outcomes, is needed to guide medical decision-making regarding treatment selection according to risk stratification.

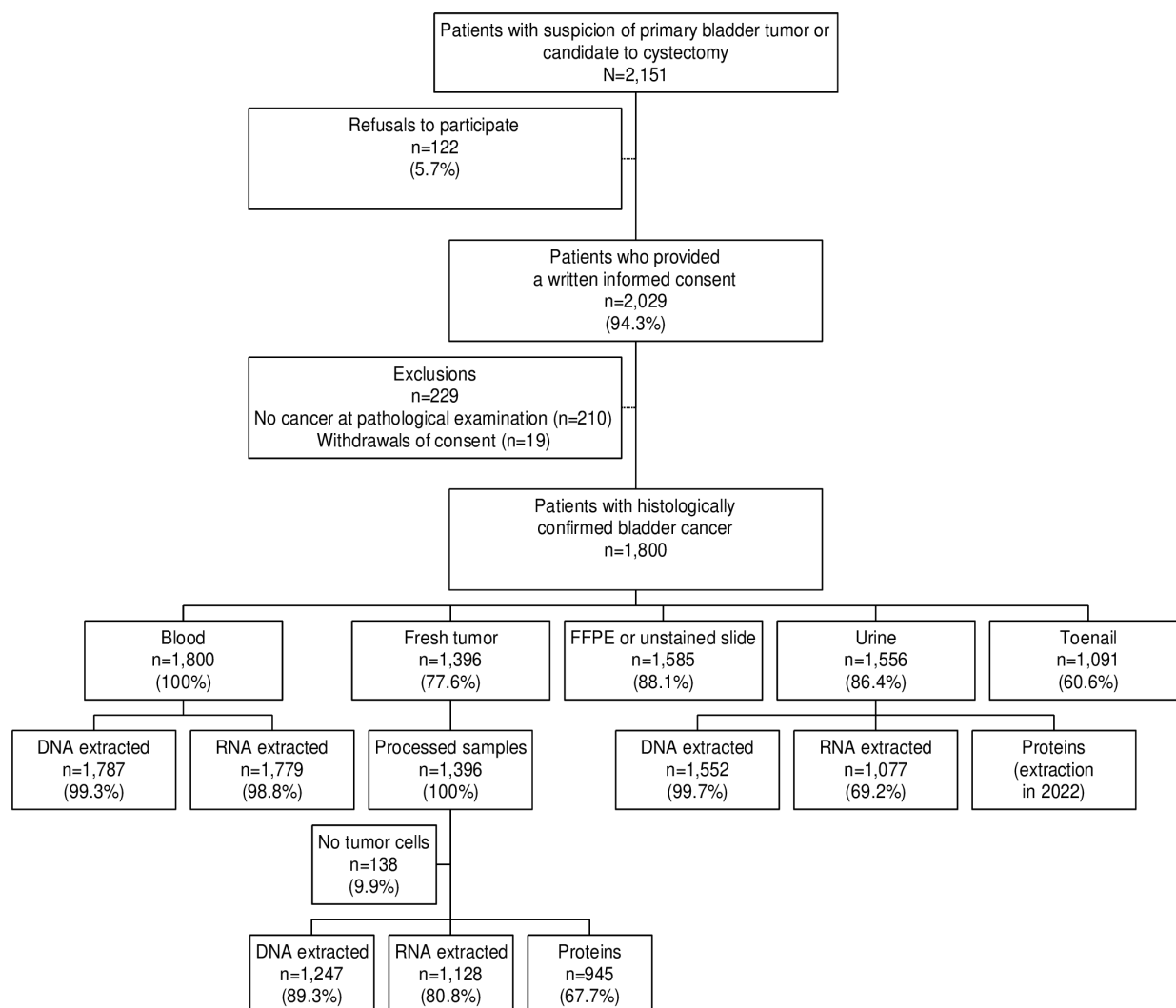
Large cohort studies with a wide range of phenotypic and environmental measures, and biological samples prospectively collected, can provide valuable resources to answer a number of clinically relevant research questions in this heterogeneous disease. However, such studies are rare because of the major efforts required for patient recruitment and data/biomaterial collection. To our knowledge, only five bladder cancer cohorts, based on 1000–1500 incident cases, with prospective data collection on lifestyle habits, tumour characteristics, treatments and outcomes, as well as biospecimen

collection (mainly blood samples), have been completed or are ongoing in Spain,<sup>4</sup> the Netherlands,<sup>5</sup> the UK<sup>6</sup> and the USA.<sup>7,8</sup> There is therefore a need for further large bladder cancer cohorts collecting extensive data and various biological samples, after diagnosis and recurrences, in order to comprehensively investigate gene-environment interactions, pathological and molecular classification and biomarker discovery, as well as to describe treatment patterns, outcomes, resource use and quality of life in a real-world setting.

Here, we describe the French national prospective Bladder Cancer Cohort COBLAnCE and report patient characteristics and treatment patterns at enrolment.

## COHORT DESCRIPTION

The COBLAnCE protocol has been previously reported.<sup>9</sup> A total of 1800 patients aged 18 years or more, who were due to undergo transurethral resection of a bladder tumour (TURBT) or cystectomy at 1 of the 14 participating centres, were enrolled in the cohort between November 2012 and June 2018, and will be followed for 6 years. Centres were selected on the basis of a high-volume



**Figure 1** Flowchart of the COBLAnCE cohort (baseline data). FFPE, formalin-fixed, paraffin-embedded.

**Table 1** Sociodemographic and lifestyle characteristics of patients with bladder cancer according to type of surgery at baseline (n=1800)

	TURB without cystectomy		Cystectomy	Total
	NMIBC (n=1114)	MIBC (n=76)	NMIBC or MIBC (n=610)	(n=1800)
Gender, n (%)				
Male	915 (82.1)	59 (77.6)	513 (84.1)	1487 (82.6)
Female	199 (17.9)	17 (22.4)	97 (15.9)	313 (17.4)
Age at interview, years, median (range)				
	68 (22–94)	75.5 (52–93)	68 (37–95)	68 (22–95)
Age at diagnosis (years), n (%)				
<40	13 (1.2)	0 (0)	1 (0.2)	14 (0.8)
40–49	48 (4.3)	0 (0)	21 (3.4)	69 (3.8)
50–59	180 (16.2)	3 (3.9)	98 (16.1)	281 (15.6)
60–69	372 (33.4)	16 (21.1)	224 (36.7)	612 (34.0)
70–79	338 (30.3)	30 (39.5)	174 (28.5)	542 (30.1)
≥80	163 (14.6)	27 (35.5)	92 (15.1)	282 (15.7)
Marital status, n (%)				
Single	82 (7.6)	9 (12.7)	42 (7.1)	133 (7.7)
Married/partnership	739 (68.7)	37 (52.1)	419 (71.0)	1195 (68.8)
Separated/divorced/widowed	255 (23.7)	25 (35.2)	129 (21.9)	409 (23.5)
Missing	38	5	20	63
Educational level, n (%)				
None or primary school	120 (11.4)	9 (11.5)	73 (12.5)	202 (11.8)
Technical/professional school	395 (37.5)	30 (43.5)	240 (41.2)	665 (39.0)
Secondary school	191 (18.1)	14 (20.3)	88 (15.1)	293 (17.2)
University degree	347 (33.0)	16 (23.2)	182 (31.2)	545 (32.0)
Missing	61	7	27	95
Job status, n (%)				
Employed	279 (26.0)	9 (12.5)	126 (21.4)	414 (23.8)
Unemployed	35 (3.3)	1 (1.4)	14 (2.4)	50 (2.9)
Retired	742 (69.1)	62 (86.1)	440 (74.6)	1244 (71.7)
Disabled/dependent	18 (1.7)	0 (0)	10 (1.7)	28 (1.6)
Missing	40	4	20	64
Monthly household income, n (%)				
<€600	18 (2.2)	2 (4.7)	7 (1.6)	27 (2.1)
€600–€1100	58 (7.0)	1 (2.3)	36 (8.2)	95 (7.2)
€1100–€1800	141 (17.0)	7 (16.3)	78 (17.7)	226 (17.2)
€1800–€2500	143 (17.2)	13 (30.2)	76 (17.3)	232 (17.7)
€2500–€3500	175 (21.1)	10 (23.3)	99 (22.5)	284 (21.6)
€3500–€4500	99 (11.9)	3 (7.0)	41 (9.3)	143 (10.9)
≥€4500	196 (23.6)	7 (16.3)	103 (23.4)	306 (23.3)
Missing	284	33	170	487
Body mass index (kg/m <sup>2</sup> ), n (%)				
<18	11 (1.0)	4 (5.7)	12 (2.0)	27 (1.6)
18–24.9	413 (38.9)	26 (37.1)	241 (41.1)	680 (39.6)
25–29.9	431 (40.6)	28 (40.0)	232 (39.5)	691 (40.2)
30–39.9	198 (18.6)	11 (15.7)	91 (15.5)	300 (17.5)
≥40	9 (0.8)	1 (1.4)	11 (1.9)	21 (1.2)
Missing	52	6	23	81

Continued

**Table 1** Continued

	TURB without cystectomy		Cystectomy	Total
	NMIBC (n=1114)	MIBC (n=76)	NMIBC or MIBC (n=610)	(n=1800)
Smoking status, n (%)				
Never smoker	209 (19.4)	12 (16.7)	105 (17.8)	326 (18.8)
Ex-smoker	521 (48.5)	34 (47.2)	320 (54.1)	875 (50.3)
Current smoker	345 (32.1)	26 (36.1)	166 (28.1)	537 (30.9)
Missing	39	4	19	62
Tobacco consumption (g/day) for ex-smokers and current smokers, n (%)				
≤20g/day	569 (69.9)	35 (62.5)	318 (69.9)	922 (69.6)
>20g/day	245 (30.1)	21 (37.5)	137 (30.1)	403 (30.4)
Missing	52	4	31	87
Alcohol intake, n (%)				
No alcohol	287 (26.5)	18 (25.0)	151 (25.5)	456 (26.1)
Moderate	518 (47.9)	33 (45.8)	270 (45.6)	821 (47.0)
Heavy	277 (25.6)	21 (29.2)	171 (28.9)	469 (26.9)
Missing	32	4	18	54
Alcohol intake: moderate consumption, <21 units in men and <14 units in women (per week); heavy consumption, ≥21 units in men and ≥14 units in women (per week)				
MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer; TURB, transurethral resection of the bladder.				

of surgery in patients with bladder cancer, and so as to include both the public and private sectors. Another selection criterion was the ability to provide good quality biological samples. Samples of peripheral blood, fresh tumour tissue, urine and toenail clippings were collected at baseline and/or during follow-up and delivered to three biological resources centres for processing and storage. The study has been approved by the French regulatory authorities and ethics committee and each patient provided written informed consent.

### Data and biospecimen collection

At study enrolment, in-person interviews were administered to patients by trained interviewers at each recruiting centre in order to collect demographic, lifestyle and medical history characteristics. Detailed clinical and pathological data at diagnosis and treatment patterns were extracted from patient medical records for the primary tumour and for all subsequent locoregional and distant recurrences. Information on health status was recorded at each follow-up visit. Finally, healthcare resource use and quality of life were collected at enrolment and regular time intervals during follow-up using the EQ-5D-5L, EORT QLQ-C30 and specific modules for MIBC and NMIBC (BLM 30 and BLS 24 questionnaires).

Blood, fresh and formalin-fixed paraffin-embedded tumour, urine and toenail clipping samples were collected at baseline.

### Data analysis

We described the study cohort according to baseline surgery and tumour type. Patients were classified into three groups: TURBT without cystectomy for patients

with NMIBC, TURBT without cystectomy for patients with MIBC and cystectomy for patients with NMIBC or MIBC. Continuous variables are summarised as the median and range, and categorical variables are shown as the frequency count and percentage. Analysis was done with SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

Regarding smoking habits, patients were considered as never smokers (less than 100 cigarettes/lifetime), former smokers (stopped smoking at least 1 year before recruitment) and current smokers (still smoking at recruitment or just stopped smoking). Complete history of tobacco smoking was ascertained separately for cigarettes, cigars and pipe for former and current smokers. To standardise consumption across products, we calculated product-specific lifetime consumption (in grams of tobacco) on the basis of International Agency for Research on Cancer estimates of average unit weights.<sup>10 11</sup> For alcohol intake, patients were classified into three groups: no consumption, moderate consumption (<21 units per week in men and <14 units in women) and heavy consumption (≥21 units per week in men and ≥14 units in women).

History of chronic disease was grouped as follows: metabolic/cardiac diseases (including arterial hypertension, diabetes, myocardial infarction, ischaemic stroke, hypercholesterolaemia and heart failure), respiratory diseases (including emphysema, chronic bronchitis and chronic obstructive pulmonary disease) and inflammatory/immune diseases (including rheumatoid arthritis, lupus, Crohn's disease, scleroderma, hyperthyroidism, hypothyroidism, rheumatoid polymyalgia and ulcerative colitis).

Pathological data were collected from primary diagnostic reports using WHO classification items (third

**Table 2** Medical history of patients with bladder cancer according to type of surgery at baseline (n=1800)

	TURB without cystectomy		Cystectomy	Total
	NMIBC (n=1114)	MIBC (n=76)	NMIBC or MIBC (n=610)	(n=1800)
Prior urinary diseases				
Urinary tract infection among men, n (%)				
No	635 (73.0)	43 (75.4)	304 (61.5)	982 (69.1)
Yes	235 (27.0)	14 (24.6)	190 (38.5)	439 (30.9)
Missing	45	2	19	66
Urinary tract infection among women, n (%)				
No	67 (34.9)	5 (35.7)	27 (28.7)	99 (33.0)
Yes	125 (65.1)	9 (64.3)	67 (71.3)	201 (67.0)
Missing	7	3	3	13
Kidney infection, n (%)				
No	1022 (96.2)	68 (95.8)	553 (94.2)	1643 (95.5)
Yes	40 (3.8)	3 (4.2)	34 (5.8)	77 (4.5)
Missing	52	6	23	80
Kidney stones, n (%)				
No	863 (81.9)	61 (85.9)	491 (84.1)	1415 (82.8)
Yes	191 (18.1)	10 (14.1)	93 (15.9)	294 (17.2)
Missing	60	5	26	91
History of chronic diseases, n (%)				
Cancer, n (%)				
No	876 (83.1)	56 (78.9)	465 (80.2)	1397 (81.9)
Yes	178 (16.9)	15 (21.1)	115 (19.8)	308 (18.1)
Missing	60	5	30	95
Asthma, n (%)				
No	974 (92.6)	68 (95.8)	544 (93.0)	1586 (92.9)
Yes	78 (7.4)	3 (4.2)	41 (7.0)	122 (7.1)
Missing	62	5	25	92
Allergies, n (%)				
No	857 (80.8)	65 (91.5)	511 (87.5)	1433 (83.6)
Yes	203 (19.2)	6 (8.5)	73 (12.5)	282 (16.4)
Missing	54	5	26	85
Respiratory diseases, n (%)				
No	929 (87.9)	61 (85.9)	512 (88.4)	1502 (88.0)
Yes	128 (12.1)	10 (14.1)	67 (11.6)	205 (12.0)
Missing	57	5	31	93
Metabolic/heart diseases, n (%)				
No	337 (31.9)	17 (23.6)	179 (30.7)	533 (31.2)
Yes	719 (68.1)	55 (76.4)	404 (69.3)	1178 (68.8)
Missing	58	4	27	89
Inflammatory/immune diseases, n (%)				
No	913 (87.5)	62 (88.6)	512 (89.4)	1487 (88.1)
Yes	131 (12.5)	8 (11.4)	61 (10.6)	200 (11.9)
Missing	70	6	37	113
Family history of cancer among FDR, n (%)				
No	434 (41.9)	36 (52.2)	236 (40.5)	706 (41.2)

Continued

**Table 2** Continued

	TURB without cystectomy		Cystectomy	Total
	NMIBC (n=1114)	MIBC (n=76)	NMIBC or MIBC (n=610)	(n=1800)
Yes	626 (59.1)	33 (47.8)	347 (59.5)	1006 (58.8)
Missing	54	7	27	88

Respiratory diseases include emphysema, chronic bronchitis and chronic obstructive pulmonary disease; metabolic/cardiac diseases include arterial hypertension, diabetes, myocardial infarction, ischaemic stroke, hypercholesterolaemia and heart failure; inflammatory/immune diseases include rheumatoid arthritis, lupus, Crohn's disease, scleroderma, hyperthyroidism, hypothyroidism, rheumatoid polymyalgia and ulcerative colitis.

FDR, first-degree relatives (parents, siblings and children); MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer; TURB, transurethral resection of the bladder.

edition for enrolment in 2012–2016 and fourth edition for 2017–2018)<sup>12,13</sup> and TNM staging (UICC 2009, seventh edition).<sup>14</sup>

### Patients and public involvement

Patients or the general public were not involved in the design or planning, recruitment or conduction of the study.

### FINDINGS TO DATE

Figure 1 shows the flowchart of COBLAnCE at baseline. A total of 2151 patients with suspicion of bladder cancer or candidates for cystectomy were eligible to be enrolled in the cohort. Among them, 122 patients refused to participate and 229 were further excluded, mainly because of the absence of cancer at the pathological examination. Thus, a total of 1800 patients with bladder cancer were enrolled in the cohort.

Patient characteristics are presented in tables 1 and 2 for the whole cohort and in each subgroup, defined by surgery at baseline and tumour type.

TURBT without cystectomy was performed in 1114 (62%) patients with NMIBC and 76 (4%) patients with MIBC, and cystectomy was performed in 610 (34%) patients with NMIBC or MIBC. Approximately 83% of patients with bladder cancer were men. The median age at enrolment was 68 years (range: 22–95). Patients with NMIBC with TURBT without cystectomy were slightly younger. Only 3.6% of the cystectomies were performed in patients younger than 50 years old.

Less than 20% of patients were lifelong non-smokers. Among the 1412 ever-smokers, 922 (70%) smoked 20 g of tobacco per day or less and 403 (30%) smoked more than 20 g. About half of the patients reported a moderate alcohol consumption. Approximately 19% of the patients had a body mass index >30.

Prior urinary tract infections were twice as common in women (67%) than in men (31%), and approximately 70% of patients reported chronic metabolic/heart diseases.

Tumour characteristics and treatment patterns in each subgroup are presented in tables 3–7.

The location of the tumour was mostly in the lateral faces (over 40%), while the urethra was only affected in 5.3%. The trigone location, with potential repercussions on the urinary

upper tract, affected 23.5% of patients. The majority of the resected tumours were solitary lesions (56.3%), and 71.7% were without basement membrane invasion (Ta and/or Tis). All of the muscle-invasive tumours were high grade. As the inclusion criteria were primary resection or cystectomy, the rate of patients with synchronous metastasis at diagnosis was low: only 4%. The majority of the tumours were urothelial (90.8%), including histological subtypes of divergent differentiation.

The non-muscle-invasive tumours were treated according to French guidelines, using only two drugs for instillation: Bacillus Calmette-Guerin (BCG) and mitomycin C. For patients with cystectomy, surgery was performed with different types of lymph node dissections, from local (298 patients) to super-extended (11 patients) dissections. For men, the prostate was removed in 96% of the patients, while 16.5% of women underwent cystectomy, 81.4% anterior pelvicotomy and 2.0% partial cystectomy. Additional synchronous excisions of the urethra (15.8%) or upper tract (1.6%) were also performed when the tumour involved the associated urothelium. After cystectomy, most of the patients had non-continent diversion (60%), including the Bricker procedure and ureterostomy. The final pathological stages are reported in table 4: 51.5% of the tumours were organ-confined carcinoma ( $\leq T2$ ).

Although radical cystectomy is the gold standard treatment for patients with MIBC, 76 patients with MIBC underwent TURB only in our study. Most of these patients could not benefit from cystectomy because of medical reasons (metastases 27%, poor global health 27% and other cancer 19%), 13% refused despite physician recommendation and 10% died before cystectomy could be performed. The prognosis of these patients is poorer; therefore, survival analyses will be adjusted accordingly.

### Strengths and limitations

COBLAnCE is a prospective cohort of 1800 patients with bladder cancer, covering both non-muscle-invasive and muscle-invasive disease, who underwent TURBT or cystectomy as the initial treatment of a bladder cancer. A follow-up of 6 years is scheduled. As of June 2022, half of the patients have completed follow-up or have died. COBLAnCE is a unique resource to develop collaborative

**Table 3** Tumour characteristics of patients with a TURB without cystectomy for NMIBC at baseline (n=1114)

Characteristics	
Number of tumour sites, n (%)	
1	580 (55.9)
2	316 (30.4)
3	98 (9.4)
4	25 (2.4)
5	9 (0.9)
6	5 (0.5)
7	5 (0.5)
Missing	76
Tumour site	
Urethra, n (%)	
No	1027 (94.7)
Yes	57 (5.3)
Missing	30
Trigone, n (%)	
No	828 (76.5)
Yes	254 (23.5)
Missing	32
Dome, n (%)	
No	934 (86.4)
Yes	147 (13.6)
Missing	33
Bladder neck, n (%)	
No	875 (80.7)
Yes	209 (19.3)
Missing	30
Right side face, n (%)	
No	635 (58.7)
Yes	447 (41.3)
Missing	32
Left side face, n (%)	
No	607 (56.3)
Yes	471 (43.7)
Missing	36
Anterior face, n (%)	
No	947 (87.8)
Yes	131 (12.2)
Missing	36
Base, n (%)	
Sessile	319 (52.1)
Pedunculated	293 (47.9)
Missing	502
Largest tumour (mm), mean (SD)	
	24.2 (20.1)
No. of resected tumours, n (%)	
1	616 (56.3)

Continued

**Table 3** Continued

Characteristics	
2–5	409 (37.4)
>5	70 (6.4)
Missing	19
Stage, n (%)	
Ta	739 (66.3)
Ta and Tis associated	60 (5.4)
T1	238 (21.4)
T1 and Tis associated	54 (4.9)
Tis isolated	15 (1.3)
Tx	8 (0.7)
Grade*, n (%)	
Low	641 (58.8)
High	450 (41.2)
Missing	23
Metastatic, n (%)	
No	1112 (99.8)
Yes	2 (0.2)
*For grading, papillary low-malignant potential tumours and low-grade papillary carcinoma are grouped together as the low-grade group; high-grade includes high-grade papillary carcinoma and flat carcinoma in situ. NMIBC, non-muscle-invasive bladder cancer; TURB, transurethral resection of the bladder.	

and multidisciplinary projects at national and international levels, including the molecular classification of bladder cancer, associations with environmental and/or genetic factors, identification of diagnostic and prognostic factors associated with recurrence and survival, healthcare resource use, costs and quality of life in a large sample of patients with bladder cancer. The aim of this paper is to present the data available, patient characteristics and treatment patterns at enrolment to enable future collaborative projects in various areas such as genetics, epidemiology, health economics and quality of life.

The COBLAnCE cohort provides valuable real-world data on bladder cancer in the French setting. Both public (n=11, including seven academic settings) and private (n=3) centres, distributed throughout the French territory, fully participated. Considering that less than 6% of patients refused to participate, the cohort provides an accurate picture of practices in patients with bladder cancer in France. Most patients (66%) included in COBLAnCE had non-muscle-invasive tumours, which is consistent with the literature.<sup>15</sup> The gender ratio in COBLAnCE is 1 female to 4.7 males, intermediate between that reported in the USA<sup>8</sup> and Spanish<sup>4</sup> cohorts (1 to 4, and 1 to 6.6, respectively). This difference in sex ratio is mostly attributable to the higher prevalence of smoking among women in the USA than in Southern European countries several decades ago.



**Table 4** Treatment characteristics of patients with a TURB without cystectomy for NMIBC at baseline (n=1114)

Characteristics	
<b>Endovesical treatment</b>	
BCG, n (%)	
No	776 (69.8)
Yes	336 (30.2)
Missing	2
Planned protocol, n (%)	
X6	
Achieved as planned	
No	18
Yes	166
Missing	5
X6+3	
Followed as planned	
No	12
Yes	72
Missing	2
X6+3+maintenance	
Followed as planned	
No	4
Yes	27
Missing	0
Other	
	23 (7.1)
Mitomycin, n (%)	
No	988 (88.8)
Yes	124 (11.2)
Missing	2
Planned protocol, n (%)	
X6	
	13 (10.7)
X8	
	105 (86.1)
X6 or X8+maintenance	
	4 (3.3)
Missing	
	2
Protocol followed as planned, n (%)	
Yes	
	112 (91.1)
No	
	11 (8.9)
Missing	
	1

BCG, Bacillus Calmette-Guerin; NMIBC, non-muscle-invasive bladder cancer; TURB, transurethral resection of the bladder.

COBLAnCE allows us to analyse if and how guidelines are followed. First, postoperative intravesical instillation of mitomycin C, which is recommended after transurethral resection of a single lesion of <3 cm, was rarely performed.<sup>16</sup> The main reason for this is probably the possible chemo-extravasation, fear of chemical cystitis, skin reaction and logistical difficulties for a modest reduction of recurrence risk and low benefit for the

**Table 5** Tumour and treatment characteristics of patients with TURB MIBC without cystectomy (n=76)

Characteristics	
Histological type, n (%)	
Urothelial	69 (90.8)
Neuroendocrine (admixed with urothelial)	3 (3.9)
Squamous (pure)	4 (5.3)
Histological subtypes or divergence of urothelial carcinoma, n (%)	
Conventional	41 (59.4)
Squamous divergence	7 (10.1)
Micropapillary	3 (4.3)
Multiple subtypes	6 (8.7)
Sarcomatoid	3 (4.3)
Plasmacytoid	1 (1.4)
Glandular divergence	2 (2.9)
Lipid-rich	1 (1.4)
Nested	1 (1.4)
Neuroendocrine (admixed with urothelial)	3 (4.3)
Poorly differentiated	1 (1.4)
Metastatic, n (%)	
No	55 (72.4)
Yes	21 (27.6)
Chemotherapy, n (%)	
No	45 (59.2)
Yes	31 (40.8)
Number of chemotherapy lines	
1	25 (80.6)
2	6 (19.4)
Cisplatin-based first-line chemotherapy	
No	14 (45.2)
Yes	17 (54.8)
Radiotherapy, n (%)	
No	64 (85.3)
Yes	11 (14.7)
Missing	1
Reason for lack of cystectomy, n (%)	
Metastases	20 (26.7)
Global health state	20 (26.7)
Other cancer	14 (18.7)
Patient refusal	10 (13.3)
Early death	8 (10.4)
Lost to follow-up	3 (4.0)
Missing	1

MIBC, muscle-invasive bladder cancer; TURB, transurethral resection of the bladder.

patients.<sup>17</sup> Second, although the optimal dose and duration of BCG treatment remain controversial, guidelines recommend long-term maintenance regimens for 1 year,<sup>18 19</sup> while in our study, less than 10% received such a treatment. The majority of patients (58.1%) had only

**Table 6** Tumour characteristics of patients with cystectomy at baseline (n=610)

Characteristics	
Lymph node dissection, n (%)	
No	45 (7.4)
Yes	565 (92.6)
Local	298
Extended	204
Super-extended	11
Missing	31
Type of cystectomy, n (%)	
Cystoprostatectomy (men)	492 (80.8)
Anterior pelvicectomy (women)	79 (13.0)
Cystectomy (men)	16 (2.6)
Cystectomy (women)	16 (2.6)
Partial cystectomy/diverticulectomy	6 (1.0)
Missing	1
Synchronous ureterectomy, n (%)	
No	511 (84.2)
Yes	96 (15.8)
Missing	3
Synchronous nephroureterectomy, n (%)	
No	598 (98.4)
Yes	10 (1.6)
Missing	2
Urinary diversion if total cystectomy, n (%)	
Bricker	322 (53.7)
Orthotopic neobladder	234 (39.0)
Skin continent diversion	6 (1.0)
Direct ureterostomy	38 (6.3)
Missing	10
Histological type, n (%)	
Urothelial	510 (95.0)
Neuroendocrine (admixed with urothelial)	11 (2.0)
Squamous (pure)	8 (1.5)
Adenocarcinoma (primary urinary bladder or urachal)	5 (0.9)
Neuroendocrine (pure)	3 (0.6)
Missing	73
Histological subtypes or divergence of urothelial carcinoma, n (%)	
Conventional	289 (55.5)
Squamous divergence	84 (16.1)
Micropapillary	36 (6.9)
Multiple subtypes	38 (7.3)
Sarcomatoid	14 (2.7)
Plasmacytoid	12 (2.3)
Clear cell	1 (0.2)

Continued

**Table 6** Continued

Characteristics	
Giant cell	3 (0.6)
Glandular divergence	13 (2.5)
Lipid-rich	1 (0.2)
Lymphoepithelioma-like	3 (0.6)
Microcystic	1 (0.2)
Nested	10 (1.9)
Neuroendocrine (admixed with urothelial)	11 (2.1)
Poorly differentiated	5 (1.0)
Stage, n (%)	
Ta	18 (3.0)
Tis	10 (1.6)
T1	53 (8.7)
T2	226 (37.0)
T3a	98 (16.1)
T3b	112 (18.4)
T4a	81 (13.3)
T4b	7 (1.1)
Tx	4 (0.7)
Associated cis, n (%)	
No	170 (38.0)
Yes	277 (62.0)
Missing	163
Grade, n (%)	
Low	18 (3.0)
High	551 (90.3)
Not available	41 (6.7)
Upfront regional and distant metastases, n (%)	
No	552 (90.5)
Yes	58 (9.5)
Lymph node status (among patients who had dissection), n (%)	
N0	432 (76.4)
N1	64 (11.3)
N2	53 (9.4)
N3	11 (2.0)
Nx	5 (0.9)

one induction instillation per week for 6 weeks, and a quarter (25.5%) had three additional instillations for 3 weeks, without 3-month, 6-month and 12-month instillations corresponding to the complete BCG treatment regimen. Despite being the most efficient, this standard regimen including maintenance is limited by major side effects that limit its use in most patients in real life. Moreover, during the inclusion period of the patients in COBLAnCE, we have suffered in France from a BCG regimen shortage due to a shutdown of Sanofi Pasteur

**Table 7** Treatment characteristics of patients with cystectomy at baseline (n=610)

Characteristics	
Chemotherapy, n (%)	
No	416 (68.1)
Yes	195 (31.9)
Number of chemotherapy lines	
1	183
2	12
First-line chemotherapy indication	
Adjuvant	92
Neoadjuvant	101
Other	1
Cisplatin-based first-line chemotherapy	
No	37
Yes	158
Radiotherapy, n (%)	
No	604 (98.9)
Yes	7 (1.1)
Neoadjuvant	3
Adjuvant	4

production. Therefore, the national guidelines recommended limiting the use of BCG, reducing dramatically the indications for maintenance treatment.

Among 610 patients who underwent cystectomy, only 101 (16.6%) received neoadjuvant chemotherapy. This first-line cisplatin-based chemotherapy continues, nevertheless, to be recommended.<sup>20</sup> To explain this low adherence in the urological community, three main reasons can be proposed. First, one-third of patients are not fit for cisplatin treatment, for reasons including kidney failure, deafness or comorbidity. Second, many urologists are not convinced by the literature concerning the benefit of neoadjuvant therapy, considering that there are a lot of biases in the two major randomised clinical trials in favour of chemotherapy prior to cystectomy, with a low absolute difference in 3-year survival of only 5%.<sup>21 22</sup> These urologists consider that adjuvant cisplatin in case of extravesical invasion is equivalent and permit it to avoid systemic treatment when unnecessary (organ confined carcinoma). Finally, many patients refuse chemotherapy and ask for primary surgery. In the future, our data will be useful as comparators for the assessment of new approaches, including neoadjuvant immunotherapy.<sup>23</sup>

COBLAnCE is a longitudinal study over 6 years that will enable description of treatment pathways, associated costs and the evolution of quality of life. These real-world data gathered since 2012 will be useful in the assessment of the efficiency of upcoming or recently approved treatments. This includes the anti-PD1/PDL1 (Programmed cell death protein 1/Programmed death-ligand 1) immunotherapies used in the metastatic setting (first line in

cisplatin ineligible patients, maintenance after first-line chemotherapy inducing disease stabilisation; second line after progression following first-line chemotherapy) or in the adjuvant setting (for high risk tumours after cystectomy), but also the currently investigated FGFR (Fibroblast Growth Factor Receptors) inhibitors and antibody-drug conjugates.

The great effort made in COBLAnCE to systematically collect blood, tumour, urine and toenail samples matched with epidemiological and clinical data was successful. DNA and RNA extracted from blood are available for most of the patients, allowing genotyping and systemic phenotyping. The collection rate of fresh tumours (>75%) was very high, allowing combined DNA, RNA and protein preparation after pathological control for large-scale molecular studies. Formalin-fixed, paraffin-embedded (FFPE) materials available at initial diagnosis for almost 90% of patients will complete these resources. The collection of tumour samples at recurrences (fresh and FFPE) is still in progress for future longitudinal investigations.

Our study cohort has some limitations that should be considered. First, in order to participate in COBLAnCE, centres had to be able to provide high-quality biological samples. These centres may not be fully representative of routine care in France. However, patient characteristics at enrolment are consistent with the literature. Second, patients were enrolled by urologists. It is possible that patients with non-resectable tumours are under-represented in the cohort. However, this fraction of patients is small in routine practice in France as the standard of care is surgery. Finally, pathological data were extracted from primary pathological reports. Although this reflects real-life practice, as clinical decisions were grounded on these data, the variability between centres and/or pathologists might introduce heterogeneity biases into the cohort. A central pathological review is ongoing to provide additional and standardised pathological annotations.

Patients in this cohort have been included before recent advances in immunotherapy for patients with bladder cancer. In particular in high-risk patients who had radical cystectomy (with or without neoadjuvant therapy), Checkmate 274 study has proven the benefit of adjuvant nivolumab treatment during 1 year.<sup>24</sup> Moreover, patients responding to chemotherapy, avelumab for maintenance treatment is now recommended<sup>25</sup> and for chemo-unresponsive patients pembrolizumab has become the second-line standard treatment.<sup>26</sup>

In conclusion, the COBLAnCE cohort, along with the wealth of epidemiological, clinicopathological, economic and biological evidence to be collected is a unique resource to enable future collaborative projects in various areas such genetics, epidemiology, health economics and quality of life. It will provide an important contribution to the much-needed improvement in the understanding of bladder cancer to guide medical decision-making.

### Collaboration

COBLAnCE welcomes requests from academic and commercial collaborators who have a valid health

research request. Regulatory procedures to access the resources of the cohort (data and/or biological samples) for conducting specific research projects are outlined in a charter that we will make available upon request to project leaders.

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**Data availability statement** Data are available upon reasonable request. Researchers may request access to data by contacting the corresponding author.

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