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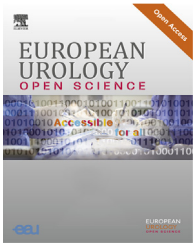

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Urothelial Cancer

Comparative Outcomes of Primary Versus Recurrent High-risk Non–muscle-invasive and Primary Versus Secondary Muscle-invasive Bladder Cancer After Radical Cystectomy: Results from a Retrospective Multicenter Study

Nico C. Grossmann [a,b,c], *Pawel Rajwa* [a,d], *Fahad Quhal* [a,e], *Frederik König* [a,f], *Hadi Mostafaei* [a,g], *Ekaterina Laukhtina* [a,h], *Keiichiro Mori* [a,i], *Satoshi Katayama* [a,j], *Reza Sari Motlagh* [a,k], *Christian D. Fankhauser* [c], *Agostino Mattei* [c], *Marco Moschini* [l], *Piotr Chlosta* [m], *Bas W.G. van Rhijn* [n], *Jeremy Y.C. Teoh* [o], *Eva Compérat* [p], *Marek Babjuk* [q], *Mohammad Abufaraj* [r], *Pierre I. Karakiewicz* [s], *Shahrokh F. Shariat* [a,h,t,u,v,w,*], *Benjamin Pradere* [a]

[a] *Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria;* [b] *Department of Urology, University Hospital Zurich, Zurich, Switzerland;* [c] *Department of Urology, Luzerner Kantonsspital, Lucerne, Switzerland;* [d] *Department of Urology, Medical University of Silesia, Zabrze, Poland;* [e] *Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia;* [f] *Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [g] *Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran;* [h] *Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia;* [i] *Department of Urology, The Jikei University School of Medicine, Tokyo, Japan;* [j] *Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan;* [k] *Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran;* [l] *Department of Urology, IRCCS San Raffaele Hospital and Vita-Salute San Raffaele University, Milan, Italy;* [m] *Department of Urology, Jagiellonian University, Krakow, Poland;* [n] *Department of Urology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [o] *S.H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China;* [p] *Department of Pathology, Medical University Vienna, Vienna General Hospital, Vienna, Austria;* [q] *Department of Urology, Hospital Motol and Second Faculty of Medicine, Charles University, Prague, Czech Republic;* [r] *Division of Urology, Department of Special Surgery, The University of Jordan, Amman, Jordan;* [s] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Centre, Montreal, Canada;* [t] *Hourani Center for Applied Scientific Research, Al-Ahliyya Amman University, Amman, Jordan;* [u] *Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria;* [v] *Department of Urology, Weill Cornell Medical College, New York, NY, USA;* [w] *Department of Urology, University of Texas Southwestern, Dallas, TX, USA*

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Abstract

Background: Radical cystectomy (RC) is indicated in primary or secondary muscle-invasive bladder cancer (primMIBC, secMIBC) and in primary or recurrent high- or very high-risk non–muscle-invasive bladder cancer (primHR-NMIBC, recHR-NMIBC). The optimal timing for RC along the disease spectrum of nonmetastatic urothelial carcinoma remains unclear.

Objective: To compare outcomes after RC between patients with primHR-NMIBC, recHR-NMIBC, primMIBC, and secMIBC.

Design, setting, and participants: This retrospective, multicenter study included patients with clinically nonmetastatic bladder cancer (BC) treated with RC.

* Corresponding author. Department of Urology, Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria. Tel. +43 1 4040026150; Fax: +43 1 4040023320.
E-mail address: shahrokh.shariat@meduniwien.ac.at (S.F. Shariat).

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Disease progression
Survival

Outcome measurements and statistical analysis: We assessed oncological outcomes for patients who underwent RC according to the natural history of their BC. primHR-NMIBC and primMIBC were defined as no prior history of BC, and recHR-NMIBC and secMIBC as previously treated NMIBC that recurred or progressed to MIBC, respectively. Log-rank analysis was used to compare survival outcomes, and univariable and multivariable Cox and logistic regression analyses were used to identify predictors for survival.

Results and limitations: Among the 908 patients included, 211 (23%) had primHR-NMIBC, 125 (14%) had recHR-NMIBC, 404 (44%) had primMIBC, and 168 (19%) had secMIBC. Lymph node involvement and pathological upstaging were more frequent in the secMIBC group than in the other groups ($p < 0.001$). The median follow-up was 37 mo. The 5-year recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were 77.9%, 83.2%, and 72.7% in primHR-NMIBC, 60.0%, 59%, and 48.9% in recHR-NMIBC, 60.9%, 64.5%, and 54.8% in primMIBC, and 41.3%, 46.5%, and 39% in secMIBC, respectively, with statistically significant differences across all survival outcomes except between recHR-NMIBC and primMIBC. On multivariable Cox regression, recHR-NMIBC was independently associated with shorter RFS (hazard ratio [HR] 1.64; $p = 0.03$), CSS (HR 1.79; $p = 0.01$), and OS (HR 1.45; $p = 0.03$), and secMIBC was associated with shorter CSS (HR 1.77; $p = 0.01$) and OS (HR 1.57; $p = 0.006$). Limitations include the biases inherent to the retrospective study design.

Conclusions: Patients with recHR-NMIBC and primHR-MIBC had similar survival outcomes, while those with sec-MIBC had the worst outcomes. Therefore, early radical intervention may be indicated in selected patients, and potentially neoadjuvant systemic therapies in some patients with recHR-NMIBC.

Patient summary: We compared cancer outcomes in different bladder cancer scenarios in a large, multinational series of patients who underwent removal of the bladder with curative intent. We found that patients who experienced recurrence of non–muscle-invasive bladder cancer (NMIBC) had similar survival outcomes to those with initial muscle-invasive bladder cancer (MIBC), while patients who experienced progression of NMIBC to MIBC had the worst outcomes. Selected patients with non–muscle-invasive disease may benefit from early radical surgery or from perioperative chemotherapy or immunotherapy.

1. Introduction

Approximately 75% of cases of urothelial carcinoma of the bladder (UCB) are diagnosed at a non–muscle-invasive stage (NMIBC) [1]. The main goal in the treatment of NMIBC is to reduce tumor recurrence and prevent tumor progression to muscle-invasive bladder cancer (MIBC). Therefore, NMIBC is classified into four groups according to the risk of progression or metastasis: low, intermediate, high, and very high-risk [2].

Considering the unpredictable, heterogeneous, and partly aggressive natural behavior of very high-risk and high-risk NMIBC (grouped together as HR-NMIBC for this study) and the dramatic impact on metastasis-free and cancer-specific survival (CSS) once the cancer reaches the MIBC stage [3], these patients deserve special consideration and close follow-up. However, while patients with low- or intermediate-risk NMIBC are treated conservatively [1] and those with MIBC are managed with radical cystectomy (RC) [4], the optimal therapy for HR-NMIBC is controversial [5,6]. Although a majority of these patients can be treated with conservative and/or intravesical strategies, others may benefit from early RC. Thus, depending on treatment and disease history, RC can be selected along the HR-NMIBC disease spectrum at diagnosis (immediate RC for primary NMIBC), at recurrence/failure of conservative measures (early RC for recurrent NMIBC), or after progression to MIBC (late RC for secondary MIBC).

Previous studies showed that patients who underwent RC for recurrent HR-NMIBC had worse oncological outcomes than those with primary HR-NMIBC [7–9]. By contrast, data comparing oncological outcomes for patients with primary and secondary MIBC are conflicting [10–13]. There are no conclusive data regarding the comparative prognosis of RC for primary HR-NMIBC, recurrent HR-NMIBC, secondary MIBC, and primary MIBC. Therefore, to fill this gap we aimed to compare oncological outcomes between these four disease states using a large multicenter cohort.

2. Patients and methods

2.1. Cohort description

This retrospective study included 908 consecutive patients who were treated with RC for diagnosis of high-risk or very high-risk NMIBC (HR-NMIBC; comprising exclusively patients with clinical T1 grade 3

disease at high risk or very high risk) or nonmetastatic MIBC (comprising patients with clinical T2–4 disease) at three expert academic centers between 2003 and 2015. Patients who received neoadjuvant chemotherapy (NAC) were not included in the analysis to allow for assessment of the natural disease history. Furthermore, patients who received perioperative radiation or had any concomitant secondary malignancies other than UCB or concomitant upper urinary tract carcinoma, and those with missing data were excluded. The study cohort was divided into four populations: (1) patients diagnosed with primary HR-NMIBC (primHR-NMIBC); (2) patients diagnosed with primary MIBC (primMIBC); (3) patients with a history of any NMIBC treated with transurethral resection (TUR) with or without intravesical therapy who experienced recurrence as HR-NMIBC (recHR-NMIBC); and (4) patients with NMIBC who progressed to MIBC during follow-up (defined as secondary MIBC, secMIBC).

The primary objective of this study was to compare survival outcomes between the four groups using recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) as primary endpoints. The secondary objective was to compare the differential rates of adverse pathological features at the time of RC, including lymph node involvement, non–bladder-confined disease (any ≥pT3N0/+), and pathological upstaging.

The study was approved by the local ethics committees of all participating institutions. All sites agreed to institutional data-sharing before study initiation.

2.2. Procedure-specific features and follow-up

The initial TUR of urinary bladder tumors was generally performed as a macroscopically complete resection of the entire tumor with a deep layer including smooth muscle. Patients diagnosed with recHR-NMIBC or secMIBC received prior intravesical therapy. Intravesical therapy was administered according to risk categories and at the physician's discretion on the basis of current guidelines. These patients received at least one induction and maintenance cycle of bacillus Calmette-Guérin (BCG; for patients at intermediate, high, or very high risk) or postoperative application of at least one course of intravesical chemotherapy (for patients at low or intermediate risk). Follow-up for these patients was based on their risk group, the institutional protocols in accordance with local guidelines at the time, or the discretion of the treating physician. In general, low-risk patients received cystoscopy at 3 mo, 12 mo, and annually thereafter up to 5 yr. Patients with HR-NMIBC were followed with cystoscopy every 3 mo for the first 2 yr, then every 6 mo up to 5 yr, and annually thereafter, as well as annual cross-sectional imaging of the abdomen.

The indication for RC in NMIBC patients with disease persistence/recurrence was persistent carcinoma in situ (CIS) at 6 mo after BCG maintenance or repeat induction, or for high-risk/very high-risk recurrence despite adequate BCG instillation therapy. Furthermore, RC was indicated in cases of BCG intolerance and evidence of high-risk persistence/recurrence, or in cases with evidence of high-risk persistence/recurrence after intravesical chemotherapy and patient preference for radical instead of BCG therapy. For patients with an initial nonmetastatic, muscle-invasive tumor stage (cT2–4N0M0), the indication for RC was immediate. The indication for RC for patients with primHR-NMIBC was based on the presence of risk factors for disease progression according to the current treatment guidelines and after shared decision-making with the patient. Preoperative tumor staging was not standardized across the centers included in the study and was at the discretion of the surgeon. When performed, staging was based on cross-sectional imaging of the chest, abdomen, and pelvis. Clinical T stage was determined on the basis of imaging and pathological findings after TUR.

RC and lymph node dissection were performed via an open approach in all patients. The extent of lymphadenectomy and the choice of urinary diversion were at the surgeon's discretion. All specimens were staged according to the 2017 American Joint Committee on Cancer TNM staging system and graded according to the 1973 World Health Organization grading system by genitourinary pathologists. Pelvic lymph node dissections were examined grossly, and all lymphoid tissue was submitted for histological examination. A positive soft-tissue surgical margin was defined as the presence of tumor at inked areas of soft tissue on the RC specimen. Urethral or ureteral margins were not considered as soft-tissue surgical margins. Lymphovascular invasion was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular walls.

For the secondary objective of the study, patients were categorized according to discrepancy between clinical and pathological TN(M) staging. Pathological upstaging was defined as higher pathological than clinical T stage (cT < pT) or the presence of positive lymph nodes in the surgical specimen (pN+) after no suspicious metastatic lymph nodes were detected on clinical staging (cN0). Pathological downstaging was defined as lower pathological than clinical stage (cT > pT) and negative lymph nodes in the surgical specimen (pN0), whereas same stage was defined as the same clinical and pathological TN(M) stage (cTN = pTN).

Adjuvant chemotherapy was administered to 157 patients (17%) according to guideline recommendations and/or at the discretion of the treating physician after shared decision-making with the patient. Oncological follow-up was not standardized and was performed in accordance with institutional protocols and contemporary guidelines. In general, patients underwent a physical examination and radiological imaging every 3 mo for the first 2 yr and then every 6 mo up to 5 yr. After 5 yr, annual follow-up was performed. Disease recurrence was defined as the presence of locoregional recurrence or distant metastasis on radiological imaging. The cause of death was determined by the responsible physicians and confirmed by chart review and/or death certificates.

2.3. Statistical analysis

Results for categorical variables are reported as frequency and proportion, and those for continuous variables as the median and interquartile range (IQR). To assess differences between groups, Pearson's χ^2 or Fisher's exact test were used for categorical variables and the Mann-Whitney U test for continuous variables. Kaplan-Meier curves and log-rank analyses were used to compare RFS, CSS, and OS between groups. Univariable and multivariable (adjusted for covariates with a significant association on univariable regression analysis) Cox and logistic regression analyses were carried out to investigate the association between disease status and RFS, CSS, OS, and adverse pathological findings, respectively. Statistical significance was set at $p < 0.05$. All tests were two-sided. All statistical analyses were performed using R v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Clinical characteristics

We included 908 patients who underwent RC for UCB, of whom 211 (23%) had primHR-NMIBC, 125 (14%) had recHR-NMIBC, 404 (44%) had primMIBC, and 168 (19%) had secMIBC. The median age was 66 yr (IQR 60–73) and 711 patients (78%) were male. Clinical and pathological demographics stratified by disease status are shown in Table 1. Patients with secMIBC had more aggressive disease, with ≥pT3 stage ($p < 0.001$), lymphovascular invasion ($p < 0.001$), and lymph node involvement ($p < 0.001$) more frequent in this group.

Table 1 – Descriptive statistics for the cohort of 908 patients treated with radical cystectomy for urothelial carcinoma of the bladder, stratified according to disease status

Parameter	Total cohort	Groups				
	n = 908	Primary hrNMIBC *n* = 211	Recurrent hrNMIBC *n* = 125	Primary MIBC *n* = 404	Secondary MIBC *n* = 168	*p* value[a]
Median age, yr (IQR)	66 (60–73)	66 (59–72)	67 (63–75)	66 (59–72)	67 (60–73)	0.3
Gender, *n* (%)						0.4
Male	711 (78)	166 (79)	100 (80)	322 (80)	123 (73)	
Female	197 (22)	45 (21)	25 (20)	82 (20)	45 (27)	
Clinical tumor stage, *n* (%)						<0.001
cTa/cTis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
cT1	336 (37)	211 (100)	125 (100)	0 (0)	0 (0)	
cT2	505 (56)	0 (0)	0 (0)	355 (88)	150 (89)	
cT3	38 (4)	0 (0)	0 (0)	29 (7)	9 (5.5)	
cT4	29 (3)	0 (0)	0 (0)	20 (5)	9 (5.5)	
Clinical tumor grade, *n* (%)						>0.9
Grade 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Grade 3	907 (99.9)	211 (100)	125 (100)	404 (100)	167 (99.4)	
Missing	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.6)	
Prior IVT, *n* (%)						<0.001
No IVT	615 (68)	211 (100)	0 (0)	404 (100)	0 (0)	
Bacillus Calmette-Guérin	195 (21)	0 (0)	88 (70)	0 (0)	107 (64)	
Other IVT	44 (4.8)	0 (0)	19 (15)	0 (0)	25 (15)	
Missing	54 (5.9)	0 (0)	18 (14)	0 (0)	36 (21)	
pT stage, *n* (%)						<0.001
pT0	57 (6)	11 (5.5)	3 (2.5)	36 (9)	7 (4)	
pTa	14 (1.5)	7 (3.5)	4 (3.5)	3 (0.5)	0 (0)	
pTis	86 (9.5)	28 (13)	18 (14)	34 (8.5)	6 (3.5)	
pT1	134 (15)	69 (33)	24 (19)	29 (7)	12 (7)	
pT2	227 (25)	38 (18)	36 (29)	108 (27)	45 (27)	
pT3	270 (30)	43 (20)	26 (21)	138 (34)	63 (37.5)	
pT4	120 (13)	15 (7)	14 (11)	56 (14)	35 (21)	
NOCD (pT3/4 and/or N+), *n* (%)	464 (51)	69 (33)	50 (40)	221 (55)	124 (74)	<0.001
pT grade, *n* (%)						0.01
Grade 1	57 (6.3)	11 (5.2)	3 (2.4)	36 (8.9)	7 (4.2)	
Grade 2	6 (0.7)	4 (1.9)	1 (0.8)	1 (0.2)	0 (0)	
Grade 3	845 (93)	196 (93)	121 (97)	367 (91)	161 (96)	
Concomitant CIS, *n* (%)	496 (55)	108 (51)	67 (54)	231 (57)	90 (54)	0.5
PSM, *n* (%)	85 (9.4)	16 (7.6)	15 (12)	33 (8.2)	21 (12)	0.2
LVI, *n* (%)	283 (31)	33 (16)	30 (24)	127 (31)	93 (55)	<0.001
Lymph nodes removed						<0.001
Median (IQR)	19 (12–32)	17 (10–27)	17 (10–30)	22 (13–33)	21 (13–33)	
Mean	23.2	20.0	20.7	25.5	23.9	
Positive lymph nodes						<0.001
Median (IQR)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–2.25)	
Mean	1.5	0.4	1.4	1.6	2.8	
LNI, *n* (%)	241 (27)	25 (12)	27 (22)	109 (27)	80 (48)	<0.001
Adjuvant CTx, *n* (%)	157 (17)	29 (14)	11 (8.8)	76 (19)	41 (24)	0.002
cT vs pT stage, *n* (%)						<0.001
Same stage	272 (30)	101 (48)	42 (34)	96 (24)	33 (20)	
Downstaging	135 (15)	11 (5.2)	3 (2.4)	102 (25)	19 (11)	
Upstaging	501 (55)	99 (47)	80 (64)	206 (51)	116 (69)	

CIS = carcinoma in situ; CTx = chemotherapy; hrNMIBC = high-risk non–muscle-invasive bladder cancer; IQR = interquartile range; IVT = intravesical therapy; LNI = lymph node involvement; LVI = lymphovascular invasion; MIBC = muscle-invasive bladder cancer; NOCD = non–organ confined disease; PSM = positive soft-tissue surgical margin.

[a] Kruskal-Wallis rank-sum test, Pearson's χ^2 test, or Fisher's exact test.

Consequently, these patients received adjuvant chemotherapy more frequently ($p = 0.002$) in comparison to the other groups. Rates of pathological upstaging were significantly higher for recHR-NMIBC and secMIBC ($p < 0.001$).

3.2. Survival outcomes

The median follow-up for our cohort was 37 mo (IQR 14–124). Overall, 304 patients (33%) experienced recurrence, 277 (31%) died from bladder cancer, and 509 (56%) died from any cause.

The 5-yr estimates for RFS, CSS, and OS were 77.9%, 83.2%, and 72.7% for primHR-NMIBC, 60.0%, 59%, and 48.9% for recHR-NMIBC, 60.9%, 64.5%, and 54.8% for primMIBC, and 41.3%, 46.5%, and 39% for secMIBC, respectively.

Pairwise log-rank analysis revealed that the recHR-NMIBC group had similar oncological outcomes in terms of RFS, CSS, and OS to the primMIBC group (all $p > 0.7$). Comparisons for the other groups showed significant differences in RFS, CSS, and OS (all $p < 0.02$; Fig. 1A–C).

Predictive factors for RFS, CSS, and OS are shown in Table 2. On univariable Cox regression analyses, recHR-NMIBC, primMIBC, and secMIBC were all predictors for shorter RFS, CSS, and OS in comparison to primHR-NMIBC. On multivariable analysis, recHR-NMIBC remained an independent predictor for shorter RFS (hazard ratio [HR] 1.64,

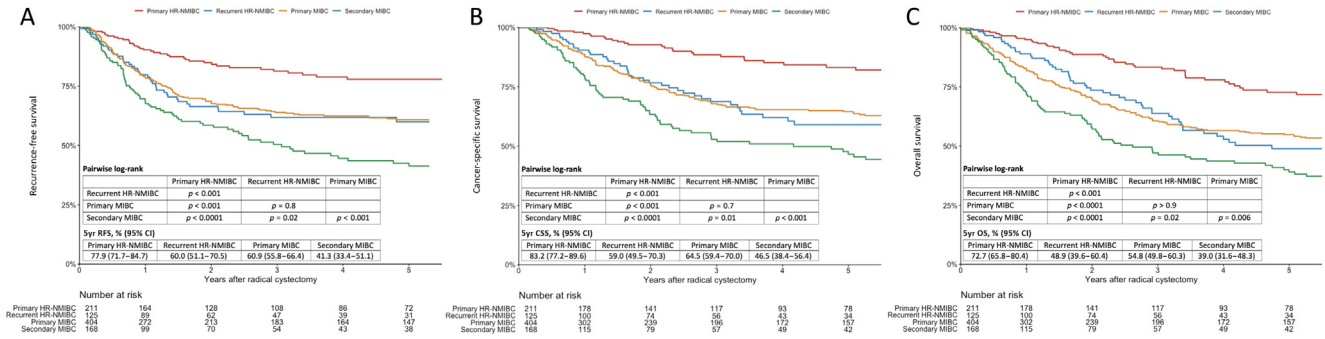

Fig. 1 – Kaplan-Meier analysis and log-rank tests for (A) recurrence-free survival (RFS), (B) cancer-specific survival (CSS), and (C) overall survival (OS) stratified by disease status. Patients with recurrent high-risk non–muscle-invasive bladder cancer (HR-NMIBC) and those with primary muscle-invasive bladder cancer (MIBC) experienced similar survival outcomes, while patients with secondary muscle-invasive bladder cancer had the worst outcomes. CI = confidence interval.

95% confidence interval [CI] 1.06–2.53; p = 0.03), CSS (HR 1.79, 95% CI 1.12–2.85; p = 0.01), and OS (HR 1.45, 95% CI 1.04–2.02; p = 0.03), while secMIBC was a predictor for shorter CSS (HR 1.77, 95% CI 1.14–2.74; p = 0.01) and OS (HR 1.57, 95% CI 1.14–2.15; p = 0.006). primMIBC was an independent predictor for shorter OS (HR 1.39, 95% CI 1.06–1.83; p = 0.02).

3.3. *Association with adverse pathological findings*

Table 3 shows predictors of lymph node involvement, ≥pT3 disease, and pathological upstaging. On univariable logistic regression analyses, recHR-NMIBC was a predictor of lymph node involvement and pathological upstaging in comparison to primHR-NMIBC, while primMIBC was a predictor for lymph node involvement and ≥pT3 disease. secMIBC was a predictor for lymph node involvement, ≥pT3 disease, and pathological upstaging. On multivariable regression analyses, recHR-NMIBC remained an independent predictor for pathological upstaging (odds ratio [OR] 2.01, 95% CI 1.23–3.30; p = 0.005). primMIBC and secMIBC were both independent predictors of lymph node involvement (OR 1.88, 95% CI 1.14–3.19; p = 0.02; and OR 3.52, 95% CI 2.02–6.26; p < 0.001, respectively) and ≥pT3 disease (OR 2.17, 95% CI 1.48–3.22; p < 0.001; and OR 2.21, 95% CI 1.38–3.57; p = 0.001, respectively), but not of pathological upstaging.

4. Discussion

In the present study, we compared oncological outcomes for four scenarios for UCB treated with RC in daily clinical practice.

The most important finding is that patients with recHR-NMIBC had similar survival outcomes (RFS, CSS, and OS) to those for patients with primMIBC.

With 5-yr CSS of 65% and OS of 55%, the oncological outcomes for our primMIBC cohort are similar to those reported for previous cohorts [14]. By contrast, we found worse oncological outcomes (5-yr CSS of 59% and OS of 49%) for our recHR-NMIBC cohort than previously described [8,9,15,16]. These differences could mainly be explained by the high heterogeneity for stage, grade, and the presence of CIS in these studies, whereas we investigated a very homogeneous population of patients with exclusively T1 grade 3 disease.

Our multivariable Cox regression analysis revealed that recHR-NMIBC was associated with shorter RFS, CSS, and OS in comparison to primHR-NMIBC. These results may indicate a more aggressive tumor biology. In this regard, previous studies have postulated that recurrent NMIBC has a more aggressive tumor biology associated with progression and worse survival outcomes in comparison to primary tumors [17]. Researchers were able to classify NMIBC into different subtypes on the basis of their molecular characteristics, which were associated with different clinical outcomes [18,19]. Furthermore, genomic alterations of well-known cancer driver genes were associated with HR-NMIBC and were independent predictors of recurrence, progression, and worse survival outcomes [18,20–22]. For example, a study by Pietzak and colleagues [21] showed that patients whose tumors harbored *ARID1A* mutations experienced significantly worse RFS after BCG induction treatment and the mutation was associated with high-grade tumors and worse survival prognosis.

Our finding of an independent association of recHR-NMIBC with pathological upstaging might be explained by the greater aggressiveness of these tumors and partly by early micrometastasis via invasion of the lamina propria. The hypothesis of early micrometastasis of these "superficial" tumors is supported by several studies reporting detection of circulating tumor cells (CTCs) in 20–40% of patients with HR-NMIBC [23–25]. For example, in a study including 102 patients with HR-NMIBC (T1 grade 3), Gazzaniga et al. [23] showed that CTC presence was an independent predictor of shorter RFS and the strongest predictor of progression-free survival. This suggests that these patients might benefit from neoadjuvant systemic therapy to eliminate micrometastatic lesions.

The phase 2 KEYNOTE-057 trial, which evaluated the efficacy of neoadjuvant pembrolizumab in HR-NMIBC for patients with BCG-unresponsive CIS with or without papillary tumors, provides promising results in this setting [26]. Moreover, several trials of neoadjuvant checkpoint inhibitors are ongoing (eg, SWOG 1605, NCT02844816; ADAPT-Bladder, NCT03317158; KEYNOTE-676, NCT03711032) as

Table 2 – Univariable and multivariable Cox regression analyses assessing the association of the four different disease scenarios with recurrence-free survival, cancer-specific survival, and overall survival among 908 patients treated with radical cystectomy for urothelial carcinoma of the bladder

Parameter	Recurrence-free survival				Cancer-specific survival				Overall survival			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Disease status vs primary hrNMIBC												
Recurrent hrNMIBC	2.10 (1.37–3.23)	<0.001	1.64 (1.06–2.53)	0.03	2.33 (1.47–3.68)	<0.001	1.79 (1.12–2.85)	0.01	1.77 (1.28–2.46)	<0.001	1.45 (1.04–2.02)	0.03
Primary MIBC	1.98 (1.39–2.81)	<0.001	1.27 (0.88–1.84)	0.2	2.16 (1.47–3.17)	<0.001	1.36 (0.91–2.03)	0.1	1.76 (1.36–2.28)	<0.001	1.39 (1.06–1.83)	0.02
Secondary MIBC	3.29 (2.25–4.8)	<0.001	1.49 (0.99–2.23)	0.06	3.87 (2.57–5.82)	<0.001	1.77 (1.14–2.74)	0.01	2.51 (1.87–3.37)	<0.001	1.57 (1.14–2.15)	0.006
Age	1.02 (1.00–1.03)	0.008	1.01 (1.00–1.02)	0.2	1.02 (1.01–1.03)	0.003	1.01 (1.00–1.03)	0.04	1.05 (1.04–1.06)	<0.001	1.04 (1.03–1.05)	<0.001
Female gender	1.51 (1.17–1.96)	0.002	1.52 (1.17–1.97)	0.002	1.68 (1.29–2.18)	<0.001	1.65 (1.26–2.16)	<0.001	1.41 (1.15–1.73)	<0.001	1.44 (1.17–1.77)	<0.001
pT stage vs ≤pT1												
pT2	2.02 (1.36–3.00)	<0.001	1.46 (0.97–2.21)	0.07	2.08 (1.38–3.16)	<0.001	1.43 (0.93–2.21)	0.10	1.61 (1.26–2.07)	<0.001	1.37 (1.05–1.78)	0.02
≥pT3	5.83 (4.17–8.15)	<0.001	3.28 (2.24–4.80)	<0.001	6.19 (4.36–8.81)	<0.001	3.20 (2.14–4.78)	<0.001	3.47 (2.78–4.33)	<0.001	2.32 (1.79–3.02)	<0.001
LNI	3.72 (2.96–4.68)	<0.001	2.08 (1.59–2.73)	<0.001	3.98 (3.13–5.06)	<0.001	2.15 (1.62–2.85)	<0.001	2.50 (2.07–3.02)	<0.001	1.87 (1.49–2.34)	<0.001
No. of LNs removed	1.00 (0.99–1.00)	0.5			0.99 (0.99–1.00)	0.2			0.99 (0.98–1.00)	<0.001	1.00 (0.99–1.00)	0.1
PSM	2.76 (2.02–3.78)	<0.001	1.41 (1.01–1.96)	0.04	3.06 (2.22–4.23)	<0.001	1.57 (1.11–2.21)	0.01	2.22 (1.67–2.94)	<0.001	1.17 (0.87–1.59)	0.3
LVI	3.00 (2.40–3.77)	<0.001	1.42 (1.09–1.84)	0.009	3.23 (2.55–4.09)	<0.001	1.48 (1.12–1.94)	0.005	2.10 (1.75–2.51)	<0.001	1.19 (0.97–1.47)	0.1
Concomitant CIS	0.90 (0.72–1.13)	0.4			0.84 (0.66–1.06)	0.1			0.97 (0.81–1.16)	0.7		
Adjuvant CTx	2.06 (1.61–2.64)	<0.001	1.00 (0.75–1.32)	>0.9	2.12 (1.64–2.75)	<0.001	1.01 (0.76–1.36)	>0.9	1.43 (1.16–1.77)	0.001	0.89 (0.70–1.14)	0.4

CI = confidence interval; CIS = carcinoma in situ; CTx = chemotherapy; HR = hazard ratio; LNI = lymph node involvement; LNs = lymph nodes; LVI = lymphovascular invasion; MIBC = muscle-invasive bladder cancer; hrNMIBC = high-risk non–muscle-invasive bladder cancer; PSM = positive soft-tissue surgical margin.

Table 3 – Univariable and multivariable logistic regression analysis predicting lymph node involvement, ≥pT3 disease, and pathological upstaging in 908 patients treated with radical cystectomy for urothelial carcinoma of the bladder

Parameter	Lymph node involvement				≥pT3 disease				Pathological upstaging			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Disease status vs primary hrNMIBC												
Recurrent hrNMIBC	2.05 (1.13–3.74)	0.02	1.76 (0.92–3.36)	0.09	1.24 (0.76–2.01)	0.4	1.07 (0.64–1.80)	0.8	2.01 (1.28–3.18)	0.003	2.01 (1.23–3.30)	0.005
Primary MIBC	2.75 (1.74–4.49)	<0.001	1.88 (1.14–3.19)	0.02	2.44 (1.71–3.51)	<0.001	2.17 (1.48–3.22)	<0.001	1.18 (0.84–1.64)	0.3	0.97 (0.67–1.41)	0.9
Secondary MIBC	6.76 (4.09–11.5)	<0.001	3.52 (2.02–6.26)	<0.001	3.69 (2.41–5.71)	<0.001	2.21 (1.38–3.57)	0.001	2.52 (1.66–3.88)	<0.001	1.45 (0.90–2.35)	0.1
Age	1.00 (0.98–1.01)	0.5			1.02 (1.01–1.04)	0.003	1.02 (1.01–1.04)	0.009	1.02 (1.00–1.03)	0.01	1.01 (1.00–1.03)	0.1
Female gender	1.50 (1.06–2.10)	0.02	1.37 (0.92–2.01)	0.1	1.18 (0.86–1.62)	0.3			1.39 (1.01–1.92)	0.05	1.30 (0.91–1.86)	0.2
pT stage vs ≤pT1												
pT2	4.58 (2.67–8.16)	<0.001	2.89 (1.64–5.28)	<0.001								
≥pT3	10.7 (6.62–18.3)	<0.001	5.54 (3.21–9.64)	<0.001								
No. of LNs removed	1.00 (0.99–1.01)	0.6			0.99 (0.99–1.00)	0.2			0.99 (0.98–1.00)	0.04	1.00 (0.99–1.01)	0.5
LVI	4.82 (3.53–6.62)	<0.001	2.54 (1.78–3.62)	<0.001	5.52 (4.07–7.53)	<0.001	5.16 (3.74–7.19)	<0.001	5.67 (4.07–8.01)	<0.001	6.24 (4.37–9.06)	<0.001
Concomitant CIS	0.65 (0.49–0.88)	0.005	0.66 (0.47–0.92)	0.02	0.60 (0.46–0.78)	<0.001	0.49 (0.37–0.96)	<0.001	0.45 (0.34–0.59)	<0.001	0.38 (0.28–0.51)	<0.001

CI = confidence interval; CIS = carcinoma in situ; LNs = lymph nodes; LVI = lymphovascular invasion; MIBC = muscle-invasive bladder cancer; hrNMIBC = high-risk non–muscle-invasive bladder cancer; OR = odds ratio.

it has been shown that a subset of BCG nonresponders have elevated PD-L1 expression [25].

However, the present study emphasizes the need for better risk stratification in NMIBC to identify the best therapeutic modality for individual patients in deciding between salvage local (ie, intravesical) therapy and systemic therapy. Given the promising results regarding the prognostic ability of genetic and protein-based tumor characteristics, prospective validation could help to refine patient selection [27].

Patients with secMIBC experienced the worst survival outcomes (RFS, CSS, and OS) and secMIBC was an independent predictor of worse CSS and OS. Previous studies reported conflicting survival outcomes for secMIBC compared to primMIBC [10–13]. The most recent meta-analysis, which included 16 studies with a total of 5270 patients, revealed no differences in 5- and 10-yr CSS and OS between these two groups [12]. Pietzak et al. [28] investigated genomic differences between secMIBC and primMIBC and found significantly more *ERCC2* mutations in primMIBC, which was previously linked to better survival outcomes [29]. These findings support our results of a more aggressive tumor biology in secMIBC, but the limited data regarding genomics for these tumors warrant further studies on their molecular characteristics to provide more accurate conclusions about their biological and clinical behavior.

Our study was able to confirm previous evidence that patients who undergo immediate RC for primHR-NMIBC experience the best survival outcomes [7–9]. However, our downstaging rate of 47% and the fact that 16% of patients died of their disease despite early RC cannot be ignored. This contrasts with the potential overtreatment in a large proportion of these patients and the fact that RC can significantly affect quality of life [30]. This underlines the need for more accurate clinical staging via imaging or biomarkers to identify patients who would benefit from bladder-preserving therapies or upfront RC.

The present study has several limitations. First, this is a retrospective, multicenter study with different surgical approaches and nonstandardized practice and follow-up patterns. Second, we had no information on initial prognostic risk factors such as tumor size, variant histology, multifocality, and prostatic involvement, which precluded precise risk profiles for the HR-NMIBC groups in the study. Furthermore, we had no information on the quality of the initial resection (whether muscle was present in the TUR specimen and if a confirmatory repeat TUR was performed in patients with T1 high-grade tumors), the time and number of recurrences after TUR, the number of TURs performed, or time to RC. Moreover, we had no information on the duration of intravesical therapy or the type of intravesical therapy if no BCG was applied. It should also be noted that we excluded patients who received NAC, which has been shown to result in downstaging of the primary tumor and a lower incidence of occult lymph node metastases [31], so the oncological and pathological characteristics of the cohort may not be consistent with the results from previous studies or real-world patient populations that generally include those patients. All the factors mentioned are known to affect oncological and pathological outcomes and should be considered when interpreting our results. Third, the retrospective study design means that some patients were followed up by physicians at a local or private practice, which contributes to the relatively short median follow-up time in this study.

However, the strength of our study is the homogeneity of our patient cohorts with primary and recurrent HR-NMIBC, which were largely heterogeneous in previous studies, making it difficult to generalize the findings to clinical practice.

5. Conclusions

The present study demonstrates that patients who underwent RC for recurrent HR-NMIBC, despite an initial conservative approach with intravesical therapy, had similar survival outcomes to patients with primary MIBC, while those who experienced a progression to MIBC had the worst survival outcomes. Recurrent HR-NMIBC and secondary MIBC are independent risk factors for worse survival outcomes, suggesting a more aggressive tumor biology that might benefit from early additional systemic therapy. However, better risk stratification is needed, particularly at the NMIBC stage, to identify patients who will benefit from bladder-preserving therapy, upfront RC, or other forms of intensified management.

Author contributions: Benjamin Pradere had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Grossmann, Pradere, Shariat.
Acquisition of data: Mattei, Moschini, Chlosta, van Rhijn, Teoh, Babjuk, Karakiewicz, Shariat.
Analysis and interpretation of data: Grossmann, Pradere, Fankhauser, Shariat.
Drafting of the manuscript: Grossmann, Pradere, Shariat.
Critical revision of the manuscript for important intellectual content: Rajwa, Quhal, König, Mostafaei, Laukhtina, Mori, Katayama, Motlagh, Fankhauser, Mattei, Moschini, Chlosta, van Rhijn, Teoh, Compérat, Babjuk, Abufaraj, Karakiewicz.
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