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Oncological Outcome of Primary versus Secondary Muscle-Invasive Bladder Cancer Is Comparable after Radical Cystectomy

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Key Words
Bladder cancer · Risk stratification · EORTC risk tables · Prognosis · Progression · Radical cystectomy

Abstract
Background: High-risk non-muscle-invasive bladder cancer (NMIBC) progressing to muscle-invasive bladder cancer (MIBC) is associated with adverse tumour biology. It is unclear, however, whether outcome of NMIBC progressing to MIBC is adverse compared to primary MIBC and whether NMIBC of higher risk of progression to MIBC is adverse compared to NMIBC of lower risk. ***Objective:*** Our objective was to assess cancer-specific survival (CSS) following radical cystectomy (RC) for primary MIBC and for NMIBC progressing to MIBC in dependence of EORTC risk score. ***Materials and Methods:*** Clinical and histopathological characteristics and CSS of 150 patients were assessed. Secondary MIBCs were stratified by EORTC risk score at the last transurethral resection of bladder tumour for NMIBC. ***Results:*** CSS did not differ significantly between primary and secondary MIBC (p = 0.521). Secondary MIBC with high EORTC score had significantly shorter CSS compared to secondary MIBC with intermediate EORTC score (p = 0.029). In multivariable analysis, pathological tumour stage (HR = 3.77; p = 0.020) and lymph node stage (HR = 2.34; p = 0.022) were significantly correlated with CSS. ***Conclusion:*** While the outcome of secondary MIBC is not generally adverse compared to primary MIBC, the EORTC risk score not only reflects high risk of progression of NMIBC to MIBC, but also worse outcome following RC for secondary MIBC. Timely RC should thus be debated in high-risk NMIBC.

Introduction

Bladder cancer is the fourth most common cancer in men with severe impact on general health; it is generally divided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) [1]. Current guidelines recommend radical cystectomy (RC) with bilateral pelvic lymphadenectomy in MIBC and in NMIBC with high risk of progression [2, 3]. Risk of progression to MIBC is usually determined by the EORTC risk score combining various clinicopathological parameters [2–4]. Risk of cancer-specific mortality following RC for MIBC is usually determined by pathologi-

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cal tumour stage and lymph node status. Since cancer-specific survival (CSS) rates vary widely, other prognostic factors have been evaluated [5, 6].

Progression of NMIBC to secondary MIBC, i.e. subsequent to preceding NMIBC as opposed to primary MIBC, could be a potential prognosticator conveying favourable outcome due to the initial non-muscle-invasive character of the bladder cancer or likewise a potential prognosticator conveying adverse outcome due to its progressive tumour biology.

The EORTC risk score predicting progression of NMIBC to MIBC could also be a potential prognosticator conveying adverse outcome by again reflecting progressive tumour biology. Should this scenario be true, debate of timely RC should be emphasized in the management of high-risk NMIBC and such debate should be based on EORTC risk scores. No conclusive data are available to date.

Currently, indications for RC for bladder cancer stages <pT2 are an issue of debate. While long-term bladder preservation is pursued for quality of life reasons, a tendency to advocate RC in case of BCG-refractory and initially recurrent T1 tumour stage is notable in the recent literature, since favourable long-term outcome has been suggested for timely radical treatment [7–11]. Due to prognostic uncertainty however the clinical management of high-risk NMIBC is demanding and any further prognosticator valuable. We presently analyse CSS in a current series of RC for primary compared to secondary MIBC to assess prognostic differences and analyse CSS in relation to EORTC risk score at the last transurethral resection of bladder tumour (TURBT) for NMIBC. No such data have been reported to date.

Materials and Methods

Patient Selection

Clinical and histopathological data of consecutive patients undergoing RC for clinically localized MIBC between 2004 and 2010 at one tertiary urological centre without neoadjuvant chemotherapy were collected. Figure 1 shows the stratification of the patients into different risk groups. Patients were subdivided into two groups: patients with primary MIBC (group 1) and patients with secondary MIBC (group 2). In order to preserve homogenous patient groups we excluded patients with secondary MIBC, if no intravesical BCG therapy had been performed (n = 11) or no re-resection at the time of T1 stage and/or CIS had been performed (n = 3). In secondary MIBC, EORTC risk scores at the time of the last TURBT for NMIBC were assessed, resulting in a score from 0 to 23 [4]: (a) number of tumours (single: 0, multiple: 3); (b) tumour size (<3 cm: 0, ≥3 cm: 3); (c) prior recurrence rate (primary: 0, recurrent: 2); (d) T category (cTa: 0, cT1: 4); (e) presence of concomitant CIS (no: 0, yes: 6); (f) grade (G1–2: 0, G3: 5). Subsequently, we devised different risk groups, as reported by Sylvester et al. [3]. Due to the frequent occurrence of high-risk patients we subdivided the high-risk group: (a) low-risk group: score <2; (b) intermediate-risk group: score 2–6; (c) high-risk group A: score 7–13; (d) high-risk group B: score 14–23. Time from diagnosis of MIBC to RC and from initial TURBT for NMIBC to RC was dichotomised at 90 days in accordance with previous reports [12–14].

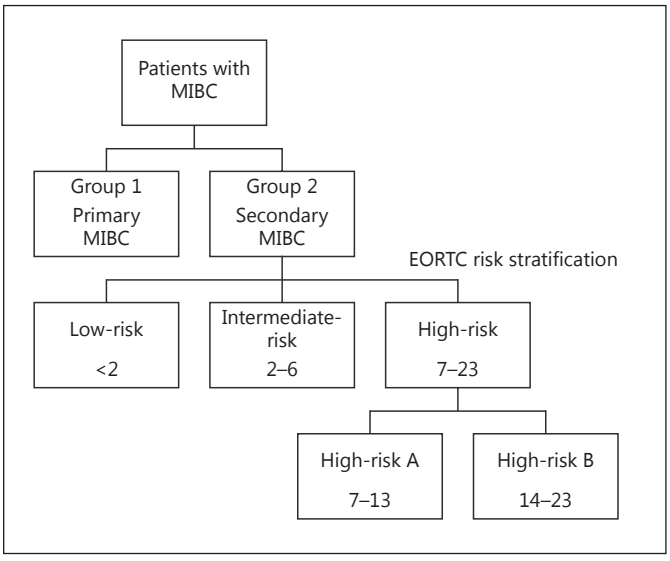

Fig. 1. Risk stratification of the patients according to EORTC.

Pathological Evaluation

Surgical specimens were processed according to standard institutional protocols. Tumour grading and staging was performed by genitourinary pathologists according to the 1973 World Health Organization (WHO) grading system and the American Joint Committee on Cancer (AJCC)-Union Internationale Contre le Cancer tumour, nodes, metastasis (TNM) classification, respectively [15, 16].

Follow-Up Regimen

Patients were followed according to institutional guidelines effective at that time largely reflecting current guidelines [2]. For the first and from the second through the fifth year after RC, follow-up visits were scheduled every 3 and 6 months, respectively, and annually thereafter with routine laboratory, ultrasound, urinary cytology, chest radiography, radiographic evaluation of the upper urinary tract and cystoscopic evaluation of the neobladder. Bone scan, computed tomography and/or magnetic resonance imagings were performed when clinically indicated. Cause of death was determined by the treating physician and death certificates.

Statistical Analysis

The hypothesis of normality for all continuous variables was tested by the Shapiro-Wilk normality test. Means and standard deviations were displayed for the continuous stable distributed variables. Medians with interquartile ranges (IQRs) were used to

Table 1. Clinical and histopathological characteristics of primary and secondary MIBC

Criteria	Entire cohort (n = 150)	Primary MIBC (n = 125)	Secondary MIBC (n = 25)	p value
Median age (IQR), years	70 (64–76)	69 (63–75.2)	71 (66.5–77.5)	0.208
Male gender	121 (80.7%)	97 (77.6%)	24 (96.0%)	0.048
cT stage, first TURBT				
<cT1	11 (7.3%)	0	11 (44.0%)	<0.001
cT1	12 (8.0%)	0	14 (56.0%)	
cT2	123 (82.0%)	121 (96.8%)	0	
cT3/4	4 (2.7%)	4 (3.2%)	0	
Number of TURBT, median (IQR)	1 (1–1)	1 (1–1)	3 (2–4.5)	<0.001
Median interval between first TURBT and RC, days (IQR)	40 (25–82)	33.5 (23.7–47.5)	539 (271.5–1,992.5)	<0.001
Interval between TURBT due to MIBC and RC ≤90 days	140 (93.3%)	118 (94.4%)	22 (88.0%)	0.371
pT stage, RC				
<pT3	57 (38.0%)	49 (39.2%)	8 (32.0%)	0.652
pT3/4	93 (62.0%)	76 (60.8%)	17 (68.0%)	
pN+ stage, RC	59 (39.3%)	50 (40.0%)	9 (36.0%)	0.824
Grade 3, RC	139 (92.7%)	114 (91.2%)	25 (100%)	0.212
Concomitant CIS, RC	72 (48.3%)	61 (49.2%)	11 (44.0%)	0.667
Lymphovascular invasion, RC	85 (56.7%)	72 (57.6%)	13 (52.0%)	0.662
Median number of lymph nodes removed (IQR)	18 (14–23)	18 (13–23)	18 (14–23.5)	0.753
Adjuvant chemotherapy	35 (23.6%)	29 (23.4%)	6 (25.0%)	1.000

present continuous not regularly distributed variables. Student's t test was applied for variables with regular and Wilcoxon rank sum (Mann-Whitney) for variables with irregular distribution, respectively. Categorical variables were compared by the χ^2 test. CSS was assessed by the Kaplan-Meier method from date of RC and impact of variables analysed by log-rank test. Impact of variables on CSS was assessed by uni- and multivariable Cox proportional Hazards regression models with backward stepwise elimination of criteria lacking significance. Subjects whose cause of death was not due to MIBC were censored at the time of death for CSS calculation. The statistical significance level was set at $p < 0.05$. All reported p values were two-sided. Statistical analysis was performed using SPSS® v19.0 (SPSS Inc., Chicago, Ill., USA).

Results

Clinical and Histopathological Outcome

Out of 150 patients, 125 (83.3%) underwent RC for primary MIBC and 25 patients (16.6%) for secondary MIBC. Clinical and histopathological characteristics are given in table 1. Mean age did not differ between primary and secondary MIBC (69; IQR 63–75.2 vs. 71; IQR 66.5–77.5; p = 0.208). Male patients were predominant in both populations (77.6 vs. 96%; p = 0.048). In secondary MIBC the median number of TURBT was 3 (IQR 2–4.5) and the median time from initial TURBT to RC was 539 days (IQR 271.5–1,992.5). No differences in the rates of delayed RC (>90 days after diagnosis of muscle invasion; p = 0.371), locally advanced tumour stages (pT3/4; p = 0.652), concomitant CIS (p = 0.667), lymph node metastasis (p = 0.824), lymphovascular invasion (p = 0.662), median number of lymph nodes removed (p = 0.753) and patients undergoing adjuvant chemotherapy (p = 1.000) were noted between primary and secondary MIBC. In secondary MIBC EORTC risk score of progression at the last TURBT for NMIBC was intermediate-risk in 6, high-risk A in 9 and high-risk B in 10 patients.

Oncological Outcome

The median follow-up was 46 months (IQR 31–62). In the entire population, CSS after 1, 3 and 5 years were 83, 67 and 59%, respectively. Pathological tumour stage pT3/4 (HR = 3.77; p = 0.020) and lymph node metastasis (HR = 2.34; p = 0.022) were independently associated with CSS in multivariate analysis (table 2). CSS did not differ significantly between primary and secondary MIBC (p = 0.521; fig. 2). Patients with secondary MIBC classified as high-risk A of progression at the last TURBT for NMIBC (14–23) showed significantly worse CSS compared to intermediate-risk or high-risk B patients (p = 0.029 and p = 0.033; fig. 3).

Table 2. Uni- and multivariable Cox regression analysis of CSS

Criteria	Univariable analysis, HR (95% CI)	p value	Multivariable analysis, HR (95% CI), backward stepwise elimination	p value
Age, cont.	1.03 (0.99–1.06)	0.128		n.s.
Female gender (referent male)	1.42 (0.68–2.94)	0.351		n.s.
Interval between first TURBT and RC, cont.	1.00 (1.00–1.00)	0.984		n.s.
Interval between TURBT due MIBC and RC >90 days (referent ≤90 days)	1.26 (0.45–3.52)	0.657		n.s.
pT3/4 stage, RC (referent ≤pT2)	8.95 (3.19–25.05)	<0.001	3.77 (1.24–11.47)	0.020
pN+ stage, RC (referent pN0)	5.05 (2.68–9.51)	<0.001	2.34 (1.13–4.84)	0.022
Grade 3, RC (referent <grade 3)	3.94 (0.54–28.56)	0.175		n.s.
Concomitant CIS, RC (referent absent CIS)	0.95 (0.53–1.70)	0.858		n.s.
Lymphovascular invasion, RC (referent absent LVI)	5.66 (2.53–12.68)	<0.001		n.s.
Number of lymph nodes removed, cont.	1.00 (0.97–1.03)	0.988		n.s.
Adjuvant chemotherapy (referent no adjuvant chemotherapy)	3.71 (2.03–6.75)	<0.001		n.s.
Secondary muscle invasion (referent primary)	0.77 (0.34–1.72)	0.524		n.s.

Discussion

Does Outcome of Primary and Secondary MIBC Differ?

No definitely conclusive data on survival rates after RC for secondary MIBC subsequent to preceding NMIBC compared to primary MIBC have been reported to date and the present literature is arbitrary. In 2002, Yiou et al. [17] compared 43 and 12 patients with primary and secondary MIBC, respectively, reporting no difference in survival. May et al. [18] compared 132 and 57 patients with primary and secondary MIBC, respectively, again finding no difference in outcome or any other clinicopathological parameter. While May at al.'s series was larger than the present one, it was assessed in retrospect from various institutions while the present series was assessed prospectively with homogeneous treatment pattern due to institutional guidelines of one centre. In analogy to the present analyses, those series found no differences in outcome between primary versus secondary MIBC [17, 18]. A more recent retrospective series by de Vries et al. [19] assessing 134 and 54 patients with primary and secondary MIBC, respectively, found comparable survival rates. The most recent series by Kotb et al. [20] analysed 1,150 patients from the Canadian Bladder Cancer Network containing 32% of patients with secondary MIBC. In this series, outcome of secondary MIBC was advantageous, as CSS at 5 years was 70% compared to 60% of primary MIBC. While age at MIBC was comparable, many other factors were adverse in primary MIBC, e.g. presence of preoperative hydronephrosis (20.8 vs. 32.6%; p = 0.0007), rate of higher pathological stage (T3/T4; 36.3 vs. 58.0%; p = 0.0001), positive lymph nodes (20.1 vs. 28.8%; p = 0.002) and rates of adjuvant chemotherapy (15.5 vs. 23.3%; p = 0.002). The authors concluded that secondary MIBC may have better clinical and pathological outcome. In contrast to the present series no details on NMIBC prior to MIBC were available and according to the authors different approaches toward early cystectomy in each centre might have biased the results [20].

In accordance with the former series and in contrast to the most recent analysis our data again do not suggest generally adverse outcome of either variation. No other factor biasing CSS was noted in the present series. The ratio of patients with secondary MIBC of all patients undergoing RC for MIBC in the present series was 25% and thus within the range of previous series (21.4 to 29.4%) [18–22]. No differences in e.g. tumours stage, lymph node status or use of adjuvant chemotherapy were noted. Thus the present homogeneous and well-controlled data, also including detailed information of NMIBC preceding MIBC, suggest comparable outcome for primary and secondary MIBC.

Does Risk of Progression of NMIBC Matter for Outcome of Secondary MIBC?

Risk of progression does convey adverse tumour biology; accordingly the outcome of RC for high-risk NMIBC is still compromised in some cases despite radical tumour removal. Accordingly, risk of progression at time of last TURBT for NMIBC prior to MIBC could reflect outcome. To date, only one series assessed risk of progression; de Vries et al. [19] stratified 54 NMIBC in one low/intermediate- and one high-risk group (n = 25 and n = 29, respec-

tively), reporting 5-year survival rates of 75 vs. 35%, respectively. While numbers are comparably small in de Vries et al.'s and our series, we found comparable CSS rates for patients with high EORTC risk scores (67% for the high-risk A group) and markedly advantageous outcome in patients with low EORTC risk scores of progression (p = 0.029).

Which Conclusions Can Be Drawn for the Management of High-Risk NMIBC?

Outcome of secondary MIBC is generally critical; some 50% of the patients with cT2N0M0 had died from disease after 5 years. While this can be partly attributed to the high rate of upstaging to tumour stages ≥pT3 and/or pN+, which is in accordance with the recent series by de Vries et al. and has been reported for up to 50% of all patients undergoing RC for MIBC [19, 22], it stresses the need for close follow-up of NMIBC at risk of progression. The present data furthermore demonstrate secondary MIBC subsequent to preceding NMIBC at high risk of progression to be brittle. Accordingly, debate of early RC should be considered previous to MIBC in high-risk NMIBC. This aspect is all the more challenging in the absence of reliable prognosticators of high-risk NMIBC. Recently, shortcomings of current grading systems for prognostic assessment were suggested [23]. Likewise, substaging of pT1 NMIBC in relation to depth of lamina propria invasion has been proposed due to inaccuracy of prognostic assessment [24, 25]. Molecular markers seem not to suffice in this regard and require further assessment [5, 26, 27]. Thus, the present data emphasize the use of the EORTC risk score of progression in high-risk NMIBC to gain some additional prognostic information.

Which Limitations of the Present Series Need to Be Taken into Account?

The present series is marked by several limitations. For one, the present dataset is small, containing but 25 patients with secondary MIBC. To date, no considerably larger dataset which is fairly homogeneous and well-controlled for biasing factors has been reported. Second, while the present data were assessed prospectively, EORTC risk scores were assigned retrospectively for the earlier years of the present series based on clinicopathological characteristics assessed at the time of TURBT. Third, while control for use of BCG therapy had been exerted in secondary MIBC, no exact control for number of doses and duration of therapy could be achieved. Fourth, no patient in the present series obtained neoadjuvant chemotherapy despite more recent respective recommendations [3], which could compromise comparability to other data.

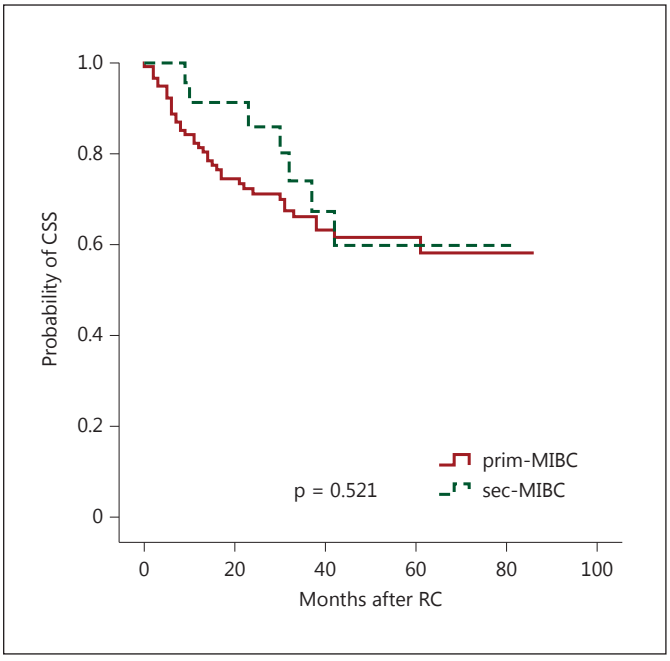

Fig. 2. Probability estimates of CSS in primary MIBC (n = 125; prim-MIBC) and secondary MIBC (n = 25; sec-MIBC).

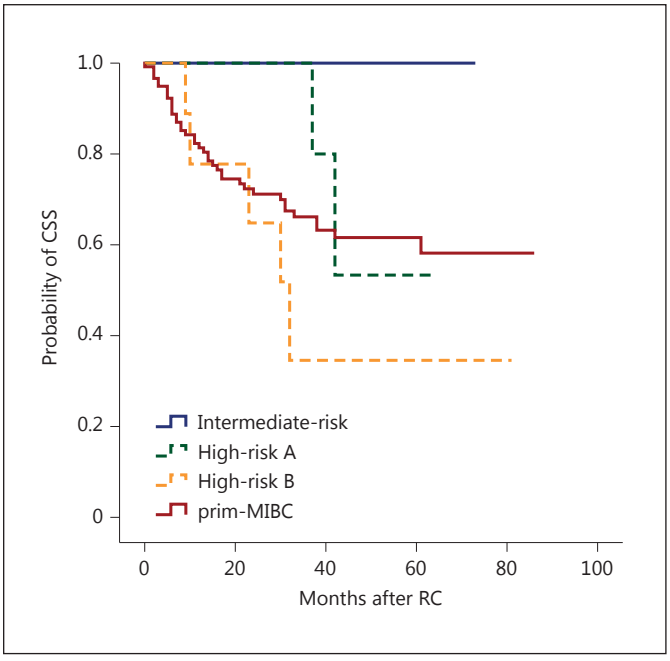

Fig. 3. Probability estimates of CSS after RC in primary MIBC (n = 125; prim-MIBC) and secondary MIBC stratified according to the EORTC risk scores of progression predicting at time of last TURBT for NMIBC [intermediate-risk group (score 2–6) n = 6 vs. high-risk A group (score 7–13) n = 9 vs. high-risk B group (score 14–23) n = 10].

Conclusions

Outcome of secondary MIBC subsequent to previous NMIBC is not generally adverse compared to primary MIBC. In high-risk NMIBC debate of early RC should be considered, since high EORTC risk scores of progression at the last TURBT for NMIBC convey poor prognosis not only for progression to MIBC but also for outcome of secondary MIBC following RC.

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