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ARTICLE

Radical cystectomy compared to intravesical BCG immunotherapy for high-risk non-muscle invasive bladder cancer – is there a long-term survival difference? A Swedish nationwide analysis

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ABSTRACT

Objectives: High-risk non-muscle invasive urinary bladder cancer (NMIBC) presents an increased risk of progression and cancer death. To reduce these risks, two different treatments are recommended – BCG or radical cystectomy (RC). The purpose of this study is to analyze cancer-specific survival of these two initial treatments.

Materials and Methods: BladderBaSe links information from the SNRUBC from 1997 to 2014, with a number of national healthcare and demographic registers. BCG was used for 3,862 patients (399 had delayed RC), while 687 had initial RC. Propensity scores were used to match the patients treated with RC and with relevant variables such as age, gender, and tumor stage with the same number treated with BCG (673 each arm). In a further comparison, an instrumental variable analysis using hospital strategy as the instrument was used.

Results: The 5-year cancer-specific survival chance was higher for the BCG group than it was for the initial RC group, 87 vs 71%, respectively. In the population with propensity score matching, 78 died from cancer in the BCG group during follow-up and 162 in the RC group. In the instrumental variable analysis, the multivariate adjusted risk difference of cancer-specific death 2 years after diagnosis was 32 per 100 treated patients, in favor of the BCG group.

Conclusions: BCG therapy had better cancer-specific survival than RC also when two different statistic methods were used to try to control for confounding. A prospective randomized trial will be necessary to rule out that selection is a major factor for the outcome.

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High-risk non-muscle invasive bladder cancer; intravesical BCG immunotherapy; radical cystectomy; long-term survival

Introduction

Urinary bladder cancer is the third most common form of cancer among men and the ninth among women in Sweden. At the time of bladder cancer detection, about 2/3 are non-muscle invasive bladder cancer (NMIBC). The high-risk NMIBC tumor types according to the Bravo Study (TaG3, T1G2, T1G3 or/and Tis) present an increased risk of progression to deep-growing cancer and metastasis [1]. To reduce the risk of progression and mortality, two different treatments are often contemplated in addition to transurethral resection (TURBT) – radical cystectomy (RC) or Bacillus Calmette-Guérin (BCG) instillation. In Sweden, it has been shown that the choice of initial treatment varies between different healthcare regions [2]. However, there is no controlled data on how cancer specific and overall survival time are affected between these two treatments.

The aim of this population-based observational cohort study was to investigate the risk of bladder cancer and all-causes death using detailed prospectively registered individual data on patient demographics, tumor characteristics, comorbidity and follow-up in patients with high-risk NMIBC, treated with BCG or RC. A secondary aim was to assess survival among patients who had delayed RC after BCG therapy.

Materials and methods

Since 1997, patients with newly-diagnosed UBC have been reported to the Swedish National Register of Urinary Bladder Cancer (SNRUBC). The national register has detailed data on an average of 97% of the bladder cancer cases newly diagnosed in Sweden. The Bladder Cancer Data Base Sweden (BladderBaSe) was created in 2015. This database links information from SNRUBC from 1997–2014, with a number of national healthcare and demographic registers noted through the use of the personal identification numbers [3]. As it is additionally linked to other national registers, information on patients' comorbidities, socioeconomics, re-admissions, adverse effects and causes of death are also available. The Charlson Comorbidity Index (CCI) is calculated with data from the Patient Register to estimate the concomitant disease burden, as described elsewhere [3].

The primary outcome was determined as death either from all causes or from bladder cancer specifically. Date and cause of death were obtained from the Cause of Death Register and death from bladder cancer was defined as International Classification of Disease (ICD)-10 code C67.

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The project was approved by the Research Ethics Board at Uppsala University, Sweden (DNR 2015/277).

Selection of study sample

Patients with high risk NMIBC (TaG3, T1G2, T1G3 or/and Tis) were selected for the current study. Data on gender, age at diagnosis, date of diagnosis, healthcare region, follow-up time, decision on type of primary treatment and timing thereof, bladder cancer death and other causes of death were registered.

Trial sample – propensity score matched

To mitigate the effects of baseline confounders, propensity scores were used to match the patients from the study sample, treated with RC and with valid values on available relevant variables with the same number of patients treated with BCG. Thus, the sample was a 1:1 match, using age at diagnosis, calendar year of diagnosis, comorbidity, gender, education, marital status and tumor type (T-stage and grade) as independent variables to calculate the propensity scores for treatment. The computer program R with its package Matchit [Ho] and type of matching set to nearest neighbor was used.

Statistical methods

The start date of the study was the date of diagnosis and the last date of the study was date of death, emigration, or 31 December 2014, whichever occurred first. Months was used as the time unit. Kaplan-Meier survival curves are presented to assess absolute risk for patients treated with BCG and RC. Hazard ratios of bladder cancer and all-cause death were calculated in Cox proportional hazards models while adjusting for covariates. The models were kept as simple as possible and non-significant ($p < 0.05$) variables were excluded, individually, model-by-model. Thus, a stepwise selection was performed, either all or a few of the following factors were included in the models: age at diagnosis, calendar year (1997–2014), comorbidity, education, gender, marital status and tumor type. In all models, the proportionality between hazard rates for BCG and RC varied with time. Therefore, a time-dependent variable was included in the models [4].

Instrumental variable analysis

To further compare survival chances of BCG with RC considering the potential problem with selection bias, we tried to mimic a randomized trial and carried out an instrumental variable analysis using hospital strategy as the instrument [5–7]. Since hospital strategy in choosing between BCG and RC is unknown, we used the proportion (0–1) of formerly RC-treated patients during the whole follow-up period in the same hospital as a proxy. The first patient at every hospital was excluded from analysis since there was no precedent for that individual. To predict risk differences, uni- and multivariable two-stage least squares regression analyses were conducted, with 2- and 5-year survival as dependent variable while adjusting for age at diagnosis, calendar year, comorbidity, education, gender, marital status and tumor type. The strength of the instrument has been tested.

Results

In 1997–2014 in Sweden, a total of 26,808 patients were diagnosed with NMIBC, of which we included 10,209 with high-risk tumor types (TaG3, T1G2, T1G3 or/and Tis). Of those, 5,750 had no further treatment and 4,459 were treated with either BCG (3,862) or with RC (687). A flow chart of the included patients is depicted in Figure 1. Baseline data show that the treatment groups differed in several aspects (Table 1). The patients in the RC group were younger (3.7 years mean age difference), had a much higher frequency of stage T1, were more common in three of six health regions and suffered slightly less from comorbidity.

The median follow-up time in the study sample was 46 months, with quartiles 1 and 3 equal to 21 and 85 months, respectively, with a range of 215 months. During that period, 608 (13%) patients died of the disease and additionally 932 (20%) patients died from other causes. The 5-year cancer-specific survival was 87% (95% CI = 86–88%) for BCG treated patients compared to cystectomized patients where survival was 71% (95% CI = 69–73%). The corresponding all-causes death survival was 72% (95% CI = 71–73%) for BCG treated patients and 61% (95% CI = 59–63%) for those cystectomized. These findings are made visible in the Kaplan-Meier survival curves presented in Figures 2 (a and b). From these figures it is also evident that the difference in absolute survival chances between treatments due to both cancer and all-causes death diminishes with increasing time and in the very long-term follow-up.

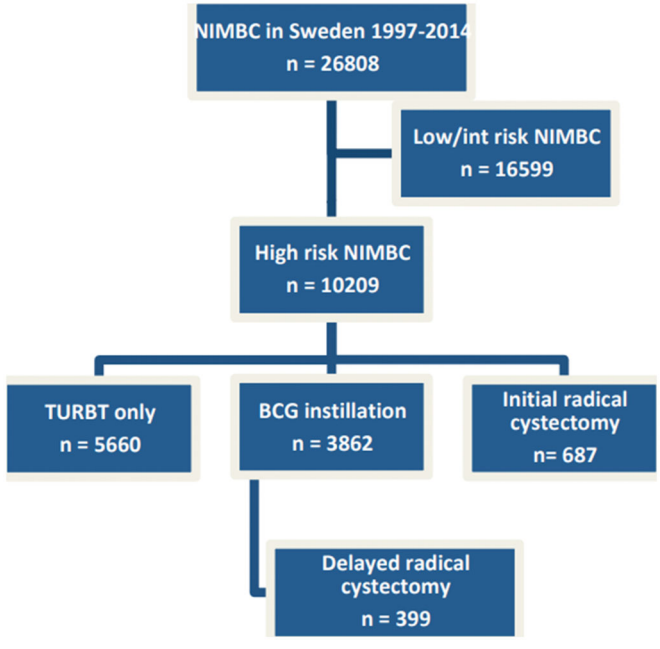

Figure 1. Flowchart showing inclusion of patient from BladderBaSe.

Table 1. Characteristics of patients with high risk NMIBC in Sweden, 1997–2014, by initial treatment.

Factor		BCG ($n = 3,862$) (%)	Initial RC ($n = 687$) (%)	Delayed RC ($n = 399$) (%)
Age	(mean, SD)	70.7 (9.7)	67.0 (9.0)	67.0 (8.1)
Age (years)	≤49	2.5	4.5	2.5
	50–59	9.8	14.3	15.6
	60–69	29.2	38.3	40.5
	70–79	39.4	37.3	37.4
	80–89	18.2	5.5	4.0
	90+	0.7	0.0	0.0
Gender	Men	81.0	80.3	81.7
	Women	19.0	19.7	18.3
Healthcare region	Stockholm	17.2	20.1	22.6
	South	24.2	19.8	18.3
	Southeast	12.3	8.9	9.0
	Uppsala-Örebro	17.9	25.8	19.0
	West	18.4	19.5	18.5
	North	10.0	6.0	12.5
Hospital type	University	37.5	37.8	38.3
	County	40.6	43.2	41.6
	District	21.9	18.9	20.1
Charlson Comorbidity Index	0	63.0	69.9	76.4
	1	17.6	12.8	13.5
	2	11.2	10.6	8.5
	3	8.2	6.7	1.5
Marital status	Married	63.7	60.2	62.8
	Divorced	14.1	17.4	15.4
	Unmarried	9.6	14.4	13.7
	Widowed	12.6	8.0	8.1
Education	Elementary	40.1	36.7	38.2
	Gymnasium	39.4	42.9	40.0
	University	20.5	20.5	21.8
Tumor type	T1 + G2,G3	70.5	91.6	71.9
	Ta + G3	17.1	6.0	13.3
	Tis + G3	12.5	2.5	14.8
Year of diagnosis	1997–2002	17.5	17.8	18.3
	2003–2008	32.9	26.2	40.6
	2009–2014	49.6	56.0	41.1

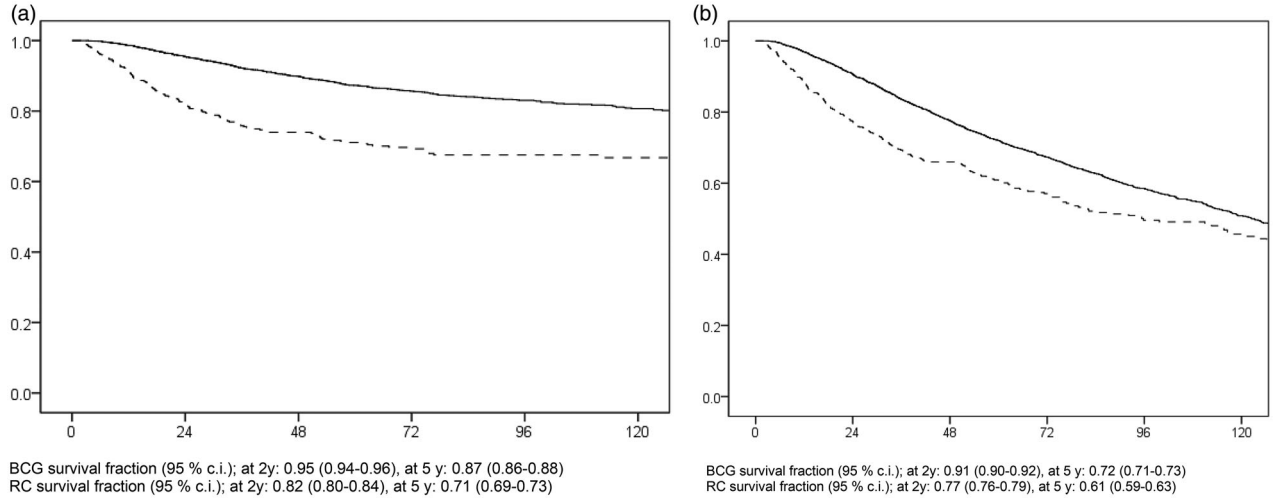

Figure 2. (a) Kaplan–Meier analysis of cancer-specific survival for patients with high risk NMIBC who underwent BCG instillation therapy (——) or initial radical cystectomy (——) in Sweden, 2007–2014. Time is from diagnosis day in months. (b) Kaplan–Meier analysis of all-causes survival for patients with high risk NMIBC who underwent BCG instillation therapy (——) or initial radical cystectomy (——) in Sweden, 2007–2014. Time is from diagnosis day in months.

Relative risks in the study sample also decreased with increasing time, as is seen in Table 2. At 2 years after diagnosis, the cancer specific death risk was 3.5-times higher for RC-treated patients than for BCG-treated patients. The corresponding hazard ratio for all-causes death was 2.6. However, after 5 years, both these relative risk estimates were no longer significantly different from one (significance level 5%).

The trial sample selected using propensity scores matching consisted of 1,346 patients (673 treated with BCG and the same number with RC) and their median follow-up time was 42 months with quartile 1 = 19 months, quartile 3 = 79 months and with a range of 213 months. In the group of patients treated with BCG, 78 and 113 patients died from the disease and from all causes, respectively, during this

Table 2. Estimates of relative risk (hazard ratios) of initial treatment (BCG or RC) for bladder cancer death and all-causes death in the study sample and propensity score matching (psm) sample using multivariate adjusted analysis at 2 and 5 years from diagnosis.

	Time from diagnosis	Study sample multivariate adjusted model	Psm sample multivariate adjusted model
Bladder cancer death, HR (95% CI)			
BCG		1, ref****	1, ref**
RC	2 years	3.52 (1.99–6.22)	3.30 (1.53–7.10)
	5 years	1.11 (0.44–2.82)	1.18 (0.36–3.92)
	Average	2.82 (2.32–3.41)*	2.64 (2.01–3.47)*
All-causes death, HR (95% CI)			
BCG		1, ref***	1, ref**
RC	2 years	2.59 (1.88–3.57)	2.17 (1.45–3.24)
	5 years	1.45 (0.90–2.32)	1.50 (0.85–2.67)
	Average	1.79 (1.55–2.06)*	1.76 (1.46–2.13)*

*Proportional hazards assumption violated.
**Adjusted for tumor type, comorbidity (cci) and age at diagnosis.
***Adjusted for sex, tumor type, comorbidity (cci), education, marital status, age at diagnosis and calendar year of diagnosis.
****Adjusted for tumor type, comorbidity (cci), marital status, age at diagnosis and calendar year of diagnosis.

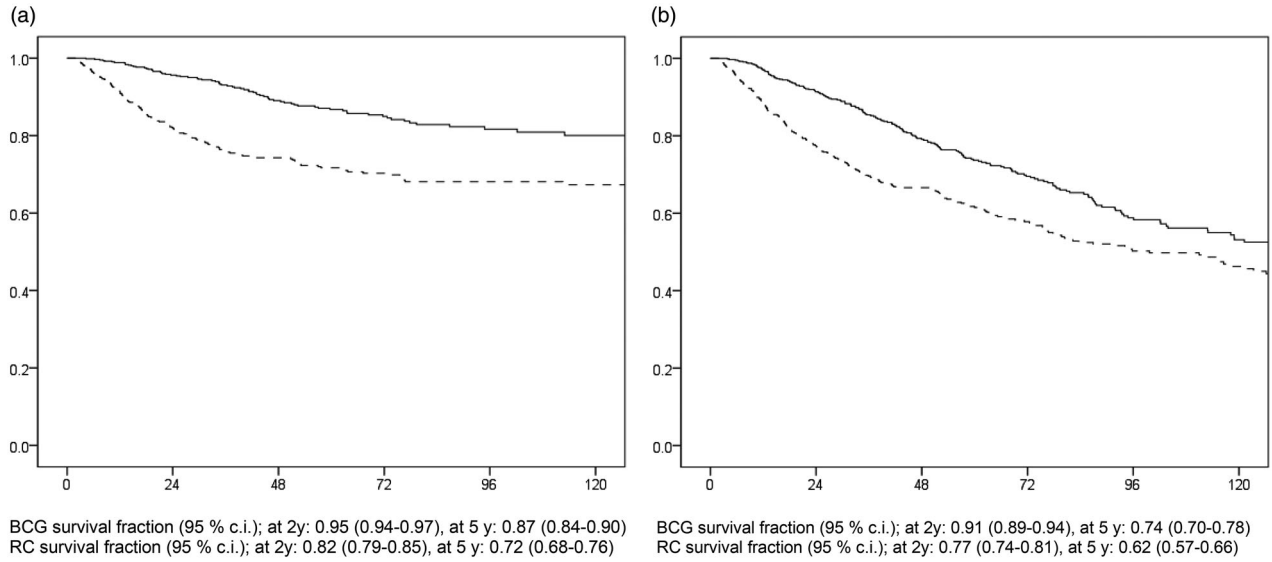

Figure 3. (a) Kaplan–Meier analysis of cancer-specific survival in the trial population with patients who underwent BCG instillation therapy (——) or initial radical cystectomy (——) in Sweden, 2007–2014. Time is from diagnosis day in months. (b) Kaplan–Meier analysis of cancer-specific survival in the trial population with patients who underwent BCG instillation therapy (——) or initial radical cystectomy (——) in Sweden, 2007–2014. Time is from diagnosis day in months.

period, and among patients treated with RC, and corresponding figures were 162 and 105. These results are depicted in the Kaplan-Meier survival curves presented in Figure 3(a and b). There were significantly higher relative risks for cystectomized patients than for those instilled with BCG, both due to the disease, HR = 3.3, and all causes, HR = 2.2, at 2 years after diagnosis. However, after 5 years, these risk differences had diminished and had become insignificant (Table 2).

In the instrumental variable analysis, the multivariate adjusted risk difference of death caused by the disease 2 years after diagnosis predicted by the model shown in Table 3 was 32.2 per 100 treated patients, in favor of BCG. The corresponding figure for all-causes risk difference was also inferior for RC compared to BCG, 19.0 patients per 100 treated patients. However, the precision was better at 2 years than 5 years, for all of the comparisons. Hence, the instrumental variable analysis conducted on the study sample confirmed the results of the regular analyses, that the inferior outcome of patients selected for RC compared to BCG in this analysis is more pronounced in the short-term.

Delayed cystectomy after BCG instillation was performed in 10% (399) of all initially BCG treated. The characteristics of these patients compared to those with initial RC are available in Table 1. Time from operation to last day of follow-up was validly registered in 598 initially and 399 delayed cystectomized patients.

Median time from diagnosis day to delayed operation was 16 months with quartile 1 and 3 equal to 11 and 29 months, respectively. The two-year cancer-specific survival was 79% compared to 81% for those who underwent initial radical cystectomy, as illustrated in Figure 4.

Discussion

In this group of patients, those with high risk non-muscle-invasive urothelial carcinoma treated with initial RC had higher risk of bladder cancer death and all-cause death as compared to those treated with BCG. In analyses considering patient selection and restricting the population to those eligible for a trial, our data still indicate superior outcomes

Table 3. Risk differences in the study sample between treatment with BCG and RC. Instrumental variable analysis with differences calculated in two-stage least squares regression models.

	Bladder cancer death		All-causes death	
Time from diagnosis	Univariate	Multivariate	Univariate	Multivariate
2 years	24.2 (10.2–38.2)	32.2 (14.5–49.9)	20.5 (2.5–38.5)	19.0 (1.0–36.9)
5 years	24.0 (5.3–42.7)	24.0 (5.2–42.8)	8.5 (-16.6–33.5)	7.8 (-16.2–31.8)

Number of patients per 100 patients (95% confidence intervals).

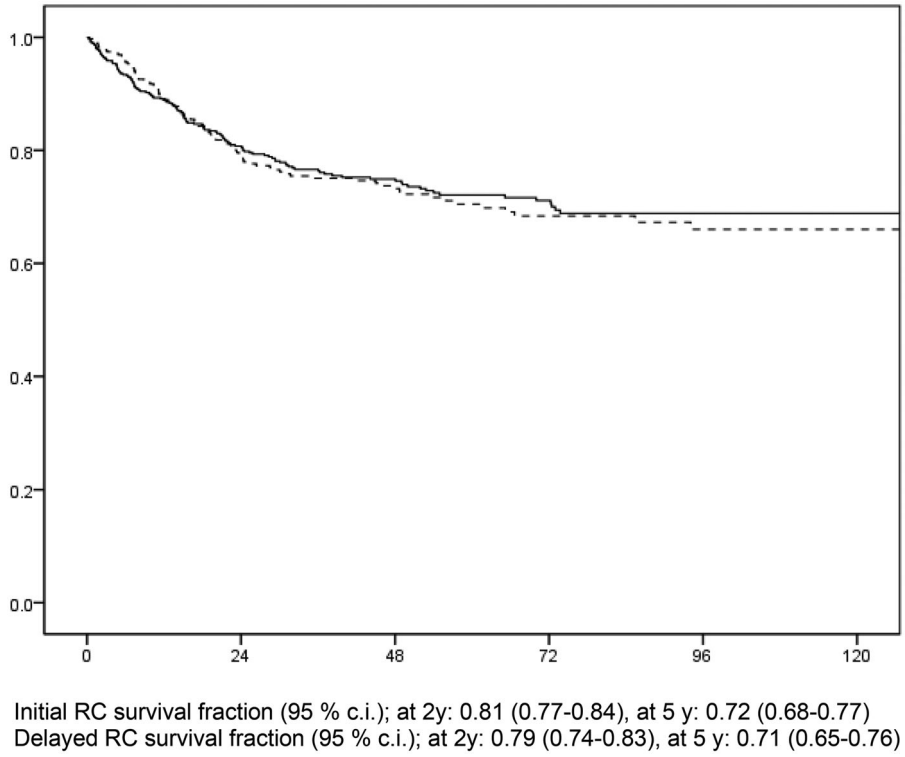

Figure 4. Kaplan-Meier analysis of cancer-specific survival in patients with high risk NMIBC who underwent initial radical cystectomy (——) or delayed cystectomy (——) in Sweden, 2007–2014. Time is from operation day in months.

among BCG treated patients. These findings are in conflict with previously expressed opinions in the community.

Due to the lack of high-level evidence, the BRAVO group initiated a feasibility study to compare RC against BCG for high-risk non-muscle invasive bladder cancer in 2015 [1]. This was in preparation for a formal randomized study. The study was prematurely stopped, reflecting the difficulties in comparing two very different management approaches. Using instrumental variable analysis, we made an attempt to simulate this kind of trial keeping the same inclusion criteria. It is natural that there is hesitancy to perform major surgery in elderly and frail patients and this is reflected in the age difference in the two treatment groups. It is also important to note that the majority of patients, constituting 55% of all high-risk non-muscle invasive bladder cancer during the studied time period, did not undergo any further treatment than TURB. The age factor, with the latter group having a 3.5 years higher median age (data on file), is obvious. The well-known toxicity of BCG is a plausible explanation for the restrictive use in this patient group. Recently systemic immunotherapy has been approved for advanced bladder cancer and one can speculate that local BCG application, with its well-known systemic toxicity, could also have a systemic antitumor efficacy. This might explain the better outcome compared to those having a cystectomy, but the evidence is controversial.

While treatment mortality with BCG is extremely rare, it is not uncommon after RC. The 90-day mortality was 4.9% according to the Swedish cystectomy registry and cannot in itself explain the survival benefit of BCG [8].

Reviews have noted superior survival for patients with T1G3 bladder cancer who undergo early cystectomy compared to delayed cystectomy [9]. Nevertheless, the authors acknowledged that the data supporting early cystectomy were from retrospective series, and thus subject to considerable potential bias.

One obvious advantage of initial cystectomies is to avoid understaging, reported to be 20% in the previous series. Unfortunately, we do not have information on upstaging in this material.

The main strengths of our study are the prospective registration, the large number of patients observed, the quality of the data and the nation-wide recruitment base. We had access to several high-quality nationwide registers with data on tumor characteristics, treatment and covariates such as hospital type and health region. Two different methods were

used to control for selection mechanisms to either treatment: propensity score matching and instrumental variable analysis. Both of them gave similar results.

As in all registry trials, there are limitations to this study. The capture rate of quality registers and how representative they are require assessment to ensure that register data are generalizable. A caveat is that other important tumor characteristics such as size and multiplicity were not registered. Hence, the selection of larger and/or multiple tumors for RC cannot be assessed and may affect the outcome. It should also be noted that the database does not document reresection, which has been recommended in recent guidelines. An earlier study from the register found large geographical differences in the use of reresection in Sweden with about half of the patients having this procedure during 2008–2009 [10]. The use of a BCG maintenance regimen or second induction courses were not registered but it was recommended in the national guidelines during the study period. The matched study cohort is likely to have included some other unrecognized patient heterogeneity in terms of demographics and overall health status. The final pathology analysis after RC were not registered in the database, which may be one of the biases for the results. The instrumental variable analysis rests on a few assumptions, some of which are difficult to assess. However, we found an association between the proportions of RC's among previous patients and the treatment for the current patient, which is important for the relevance of the instrument. We could also confirm no association between the instrument and measurable covariates and events of death, which is indicative but not evidence for the instrument to be only associated with the outcome through the actual treatment.

The argument for individualized treatment has many proponents, but there is no consensus how this should be done. The EAU guidelines have characterized a subgroup of highest-risk tumors being those with concurrent bladder CIS, multiple and/or large tumors, location with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma and lymphovascular invasion. The AUA guidelines also mention diffuse disease or tumor location in a site not amenable to complete resection. We earlier reported from the Nordic T1 trial that concomitant carcinoma *in situ* was not predictive of failure of BCG therapy [11]. The only independent factor for treatment failure in that study was remaining T1 stage at second resection. Unfortunately, no biomarker has yet proven effective as a reliable predictor of BCG response.

In this study, RC is associated to poorer oncological outcomes compared to previously reported cohorts from highly specialized centers. For example, Hautmann [12] showed a 93% CSS survival rate at 5 years for NMIBC patients. However, population-based studies have shown corresponding rates of 40 – 71%, which is in line with our 71% CSS [13,14].

One of the main findings of our study is the relatively poor outcome with initial cystectomy in a group of patients with presumably localized disease. Neoadjuvant chemotherapy has a survival benefit in muscle infiltrating bladder cancer. In an early Nordic neoadjuvant study the T1 category was included, and a similar survival advantage as that in the more advanced tumors was found but could not be proven statistically [15]. Thus, additive treatment to RC even in NMIBC should be considered in the future. We recognize that a randomized prospective trial is needed to get high-level evidence of the outcome of initial treatment with RC or BCG of high-risk non-muscle invasive bladder cancer. Until then the results of our study are thought-provoking.

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Author contributions

Eugen Wang had full access to all the data in the study and takes responsibility for the integriy of the data and the accuracy of the data analysis. Study concept and design: Malmström. Acquisition of data: Gårdmark, Malmström. Analysis and interpretation of data: Wang, Larsson, Malmström. Drafting of the manuscript: Wang, Larsson, Gårdmark, Malmström. Critical revision of the manuscript for important intellectural content: Wang, Larsson, Gårdmark, Malmström. Statistical analysis: Larsson.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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