



Recurrent Bacteriuria as a Prognosis Marker in the Adjuvant Treatment of Non-Muscle Invasive Bladder Cancer

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Abstract

Bacteriuria may affect the response to adjuvant therapy in non-muscle invasive bladder cancer. We developed a prospective observational study including women with bladder cancer treated with intravesical treatment. The presence of significant bacteriuria was analysed. Female patients with RB had a better response to adjuvant treatment for NMIBC. The RB group showed lower rates of tumor recurrences and progression.

Purpose: Bacteriuria may affect the response to adjuvant therapy in non-muscle invasive bladder cancer (NMIBC). The main aim of this study was to examine the effect of recurrent bacteriuria (RB) on the prognosis of NMIBC in women receiving intravesical therapy. **Materials and Methods:** We designed a prospective observational study from 2012 to 2019. We included women with bladder cancer treated with transurethral resection of the bladder (TURB) and adjuvant intravesical treatment. Significant bacteriuria was defined as a presence in urine cultures at or above 100,000 colony-forming units per millilitre. The recurrent bacteriuria group included patients with significant bacteriuria in at least two determinations in 6 months or in 3 or more determinations in a year. The institutional board approved the study. **Results:** One hundred thirty-six patients diagnosed with NMIBC participate in the study, of whom 100 met the inclusion criteria. During follow-up, 48 were categorized in the RB group and 52 formed the non-bacteriuria group (NB). **RB Group Had a Better Outcome:** Eight patients (16.67%) experiencing a recurrence of the same grade, with no progression to a higher-grade tumor or muscle-invasive tumor. In the NB group, 18 (34.6%) patients presented a recurrence ($P = .001$) and 22 (42.3%) progressed to a higher-grade tumor or muscular invasion ($P = .001$). The presence of RB was identified as a predictor of good response in multivariate regression with a relative risk of 0.13 ($P = .018$). **Conclusions:** Female patients with RB had a better response to adjuvant treatment for NMIBC. The RB group showed lower rates of tumor recurrences and progression.

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Introduction

Bladder cancer (BC) is the most prevalent malignant tumor of the urinary tract.¹ While it is more commonly diagnosed in males, the incidence of BC is rising among women in developed countries.²

Non-muscle-invasive bladder cancer (NMIBC) represents over 70% of all cases and encompasses papillary tumors (Ta), carcinoma-in-situ, and invasion of the lamina propria (T1).³ Risk stratification is based on the anatomical and histopathological grading of the tumor. The European Association of Urology (EAU) guidelines recommend intravesical chemotherapy for intermediate-risk NMIBC and bacillus Calmette-Guérin (BCG) for intermediate or high-risk NMIBC.⁴

Herr investigated the impact of asymptomatic bacteriuria (ABU) on the response to adjuvant therapy with BCG treatment. The results indicate that the presence of ABU during BCG enhances the immune response, resulting in a more robust response to therapy, tumor cell eradication, and a reduction of recurrences.⁵ Also, in low-grade tumors, bacteriuric patients exhibited fewer low-grade papillary recurrences compared to non-infected patients.⁶

Further investigation of this effect should focus on the female population, who have a higher risk of infection compared to

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males.⁷ In NMIBC, women often exhibit a worse prognosis and higher-grade tumors.^{4,8} The increased risk of infection in women could contribute to this poorer outcome. Therefore, studies should consider sex as a potential factor influencing the relationship between infection and NMIBC prognosis.⁸

The main aim of this study was to examine the effect of recurrent significant bacteriuria on the prognosis of NMIBC in women receiving adjuvant intravesical therapy.

Materials and Methods

Prospective observational study of women who underwent transurethral resection of the bladder (TURB) from 2012 to 2019. The inclusion criteria were¹ age more than 18 years old,² primary NMIBC treated with transurethral resection of bladder (TURB) and³ who received a full cycle of adjuvant treatment with bladder instillation (induction and maintenance). We exclude patients with¹ recurrent tumors,² emergency procedures and³ palliative surgery. All patients were treated according to the standard treatment protocol of bladder non-muscle invasive cancer.

After a TURB, 4 weeks later the adjuvant therapy was begun. The cultures were obtained before each instillation and before a surveillance cystoscopy. We defined significant bacteriuria as a presence in urine cultures at or above 100,000 colony-forming units per millilitre of urine (CFU/cc). The patients were divided into two groups according to the presence of significant bacteriuria during the bladder adjuvant treatment. Since there is no established definition of recurrent ABU, we follow the EAU definition of recurrent urinary tract infection in order to establish group of recurrent ABU.⁹ The recurrent bacteriuria group (RB) included patients with significant bacteriuria in at least two determinations in 6 months or in 3 or more determinations in a year. No bacteriuria group (NB) included those who do not meet criteria of significant bacteriuria. However, in NB there could be patients with positive urine culture with symptoms (less than 2 in 6 months or 3 in 1 year). ABU without urinary tract infection (UTI) criteria was not treated. Adjuvant treatment protocols were not discontinued due to ABU.

Patients' epidemiological and clinical data were identified: sex, age, body mass index (BMI), American Anaesthesiology Association (ASA) scores, smoking history, hormonal treatment (general or topical), and UTI prior to diagnosis of bladder cancer. Onset symptoms were identified. The diagnostic test performed were collected. First, TURB data was collected: date, hospitalization days and tumor classification according to TNM of bladder cancer.¹⁰ Adjuvant intravesical treatment for bladder cancer was revised (mytomicin, epirubicin, or BCG). Data on evolution, such as recurrence or progression during the follow-up was recollected. Good evolution was defined as a remission of the tumor or recurrence of equal or lower grade. Bad evolution was a higher-grade recurrence or progression to a muscle-invasive tumor. The evolution was taken into account according to recurrence at one year, or the minimum follow-up time. If the patient had a tumor recurrence, it was considered bad evolution, with a minimum follow-up period of one year.

All procedures were conducted under the Declaration of Helsinki and Spanish legislation. The study protocol was reviewed and approved by the institutional research ethics committee (PI 2021

10 890 approval code). Informed consent was obtained from each of the participants.

Mean and standard deviation (SD) were reported for continuous variables and proportions and percentages for categorical variables. The univariate analysis of the groups was performed with the Student's *t*-test (numerical variables with normal distribution) and ANOVA analysis of variance (with Scheffe's test for normal samples and Kruskal Wallis for other distributions); and for categorical variables, Chi-square and Fisher's exact test were employed. Additionally, we conducted a multivariate logistic regression analysis. The statistical significance threshold was set at $P < .05$. The analysis was performed with SPSS 25.0 (IBM, Chicago, IL, USA).

Results

A total of 136 patients who underwent TURB agreed to participate in the study, of whom 100 met the inclusion criteria. During follow-up, 48 (48%) of these patients were categorized as the recurrent bacteriuria group (RB), while the remaining 52 (52%) patients formed the non-bacteriuria group (NB).

Table 1 displays the demographic characteristics of both groups, revealing no significant differences in terms of mean age, BMI, ASA class and the prevalence of smoking. However, the RB group had a lower percentage of patients in ASA class II (41.6% vs. 57.7%), a higher percentage in ASA class III (50% vs. 26.92%) and a significantly higher proportion of ex-smokers (25% vs. 7.69% in the NB group, $P = .028$). No patient in this study was receiving general or topical hormonal treatment.

Prior to bladder cancer diagnosis, 20 of the 48 patients (41.6%) in the RB group had urine culture in the year prior to the diagnosis of bladder cancer, with positive results in 18 of the 20. In the NB group, 23 of the 52 patients (44.2%) had urine culture in the year prior to diagnosis, with positive results in 3 patients. The diagnosis of bladder cancer did not alter the bacteriuria status of the patients. All urine cultures performed prior to the diagnosis of bladder cancer were performed for urinary symptoms, and the episodes were classified as urinary tract infection.

The onset symptoms of the patients in the RB and NB groups were comparable, with haematuria being the most frequent. However, a significant difference was observed between the groups in terms of the prevalence of infection before diagnosis. The RB group had a much higher percentage (58.3%) of patients with infection before diagnosis, compared to only 3.85% in the NB group ($P = .001$). At the time of diagnosis, positive cytology was observed in 25% of patients in the RB group and 23% in the NB group. A significantly higher number of patients (66.6%) in the RB group had leukocyturia on cytology, compared to 14 patients (26.9%) in the NB group ($P = .001$). Complementary tests revealed that ultrasonography showed bladder lesions in 66.6% of patients in the RB group and 38.5% in the NB group ($P = .005$). All onset symptoms and complementary test results are presented in Table 2.

Following TURB, the anatomopathological specimen showed that 32 patients had a Ta stage (14 in RB, 18 in NB, $P = .668$) and 68 had a T1 stage (16 in RB and 22 in NB, $P = .668$). All patients had a complete TURB (R0). There were no differences in tumor baseline characteristics between RB and NB groups. Variables

Table 1 Patients and Tumor Baseline Characteristics

	Recurrent Bacteriuria (n = 48)		No Bacteriuria (n = 52)		P-Value
Age (years), mean ± SD	71.36 ± 10.61		70.07 ± 10.56		.254
Body mass index (kg/m ²), mean ± SD	26.69 ± 3.48		26.37 ± 3.54		.339
ASA (n, %)					
I	4	8.3%	6	11.5%	.743
II	20	42.6%	40	57.6%	.161
III	24	50%	14	26.9%	.023
IV	0		2	3.8%	.496
Smoking habit (n, %)					
Never smoker	24	50%	32	61.5%	.314
Smoker	12	25%	16	30.7%	.656
Ex-smoker	12	25%	4	7.6%	.028
Tumor size (cm) mean ± SD	2.09 ± 1.72		3.071 ± 0.06		.613
Focality (number of tumors) mean ± SD	2.01 ± 0.06		1.98 ± 0.58		.452
T tumor stage (n, %)					
Ta	14	29.1%	18	34.6%	.668
T1	34	70.8%	34	65.3%	.668
Grade of tumor (n)					
Grade 1	23	Ta = 14 T1 = 9	25	Ta = 18 T1 = 7	1
Grade 2	6	T1 = 6	6	T1 = 6	1
Grade 3	16	T1 = 16	18	T1 = 18	1
Associated CIS (n)					
Yes	3	T1 = 3	3	T1 = 3	1
No	45		49		1
Presence of bacteriuria 10000-99999 (n, %)	0	0	4	7.69%	.118

Abbreviations: ASA = American Anaesthesiology Association.

Table 2 Initial Diagnosis of Bladder Cancer

	Recurrent Bacteriuria (n = 48)		No recurrent Bacteriuria (n = 52)		P-Value
	N	%	N	%	
Symptoms					
Pain	4	8.33	10	19.23	.1530
Infection	28	58.33	2	3.85	.0001
Haematuria	48	100.00	50	96.15	.4958
Microhaematuria	24	50.00	24	46.15	.8414
Macrohaematuria	24	50.00	26	50.00	1
Cytology					
Positive for malignant cells	12	25.00	12	23.08	1
Cytology haematuria	8	16.67	10	19.23	.7988
Cytology leukocyturia	32	66.67	14	26.92	.0001
Positive complementary test					
CT scan	20	41.67	16	30.77	.3004
Ultrasound scan	32	66.67	20	38.46	.0055

such as size, number of tumors, grade and associated CIS for each group are listed in Table 1.

Four patients had a 10,000-100,000 ABU, they were included in NB group. The baseline characteristics did not differ from NB group in age ($P = .895$), BMI ($P = .587$) ASA ($P = .42$), smoking

status ($P = .52$). The characteristics, such as size ($P = .567$) and focality ($0 = 0.06$) were comparable among the tumors.

Adjuvant treatment was administered to 62 patients with mitomycin, 24 patients with BCG, and 10 patients with epirubicin, based on the bladder cancer treatment protocol. There were

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Table 3 Adjuvant Treatment Received

Adjuvant treatment	Recurrent Bacteriuria, n = 48		No Recurrent Bacteriuria n = 52		P-Value
	N	%	N	%	
MMC	34	70.08	32	61.53	.3997
BCG	10	20.83	14	26.92	.4938
Epirrubicin	4	8.33	6	11.54	.7429
Disease at the first 3-month post treatment cystoscopy	N		N		P-Value
Presence	9	18.75%	11	21.15%	
Absence	39	81.25%	41	78.84%	.807

Abbreviations: BCG: bacillus Calmette-Guérin; MMC = Mitomycin-C.

Table 4 Evolution of Bladder Cancer, Recurrence, and Rate of Progression in NB and RB Groups

	Recurrent Bacteriuria N = 48		No Bacteriuria N = 52		P-Value
	N	%	N	%	
Good evolution	48	100.00	30	57.69	.001
Complete response	40	83.33	12	23.07	.001
Recurrence	8	16.67	18	34.62	.0668
Progression	0	0.00	22	42.31	.001

Good evolution: no relapse or recurrence of the same or lower grade. Complete response: no recurrence. Recurrence: the same grade or lower tumor during follow-up. Progression: higher grade tumor or T2.

no significant differences in the treatments administered between the RB and NB groups (Table 3).

The mean RB group had a longer average follow-up duration, 1723 days (SD ± 527), when contrasted with the NB group, which had 965 days (SD ± 292) ($P = .001$). Four patients had a minimum follow-up of less than one year, 2 in the non-bacteriuria group and 2 in the bacteriuria group, with no differences between groups ($P = .597$). During the follow-up, 48 patients experienced bacteriuria. Before the administration of adjuvant treatments, urine cultures of the RB group showed that 33.3% presented *Escherichia coli*, 20.8% *Enterococcus faecalis*, 8.3% *Klebsiella sp.*, and 37.5% two or more bacteria without reaching contamination.

In the RB group, there were 4 patients who, in addition to bacteriuria, exhibited symptoms of urinary tract infection. Only those patients were treated with antibiotics. ABU was not treated with antibiotics. Patients treated with antibiotics still presented ABU at follow-up. These patients continued to be included in the RB group.

In the NB group, there were 3 patients who had bacteriuria along with symptoms of urinary tract infection. However, at follow-up, they did not show bacteriuria again; therefore, they continued to be included in the NB group.

Patients in the RB group had a better outcome, with all patients experiencing a good evolution. Only 8 patients (16.67%) experienced a recurrence of the same grade, with no progression to a higher-grade tumor or muscle-invasive tumor. Patients in the NB group had a worse outcome with only 30 patients (57.69%) achieving a good evolution, 12 patients (23.05%) had complete response during follow-up, 18 (34.6%) experienced a recurrence of equal or lower grade and 22 (42.3%) progressed to higher-grade tumor or muscle-invasive disease. A trend towards significance was observed

for recurrence ($P = .0668$), with significant differences for good evolution ($P = .001$) and progression ($P = .001$) (Table 4).

The multivariate logistic regression analysis revealed that several variables were significantly related to a good evolution after treatment for bladder cancer. A presence of recurrent bacteriuria (RR = 0.13, $P = .018$), absence of leukocyturia on urine cytology (RR = 0.05, $P = .001$), and smaller cystoscopy size of tumor (RR = 0.009, $P = .018$) were all associated with a good evolution. Conversely, pain as an initial symptom (RR = 5.66, $P = .022$) was linked to not achieving a good evolution. Detailed data are shown in Table 5.

Discussion

UTI has been investigated as a potential risk factor for the development of NMIBC. *Schistosoma haematobium* infection is a well-established risk factor for squamous cell carcinoma of the bladder. A meta-analysis conducted by Bayne et al. aimed to elucidate the association between UTI and NMIBC and resulted in a calculated relative risk (RR) of 1.33. However, the presence of study heterogeneity and confounding variables limits the strength of these findings, as evidenced by a calculated RR of 0.38 when biased studies were excluded.¹¹

Our study did not examine UTI as a potential risk factor for the development of BC. However, we did observe that infection was the second most common presenting symptom in the patient with RB, following haematuria. This suggests that individuals in this subgroup may have an underlying predisposition to infections, which could impact their response to adjuvant bladder treatment.

In previous studies involving patients with infiltrating bladder cancers, significant bacteriuria was found to be associated with

Table 5 Logistic Regression Analysis for Good Evolution (Defined As No Relapse or Recurrence of the Same or Lower Grade)

Variables	RR	95% IC		P-Value
		Lower	Upper	
Pain	5.669	1.287	0.022	24.979
Recurrent bacteriuria	0.136	0.026	0.018	.715
Cytology leukocyturia	0.054	0.009	0.001	.324
Tumor size in first cystoscopy	0.095	0.014	0.018	.664

Abbreviations: IC = confidence Interval; RR = relative risk.

a worse prognosis for bladder cancer. However, when studying only superficial bladder cancers, asymptomatic bacteriuria has been found to be associated with a better prognosis.¹² Thus, this is an intriguing finding: the inflammatory status in the case of superficial cancer could be beneficial for the prognosis of cancer, whereas in the case of infiltrative cancer, significant bacteriuria is associated with a worse prognosis.

Efforts have been undertaken to identify non-invasive prognostic markers for NMIBC. The macrophage-mediated inflammatory response has been proposed as a crucial factor in response to infections and tumors, as these cells secrete chemokines that contribute to inflammation and immune modulation.¹³

Pyuria has been proposed as a potential predictor of treatment response in several studies involving patients treated or not with bacillus Calmette-Guérin (BCG). Pyuria has also been associated with increased tumor recurrence.¹⁴⁻¹⁶ While our study did not specifically examine pyuria, we did observe more frequently the presence of leukocyturia in the RB group, which exhibited better outcomes.

ABU has been suggested to confer protection against infection through colonization-induced immunomodulation of the urothelium via neutrophil chemokines.¹⁷ Patients with ABU have been observed to exhibit higher circulating neutrophil counts and a greater prevalence of pyuria.¹⁸ Administration of adjuvant BCG treatment has not been observed to increase infection rates in patients with ABU.¹⁹ Prophylactic antibiotic therapy is not indicated before BCG instillation.²⁰

BCG demonstrated the potential of eradicating ABU, likely due to the increased inflammatory activity associated.²¹ In our study, we ensured a consistent condition by selecting patients with RB throughout the study, following established inclusion criteria.

The influence of ABU on the prognosis of BCG-treated bladder cancer has been studied by Herr. In low-grade tumors treated with surgery alone, bacteriuria was found to reduce the number of recurrences.⁶ In another study, that included all tumor stages treated with BCG, patients with ABU had a higher complete response at first control than those without ABU. Additionally, patients with ABU had a lower rate of tumor recurrence and recurrence-free survival at three years, with no differences observed based on sex, tumor stage, or presence of Tis. However, no differences were observed in the progression to a higher grade of disease.⁵

Our study confirms Herr's findings. Patients with RB had a more favourable response to adjuvant treatment with fewer recurrences (8 vs. 18 in NB). All recurrences in RB were of equal grade with no patient progressing. In contrast, patients in the NB group had

a higher percentage of recurrences of the same grade and a higher association with disease progression. Therefore, our results suggest that RB may facilitate a greater response during intravesical treatment. Logistic regression confirmed this association, with recurrent bacteriuria having an RR of 0.136 (95% CI: 0.026-0.018).

Recent advances in rRNA sequencing have enabled the identification and characterization of the commensal microbiome inhabiting the bladder. Research is currently underway to explore the potential influence of the bladder microbiome, as well as its correlation with the gut microbiome. The response to BCG therapy and novel treatments such as PD-1 and PDL-1 inhibitors could be affected by the microbiome. The response to BCG, by alterations in binding sites, could be linked to changes in response caused by the microbiome. Furthermore, novel treatments targeting PD-1 and PDL-1, could also modify their functions due to microbiome. Andolfi et al. have reported higher rates of recurrence in BCG-treated patients with Enterobacteriaceae and lower recurrence rates with *Lactobacillus*, although the sample size was small. Therefore, more comprehensive, and long-term studies are required to evaluate the role of the bladder microbiome in treatment response.²²

We acknowledge the limitations of our study. We do not adhere strictly to the definition of asymptomatic bacteriuria, adapting the definition of recurrent bacteriuria and ensuring that bacteriuria was recurrent (2 episodes in 6 months and 3 in a year). The follow-up time was longer for the RB group, although this did not affect the results as none of these patients showed disease progression. Regarding the follow-up tests, uniformity was not maintained across all groups, particularly for high-risk patients who necessitated more frequent cystoscopy revisions. This increased frequency of revisions has the potential to elevate the risk of bacteriuria. Nevertheless, it is noteworthy that both groups were well-balanced in terms of Ta and T1 grade. Also, we did not determine the bladder microbiome using RNA sequencing, which could have identified specific bacteria associated with a better response to treatment.

Conclusions

Female patients with RB had a better response to adjuvant treatment for NMIBC. The RB group showed lower rates of recurrences and progression. The RB showed to be an independent predictor of good evolution.

Clinical Practice Points

- Asymptomatic bacteriuria can influence the response to adjuvant therapy with BCG treatment.

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- Recurrent bacteriuria could be a response marker during the adjuvant intravesical treatment. Patients with recurrent bacteriuria had a more favourable response to adjuvant treatment with fewer recurrences.
- The influence of bladder microbiome in the response should be studied.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

Juliusz J. Szczesniewski: Conceptualization, Validation, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Magaly T. Márquez-Sánchez:** Methodology, Software, Formal analysis, Investigation, Resources. **Bárbara Padilla-Fernández:** Writing – review & editing, Supervision. **Luis Llanes-González:** Writing – review & editing, Supervision. **María E. Lorenzo-Gómez:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

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