

# Reduced Recurrence of Low-Grade Ta Bladder Tumors Associated with Asymptomatic Bacteriuria



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## Abstract

Asymptomatic bacteriuria (ABU) is common in bladder tumor patients. ABU causes local inflammation that may have an antitumor effect. In patients with low-grade, papillary (TaLG) bladder tumors, we found that bacteriuric patients had fewer recurrences and longer recurrence-free survival times than uninfected patients. Reduced tumor recurrence was associated with higher absolute neutrophil counts and pyuria, surrogate indicators of an inflammatory immune response in the bladder.

**Background:** Microbes in the urine trigger immune responses similar to intravesical BCG, which destroys bladder cancer. Asymptomatic bacteriuria (ABU) is common in bladder cancer patients, suggesting resident bacteria may also have an antitumor effect. We investigated the frequency of tumor recurrences in bacteriuric and uninfected patients.

**Methods:** We determined recurrence rates in 367 patients with low-grade, papillary non-muscle-invasive bladder tumors (TaLG), with and without asymptomatic bacteriuria (ABU). They were followed every 6 months for 36 months and did not receive antibiotics or intravesical chemotherapy. Recurrent tumors were treated generally by outpatient fulguration. Before cystoscopy, patients submitted a voided urine sample for culture, stratified as no growth (or mixed flora), or  $>10^4$ CFU/ml single organism. We also measured absolute neutrophil counts (ANC) and the presence of pyuria, as surrogate indicators of bladder inflammation.

**Results:** Of the 367 cases, 96 (26%) had ABU. With absolute 3 year follow-up, 74% of patients with ABU survived tumor-free compared to 52% of uninfected patients ( $P=0.001$ ). Forty-eight per cent of patients with negative cultures recurred versus 26% with  $>10^4$  or  $>10^5$ CFU/ml. ( $P=0.001$ ). Mean number of recurrent tumors in colonized patients was 1.9 vs 3.4 in uninfected patients. ANC averaged 6.0K/mcL in bacteriuric vs. 4.5K/mcL in uninfected patients ( $P=0.03$ ).

**Conclusion:** Patients with papillary TaLG tumors and chronic asymptomatic bacteriuria had fewer recurrences, fewer numbers of recurrent tumors, and longer tumor-free survival times than similarly staged uninfected patients. Bladder-resident bacteria may reduce bladder tumor recurrences through local immune mechanisms.

**Keywords:** Asymptomatic bacteriuria; Bladder tumor; Uropathogens

**Abbreviations:** ABU: Asymptomatic Bacteriuria; ANC: Absolute Neutrophil Counts; BCG: Mycobacteria

## Introduction

Low-grade, papillary bladder tumors (TaLG) are common neoplasms, especially in the elderly, and they frequently recur [1]. Asymptomatic bacteriuria (ABU) is also common in bladder tumor patients [2]. Uropathogens activate neutrophil-driven innate immunity to protect the host against acute infection and is capable of destroying nascent tumor cells [3]. Absolute neutrophil counts (ANC) and pyuria are signs of local immune activity and favorable outcomes in cancer patients with ABU [4]. Mycobacteria (BCG) instilled in the bladder stimulate the immune system to destroy high grade urothelial cancers and prevent their recurrence. This prompted us to investigate

whether chronic bacteriuria may have similar antitumor effects against surgically-treated TaLG tumors.

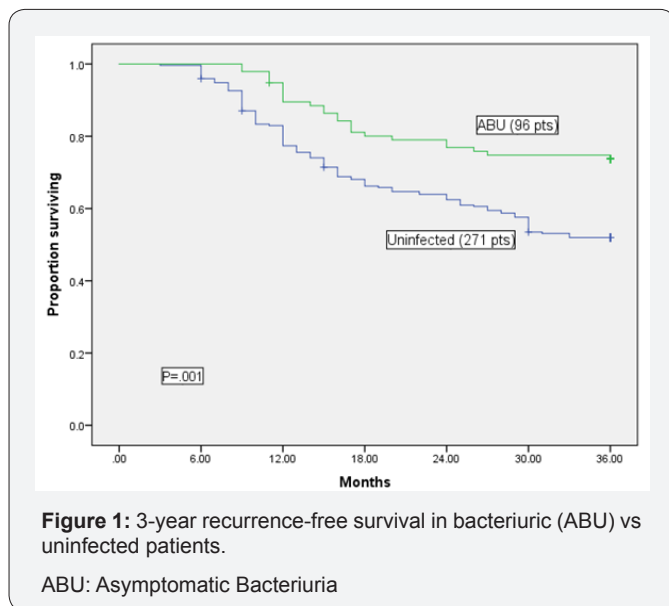
## Methods

In an institutional review board approved study, we evaluated 367 patients with multiple ( $>1$ ) and recurrent (1 or more recurrence per year) TaLG bladder tumors from 2009 to 2013 at our cancer center. After initial transurethral resection, they were followed by outpatient white-light and narrow-band cystoscopy every 3 to 6 months for 36 months. Recurrence rate in this population was estimated at 56% within 3 years [5].

None of the patients received antibiotics, before or immediately after cystoscopy. Post-procedure or adjuvant intravesical chemotherapy was not used. Recurrent tumors were generally treated by outpatient fulguration. Before each cystoscopy, patients submitted voided urine samples for culture, quantified as no growth or mixed flora (uninfected) or >104 or >105CFU/ml single isolated organism (ABU). At least 4 cultures (average 5.5) were obtained during follow-up. Patients were classified according to predominant bacterial burden on serial cultures. Blood and urine specimens were also obtained to measure absolute neutrophil counts (K/mcL) and to detect pyuria (10 or more white blood cells per mm<sup>3</sup>).

Sample size was based on a projected proportion of 20% to 25% of patients with ABU, at least 40% developing a tumor recurrence in 3 years, and a 20% difference in tumor recurrence rate between infected and uninfected patients. The end points of the study were frequency of tumor recurrences and 3 years recurrence free survival in bacteriuric and uninfected patients. X<sup>2</sup> and Student's t-test were used to test the correlation of bacteriuria with patient characteristics and tumor recurrence rate. Kaplan-Meier curves were constructed for 3-year recurrence-free survival times and compared using the log-rank test. P-values (2-sided) less than .05 were considered significant.

**Results**



**Figure 1:** 3-year recurrence-free survival in bacteriuric (ABU) vs uninfected patients.

ABU: Asymptomatic Bacteriuria

The median age was 64 (29-93) years, and 63% were men. Of the 367 cases, 96 (26%) had chronic ABU (predominantly Enterococcus and E. coli on serial cultures) and 271 (74%) were uninfected. The median age of patients with ABU was 66 (36-98) years vs. 63 (22-93) years in uninfected patients; 53% ABU patients were >65 years. Proportionately more females had ABU than men (37% vs. 20%). With an absolute follow-up of 3 years, 42% of patients recurred (median, 14 months). Of 96 patients with ABU, 25 (26%) recurred vs. 129 of 271 (48%) uninfected

patients (odds ratio=.39; 95% CI, .23-.65; P=.001). Of 51 patients 65 years or older who had ABU, 37% recurred vs. 70 of 125 (56%) elder patients who did not have ABU (P=.02) (Figure 1). The median time to recurrence in older patients was 28 months. In the entire cohort, three-year recurrence-free survival was 74% in infected vs 52% in uninfected patients and survival time was longer (P=.001) in patients with ABU (Figure). In elderly patients, 3-year recurrence-free survival was 63% in infected vs 44% in uninfected patients (P=0.01). Mean number of recurrent tumors was 1.9 in bacteriuric patients vs 3.4 in uninfected patients (P=0.01).

Absolute neutrophil count (ANC) averaged 6.7K/mcL in bacteriuric patients vs. 4.7K/mcL in uninfected patients (P=0.008). ANC averaged 6.0K/mcL in tumor-free patients vs 4.5K/mcL in patients with recurrence (P=0.03). Pyuria occurred in 142 patients (38%); 28% recurred vs 51% patients who had no pyuria (P=0.001). Of 56 patients (ABU, pyuria, median ANC >5), 3-year recurrence-free survival was 66% vs 39% in 99 patients (no ABU, no pyuria, median ANC<5) (P=0.001).

A multivariable analysis of significant factors associated with recurrence-free survival included age >65 years (P=0.01), ABU (P=0.03), Average ANC >5 (P=0.02), and pyuria (P=0.02).

**Discussion**

The major finding of our study is that patients with recurrent low-grade papillary bladder tumors and chronic bacteriuria had fewer recurrences, fewer numbers of recurrent tumors, and longer tumor-free survival times than similarly staged uninfected patients receiving the same local treatment and follow-up schedule. A plausible explanation is that chronic bacteriuria may reduce bladder tumor recurrences by local inflammatory immune mechanisms [6,7]. Bacteriuric patients had higher numbers of neutrophils in the blood and pyuria compared with uninfected patients, supporting the hypothesis that ABU is associated with inflammatory immune responses in the bladder, which may have antitumor effects. Another explanation is bacteria generate nitrite, which can inhibit urothelial cancer cell growth [8]. A lesser possibility because of enhanced optical technology used in this study is that bacteria-induced pyuria (cloudy urine and debris) may simply obscure visible detection of small tumors, artificially lowering true recurrence rate.

The study is limited by retrospective analysis of patients from a single center, and half the patients remained tumor-free, suggesting a favorable cohort less likely to recur. However, we found in a prior study of TaLG patients that 62% recurred over 3 years using both white light and narrow band imaging for treatment and follow-up [9], similar to our current results in uninfected patients. Bacteria may decrease implantation of viable tumor cells, or influence tumor growth through cytokines. We did not measure urinary cytokines, which may have strengthened the nexus between bacterial inflammation and antitumor immunity.

## Conclusion

Bacteriuric bladder tumor patients had fewer low-grade papillary tumor recurrences than uninfected patients. Bacteriuria may impact tumor recurrences by immune mechanisms. Bacterial priming of complex immune responses acting to retard tumor growth in the bladder is a plausible, yet unproved, explanation, but is worthy of further study. The data also suggest that since only a third of older patients with chronic bacteriuria recur, generally after one year and with few tumors, they may be followed annually, reducing the overall burden of cancer care in the elderly population.

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