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Clinical-Bladder cancer

# Association of smoking status and recurrence of non-muscle invasive bladder cancer among patients managed with blue light cystoscopy

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**Abstract**

**Purpose:** Smoking has a strong causal association with bladder cancer but the relationship with recurrence is not well established. We sought to assess the association of smoking status on recurrence of non-muscle invasive bladder cancer (NMIBC) in a contemporary cohort of patients with predominantly high-risk, recurrent NMIBC managed with photodynamic enhanced cystoscopy.

**Materials and methods:** We performed a retrospective study of patients with NMIBC included in a multi-institutional registry. Our primary exposure of interest was smoking status. Our primary outcome was first recurrence of NMIBC. Kaplan-Meier analysis was used to calculate recurrence free probabilities and Cox proportional hazards regression was used to evaluate the impact of smoking status on recurrence free survival.

**Results:** Our analytic cohort included 723 adults with bladder cancer, 11.5% with primary NMIBC and 88.5% with recurrent NMIBC. The majority of patients were white, male, and had high-risk NMIBC (72.6%). 52.6% of included patients were former smokers and 12.7% were current smokers. During the three-year study period, there was a NMIBC recurrence in 259 of the 723 patients (35.8%). The 1- and 3-year probability of recurrence was 19% and 44%, respectively. The grade and stage of recurrences were 28.9% LG Ta, 34.4% HG Ta, 15.8% pure CIS, 0.3% LG T1, 15.4% HG T1, and 5.4% unknown. After adjustment for *a priori* clinical and demographic factors, smoking status had no significant association with recurrence.

**Conclusion:** Smoking status was not significantly association with recurrence in a study of patients with predominantly high-risk recurrent NMIBC managed with photodynamic enhanced cystoscopy. 

*Keywords:* Smoking cessation; Bladder cancer; Recurrence

## Introduction

Smoking has a well-established causal relationship with the development of urothelial cancer [1]. Most new urothelial cancers are localized to the bladder and are non-muscle invasive (NMIBC) at the time of diagnosis. NMIBC frequently recur and there are several established factors that increase the probability of recurrence [2–4]. Smoking status has been linked to increased aggressiveness at the time of bladder cancer diagnosis [5] but its effect on recurrence patterns in NMIBC is conflicting and prior studies have limitations that prevent generalizability for contemporary management [6-10]. Fluorescence-based photodynamic enhanced or Blue Light cystoscopy (BLC) has been shown to decrease recurrence rates in some types of NMIBC due to improved cancer detection abilities [11]. To date, there has not been any exploration of the relationship between smoking status and risk of NMIBC recurrence among

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patients managed with this new technology and emerging standard of care. Improving our understanding of the relationship between smoking and NMIBC recurrences may help tailor treatment and surveillance protocols for patients.

Patients who have undergone Blue Light photodynamic enhanced cystoscopy with Cysview (Photocure, Norway) are entered into a multi-center registry that collects several important bladder cancer patient factors and outcomes. This registry includes detailed information about patient demographics, risk factors including smoking history, stage at diagnosis, treatments, and long-term outcomes. Using this data source, we sought to assess the association of smoking status on recurrence rates in a cohort of adults with predominantly high-risk recurrence NMIBC managed with photodynamic enhanced cystoscopy. Our goal was to further assess this relationship in order to help inform risk-stratification algorithms, management decisions, and surveillance protocols.

## Patients and methods

### *Data Source*

Following local IRB approval at each participating center and after informed consent, patients undergoing BLC at 15 participating centers in the United States were enrolled in a registry starting in 2014. Patients were included in the registry if they had suspected or known NMIBC based on a prior cystoscopy or imaging and were a candidate to undergo Blue Light Cystoscopy (BLC) with Cysview. Enrollment was expanded to include patients with a history of NMIBC undergoing surveillance BLC after the Cysview regulatory indication was expanded to include such patients. Several publications have previously validated the use of this registry for research purposes and have reported the protocol for use of BLC [12–14]. This study was conducted using de-identified data from the registry and was IRB approved locally at NYU Grossman School of Medicine (#S19-00795). This study is reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria [15].

### *Patient population and analytic cohort*

All patients included in the registry as of September 21, 2020 were assessed. Inclusion criteria included a primary or recurrent diagnosis of non-muscle invasive (Tis, Ta or T1) urothelial cell carcinoma of the bladder. Patients were excluded if: 1) they had no history of bladder cancer recorded in the registry or had no pathology results reported in the registry confirming bladder cancer, 2) they lacked surveillance follow up or records following primary diagnosis, 3) they had a missing or an implausible diagnosis or outcome dates, 4) if they had missing staging data that precluded the ability to assign an American Urological Association (AUA) risk group, or 5) smoking status was unknown. Patients were followed from the date of initial diagnosis until they reached censorship criteria. Censorship was at either their last recorded urology follow-up visits or at 3 years following index diagnosis (the end of our study period). Patients were termed "primary," or "recurrent," bladder cancer patients based on bladder cancer history taken at enrollment into the registry. Surveillance cystoscopy schedule and follow up was not standardized but all participating centers and urologists' practices aligned with management recommendations put forth by the AUA and National Comprehensive Cancer Network (NCCN).

### *Exposure, outcomes, and measures*

Our primary exposure of interest was smoking status at the time of entry into the dataset. Patients were categorized as never, former, or current smoker. Intensity of smoking history in the form of pack-years smoked was assessed. Our primary outcome was first NMIBC recurrence. All patients who were identified as experiencing a recurrence had biopsy proven pathologic diagnoses from each participating institution's pathology department. Time to recurrence for patients in the registry with "primary," bladder cancer was based on time from initial bladder diagnosis to first recurrence in the registry. Patients in the registry with "recurrent," bladder cancer had time to recurrence calculated from the date of their most recent prior bladder cancer finding to the first subsequent recurrence in the registry.

Patients were assigned to 1 of 3 risk groups (low, intermediate or high) according to the AUA/Society of Urologic Oncology (SUO) NMIBC guidelines [16]. Patients who had multifocal tumors with different size, stage, or grade were designated according to the characteristics of the highest risk tumor. Patients with a missing tumor size were similarly stratified to the highest AUA/SUO associated risk category for which they qualified independently of tumor size. Additional covariates of interest included: History of intravesical treatment (none, BCG, intravesical chemo, multiple) and use of prior BLC (yes/no). Prior BLC was defined as exposure to Blue Light Cystoscopy with Cysview, prior to registry participation. Prior BLC was assessed as part of patient history at enrollment. Prior BLC use was included as a variable due to the potential confounding influence that diagnostic or surveillance BLC has on cancer detection. Demographic covariates included patient gender, age, and race/ethnicity (dichotomized as white and non-white).

### *Statistical analysis*

Descriptive statistics were used to report baseline variables. Kaplan-Meier analysis was used to calculate recurrence free probabilities over 3 years following study inclusion. A Cox proportional hazards regression model was used to conduct multivariate analysis evaluating the impact of variables chosen *a priori* on recurrence free

survival. Variables included as potential confounders in our model were selected based on the extent literature of bladder cancer recurrence risk factors and included AUA risk category, smoking status, history of blue light cystoscopy, age, gender, and race. A cutoff of $P < 0.05$ was used for significant difference in outcomes. All analyses were done in R, version 3.6.3 (https://www.R-project.org/).

## Results

### *Description of cohort*

Our initial cohort included 1,030 adults from the registry (drawn from a registry that overall included 1,844 patients) who met initial inclusion criteria and had complete pertinent data. Participants were further excluded from this group of patients if they had missing data on smoking history ($n = 307$) since this was our primary exposure of interest. Thus, our final analytic cohort included 723 adults with bladder cancer (Figure 1). There were 83 (11.5%) of patients who entered the registry with a primary diagnosis of NMIBC and 640 (88.5%) who had a history of recurrent NMIBC. The majority of patients were white, male, and had AUA high-risk NMIBC (72.6%). Median follow up time for the entire cohort was 717 days (IQR 321-1096 days). Of all included patients, 60.6% ($n = 438$) previously received intravesical treatment (Table 1), most of which was BCG.

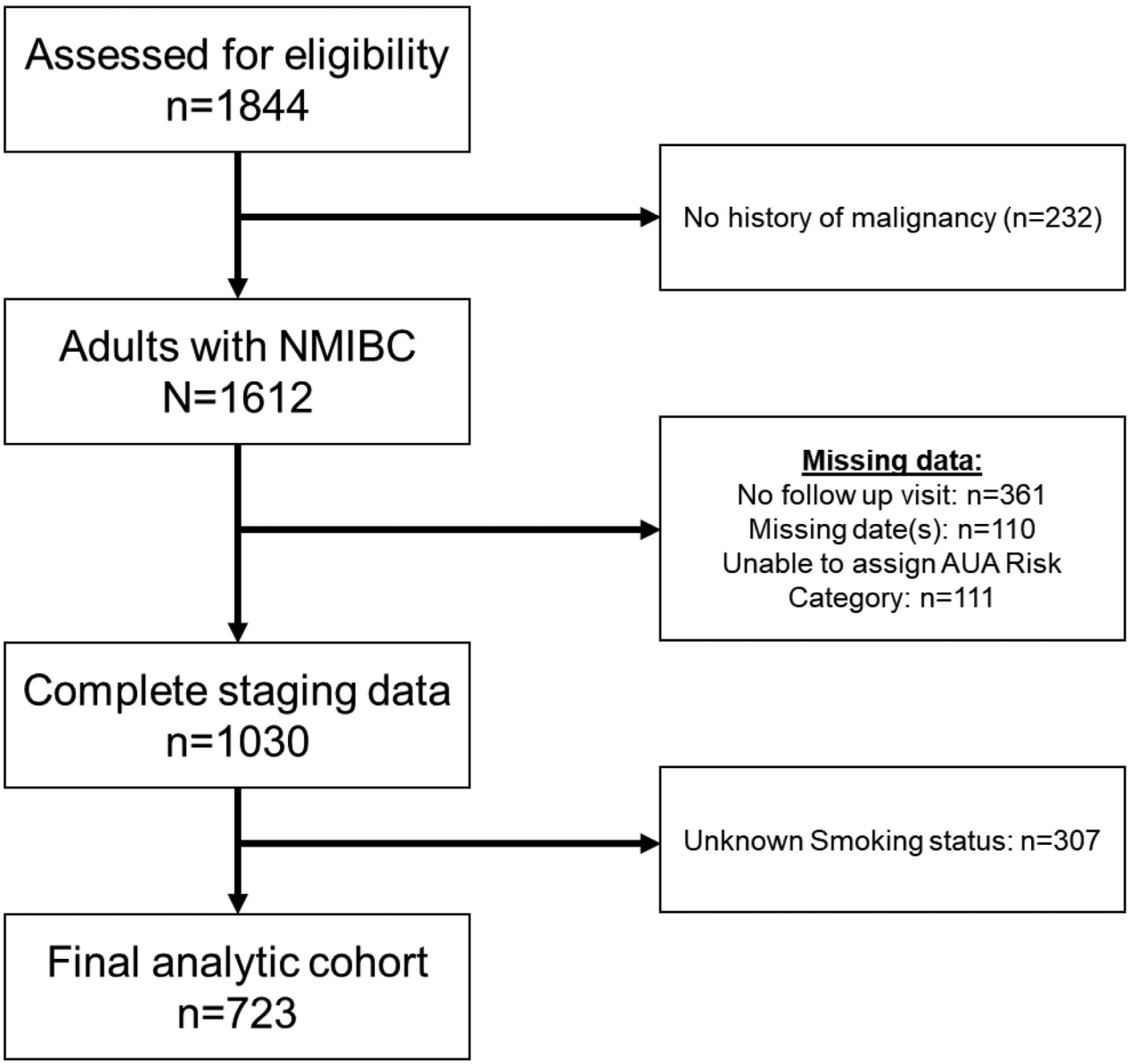


Fig. 1. Development of analytic cohort with exclusions.

Table 1
Demographics and bladder cancer history of 723 patients with NMIBC that comprised our analytic cohort

| | *n* (%) |
|---|---|
| Male gender | 596 (82.4) |
| Age, >65 years old | 546 (75.5) |
| Race | |
| White | 588 (81.3) |
| Non-White or Unknown | 135 (18.7) |
| Smoking history | |
| Current | 92 (12.7) |
| Former | 380 (34.7) |
| Never | 251 (52.6) |
| AUA Risk Category | |
| Low | 73 (10.1) |
| Intermediate | 125 (17.3) |
| High | 525 (72.6) |
| Bladder Cancer History | |
| Primary | 83 (11.5) |
| Recurrent | 640 (88.5) |
| History of intravesical treatment | |
| No | 178 (24.6) |
| Yes | 438 (60.6) |
| Chemotherapy[a] | 75 (17.1) |
| BCG[a] | 248 (56.6) |
| Multiple[a] | 90 (20.5) |
| Unknown[a] | 25 (5.7) |
| Unknown | 107 (14.8) |

[a] percentage among those who received any intravesical therapy ($n = 438$)

### *Smoking details*

Over half of the included patients were former smokers (52.6%) and 12.7% were smokers at the time of entry into the registry (Table 2). Most current smokers reported between 11−50 pack years (56.5%) or greater than a 50-pack year smoking history (30.4%). Of former smokers with available pack-year data, the majority smoked between 11−50 pack-years. Of the 92 patients who were current smokers upon entry into the registry, 9 (9.8%) quit at their 6 months follow up visit.

### *Risk of recurrence*

During the three-year study period, there was a NMIBC recurrence in 259 of the 723 patients (35.8%). The 1- and 3-year probability of recurrence was 19% and 44%, respectively. There were no differences in recurrence-free survival probability for adults when stratified by smoking status, gender, or age category. Adults with AUA low risk NMIBC had higher recurrence free survival probability compared to those with AUA intermediate and high risk NMIBC ($P = 0.006$) (Figure 2). Additionally, those who had a history of prior BLC also had a higher recurrence free survival probability ($P = 0.005$), which was most pronounced among those with intermediate and high risk NMIBC (Supplement). The grade and stage of initial recurrences were 28.9% LG Ta, 34.4% HG Ta, 15.8% pure CIS, 0.3% LG T1, 15.4% HG T1, and 5.4% unknown.

After adjustment for *a priori* clinical and demographic factors, baseline smoking status had no significant association with recurrence (Figure 3). However, there was a significant association between higher AUA risk group and increased risk of recurrence. Additionally, prior BLC usage was associated with lower risk of recurrence (HR 0.6, 95% CI 0.4−0.8). Sensitivity analyses, which included patients with unknown smoking history included in the analytic cohort, did not demonstrate differences in any outcomes (Supplement).

Within the three-year window, there were 18 patients (2.5%) who progressed beyond non-muscle-invasive disease. Eight of these 18 patients had a NMIBC recurrence prior to progression. Sixteen of these patients progressed to pT2 and 2 progressed to pT4. Four additional progressions occurred after our thee-year study window. All of the patients who experienced progression were high-risk as defined by the AUA/SUO.

## Discussion

In this analysis of a large multi-center registry of patients with predominantly high-risk recurrent NMIBC managed with BLC, we did not find a significant association between smoking status and subsequent NMIBC recurrence. The strengths of our analysis are the multi-center nature of the registry, the centers of excellence that contribute patients to the registry, use of BLC in the cohort, availability of long term follow up, and ability to stratify according to contemporary and clinically applicable AUA risk categories. Additional notable findings include further confirmation of disparate recurrence rates among patients with AUA high/

Table 2
Smoking history and pack-year intensity of smoking for analytic cohort

| Smoking Status (pack-y) | 0 − 1 | 2 − 10 | 11 − 50 | >50 | Unknown |
|---|---|---|---|---|---|
| Current ($n = 92$) | 3.2% (3) | 4.3% (4) | 56.5% (52) | 30.4% (28) | 5.4% (5) |
| Former ($n = 380$) | 1.3% (5) | 14.5% (55) | 33.4% (127) | 10.3% (39) | 40.5% (154) |
| Never ($n = 251$) | - | - | - | - | - |

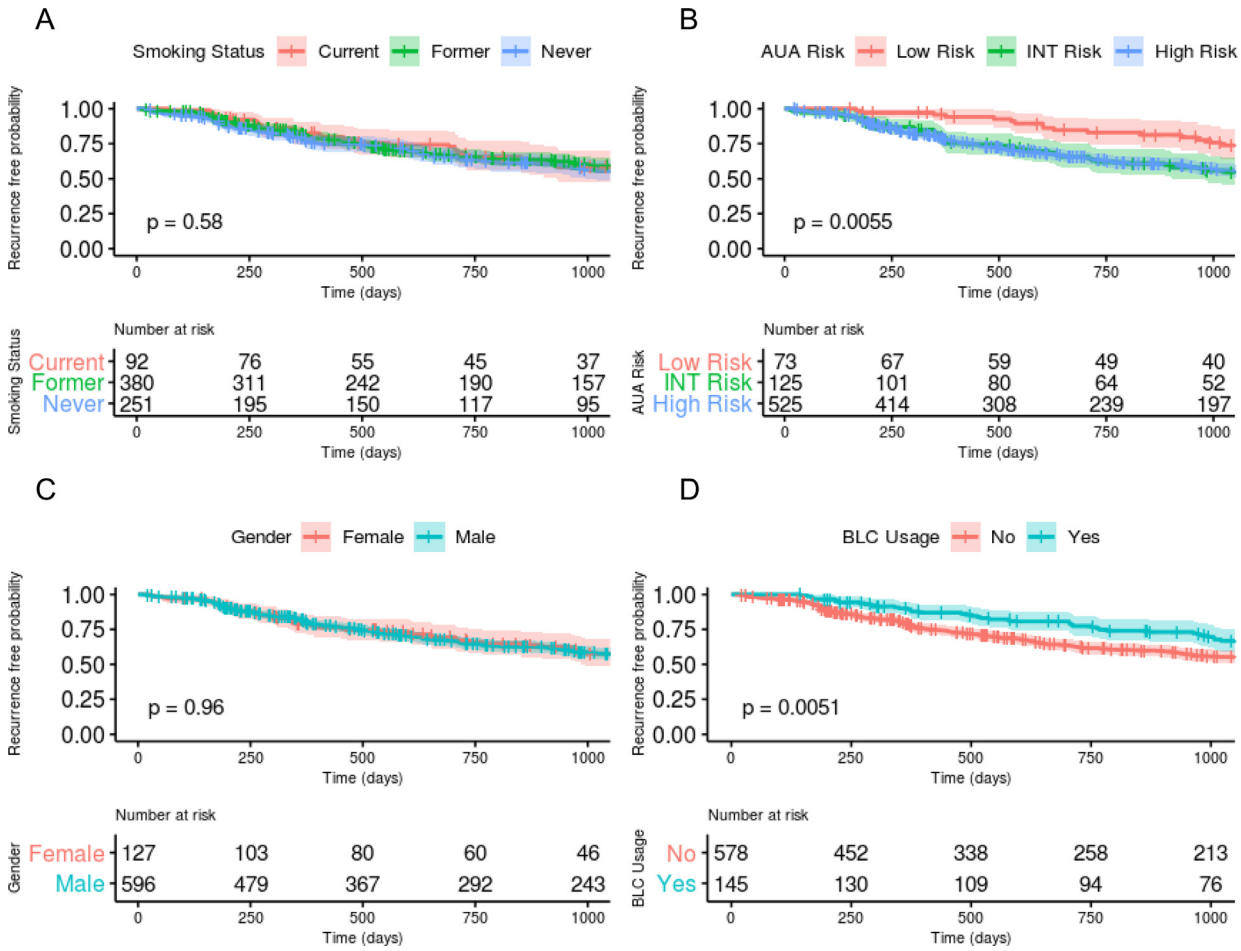


Fig. 2. Unadjusted recurrence-free survival based on (A) smoking status, (B) AUA risk category, (C) gender, and (D) history of blue light cystoscopy (BLC) (Color version of the figure is available online.)

intermediate risk NMIBC (compared with low-risk patients) and a decreased risk of recurrence among those patients who had a previous BLC.

Previous studies have found equivocal associations between smoking status and NMIBC recurrence patterns [17]. In general, there are unique aspects of those patient cohorts and differences in study design that make our findings complimentary and contributory to the literature on this topic. A secondary analysis of approximately 700 participants in a European prospective adjuvant intravesical chemotherapy trial found that current and former smokers had a slightly higher risk of recurrence when compared to never smokers [18]. However, the authors did not assess former and current smokers independently, as we have. Conversely to this study but similar to our findings, smoking was not determined to be independently associated with recurrence in several additional studies [8,19,20]. In a multi-center retrospective study of over 2,000 adults with primary NMIBC, former and current smoking (compared to never smoking) was not associated with recurrence [8]. Since patients included in this study were newly diagnosed, many had lower grade and stage disease than our cohort while only ~20% received any intravesical therapy throughout the course of the study. In our study, the vast majority of included patients were high-risk and already had a history of recurrent NMIBC. The differences in disease severity and therefore risk of recurrence among the patients included in our studies compared to others is likely related to referral bias within our cohort from higher volume centers. However, our findings add additional data to support a lack of association between current smoking status and recurrence among a group of high-risk patients.

We report 2 additional important findings not related to our primary analysis. First, we by stratifying recurrence risk among AUA NMIBC categories, we have demonstrated that these category designations may differentiate recurrence risk to some degree. These findings are similar to 2 prior reports that showed that intermediate and high-risk patients had similar recurrence rates but these were significantly different than low risk patients [21,22]. It may be

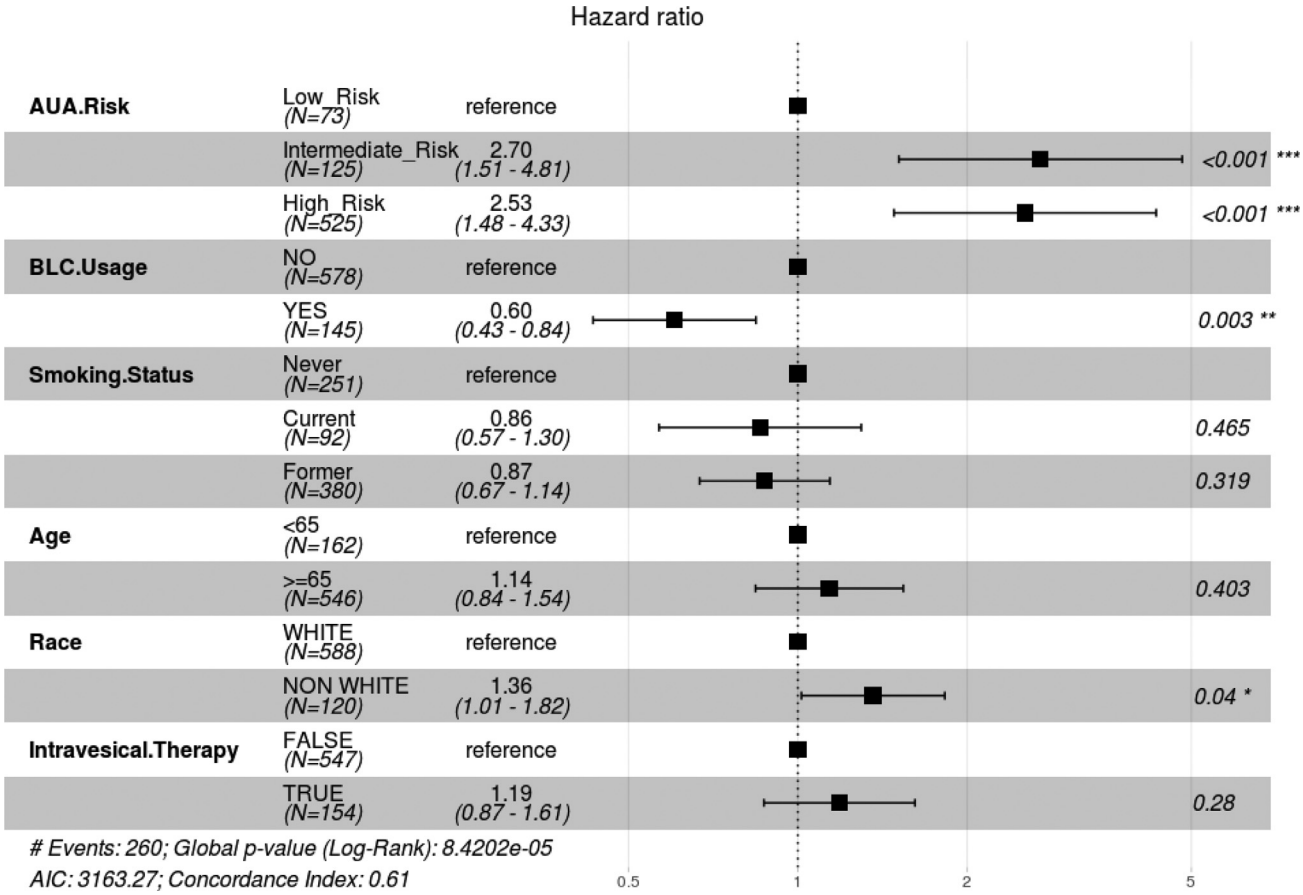


Fig.3. Forest plot of Cox proportional hazard ratios for multivariable model assessing association between smoking status and NMIBC recurrence adjusted for *a priori* covariates.

possible that there is significant overlap in risk between the proposed intermediate and high-risk strata. This may necessitate revisions to these criteria in the future. However, it is important to note that although intermediate and high-risk patients had no significant difference in recurrence rates, only high-risk patients progressed. These findings are also consistent with past studies of the AUA/SUO risk categories appropriately stratify patients according to risk of NMIBC progression [19,20]. Second, we demonstrate a recurrence free survival benefit for patients who had previously had bladder cancer diagnosed or surveilled with BLC. Though use of BCL has been associated with increased detection of bladder cancer, particularly CIS [23,24], our findings demonstrate long term benefit of this technology.

The relationship between smoking and bladder cancer remains underappreciated but is an essential component of cancer survivorship [25,26]. Our findings should not be used to minimize the need for urologists to educate and counsel smokers who are diagnosed with bladder cancer. Smoking cessation is critically important given the myriad health benefits of smoking cessation and all urologists should be screening for tobacco use during visits and improving how they help patients quit [27]. However, many questions remain unanswered about complex relationship between smoking and bladder cancer recurrence. These include the influence and timing of quitting, the differential risk related to duration of exposure vs. intensity of exposure, and whether certain intravesical treatment agents may be more or less effective among smokers. Recently, a Danish study reported improved effectiveness of Mitomycin among current smokers [28]. Interestingly, the Rink et al. study found that smoking cessation 10 years prior to diagnosis was associated with a lower risk of recurrence [9]. This is in contrast to a population-based study conducted in the Netherlands which reported no difference in recurrence or progression among never, former, current smokers, and no significant effect of remote quitting [20]. A prospective study in UK of 722 NMIBC of adults who quit at the time of diagnosis vs those who continued smoking showed no difference in risk of recurrence, though this was somewhat limited by how few people quit smoking at the time of diagnosis [19]. It is possible that the high-risk, recurrent nature of disease in our cohort obscured the influence smoking has on recurrence rates

due to selection bias. Similarly, perhaps tobacco-use has a differential influence on the varying molecular biology of NMIBC, which we were unable to assess, thereby confounding recurrence patterns [29].

Limitations of our study include lack of granular data on smoking history, including nearly one third of patients that were excluded for having no smoking related information entered into the registry. In order to account for this, we performed unadjusted and adjusted analyses with unknown smoking status patients included in the cohort, demonstrating no differences. Timing of the quit attempt also has had equivocal associations with NMIBC recurrence outcomes [20,30] and we were unable to account or assess this as the data were not available. Additionally, the heterogeneity of NMIBC treatment strategies required creating covariates that may not completely capture the nuanced details of treatment with intravesical therapies. This type of residual confounding is largely related to the differences between intravesical chemo and immunotherapies and those who did or did not meet "adequate," intravesical treatment criteria. If we accounted for this, we would have considerably limited our statistical power to assess our primary exposure, which was smoking status. We were also unable to assess factors associated with progression, a critical second component of NMIBC outcomes, in this cohort due to low frequency of progression events. The low frequency of recurrence and progression events in this study, despite the duration of follow up and the cohort being comprised largely of patients with high-risk recurrent disease, is likely multifactorial. Historical progression rates are likely higher than what we now see in contemporary practice [31] and our findings may be related to improved treatment or surveillance strategies at the high-volume centers who contribute to the registry or improved detection of disease through the use of BLC [14]. Lastly, the patients included in this registry come from a diverse mix of institutions, but are largely reported from academic centers of excellence with considerable experience managing recurrent, high risk NMIBC which may have influenced our findings. However, this can be considered evidence that contemporary outcomes at high volume centers are superior to historical recurrence and progression rates but also that our findings may be less generalizable to all patients with NMIBC.

## Conclusion

Smoking status did not have a significant association with NMIBC recurrence rates in our analysis of a multicenter registry of patients with predominantly high-risk recurrent bladder cancer managed with BLC. Additional findings include differentiate recurrence rates among AUA low and intermediate/high risk patients and a possible recurrence-free survival benefit among patients surveilled or diagnosed with enhanced cystoscopy.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2021.04.028.

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