**Surveillance for low and low-intermediate risk non-muscle invasive bladder cancer: A Pilot Study**

**Protocol # 2013-0177H**

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**Study Schema**

\*If patient presenting for initial 3 month cystoscopy following tumor resection, perform cystoscopy and if NEGATIVE, follow nomogram.

NO

Not Eligible\*

Does the pt have at least ONE negative surveillance cystoscopy following the most recent biopsy?

NO

Not Eligible

YES

Does the patient have low/low intermediate NMIBC?

YES

NO

Not Eligible

NO

Was the most recent tumor 12 to 48 months ago?

Was the most recent tumor < 12 months ago?

YES

YES

Randomization

Randomization

Sign Informed Consent

Sign Informed Consent

**AUA (Control Arm)**

Participant will undergo cystoscopy every 3 months (± 1.5 months) for the first 2 years after most recent biopsy and transition to cystoscopy every 6 months when 24 months after biopsy.

Participant will be followed for 2 years from the day of study enrollment.

**EAU (Intervention Arm)**

Participant will undergo cystoscopy 12 month (± 1.5 months) from most recent biopsy, and then yearly (± 1.5 months).

Participant will be followed for 2 years from the day of study enrollment

**EAU (Intervention Arm)**

Perform 12 month post-biopsy cystoscopy if not already completed and participant will undergo cystoscopy yearly (± 1.5 months).

If most recent biopsy is ≥ 12 months after initial diagnosis, participant will undergo cystoscopy yearly (±1.5 months)

Participant will be followed for 2 years from the day of study enrollment

**AUA (Control Arm)**

Participant will continue to undergo cystoscopy every 3 months (± 1.5 months) for the first 24 months after most recent biopsy, then every 6 months (± 1.5 months) for the next 24 months, then yearly after 4 years.

Participant will be followed for 2 years from the day of study enrollment

1. **Objectives**

1.1 The primary objectives of the study are to:

1. Demonstrate feasibility of study recruitment and retention in order to help plan for subsequent phase III study
2. Develop methods for assessing patient satisfaction and costs associated with cystoscopy during bladder cancer surveillance

1.2 Secondary objectives of the study are to:

1. Capture preliminary data regarding number of procedures and direct and indirect cost differences between study arms
2. Compare proportion of patients experiencing disease progression and recurrence at 2 years following most recent biopsy under two different surveillance approaches

2.0 Background

2.1 Overview

Urothelial carcinoma of the bladder (UCB) accounted for 70,530 new cases of cancer and 14,680 cancer-related deaths in the United States during 2010[1](#_ENREF_1). Of these new cases, approximately 25% presented as invasive tumors involving the muscular wall of the bladder and 75% present as non-muscle invasive bladder cancer (NMIBC). Transurethral resection of bladder tumor (TURBT) is an endoscopic procedure that allows for histopathologic assessment and disease staging. TURBT is the primary diagnostic procedure for new and recurrent bladder tumors. TURBT can also be therapeutic for small or non-muscle invasive tumors.

Due to the high likelihood of disease recurrence after initial treatment and the possibility of disease progression, bladder cancer patients require frequent and long-term endoscopic evaluations. As a result, bladder cancer has been identified as the **most expensive** cancer to manage and is an enormous burden to our health care system[2](#_ENREF_2). The depth of tumor invasion into the bladder wall determines the stage of bladder cancer. Non-muscle invasive (previously termed “superficial”) tumors don’t invade the bladder muscularis propria and are usually managed with transurethral surgery with bladder preservation. Fortunately, the majority of bladder cancer patients are initially diagnosed with non-muscle invasive disease. Following transurethral bladder tumor removal, there are two major unfavorable outcomes to avoid. The cancer may recur/persist or it may progress to more advanced disease. Tumor recurrence/persistence is agonizing for the patient and tumor progression is life threatening.

In the U.S., guidelines for following patients with non-muscle invasive bladder cancer indicate that patients should undergo cystoscopy every 3 months for the first 2 years after diagnosis, then every 6 months for the next 2 years, and then yearly. This recommendation is based on expert opinion (Level 4 evidence). The European Association Urology (EAU) recommends a less frequent follow-up scheme (see Treatment plan below). Although such an approach could considerably decrease costs and burden during the follow-up period by examining patients less frequently, to date these surveillance approaches have never been assessed in a prospective manner.

2.2 European Urologic Association (EAU) Guidelines

Surveillance strategies for detection disease recurrence in patients with NMIBC in Europe and U.S. largely rely on cystoscopy as the principal means for identifying tumors. The EAU guidelines provide a risk-adapted surveillance cystoscopy program for patients with a history of bladder cancer[3](#_ENREF_3). In the first step, a weighting system is used to calculate the risk of disease recurrence and progression[3-5](#_ENREF_3). Then, the scores are used to determine a patient’s risk for disease recurrence and progression into a three tiered classification system (low-, intermediate-, and high-risk) disease. Surveillance strategy is variable based on disease risk as follows:



2.3 The American Urologic Association (AUA) Guidelines

Surveillance strategies for bladder cancer in the U.S. advise cystoscopy every 3 months for the first 2 years, then every 6 months for 2 years, then annually, resetting the clock with each newly identified tumor. Although the accuracy of cystoscopy relies on the subjective and operator-dependent interpretation of visible findings, it is widely accepted as the “gold standard” for diagnostic evaluation of bladder cancer[6](#_ENREF_6).

3.0 Staging Criteria

Bladder cancer

Primary Tumor (T)

Clinical Stage

cT1 Invades subepithelial connective tissue (lamina propria)

cT2 Muscle-invasive

cT3 Residual mass on exam under anesthesia following TURBT

cT4 Clinically fixed disease on exam under anesthesia

Pathologic Stage

 pT1 Invades subepithelial connective tissue (lamina propria)

pT2 Muscle-invasive

pT3 Invades perivesicle fat

pT4 Invades adjacent organs (prostate, vagina, uterus, bone, etc…)

Histologic subtypes

 Urothelial cell carcinoma (Transitional cell carcinoma)

 Squamous cell carcinoma

 Adenocarcinoma or glandular carcinoma

 Sarcomatoid carcinoma

 Micropapillary carcinoma

Histologic grade

High-grade Poorly- or un-differentiated

4.0 Inclusion Criteria

The patient must:

4.1 Have one negative cystoscopy 3 months following most recent biopsy

4.2 Be able to give informed consent

4.3 Be age 18 or older

4.4 Be at low- or low-intermediate risk for disease recurrence and progression according to the EAU guidelines (see Table below)

|  |  |  |
| --- | --- | --- |
| **Factor** | **Recurrence** | **Progression** |
| No. of tumorsSingle2-7>7 | 036 | 033 |
| Tumor diameter<3cm≥3cm | 03 | 03 |
| Prior recurrence rate Primary1 recurrence per year>1 recurrence per year | 024 | 022 |
| CategoryTaT1 | 01 | 04 |
| Concomitant CISNoYes | 01 | 06 |
| Grade (1973 WHO)G1G2G3 | 012 | 005 |
| Total score | 0-17 | 0-23 |
|  |  |  |
| Risk Group | Recurrence score | Progression score |
| Low | 0 | 0 |
| Low-intermediate | 1-4 | 2-6 |
| High-intermediate | 5-9 | 7-13 |
| High | 10-17 | 14-23 |

5.0 Exclusion Criteria

5.1 Have a history of invasive (≥T1) bladder cancer

5.2 Have a history of carcinoma-in-situ (CIS)

5.3 Unable to give informed consent

5.4 < 18 or younger

5.5 Have variant histology (micropapillary, nested variant, non-urothelial cell carcinoma elements)

6.0 Study Procedure

 6.1 Study Design

 This is a two-arm, randomized-controlled study. For the purposes of enrollment “intervention” refers to surveillance based on the EAU guidelines (see study schema and calendars) and “control” refers to surveillance based on the AUA guidelines (see study schema and calendars).

6.2 Recruitment

Patients will be recruited through the urology outpatient clinics at the UTHSCSA Medical Arts and Research Center (MARC) and RBG GU clinic, and VA Urology clinic.

Attending physicians in the Department of Urology, and selected other personnel who also serve as research staff for this study, will identify prospective study participants/ candidates. Study eligibility will be determined by investigators and research staff with legitimate access to patient PHI due to their clinical role and/or as members of the research team. In the event approved study staff cannot reach treating physician/investigator in person due to clinic schedule, a secure e-mail correspondence containing initials and medical record number of eligible patient will be sent securely to treating physician/investigator through UTHSCSA e-mail system so that they may notify patient of research opportunity. The principle investigator/sub-investigators will also forward a copy of upcoming Urology clinic and/or OR schedule and give to an approved research staff to identify and screen potential participants. This schedule may be disclosed physically or electronically. If electronically, it will be sent via a secure e-mail correspondence. . Disclosure applies to VA site only as e-mail will not be within VA e-mail system (physician study staff have VA privileges but do not have VA e-mail). Secure e-mail correspondence will be maintained behind HSC firewall.

Any patient who presents with non-muscle invasive bladder cancer and meets the inclusion/exclusion criteria will be given an option to participate in the study. The inclusion of patients or refusal to participate by patients eligible for this study will in no way compromise the quality of health care they will receive.

A list of candidates who meet the eligibility criteria will be given to the principle investigator or Sub-PI for review. The PI/Sub-PI would then attempt to recruit all potential candidates via phone. Research objectives, risks vs. benefits of study participation, alterative treatment plan, randomization process, and study participants’ rights and responsibilities will be explained. If the candidate is interested, a copy of IRB-approved informed consent will be given (via USPS, email, or in-person) for review prior to the candidate’s routine surveillance cystoscopy. In the event that neither the PI nor the Sub-PI can’t reached the potential candidates over the phone, an IRB approved research staff will approach the candidate during his/her next follow-up appointment.

The candidate will be approached again by either study staff or the PI/Sub-PI after the candidate’s routine surveillance cystoscopy has been determined “negative” or “normal”. The study staff/PI will reiterate the research objectives, risks and benefits of study participation, alternative treatments available, randomization process, and the subjects’ rights and responsibilities. If the candidates agree to participate, informed consent will be obtained and randomization will occur.

Eligible candidates will be approached and consented in a private consult room located within the GU clinic at the UTHSCSA MARC and RBG and VA. Usual privacy policy practices will be followed. Study participants will also be given contact information for someone they can call with any questions that may arise.

 6.3 Study Intervention (Surveillance cystoscopy)

After signing the informed consent, participants will be randomized to either the intervention arm or the control arm. Regardless of group assignment, participants will undergo cystoscopy in clinic as per usual care.

If the participant is randomized to the **intervention arm**, surveillance cystoscopy will be performed following the EAU guidelines as determined by the time from the last tumor. Please see Study Calendar for guidance.

If the participant is randomized to the **control arm**, surveillance cystoscopy will be performed following the AUA guidelines, which is every 3 months (± 1.5 mons) for 2 years, then every 6 months (± 1.5 mons) for the next 2 years, and then yearly (± 1.5 mons) following the diagnosis of bladder cancer. Please see Study Calendar for guidance.

Because use of cytology is variable among the participating urologist, the utilization of cytology will be at the treating urologist’s discretion as per usual standard care. Study duration will be 2 years from the time of study enrollment.

 6.4 Patient satisfaction and Cost

* 1. Participants will be administered self-reported questionnaires after each cystoscopy visit which aims to capture their overall attitudes and satisfaction/dissatisfaction regarding the follow-up regimen for their bladder cancer. The questionnaire will aim to gather the following data elements:
		1. Bother associated with cystoscopy visits –travel time, waiting room.
		2. Bother associated with cystoscopy procedure – including level of pain, , frustration, etc.. (see appendix)
		3. “Do you feel better after cystoscopy as a means to make certain there are no tumors present” (see appendix)
		4. Do you think cystoscopy is too much of a burden for the patient (see appendix)
	2. Cost (see appendix) - Participants will provide an estimate of indirect costs associated with the procedure including, but not limited to the following:
		1. Time away from work
		2. Gas/bus ticket
		3. Food
		4. Bladder cancer related costs (surgery, cystoscopy, hospitalization, imaging, anesthesia, etc.)
		5. Ancillary costs: lost work and time off for others who may drive patients and take time off to care for them
		6. Other

 6.5 Cancer-related Outcomes

* 1. Disease recurrence- this will include tumors confirmed by pathologic assessment. We expect recurrence rates within 2 years to be approximately 15% and to be similar between the two groups.
	2. Number and size of recurrent tumors. Because the participants in the intervention group will undergo less cystoscopies compared to the “control” group, we will track the number and size of all recurrent tumors in both groups. The size is estimated (in centimeters) based on the treating urologists tumor size estimation during cystoscopy. We expect that the number and size of recurrent tumors will be similar between both groups.
	3. Disease progression – defined as increase grade (low grade to high grade), or increase stage (Ta to CIS, ≥T1). We expect progression rates to be low in this population (<5%) and similar between the two study arms.
	4. Case report forms are provided in the appendix

6.6 Feasibility Assessment

1. Adherence to protocol regimen – the number of cystoscopies scheduled and completed will be recorded by the study coordinator.
2. Study feasibility – the number of patients with bladder cancer undergoing bladder biopsy or transurethral resection will be reviewed and tracked. From these patients, we will track the number of patients that are eligible for the study and this will be logged. The number of patients approached and the number of patients enrolled will be tracked to provide an estimation of study feasibility and accrual potential. This information will be critical for subsequent proposal for a large multi-center study.

7.0 Study Calendar

Please refer to the following study calendars pending on the participant’s randomization result

7.1 Control Arm (AUA Guideline)

AUA Guideline (Control Arm): Cystoscopy every 3 months (± 1.5 mons) for the first 2 years, then every 6 months (± 1.5 mons) for the next two years, and then yearly (± 1.5 mons).

|  |  |
| --- | --- |
| Study Entry Time Point | AUA Recommended Guideline: Cystoscopy every 3 months (± 1.5 mons) for the first 2 years, then every 6 months (± 1.5 mons) for the next two years, and then yearly (± 1.5 mons). |
| Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
| Mon6 | Mon9 | Mon12 | Mon15 | Mon18 | Mon21 | Mon24 | Mon30 | Mon36 | Mon42 | Mon48 | Mon60 | Mon72 |
| @ Mon 3 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 6 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 9 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 12 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 15 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 18 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 21 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 24 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 30 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 36 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 42 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| @ Mon 48 |  |  |  |  |  |  |  |  |  |  |  |  |  |

During each of these visits, participants will have the following procedures done:

* Surveillance cystoscopy (Standard of Care)
* Study eligibility assessment (Research only)
* Satisfaction questionnaire (Research only)
* Cost questionnaire (Research only)
* FACT-Bl questionnaire (Research only)

7.2 Intervention Arm (EAU Guideline)

EAU Guideline (Intervention Arm): Cystoscopy at month 3 (± 1.5 mons), then at 12 months (± 1.5 mons), and yearly (± 1.5 mons) for five years.

|  |  |
| --- | --- |
| Study Entry Time Point | EAU Recommended Guideline: Cystoscopy at 3 month (± 1.5 mons), then at 12 months (± 1.5 mons), and yearly (± 1.5 mons) for five years. |
| Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
| Mon12 | Mon24 | Mon36 | Mon48 | Mon60 | Mon72 |
| @ Mon 3 |  |  |  |  |  |  |
| @ Mon 6 |  |  |  |  |  |  |
| @ Mon 9 |  |  |  |  |  |  |
| @ Mon 12 |  |  |  |  |  |  |
| @ Mon 15 |  |  |  |  |  |  |
| @ Mon 18 |  |  |  |  |  |  |
| @ Mon 21 |  |  |  |  |  |  |
| @ Mon 24 |  |  |  |  |  |  |
| @ Mon 30 |  |  |  |  |  |  |
| @ Mon 36 |  |  |  |  |  |  |
| @ Mon 42 |  |  |  |  |  |  |
| @ Mon 48 |  |  |  |  |  |  |

During each of these visits, participants will have the following procedures done:

* Surveillance cystoscopy (Standard of Care)
* Study eligibility assessment (Research only)
* Satisfaction questionnaire (Research only)
* Cost questionnaire (Research only)
* FACT-Bl questionnaire (Research only)

8.0 Criteria for Evaluation and Oncologic Endpoint Definitions

8.1 Recurrence

a. Visible –urologist documents presence of a bladder tumor on cystoscopy.

b. Pathologic- following transurethral resection of the bladder tumor, recurrence is confirmed based on pathologic interpretation of the specimen

8.2Progression

 a. Grade progression- patient experiences an increase in tumor grade (low grade to high grade)

 b. Stage progression – patient experiences an increase in the tumor stage (Ta to CIS or ≥T1)

9.0 Statistical Considerations

9.1 Sample Size Determination

This is a pilot study, which aims to assess the feasibility of the steps that need to take place as part of the subsequent large study.  As a primary objective, we aim to determine the recruitment and retention rates to help power the subsequent phase III trial. We use completion of the assessment form as a surrogate for recruitment and retention.  Based on accrual rate and study duration, we have selected a sample size of 45 which will provide sufficient data to contribute to the pilot project.  We will plan to enroll a total of 50 patients to assume a drop/withdrawal of 10%.

10.0 Data analysis

The number screened, the number of screen failures by reason, the number randomized to each arm, the number lost to follow-up by arm, and the number completing the study by arm will be tabulated. Tabular summaries of baseline characteristics, and numeric outcomes pertaining to all primary and secondary end points will be summarized by study arm. Intervention and control arms will be contrasted on binary and categorical outcomes with Fisher’s Exact Test and on continuously distributed outcomes with t-tests or Wilcoxon tests as appropriate. Continuously distribution data may be log transformed prior to analysis to achieve approximate normality. All statistical testing will be 2-sided with a significance level of 5%. 95% confidence intervals for parameters will be displayed. Corrections for multiple testing will not be applied. SAS Version 9.3 for Windows (SAS Institute, Cary, NC) or R will be used throughout.

11.0 Registration Guidelines

Patients must be registered after enrollment.

12.0 Ethical and regulatory

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

13.0 Data and Safety Monitoring Oversight

A Data and Safety Monitoring Plan (DSMP) is required for all an individual protocols conducted at CTRC. All protocols conducted at CTRC are covered under the auspices of the CTRC Institutional Data Safety Monitoring Plan.

The CTRC Institutional DSMP global policies provide individual trials with:

• institutional policies and procedures for institutional data safety and monitoring,

• an institutional guide to follow,

• monitoring of protocol accrual by the CTRC Protocol Review Committee,

• review of study forms and orders by the Forms Committee,

• tools for monitoring safety events,

• monitoring of UPIRSO’s by the Director of Quality Assurance and DSMC,

• determining level of risk (Priority of Audit Level Score – PALS) ,

• oversight by the Data Safety Monitoring Committee (DSMC), and

• verification of protocol adherence via annual audit for all Investigator Initiated Studies by the CTRC Quality Assurance Division.

**Monitoring Safety**

Due to the low risk associated with participation in this protocol, The Principal Investigator will conduct independent annual review and report any findings to the CTRC Data Safety Monitoring Committee (DSMC) and the UTHSCSA IRB. It is not anticipated that any safety issues will arise from this study because of the study design.

 **Reporting Requirements**

As per the CTRC DSMP, any protocol modifications, problematic safety reports, unanticipated problems, and suspension or early termination of a trial must be reported to all members of the research team. Suspension and early termination of a trial must also be reported immediately to the Director of Quality Assurance (DQA) who will promptly notify the sponsor and the UTHSCSA IRB.

 **Assuring Compliance with Protocol and Data Accuracy**

As with all studies conducted at CTRC, the PI has ultimate responsibility for ensuring protocol compliance, data accuracy/integrity and responding to recommendations that emanate from monitoring activities. **Source verification of data will be performed every twelve months***.* Protocol compliance, data accuracy and reporting of events is further ensured by an annual audit conducted by the Data Safety Officer, whose audit report is shared with the PI, the research team, and will be reviewed by the CTRC DSMC.

 Safety Definitions:

 For this study, the following safety definitions will be applicable:

|  |
| --- |
| **UTHSCSA UPRISO REPORTING REQUIREMENTS** |
| Type Event | Report to | Timeframe |
| UPIRSO - life threatening | UTHSCSA IRB and QA Director | within 48 hours of the PI determining a UPIRSO exists |
| UPIRSO - non-life threatening | UTHSCSA IRB and QA Director | within 7 days of the PI determining a UPIRSO exists |

Unanticipated Problems Involving Risks to Subjects or Others Definition: Unanticipated problem involving risk to subjects or others includes any incident, experience or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied (note: the unfounded classification of a serious adverse event as “anticipated” constitutes serious non-compliance);
2. definitely related or probably related to participation in the research; and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

All UPRISO’s will be reported following CTRC and UTHSCSA institutional guidelines.

 References

# 1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin.* Sep-Oct 2010;60(5):277-300.

# 2. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: a comprehensive review of the published literature. *Pharmacoeconomics.* 2003;21(18):1315-1330.

# 3. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol.* Mar 2006;49(3):466-465; discussion 475-467.

# 4. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Bohle A, Palou-Redorta J. EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder. *Eur Urol.* Aug 2008;54(2):303-314.

# 5. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Bohle A, Palou-Redorta J. [EAU guidelines on non-muscle-carcinoma of the bladder]. *Actas Urol Esp.* Apr 2009;33(4):361-371.

# 6. Brown FM. Urine cytology. It is still the gold standard for screening? *The Urologic clinics of North America.* Feb 2000;27(1):25-37.

**List of Abbreviations**

AUA –American Urologic Association

DLT – Dose-limiting toxicity

EAU – European Association of Urology

FACS - Fluorescence-activated cell sorting

NIMBC – non-muscle invasive bladder cancer

T- tumor

TURBT – transurethral resection of bladder tumor

UCB – urothelial cell carcinoma of the bladder

Participant Study ID:

Date of Form Completion:

Visit #:

Age of Participant:

**Screening Visit**

**Bladder Cancer History**

*(questions relate to most recent tumor)*

Date of Biopsy:

Pathologic Stage:

Pathologic Grade:

Number of Tumors:

Size (cm):**Histiologic Subtype:**

* Urothelial Cell Carcinoma
* Urothelial Squamous Cell Carcinoma
* Urothelial Transitional Cell Carcinoma
* Urothelial Adenocarcinoma
* Other, \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Number of Tumors Over the Last Year: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Demographics**

1. What is your gender? 🞏 Male 🞏 Female

2. Do you currently use tobacco in any form? 🞏 Yes 🞏 No

3. Did you use tobacco in the past? 🞏 Yes 🞏 No

4. What types of tobacco do/did you use regularly?

 🞏 Cigarettes 🞏 Cigars 🞏 Chew 🞏 Snuff 🞏 Dip 🞏 Other, \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

5. Approximately how long have you used tobacco? \_\_\_\_Years \_\_\_\_Months 🞏 N/A

6. On average how much tobacco do you use? \_\_\_\_ packs per \_**day/week/month**

7. Do you know that tobacco use may increase risk of bladder cancer?

🞏 Yes 🞏 No

8. Do you have a history of bladder cancer? 🞏 Yes 🞏 No

9. What type of insurance do you have?

* Private Insurance, \_\_\_\_\_\_\_\_\_\_\_\_\_\_
* Medicaid
* Medicare
* Carelink
* None/Private Pay
* Other, \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Participant Study ID:

Date of Cystoscopy:

Visit #:

**Cystoscopy**

**Findings**

Tumor: 🞏 Yes 🞏 No

Size (cm):

Number:

Location:

Appearance:

* Papillary
* Sessile
* Diffuse/CIS
* Other,describe: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Subsequent Biopsy (if applicable)**

Date of Biopsy:

**Findings**

Tumor: 🞏 Yes 🞏 No

Size (cm):

Number:

Location:

Appearance:

* Papillary
* Sessile
* Diffuse/CIS

Other,describe: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Pathology Results:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Treatment administered immediately following biopsy: 🞏Yes 🞏 No

If yes, please specify: (i.e. intravesicle therapy, dosage)

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Participant Study ID:

Date of Form Completion:

Visit #:

**Patient Satisfaction Questionnaire**

*To be administered after the cystoscopy procedure.*

**1. Discomfort associated with the procedure, please circle one:**



**2. Bother associated with the procedure, please circle any that apply or provide your own explanation.**

1. I feel better after this procedure because I feel that I’m taking good care of myself.
2. I am frustrated by this procedure and feel that it is performed too often and is not necessary.
3. Other, please explain: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Participant Study ID:

Date of Form Completion:

Visit #:

**Patient-reported Cost Assessment**

**Time**

Did you take time off of work for this procedure?

🞏 Yes 🞏 No

If **YES**, how much time? (please indicate in hours): \_\_\_\_\_\_\_\_\_\_\_\_\_\_

Did someone accompanying you take time off of work for this procedure?

* Yes 🞏 No

If **YES**, how much time? (please indicate in hours): \_\_\_\_\_\_\_\_\_\_\_\_\_

**Transportation**

How did you get to this appointment? (select all that apply):

* Drove
* Took public transportation, such as a bus
* Took a cab
* Walked
* Other, explain: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

If you drove, what is the total mileage (round trip) driven for this appointment: \_\_\_\_\_\_\_\_\_ Miles

What was your total (round trip) travel time: \_\_\_\_\_\_\_\_\_ Hour(s)\_\_\_\_\_\_\_\_\_Minutes

**Money**

How much money do you estimate this appointment cost you personally?

(Assuming insurance covers what they are supposed to cover)

Any other expenses or time that we should account for because of this appointment that we missed from the above questions?

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_