

PlasmaKinetic (PK) Button Vaporization Electrode for Treatment of Bladder Tumors

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PK Button Vaporization Electrode for Treatment of Bladder Tumors
Clinical Protocol Outline

Approvals	Print Name	Signature	Date
Regulatory/ Clinical Affairs	Laura Storms		
Marketing	Namrata Hazariwala		
Principal Investigator	Kenneth Ogan, MD		

Title: PK Button Vaporization Electrode for Treatment of Bladder Tumors

Principal Investigator: Kenneth Ogan, MD

Sub Investigator: Adeboye Osunkoya, MD

Co-Investigators: Daniel Canter, MD, Viraj Master, MD PhD, Peter Nieh, MD, Kenneth Ogan, MD, John Pattars, MD

Study-Supporter: Olympus78

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1. Hypothesis:

It is hypothesized that the PK Button Vaporization Electrode is a non-inferior device in terms of composite complication rates when compared with traditional monopolar electrocautery in the treatment of patients with bladder cancer.

2. Abstract:

The current treatment standard of care for patients who present de novo or with a recurrent bladder tumor is transurethral resection of the bladder tumor (TURBT) using monopolar electrocautery in the form a 90-degree loop electrode and has been used since its introduction in 1952. This intervention, accomplished endoscopically through the urethra, is both diagnostic and potentially therapeutic. Although usually safe and sufficient, this technique can create technical challenges which in this study are to be compared to the use of bipolar energy in TURBT. Bipolar energy has been available for many years and has been readily adopted for the surgical treatment of benign prostatic enlargement and may provide advantages and solutions to the technical challenges of monopolar electrocautery. A further refinement on bipolar energy has been the recent introduction of the PK Button Vaporization electrode which will be used in the intervention arm of this study. A minimum of 120 patients over approximately 2.5-3.0 years will be enrolled and randomized onto one of the two study arms (control-monopolar electrocautery vs. intervention-PK Button Vaporization). The purpose of this study is to measure the procedural (intraoperative), short term, as clinically indicated, (4-6 weeks), and long-term (3 months) outcomes of TURBT using the PK Button when compared to traditional monopolar loop electrocautery. The goal of the study will be to prove equivalence in outcomes between the two techniques based on the comparison of complication rates. The control arm of the traditional monopolar loop electrode is expected to have a composite complication rate of 10-15%. It is hypothesized that the PK Button Vaprization Electrode is a non-inferior device in terms of overall complication rates when compared with traditional monopolar electrocautery in TURBT procedures.

3. Background:

The burden of bladder cancer in the United States is enormous. In 2011 alone, there will be nearly 70,000 new cases with approximately 15,000 deaths.ⁱ These statistics do not account for the huge number of patients with superficial or non muscle-invasive bladder cancer (NMIBC) who require continual cystoscopic surveillance and tumor resection when recurrences occur.

The current treatment standard of care for patients who present de novo or with a recurrent bladder tumor is transurethral resection of the bladder tumor (TURBT). This intervention, accomplished endoscopically through the urethra, is both diagnostic and potentially therapeutic. An adequately performed TURBT will provide the pathologist with enough tissue to provide tumor grade and stage information. Adequate cancer staging is the most important component in determining the correct treatment paradigm for any patient with a bladder tumor.ⁱⁱ If the tumor invades the muscularis propria--the muscular wall of the bladder--a radical cystectomy with urinary diversion is the current gold standard therapy. For patients in whom the tumor does not extend into the muscularis propria, complete TURBT with or without intravesical chemo/immunotherapy is recommended.ⁱⁱ above

Currently, TURBT using monopolar electrocautery in the form a 90-degree loop electrode has been used since its introduction in 1952. Although usually safe and sufficient, this technique can create technical challenges because it can be difficult to position the loop electrode in a dynamically changing cylindrical space (the bladder). Specifically, especially with larger bladder tumors, intraoperative bleeding can obscure visualization and result in incomplete tumor resection as well as inadequate sampling of the layers of the bladder needed to establish tumor stage. Furthermore, monopolar current can result in stimulation of the obturator nerve during resection of lateral wall tumors, resulting in violent adduction of the leg with potential bladder perforation as well as possible iliac vessel injury.ⁱⁱⁱ below

Conversely, bipolar energy, which has been available for many years, has been readily adopted for the surgical treatment of benign prostatic enlargement.ⁱⁱⁱ The advantages of a bipolar electrical current include the direct return of current to the loop rather than to the grounding pad placed on the patient's skin. This has the theoretical value of limiting the diffusion of current, and therefore heat, to the surrounding tissue. A further refinement on bipolar energy has been the recent introduction of the PK Button Vaporization electrode.ⁱⁱⁱ above The semi-spherical design of the electrode creates a plasma arc that glides over the tissue, transmitting energy to the cell layers adjacent to the arc which are then quickly vaporized. Coupling bipolar energy into the Button electrode would not only harness the benefits of less thermal spread but also would obviate the geometric challenges associated with loop electrodes during resection of bladder tumors. Procedural advantages would potentially include minimal bleeding, good visualization, and a reduction in the occurrence of the obturator reflex and concomitant bladder perforation.ⁱⁱⁱ above

4. Objective:

Currently, monopolar electrocautery is the goal standard in treating patients with bladder tumors mainly due to its extensive use since being introduced in 1952. While other devices, such as the PK Button, are now available, there have not been any US studies done in order to assess non-inferiority. The purpose of this study is to measure the procedural (intraoperative), short term, as clinically indicated, (4-6 weeks), and long-term (3 months) outcomes of TURBT using the PK Button when compared to traditional monopolar loop electrocautery. The goal of the study will be to prove equivalence in outcomes between the two techniques by comparing the rate of complications between the two arms.

3.1 Primary Objective

The primary endpoint will be the measurements of procedural complications, which include post-operative bleeding, need for blood transfusion, bladder perforation, obturator nerve stimulation, or need for hospitalization or bladder irrigation. The expected rate of composite complications is 10-15%. If one or more of the aforementioned complications occur, then the case will be recorded to have a complication.

3.2 Secondary Objective

The secondary endpoints will be the assessment of operative time, tumor recurrence, catheterization time, and amount of thermal spread or cautery artifact in biopsies of tumor base.

It is hypothesized that the PK Button VapORIZATION Electrode is a non-inferior device in terms of complication rates when compared with traditional monopolar electrocautery in TURBT procedures.

5. Study Design:

The number of subjects will be a minimum of 120 patients. This is the **first US study** comparing the use of the PK Button electrode for the ablation/treatment of bladder tumors to the traditional monopolar loop electrocautery. The goal will be to collect data to confirm the efficacy and safety of the PK Button electrode vaporization procedure. The primary endpoint of the study is to verify equivalence or non-inferiority to monopolar loop electrocautery technique as measured by comparing the rate of complications from postoperative bleeding, need for blood transfusion, bladder perforation, obturator nerve stimulation, and need for hospitalization. Secondary endpoints will include operative time, tumor recurrences (overall, at original TUR site, and elsewhere), catheterization time, and amount of thermal spread detectable in biopsies of tumor base. It is expected that the monopolar loop electrocautery arm will have a composite complication rate of 10-15% based on clinical experience, though this number is often inconsistently reported based on the subjective analysis of the degree of complication. It is hypothesized that the PK Button Electrode arm will have the same or lower rate of composite complications during the procedure.

Pre-operative, intraoperative, short term as clinically indicated (4-6 weeks), and long-term (4 months) criteria will be measured.

The study will be performed at Emory University Hospital, Saint Joseph's Hospital, and Grady Hospital, Atlanta, Georgia.

The estimated time frame needed to include the number of subjects is 24-30 months.

The type of investigation will be a two arm randomized study with patient treatment consisting of TURBT using the PK Button Electrode and the control group undergoing TURBT using the monopolar loop electrode. The goal will be to collect procedural, short

term, and long term follow up data to compare the bipolar vaporization and monopolar electrocautery data. The primary and secondary endpoints of the study

- Primary endpoint: the composite complication rate assessing the occurrence of one or more of the following:
 - Post-operative bleeding
 - Need for blood transfusion
 - Bladder perforation based on surgeon's examination of bladder
 - Obturator nerve stimulation
 - Need for hospitalization; need for continuous bladder irrigation
- Secondary endpoints:
 - Operative time
 - Tumor recurrence
 - Catheterization time
 - Amount of thermal spread/cautery artifact in biopsies of tumor base

Measures will be taken to minimize and avoid bias. The patients will be randomized and care will be taken to match cohorts for age, co-morbidity, tumor size, tumor number, tumor location, and tumor stage. Randomization will occur after the informed consent has been obtained from the patient and the process has been documented. Patients will be randomized 1:1 (monopolar loop vs. pk button). Study coordinator will place six pre-labeled pieces of paper (three monopolar loop and three pk-button) in an envelope. Each time patient consents to participate in the study, study coordinator will randomly pick a paper from the envelope which will have the randomization arm written on it. Study coordinator will not place the paper back into the envelope in order to ensure true 1:1 randomization for six patients at the time. Once all six papers have been picked from the envelope, the process will be repeated.

Measurements will include:

Patient Measurements:

- Pre-operative:
 - Cystoscopic confirmation of papillary bladder tumor requiring TURBT
 - Urine cytology
 - Upper tract study/cross-sectional imaging to exclude nodal/metstatic disease
 - CBC, comprehensive metabolic panel, coagulation studies
- Intra-operative/peri-operative:
 - Operative time
 - Post-operative bleeding
 - Need for blood transfusion
 - Bladder perforation
 - Obturator nerve stimulation
 - Catheterization time
 - Need for hospitalization; need for continuous bladder irrigation

- Short-term (4 weeks or closest standard of care (SOC) visit) as clinically indicated for subjects with high-grade T1 disease who require re-resection after initial pathologic review:
 - Repeat cystoscopic exam to determine residual/recurrent disease at original TUR site and elsewhere in bladder
 - Biopsy of tumor base to re-assess thermal spread/cautery artifact
- Long-term (4 months or closest standard of care (SOC) visit):
 - Repeat cystoscopic exam to determine presence of recurrent disease

Safety Measurements:

- Complication Rate: Intraoperative complications include obturator nerve reflex, bladder perforation, and bleeding. Immediate post-op complications include bleeding and electrolyte change.
- Operative Time (minutes): measured from scope insertion to scope removal.
- Transfusion Rate
- Catheterization Time (days)
- Need for hospitalization based on intraoperative bleeding, electrolyte monitoring, or bladder perforation.
- Serum hemoglobin/electrolyte levels will only be monitored as clinically indicated.

Subjective Physician Intraoperative Criteria (Rated 1-5, 1 being “Excellent”, 5 being “Unacceptable”)

- Intraoperative level of bleeding
- Quality of Visualization
- Ease of Use
- Actual duration measured above.
- All of above measurements will be taken on an intraoperative basis.

Comparisons to be made to the control. The control data will be collected in patients treated with the traditional monopolar loop electrocautery. True positives and false positives will be assessed in the statistical consideration.

Duration of the investigation will be approximately 2.5-3.0 years. If there are unforeseen complications resulting in patient cases, investigators will discontinue enrollment. This case will be discussed at weekly Urology research meetings as well as monthly GU multidisciplinary meetings.

6. Summary of Measurements

Measurement Description	Pre-Op	Intra-Op	Immediate Post-Op	4 weeks Post-Op (or closest SOC visit)	4 months Post-Op (or closest SOC visit)
Cystoscopy confirming bladder tumor	X			X	X
Biopsy of tumor base and resection of new tumors				X	
Urinary cytology	X				
CBC, comprehensive metabolic panel	X				
INR Anticoag Measurement	X				
Upper tract/cross-sectional imaging to exclude nodal/metastatic disease	X				
Complication Rate		X			
Operative Measurements Operative Time, Blood Loss, Transfusion Rate, Bladder perforation, obturator nerve stimulation, need for continuous bladder irrigation		X	X		
Catheterization Time		X	X		
Need for hospitalization					
Operative Subjective Measurements Visualization, Ease of Use, Duration		X			

7. Study Equipment

a. Cysto-Resection PK Button Equipment

Each physician will use the following set of cysto-resection equipment for the PK Button portion of the study.

Description (can be changed)	Item Number
SuperPulse Generator with Footswitch	
Elite 1 Continuous Flow Rotating Inner Sheath	ERIS-CF25
Elite 1 Continuous Flow Rotating Outer Sheath	EROS-CF25
Visual Obturator for Inner Sheath	ERTO-CF25
Standard Obturator for Inner Sheath	ERSO-CF25
Iglesias PK Front Loading Working Element	EIWE-PKFL
M3 Gold 30 Degree Telescope	M3-30A
PK Button Electrode with Cable	786500

b. Traditional monopolar loop electrocautery available in OR at Emory University Hospital or Grady Hospital.

8. Study Participation:

The number of subjects will be a minimum of 120 patients. Duration of the investigation will be approximately 2.5-3.0 years.

Inclusion criteria

- Patients with cystoscopically detected bladder tumors requiring TURBT
- Patients with bladder tumors which are endoscopically resectable by surgeon's judgment with only one trip into the operating room.
- Age \geq 18 years

Exclusion criteria

- Patients with clinical evidence of locally advanced, nodal, or metastatic bladder cancer
- Patients with hydronephrosis secondary to bladder cancer
- Patients with diffuse tumor throughout bladder that is deemed unresectable by surgeon

Recruiting tools will not be formally utilized.

Screening procedures

- Local cystoscopy
- Upper tract/cross-sectional imaging to exclude locally advanced/nodal/metastatic bladder cancer

Subject withdrawal and replacement criteria

- Subjects that withdraw prior to undergoing treatment will be excluded from analysis and will be replaced by an additional subject.
- Subjects that are lost to follow-up after treatment will also be excluded from analysis and will be replaced by an additional subject.

9. Study Methods:

Description of device preparation

- The investigational device and the monopolar loop electrocautery equipment will be prepared in a standardized fashion and all equipment will be autoclaved prior to each use:

- Working elements, telescopes, and sheaths, cables, and accessories will be removed from original packaging (if applicable) and inspected for integrity.
- Working elements, telescopes, and sheaths, cables and accessories will loaded into sterilization trays. All devices will then be sterilized in an autoclave steam sterilizer per parameters in the instructions for use.
- After sterilization the devices will be stored or transported to the operating room.
- Once in the OR, the devices will be transferred to the sterile table using accepted OR procedure for the handling of surgical devices. The Resectoscope will be assembled by the physician or the operating room staff..
- The disposable devices will be transferred to the sterile field using accepted practice and assembled into the Resectoscope.
- After the procedure the disposable product will be inspected and discarded. The surgical devices undergo cleaning and sterilization according to the guidelines in the Olympus/ACMI resection equipment Instructions for Use.

The procedural use of the device(s)

- The TURBT Button Vaporization technique will be standardized for each patient. Prior to beginning vaporization, a bladder wash and a cold-cup biopsy of the primary tumor will be taken in order to obtain tumor grade information. Since tumor vaporization results in no pathologic tissue for review, this step is necessary in order to obtain adequate grade information for each individual patient. Tumor vaporization will then proceed systematically down to the tumor base. At this point, multiple biopsies of the tumor base will be obtained either with the cold-cup biopsy forceps or a bi-polar loop as determined by clinical judgment to ensure adequate stage information.
- Traditional monopolar loop electrocautery TURBT will be performed in the usual fashion.
- Regardless of procedure used, all patients will receive intravesical mitomycin-C chemotherapy in the PACU post-operatively unless there is surgical concern for bladder perforation which is a contraindication for its use.

The procedure that the patient undergoes including any medication

- All patients will receive peri-operative antibiotics
- Hospital admission for overnight observation following surgery will be determined post-operatively and will be on an as needed basis. The intent is for all study patients to be discharged home the same day as the procedure unless there is concern for bleeding or it is felt the patient requires overnight observation (e.g. perforation, etc.)
- Foley catheter will be discontinued after post-operative intravesical therapy unless prolonged drainage is clinically indicated.
- Patients will be prescribed pain medications, bladder spasm medications, and stool softeners as needed post-operatively

10. Statistical Consideration

Power estimation: this study is designed to establish the non-inferiority of PK Button Vaporization Electrode (arm 1) compared to the traditional monopolar loop electrode (arm2) in terms of complication rate. Based on the historical data, we assume that the complication rate in arm2 is 15% and the highest acceptable complication rate for claiming non-inferiority in arm 1 is 20%. By a sample size of 60 patients per group, we have 84% of power to detect a difference of -9% when the actual complication rate in arm1 is 6% by the one-sided Z test (pooled) at significance level of 0.05.

Statistical analysis plan:

- The primary analysis will be conducted by pooled z test for comparison of complication rate in two arms.
- For the secondary endpoints, the comparison between the two arms will be done using two-sample t-test/Wilcox sum rank test for continuous measurements, e.g. operative time, and Chi- square test/Fisher's exact test for categorical ones, e.g. post-operative bleeding (Yes/No). Log-rank test will be performed for any time-to-event outcome, e.g. time to recurrence. Multivariable regression model may be used to take potential confounders into account. For repeated measured outcomes, e.g. AUA/IPSS score over time, GEE model will be considered.

11. Protocol Deviations

Any deviations to the protocol will be noted and require approval of the study coordinators and appropriate Olympus personnel.

12. Reference to Data Collection, Management and Analysis

Data will be collected on individual data sheets for each patient. The collected data will be entered into an excel spreadsheet for analysis and comparison to existing published data. Statistical analysis will be performed on the data to determine means, standard deviation, and range.

13. Acceptance criteria

- Comparable intra-operative/peri-operative outcomes as detailed above
- Comparable or improved IPSS scores post-operatively
- Comparable or improved recurrence rates at 4 weeks or 4 months from original TURBT
- Comparable or improved thermal spread/cautery artifact as reported by histologic review

14. Risk Analysis

Prior studies have shown that bipolar TURBT appears to be as safe as traditional monopolar TURBT with potentially less thermal spread/cautery artifact, which complicates pathologic review. Furthermore, one recent European study recently reported improved intra-operative/peri-operative

results with Button TURBT as compared to monopolar TURBT. Also, in that study, there was the suggestion that recurrence rates were improved when using the Button.

15. Publication Plan

We plan to use the data from the study to write 2-3 manuscripts. Initially, since this is a relatively novel approach to the resection of bladder tumors, we plan to report the technique for dissemination among the urologic community. Once the study concludes, we would then plan on writing at least one manuscript detailing the intra-operative/peri-operative, oncologic, and histopathologic results of the study. Depending on the robustness of the data, a second manuscript could be prepared describing post-operative urinary bother between the two groups combined with thermal spread/cautery artifact data.

16. IRB

This protocol and study will be submitted for IRB approval.

Any adverse events, protocol deviations, or reportable events will be reported to the IRB promptly and followed-up by investigators until resolved or stable.

17. Informed Consent

Consent will be obtained from each patient included in the study. Approval of a consent form by the patient will be required and will be documented prior to inclusion in the study.

Investigator will disclose any financial interests with Olympus or any other contributor during the course of the study.

18. Monitoring Procedures

The safety of the TURBT Button Vaporization technique will be monitored during the study on a regular basis by the study coordinators. Also, all other documentation required by part of the investigation should be monitored. This may include informed consent documents, patient case history files, enrollment questionnaires (inclusion/exclusion criteria is assessed), case report forms, adverse event report forms, post-op test results and questionnaires (these will be followed per protocol).

Appendices

The following will be provided by the principal investigator prior to the start of the study:

Patient Consent Form.

Patient Data Sheet

Approval:

Senior Management of QA/RA

Responsible Marketing Manager

Investigator

Participating IRB(s)

ⁱ Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.

ⁱⁱ Hall MC, Chang SS, Guido D, Pruthi RS, Seigne JD, Skinner EC, Wolf JS, Schellhammer PF: Guideline for the Management of Nonmuscle Invasive Bladder Cancer (Stages Ta, T1, and Tis), Chapter 1- Diagnosis and Treatment Options: 2007 Update. American Urological Association Education and Research, Inc. 2007; 15:51.

ⁱⁱⁱ Issa MM. Technological advances in transurethral resection of the prostate: bipolar versus monopolar TURP. *J Endourol*. 2008;22:1587–1595.

^{iv} Bipolar transurethral resection of prostate: Current status in the management of bladder outflow obstruction..Bolgeri M, Naji S, Sahai A, et al. BRITISH JOURNAL OF MEDICAL AND SURGICAL UROLOGY . 2012;5(3):105-10.