Efficacy and Safety of Potassium–Titanyl-Phosphate Laser Vaporization for Clinically Non-Muscle Invasive Bladder Cancer

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Purpose: Although transurethral resection of the bladder tumor (TURBT) is still regarded as the gold standard for the treatment of clinical non-muscle invasive bladder cancer, alternative surgical options remain investigating. Our aim was to evaluate the efficacy and safety of potassium–titanyl-phosphate (KTP) laser for the treatment of primary, clinically non-muscle invasive bladder cancer compared with standard transurethral resection of bladder tumor.

Materials and Methods: The data of primary non-muscle invasive bladder cancer patients treated by either KTP laser vaporization (PVB group) or TURBT were analyzed retrospectively. The preoperative conditions and intraoperative complications such as obturator nerve reflex and bladder perforation and postoperative characteristics such as catheterization time and tumor recurrence were compared.

Results: The patients' demographics and tumor characteristics in the two groups were comparable. PVB was superior to TURBT in terms of intraoperative complications such as obturator nerve reflex ($P = .0289$), postoperative bladder irrigation ($P = .038$) and postoperative catheterization time ($P < .0001$). Recurrence rate after PVB was also lower than that after TURBT.

Conclusion: Our results indicated that PVB is a feasible, safe and effective alternative surgical approach for the management of primary, clinically non-muscle invasive bladder cancer, especially for those with lifetime oral taken anticoagulation medicine, with fewer perioperative complications and lower recurrence.

Keywords: urinary bladder neoplasms; laser therapy; neoplasm invasiveness; neoplasm recurrence; surgery.

INTRODUCTION

Bladder cancer is the most common cancer in genitourinary system. In USA, an estimated 73510 new cases of bladder cancer and 14,880 bladder cancer related deaths are expected to occur in 2012.[1] Most newly diagnosed bladder cancers (75%) are non–muscle invasive bladder cancer (NMIBC),[2] and can be treated by transurethral resection of the bladder tumor (TURBT). But when the lesions were located in the lateral bladder wall or near ureter orifice and treated by TURBT, complications, such as bleeding, bladder perforation and obturator nerve reflex (ONR) even hydronephrosis would occur.[3] On the other hand, some bladder cancer patients are using coumarin derivatives and platelet aggregation inhibitors because of cardiac and cerebrovascular events, interruption of long-term anticoagulation in these patients creates a paradox situation in which competing risks of thrombosis and hemorrhage must be managed. Therefore, alternative surgical options such as laser resection have advantages for the treatment of such cases. Until now, holmium and thulium laser resection of bladder tumor are the most frequent used surgery for the treatment of NMIBC and provide satisfactory outcomes.[4,5,6] However, whether it is suit for those with anticoagulation medicine is not reported.

Potassium-titanyl-phosphate (KTP) laser is 532 nm laser which was transformed from 1064 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser by potassium-titanyl- phosphate crystine. In 1995, Malek and colleagues introduced the 80 W KTP laser for photoselective vaporization of prostate (PVP) and subsequently reported its results 5 years after surgery.[7,8] Nowadays, this method has become an alternative choice for those who suffer from lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia and need surgical intervention,[9,10] especially PVP is more benefit for those with oral anticoagulation medications, because anticoagulation medications withdrawal would have posed a considerable risk for thromboembolic events.[11] However, the efficacy and safety of KTP laser used for the treatment of NMIBC, especially when the lesion is located in the lateral wall of the bladder or near the ureter orifice, for those using oral anticoagulation medications, is still remain further investigation.

In the present preliminary study, we evaluated the efficiency and safety of the KTP laser for bladder tumor resection via a continuous cystoscope for the treatment of NMIBC, and we called it as photoselective vaporization of bladder cancer (PVB), and the results compared with conventional TURBT in terms of intra-operative complications, postoperative characteristics and efficacy as determined by the tumor recurrence.

MATERIALS AND METHODS

Study Population

From August 2004 to December 2010, bladder cancer patients treated with either TURBT or PVB at the author's institution were retrospectively analyzed. The inclusion criteria for this investigation must meet the following standards: primary, not the recurrent bladder cancer, the diameter of the tumor was less than 4 cm with no upper urinary tract tumor, the pathological result was non-muscle invasive bladder cancer with no carcinoma in situ (CIS).

The detail history of all patients has been obtained preoperatively. Ultrasonography, intravenous urography, computerized tomography, and cystoscopy have been routinely performed to exclude upper urinary tract tumors, to determine the location, number, and volume of the tumor and to evaluate the clinical stage of tumor preoperatively. Random bladder biopsies before the operation were obtained to diagnose pathological characterization of bladder cancer and to detect CIS. In order to try to avoid missing high-grade tumor, we routinely biopsied at least three lesion in the bulking mass for pathological diagnosis. All patients chose the surgical strategy with written informed consent. And all the operations were performed by three expertise (Y Shan, D Yang, and B Xue) with standard procedure to get a comparable result.

Surgical Procedure

For the PVP group patients were under general or continuous epidural anesthesia and positioned in a routine lithotomic position. The equipment involved in the PVB procedure was described elsewhere.[9] Continuous flow laser cystoscope was inserted into the bladder cavity via a video system and the bladder cavity was examined to verify the previous cystoscopic examination results. The laser fiber was inserted through the working channel of the continuous cystoscope. The power is set at 60 W – 80 W for laser vaporization and 50

W – 60 W for laser coagulation. At the beginning of the surgical procedure, a circular coagulation blockage mark about 1.5 cm away from the tumor edge was made around the lesion. The resection procedure was somewhat different according to the characterization of the lesion. If the tumor was papillary with a long tip and a small volume, the tip was vaporized first to resect the body of the tumor. Then the basement of the lesion was vaporized gradually until the underlying detrusor muscle layer was visible. If the tumor was sessile or had a bigger volume, the vaporization was begun from the surface of the lesion till the muscle layer was seen. During the procedure, three or four specimens from endoscopically "normal" appearing areas from the bottom and the margin of the tumor were biopsied via the working channel of the cystoscope for pathological examination to verify whether there was any tumor residual so as to determine the finally clinical stage of the cancer. After the exposure of deeper detrusor muscle, careful vaporization of the underlying muscle and surrounding mucosa that marked at the beginning of the operation was performed. Then the floating tissues in the bladder cavity were retrieved by using an Elik's evacuator. After verifying the lack of perforation or hemorrhage, a catheter was inserted and indwelled as demand.

The TURBT was performed using an ACMI 25.6 French (F) continuous flow resectoscope with loop electrode (Richard Wolf GmbH, Knittlingen, Germany) and a cutting and coagulation power set at 160 W and 80 W respectively. A traditional piece-by-piece resection to the muscle layer was performed.[4] Three or four loci of the basement of the resection zone was biopsied as that was done in PVB group for pathological examination. The surrounded bladder mucosa about 1.5 cm away from the tumor base was also electrocauterized. After the operation, a catheter was inserted and indwelled as did in PVB group.

Postoperative Followup

The postoperative management included bladder irrigation when bleeding is obvious, and the urethral catheter was removed when the urine became clear. The intravesical instillation regimen was epirubicin, started within 24 hours after surgery for the first time, thereafter 40 mg weekly for 8 weeks, followed by monthly maintenance up to 1 year post-operatively. All the patients were followed up in the outpatient clinical at regular intervals. Patients were required to do ultrasonography and cystoscopy every 3 months after the surgery, for which we adhere the 2011 guideline of the Chinese Urologic Association for non-muscle invasive bladder cancer. The data regarding operation time, complication such as obturator nerve reflex, bladder perforation and catheterization time, the recurrences or recurrence location were recorded.

Statistical Analysis

Continuous data were summarized using the mean ± SD and compared by non-parametric *t* test. Categorical variables were compared using the chi-square test or Fisher's exact test. The statistical package for the social science (SPSS Inc, Chicago, Illinois, USA) version 16.0 was used for statistical analysis. $P < .05$ was considered as statistical significance.

RESULTS

From August 2004 to December 2010, a total of 287 patients were diagnosed as bladder cancer and treated either by TURBT or by PVB at the author's institution. Only 60 patients met study criteria and were enrolled in this investigation. The data of 60 patients and tumor characteristics in the PVP and TURBT groups were comparable for sex, age, tumor multiplicity, tumor size and grade. *P* values regarding all listed variables were > .05 (Table 1). But 6 patients with lifetime oral taken aspirin or warfarin because of cardiac and cerebrovascular problems were enrolled in the PVB group, and during the operation the medications did not discontinued.

Table 2 lists the intra- and postoperative characteristics of PVB vs TURBT. The number of lateral lesion in the PVB group and TURBT group were 22 and 17, respectively. However no ONR and bladder perforation occurred in the PVB group. On the contrary, 3 of 17 patients in the TURBT group had ONRs (0/22 vs. 3/17, $P = .0289$, Fisher's exact test), which have statistical significance. Although of patients in TURBT group, 2 had bladder perforation, but with no statistical significance (0/28 vs. 2/32, $P = .18$, Chi-square test). The proportion of patients needed postoperative bladder irrigation in the PVB group was also lower than that in the TURBT group (1/28 vs. 7/32, Chi-square test, $P = .038$). The PVB group was associated with a shorter operative time

Table 1. Patient demographics and tumor characteristics.*

Variables	PVB	TURBT
Sex, no	28	32
Male	22	25
Female	6	7
Age, Mean ± SD	45.3 ± 8.3	42.5 ± 9.2
Tumor multiplicity		
Single	22	24
Multiple	6	8
Tumor size, cm		
≤ 3	24	26
3-4	4	6
Location		
Lateral	22	17
Other	6	15
T stage		
Ta	8	7
T1	20	25
Grade		
1	15	16
2	10	10
3	3	6

Key: TURBT, transurethral resection of the bladder tumor; PVP, KTP laser vaporization.
*In the PVP and TURBT groups, sex, age, tumor multiplicity, tumor size and grade were comparable, $P > .05$.

and postoperative catheter drainage period as compared with TURBT group ($P < .0001$, non-parametric t test). No blood transfusion were needed in both groups.

All patients were followed for 20 to 64 months after surgery (the mean follow up were 38.5 months in TURBT group and 38 months in PVB group). Among patients involved in this study, an 83 years old patient with multiple lesions was recurred in new site 6 months after the PVB surgery and treated by PVB again. This patient had coronary artery stent with lifetime aspirin taken. No other recurrence was found in PVB group in the following period. But 3 cases had cancer recurrence in the TURBT group, among which 2 recurrences were found at another site in the bladder wall and retreated by TURBT.

DISCUSSION

The primary approach to the management of non–muscle invasive bladder cancer (NMIBC) is TURBT followed by intravesical therapy with either chemotherapeutic agents or Bacillus Calmette-Guerin (BCG). Currently, the European Association of Urology (EAU), the First International Consultation on Bladder Tumors (FICBT), the National Comprehensive Cancer Network (NCCN), and the American Urological Association (AUA) guidelines still recommend TURBT as the gold standard for the initial diagnosis and treatment of NMIBC.[12] However, the intra- and postoperative complication and the ultimate efficacy of TURBT largely depend on the appropriate resection techniques, the experience of individual surgeons and the pathological characterization of NMIBC.[3,4,13-15] For example, relatively shallow depth resection can cause an incomplete initial resection, such patient also need re-TURBT,[13,16] on the other hand, deeper resection would lead to higher risk of bladder perforation and severe bleeding, especially when the lesion was located in the lateral bladder wall and was resected by TURBT. In such cases, obturator nerve would ultimately be stimulated by the current flow, the obturator spasm and leg jerk would occur and bladder perforation sometimes occurred. When the lesion's location was less than 2 cm away from the ureter orifice and were treated with TURBT, ureteral stricture and scarring of the ureteral orifices could occurred and potentially lead to ureteral obstruction and hydronephrosis,[6] and in such situation, the lesion were often resected by open surgery.

The use of lasers such as holmium:YAG and thulium for treating bladder cancer especially non-invasive bladder cancer have been confirmed to be safe and minimally invasive and the success rate is at least as good as those of standard TURBT.[4,5] But the holmium:YAG laser was usually produced by pulse mode. During the surgical procedure, it is not so easy to control obviously bleeding because the fiber was easily to move away from the wanted location.

The 80 W potassium–titanyl-phosphate (KTP) laser was first reported in 2003 in a pilot study for the treatment of BPH with good outcome and minimal morbidity.[7] Nowadays it was proved to be an efficacy and safety alternation for the treatment of benign prostatic hyperplasia (BPH), especially for those patients on anticoagulation therapy, including aspirin, coumadin, and clopidogrel, that is not suitable for routine methods such as TURP or TVP.[10]

Table 2. Intra- and postoperative characteristics of PVP group vs. TURBT group.

Variables	PVB	TURBT	*p*
Number	28	32	
Operation time (min)	22 ± 8.3	27 ± 7.8	.019
Complications, no			
Obturator nerve reflex	0	4	.028
Bladder perforation	0	2	NS
Postoperative bladder irrigation, no	1	7	.038
Catheterization time (days)	3.24 ± 1.2	5.73 ± 0.9	.0001
Recurrence, no	1	3	NS

Key: TURBT, transurethral resection of the bladder tumor; PVP, KTP laser vaporization, NS, not significant.

In the author's department, KTP laser was initially used for the treatment of BPH in August 2004. We thought that KTP laser was produced by Green Light KTP laser system (laserscope) without any current flow going through the human body, if it was used for the treatment of NMIBC that located in the lateral wall, might not occurred. In our pilot study when we first used it for the resection of the lateral bladder wall lesion, no ONRS were observed. Because of the laser beam has a forward deflection of 70° and a divergence angle of 15°, for those tumors located in special site such as in the dome that cannot so easily be resected by routine TURBT technical, the PVB can performed successfully. Thirdly, the unique 532 nm wavelength that the laser operates at is highly absorbed by hemoglobin and minimally absorbed by water, which limits the optical penetration depth of the KTP laser to 0.8 mm.[7,9] The heat remaining in the tissue induces a coagulation zone of only 1~2 mm thickness. So in PVB group, bladder perforation was not happened and serious bleeding needed bladder irrigation was not so common as compared with that in TURBT group. These advantages made it more suitable for the treatment of the lesion located in the lateral bladder wall and near the ureter orifice to prevent ONRs and potential hydronephrosis secondly to ureteral stricture which can be caused by TURBT.[6] Finally, for those bladder cancer patients with anti-coagulation therapy, PVB is superior to TURBT, because no perioperative discontinuation in drug administration needed.

In order to prevent or delay tumor recurrence, transurethral resection followed by intravesical therapy is considered as standard treatment strategy for NMIBC, the majority intravesical medicine used are BCG or chemotherapeutic drugs such as thiotepa, mitomycin C, doxorubicin (adriamycin), pirarubicin and epirubicin.[12] But the strategy used for the treatment of NMIBC sometimes varies according to the EAU, FICBT, NCCN and AUA guideline.[13] For example, for low risk NMIBC, a single immediate postoperative instillation of chemotherapeutic agents after TURBT is recommend enough, but for intermediate and high risk of NMIBC, BCG (rather than other chemotherapeutic medicine) is recommended as the most useful medicine. Since BCG is not commercial provided in our nation, and there are still 40–80% of tumors recurrence in spite of complete resection,[17] we performed an intravesical instillation with epirubicin within 24 hours plus one year maintenance postoperatively. The follow up results indicated that the recurrence number in PVB group is also less than that in TURBT group.

The major drawback of PVB is the lack of tissue for histological examination because all the tumor was vaporized by KTP laser unless we do biopsy pre-operation and intro-operation. In order to determine the infiltrate depth, we routinely

get biopsy sample before the operation, and when vaporized layer was reached the muscle, we did biopsy from the muscle layer beneath the vaporized lesion via the working channel of the continuous cystoscope. If no residual cancer was found in this layer, we defined it as NMIBC.

CONCLUSION

In conclusion, PVB via continuous cystoscopy is a safe and effective treatment for NMIBC. It is a promising treatment option due to the precise incision, lower complication rate and excellent hemostasis. Long-term prospective randomized studies will be needed to confirm these promising preliminary results.

CONFLICT OF INTEREST

None declared.

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