Two-micrometer thulium laser resection of the prostate-tangerine technique in benign prostatic hyperplasia patients with previously negative transrectal prostate biopsy

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The 2-µm thulium laser resection of the prostate-tangerine technique (TmLRP-TT) has been introduced as a minimally invasive treatment for benign prostatic hyperplasia (BPH). This study was undertaken to assess the clinical efficacy and safety of TmLRP-TT for the treatment of BPH patients with previously negative transrectal prostate biopsy. A prospective analysis of 51 patients with previously negative transrectal prostate biopsy who underwent surgical treatment using TmLRP-TT was performed from December 2011 to December 2013. Preoperative status, surgical details, and perioperative complications were recorded. The follow-up outcome was evaluated with subjective and objective tests at 1 and 6 months. TmLRP-TT was successfully completed in all patients. Mean prostate volume, operative duration, and catheterization time were 93.3 ± 37.9 ml, 69.5 ± 39.5 min, and 6.5 ± 1.3 days, respectively. The mean International Prostate Symptom Score, quality of life score, maximum urinary flow rate, and post-void residual urine volume changed notably at 6-month follow-up (22.5 ± 6.9 vs 6.1 ± 3.2, 4.8 ± 1.3 vs 1.1 ± 0.9, 7.3 ± 4.5 vs 18.9 ± 7.1 ml s⁻¹, and 148.7 ± 168.7 vs 28.4 ± 17.9 ml). Two (3.9%) patients required blood transfusion perioperatively, while 3 (5.9%) patients experienced transient hematuria postoperatively, and 2 (3.9%) patients received 3 days recatheterization due to clot retention. TmLRP-TT is a safe and effective minimally invasive technique for patients with previously negative transrectal prostate biopsy during the 6-month follow-up. This promising technology may be a feasible surgical method for previously negative transrectal prostate biopsy in the future.

Keywords: 2-µm thulium laser resection of the prostate-tangerine technique; benign prostatic hyperplasia; laser surgery; prostate biopsy; thulium laser

INTRODUCTION
Benign prostatic hyperplasia (BPH) is becoming a common disease with the increasing aging population in China.¹ It can lead to more severe complications, such as acute urinary retention (AUR), kidney dysfunction, and hematuria.² The current clinical approach requires patients to be scheduled for biopsy in the case of an elevated serum prostate-specific antigen (PSA) level, which is confirmed routinely before surgery. In most published randomized clinical trials, patients with an abnormal digital rectal examination (DRE), an abnormal elevation of total PSA levels, or suspicious and irregular needle echogenicity were subjected to transrectal ultrasound (TRUS)-guided prostate biopsy. Patients were excluded if pathology results confirmed prostate cancer.³ However, most patients would have likely been diagnosed with only BPH given the relatively low specificity of both PSA and DRE testing in these studies.⁴ ⁵

Currently, published reports on the surgical efficacy and safety in BPH patients with previously negative prostate biopsy are still rare. In our previous report, on the treatment of BPH patients with AUR, we found that operative morbidity, including bleeding and high fever, in BPH patients with previously negative prostate biopsy was higher than that in patients who did not undergo biopsy:⁶ Thus, an ideal treatment for this particular group of patients should be introduced as soon as possible.

Based on its superior characteristics to transurethral resection of the prostate (TURP), the 2-µm thulium laser resection of the prostate-tangerine technique (TmLRP-TT) was recently designed for the surgical treatment of BPH and had shown promising results in our previous multi-center study and systematic review.⁶ ⁷ This procedure had been shown to be efficient and safe with faster hemostasis, higher precision, and lower perioperative morbidity, but also shown to have a greater superiority in the treatment of BPH.⁸ The aim of our current study was to investigate the therapeutic efficacy and safety of TmLRP-TT in the treatment of BPH patients with previously negative transrectal prostate biopsy.

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MATERIALS AND METHODS

Patients
Fifty-one consecutive BPH patients (mean age 67.4 ± 6.5, range 57–83 years) were enrolled to undergo surgical treatment with TmLRP-TT from December 2011 to December 2013. The study was approved by the Hospital Ethics Committee and written informed consent was obtained from all patients before the surgery.

All enrolled patients were suspected to have prostate cancer based on previously determined criteria (abnormal DRE findings, PSA level elevation, or suspicious and irregular needle echogenicity upon transrectal examination). Ultrasound-guided transrectal 12-core needle biopsy of the prostate was performed at diagnosis and negative pathology results were confirmed.

Exclusion criteria included neurogenic bladder dysfunction, urethral stricture, and any previous prostatic, bladder neck, or urethral surgery.

All patients were evaluated preoperatively by scoring subjective symptoms with the International Prostate Symptom Score (IPSS) and quality of life score (QoLs), both of which were completed at follow-up visits or by mailed questionnaires up to 6 months after surgery. In addition, physical examination by DRE; laboratory investigations with complete blood count, determination of clinical chemistry parameters, serum creatinine level, routine urinalysis, and urine culture, PSA level before DRE; kidney-bladder ultrasound; and TRUS measurement of prostate volume, PVR volume, and Qmax values were determined for all patients.

Instrument and surgical techniques
The study was approved by the Hospital Ethics Committee and written informed consent was obtained from all 51 patients before TmLRP-TT.

All procedures were performed by experienced attending urologists at the Department of Urology, Shanghai General Hospital. All patients were placed in the lithotomy position, and the procedure was performed under general anesthesia. Subsequently, the Tm:YAG laser (Revolix, LISA laser products, Katlenburg, OHG, Germany) was operated in continuous-wave mode with a wavelength of 2.013 µm for the TmLRP-TT procedure. The power setting used for cutting was 120 W. The energy was delivered via 550-mm end-firing PercuFlex fibers with tissue damage restricted to <1 mm beneath the cut. The laser fiber was introduced via a Karl Storz 26F continuous flow resectoscope. Isotonic saline irrigation at room temperature was used in all cases at the height of 60 cm. The entire procedure was similar to the peeling of a tangerine and had been previously described in detail. Briefly, the incisions were made at 5 and 7 o’clock with sufficient depth to reach the surgical capsule from the bilateral bladder neck to the verumontanum. Next, the median lobe was removed through a transverse section. The lateral lobes were resected by cutting in a large curve after making a transverse incision. The prostatic tissue was dissected off the surgical capsule and resected into small pieces using a combination of semicircular and transverse incisions. At the end of the procedure, a 22F triple lumen catheter was inserted into the bladder. All tissue retrieved from each patient was investigated histologically. Bladder irrigation was maintained if patients experienced significant hematuria. The feasibility of catheter removal and suitability for discharge home were assessed between 7:00 a.m. and 9:00 a.m. each postoperative day. Catheters were removed if the urine color was satisfactorily light. If the catheter could not be removed, the patient remained in the hospital another night and was reassessed the following day. Therapeutic effects and complications were monitored. Patients were discharged only in the absence of significant hematuria or fever.

Assessment
Perioperatively, the primary outcomes measured included operative duration (time that the resectoscope sheath remained within the urethra), hemoglobin levels, decrease in serum sodium and potassium levels, postoperative catheterization time, and number of postoperative hospital day. IPSS, QoLs, Qmax, and PVR volumes were evaluated at 1 and 6 months postoperatively. All perioperative and postoperative complications were recorded up to 6 months after TmLRP-TT.

Outcome analysis
The study data were expressed according to mean ± standard deviation (range). The paired sample t-test was used to compare preoperative and postoperative data. Statistical tests were performed using SAS System 8.0 (SAS Institute Inc., NC, USA) software for Windows 7. Two-sided tests with \( P < 0.05 \) were considered statistically significant.

RESULTS
All patients underwent prostate biopsy 7 to 14 days before the TmLRP-TT surgery. The TmLRP-TT procedure was completed successfully in all patients. Table 1 lists medical comorbidities, perioperative data, and complications of the patients.

All 51 patients had successful voiding postoperatively and completed the 6-month assessment. As shown in Table 2, patients exhibited notable improvement in obstructive voiding symptoms. The mean IPSS and QoLs decreased significantly from 22.5 ± 6.9 to 6.3 ± 3.5 and 4.8 ± 1.3 to 1.4 ± 1.1, respectively. The mean residual volume decreased from 148.7 ± 168.7 to 25.6 ± 16.2 ml. The mean Qmax increased from 7.3 ± 4.5 to 19.5 ± 5.3 ml s\(^{-1}\) (\( P < 0.05 \)) after the TmLRP-TT treatment. Bladder outlet obstruction was clearly resolved at the 1-month follow-up visit and maintained throughout the study period.

Table 1 also lists adverse events. No case of transurethral resection syndrome (TURS) was observed. Two (3.9%) of the patients required blood transfusion post the procedure. Three (5.9%) of the patients experienced transient hematuria postoperatively, of these 2 (3.9%) received 3 days recatheterization due to clot retention. One patient (2.0%) who had undergone TRUS-guided prostate biopsy 9 days before the procedure had prostate surgical capsule perforation. Ten (19.6%) patients had leukocyturia, of these 3 (5.9%) required antibiotic treatment following definite diagnosis of UTI.

Postoperatively, 8 (15.7%) patients complained of some degree of urinary incontinence within the first month following the procedure. These symptoms were alleviated effectively following treatment with Chinese traditional medicine (Wonglitong, orally after meal) and no case of permanent incontinence was observed. Of the 41 sexually active patients, 20 (48.8%) reported retrograde ejaculation postoperatively. During the 6-month follow-up, 3 (5.9%) urethral strictures requiring internal urethrotomy due to meatal stenosis were observed. None of the patients experienced bladder neck contracture or reoperation during the follow-up period. Postoperatively, the histological examination of the resected prostatic tissue revealed the absence of prostate malignancy in all patients.

DISCUSSION
The incidence of BPH has been increasing in China. When preparing transurethral prostatectomy for patients with serious Lower Urinary Tract Symptoms (LUTS), the urologist often encounters patients with elevated and/or rising PSA levels. With the recent advances in biopsy instruments and prostate ultrasound, prostate biopsy is of now a relatively safe procedure in most cases. However, if the observed increase in PSA levels is mainly attributable to BPH, the biopsy may
Table 1: Perioperative patients' characteristics

| Variable                        | TmLRP-1TT              |
|---------------------------------|------------------------|
| Patient (n)                     | 51                     |
| Comorbidities, n (%)            |                        |
| Hypertension                    | 23 (45.1)              |
| Heart disease                   | 10 (19.6)              |
| Diabetes                        | 9 (17.6)               |
| Hyperlipidemia                  | 18 (35.3)              |
| Cerebral infarction             | 2 (3.9)                |
| Renal failure                   | 5 (9.8)                |
| Urine inflammatory              | 13 (25.5)              |
| Urinary tract infection         | 10 (19.6)              |
| Urinary attention               | 19 (37.3)              |
| Perioperative, mean±s.d. (range)|                        |
| Age (year)                      | 67.4±6.5               |
| Prostate volume (ml)            | 93.3±37.9              |
| PSA (ng ml⁻¹)                   | 11.2±7.8               |
| Preoperative stay after biopsy (day) | 8.3±1.97               |
| Operative time (min)            | 69.5±39.5              |
| Hemoglobin decrease (g dl⁻¹)    | 1.21±1.27              |
| Serum sodium decrease (mmol l⁻¹) | 3.07±0.05              |
| Serum potassium decrease (mmol l⁻¹) | 0.12±0.38              |
| Catheter removal (day)          | 6.5±1.3                |
| Hospital stay (day)             | 7.4±1.4                |
| Complications and medication use, n (%)       |
| Transient hematuria             | 3 (5.9)                |
| Blood transfusion               | 2 (3.9)                |
| Prostate surgical capsule perforation | 1 (2.0)               |
| Recatheterization               | 2 (3.9)                |
| Transient urge incontinence     | 8 (15.7)               |
| Permanent incontinence          | 0                      |
| Urine inflammatory              | 10 (19.6)              |
| Urinary tract infection         | 3 (5.9)                |
| Urethral stricture requiring internal urethrotomy | 3 (5.9) |
| Bladder neck stricture          | 0                      |
| Reoperation                     | 0                      |
| Retrograde ejacuure            | 20 (48.8)              |

s.d.: standard deviation; TmLRP-1TT: 2-µm thulium laser resection of the prostate-tangerine technique

Table 2: Follow-up data

| Parameter        | Baseline | 1-month | 6-month | P       |
|------------------|----------|---------|---------|---------|
| IPSS             | 22.5±6.9 | 6.3±3.5 | 6.1±3.2 | <0.001  |
| QoLs             | 4.8±1.3  | 1.4±1.1 | 1.1±0.9 | <0.001  |
| Qmax (ml s⁻¹)    | 7.3±4.5  | 19.5±5.3| 18.9±7.1| <0.001  |
| PVR (ml)         | 148.7±168.7| 25.6±16.2| 28.4±17.9| <0.001  |

The paired sample t-test was used to compare pre- and post-operative parameters. IPSS: International Prostate Symptom Score; QoLs: quality of life score; Qmax: maximum flow rate; PVR: post-void residual volume

According to our initial clinical experience, hemoglobin loss in patients with biopsy history was significantly higher than that in those who did not undergo prostate biopsy (1.15 g dl⁻¹ vs 0.75 g dl⁻¹). Thus, a feasible surgical method is required for patients with history of biopsy. TmLRP-1TT presents many advantages over TURP. It can provide a combination of excellent hemostasis and rapid vaporization when resecting the prostate tissue. Therefore, we attempted to use this method to resolve this clinical issue.

It is well-known that hematuria is a common complication of prostate biopsy. Biopsy may also stimulate prostate tissue hyperemia-edema, which can easily cause bleeding and oozing. For this reason, both biopsy and the resection operation were not performed simultaneously in this study. Indeed, patients usually underwent TmLRP-1TT 7 to 14 days after the biopsy when the prostate tissue hyperemia-edema should have been considerably reduced. Meanwhile, the pathological results of the biopsy would have confirmed a benign hyperplasia, thus making our subsequent operation more acceptable and appropriate.

Although there was no control group in our study, we were able to confirm that perioperative bleeding occurred more frequently than patients without history of biopsy. We found an average decrease of 1.21 g dl⁻¹ in hemoglobin levels during the operation and subsequent blood transfusion were AUR patients. AUR and catheterization were more likely to lead to elevated PSA values and subsequent biopsy and in our study, AUR cases accounted for 37.3% of patients. In addition, patients with AUR had been reported to be more vulnerable to UTI and have larger prostate volumes and were more likely to undergo bleeding. In our study, we found that there was an average decrease of 1.34 g dl⁻¹ (19 cases) versus 1.14 g dl⁻¹ (32 cases) in hemoglobin levels for patients with or without preoperative AUR, respectively. Second, the impact of prostate volume should also be taken into account. PSA levels and prostate size are correlated in men diagnosed with BPH and without evidence of prostate cancer. Gross et al. had previously reported an average decrease of 1.4 g dl⁻¹ in hemoglobin in 266 cases with prostate volumes larger than 80 ml. In our study, 29 (57%) patients had gland volumes <100 ml and 22 (43%) had glands larger than 100 ml, respectively. We performed subgroup analysis according to the impact of prostate volume and analyzed the hemoglobin loss. Patients with larger prostate volume (>100 ml) suffered from greater blood loss (1.31 g dl⁻¹, 22 cases >100 ml vs 1.14 g dl⁻¹, 29 cases ≤100 ml), so larger prostate volumes may indicate a greater likelihood of postoperative hemorrhage.

UTI was confirmed by bacterial culture, treated with antibiotics, and recorded. Chen et al. found a significantly higher rate of UTI (19%, 4/21) in an intervention group performing simultaneous TURP and biopsy. Furthermore, these patients had a prolonged hospital stay and displayed higher hematuria and fever rate. In our study, the incidence of UTI was successfully reduced to 5.9%, and this was attributed to the rational and effective administration of antibiotics after biopsy, but before TmLRP-1TT. The fever associated with UTI normalized in 3 days after antibiotic therapy. However, a leukocyturia reaction or urine sterile inflammation (USI) seemed to occur very commonly in the study. We found excessive white cells in the urine test in 13 (25.5%) patients preoperatively and in 10 (19.6%) patients postoperatively. Based on our experience, antibiotics had no curative effect on USI but traditional Chinese medicine might help. As far as
we were concerned, the two conditions mentioned above were not the same because they were different in terms of etiology and pathology, although both lead to higher PSA levels and likely more blood loss during the operation. Coagulative necrosis occurred in deep tissues during the operation and a longer period was required for postoperative eschar sloughing. Thus, most of these patients exhibited a leukocyturia reaction, but had a negative urine culture postoperatively and did not require antibiotic therapy. We believed catheterization and urethral secretions might be the main factors of pre- and post-operative USI. Postoperatively, we usually used AnEr iodine to clean orificium urethrae externum secretions and applied Occlusent aureomycin at the external orifice of the urethra (twice a day) until the catheter was removed. We believed these measures could reduce the incidence of USI, UTI, as well as urethral and bladder neck stricture during the prostatectomy surface repair time.

Another key problem we faced was the diagnosis of incidental prostatic carcinoma. We observed that AUR patients accounted for a substantial proportion in our study. In clinical practice, the standard indication for prostate biopsy of the catheterized patient is not clear because PSA is influenced by numerous factors including catheterization, USI, UTI, and larger prostate volume. In our study, we performed biopsy according to guidelines. Three cases with biopsy-confirmed prostate cancer were excluded from the study before TmLRP-TT was performed. All 51 patients were diagnosed with BPH postoperatively by pathological examinations and had no sign of malignancy over the 6-month follow-up. However, during the operation, the thulium laser vaporized most of prostate tissue, leaving less tissue sample for subsequent histological examinations compared with samples obtained following TURP. As a result, close monitoring of PSA levels was warranted after the surgery.

Our study was the first to analyze the outcomes of thulium laser resection of the prostate with previous biopsy. In patients with a mean prostate volume of 93.3 ml, we recorded a significant improvement of 12.2 ml s$^{-1}$ in the mean Qmax and a reduction of 16.2 points in the mean IPSS at 1-month follow-up. The clinical effects remained stable over a 6-month surveillance. These results were quantitatively similar to those described in clinical trials analyzing BPH resection only caused by LUTS and performed by KTP, HoLEP, or TURP. Admittedly, there were some flaws in our study. The follow-up period (6 months) was short, and the sample size (51) was small. In addition, the study also lacked randomized controls. These shortcomings would be overcome in a future study.

CONCLUSIONS

TmLRP-TT is a safe and effective minimally invasive technique for patients with previously negative transrectal prostate biopsy during a 6-month follow-up. It is a promising technology, which should be considered a feasible surgical method for patients with a confirmed negative transrectal prostate biopsy in the future. However, larger-scale and randomized controlled trials with longer regular follow-up periods are needed to confirm the stability of the result.

AUTHOR CONTRIBUTIONS

JL and SJX had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. JL and SJX conceived the study and the study design. JZ and FZ acquired the data. HBW analyzed and interpreted the data. HBW and XWS performed the statistical analyses. JZ drafted the manuscript. HTL, FJZ, and BMH performed the surgical procedures. XWS, JLL, and SJX provided critical revision of the manuscript for important intellectual content.

COMPETING INTERESTS

All authors declared no competing interests.

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