Transurethral resection in women with symptomatic keratinizing squamous metaplasia of urinary bladder: A retrospective study of 92 cases

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Abstract

Objectives: To investigate the efficacy of transurethral resection (TUR) on relieving urinary symptoms in patients with keratinizing squamous metaplasia (KSM) of the urinary bladder.

Methods: Data were analyzed from a retrospective study of patients receiving transurethral bipolar plasma resection (bi-TUR) treatment for symptomatic KSM. Urinary symptoms were assessed by the International Prostate Symptom Score (IPSS) and a numeric rating scale pain score. Efficacy was assessed using the IPSS to determine changes from baseline in lower urinary tract symptoms (LUTS). Self-reported quality of life (QoL) was assessed by the last question of the IPSS questionnaire.

Results: A total of 92 female patients were included in the analysis. The median age was 42 years. LUTS, pain, and hematuria were the most common symptoms that affected patients. The median follow-up duration was 51 months. There were significant improvements in LUTS from baseline IPSS after TUR (P < .001). The percentage of the patients with moderate to severe LUTS went down from 52.2% to 18.5%. The median Numeric Rating Scale (NRS)-11 pain score reduced from 3 at baseline to 0 at the last visit. Twenty-one out of 40 patients reported that the pain symptoms disappeared completely. No patients reported hematuria symptoms at the final follow-up. Improvement of self-reported QoL was significant (P < .001). A total of 57.6% of patients reported an improvement, 26.1% of patients reported no improvement, and 16.3% reported deterioration.

Conclusions: Bi-TUR therapy significantly relieved urinary symptoms in women with KSM. Improvement of QoL was acceptable with a success rate of 57.6%. Considering the very low complication rate, our study supported bi-TUR as an alternative treatment for patients who are resistant to medical therapy.

KEYWORDS
female, LUTS, squamous metaplasia, transurethral resection
1 | INTRODUCTION

Keratinizing squamous metaplasia (KSM) of the urinary bladder, also known as vesical leukoplakia, is an abnormality of the urothelium in which the urothelium is transformed into a squamous cell epithelium beneath a layer of keratin. Most KSM patients typically present with non-specific urinary symptoms, including frequency, urgency, and other lower urinary tract symptoms (LUTS), macroscopic/microscopic hematuria, and genitourinary discomfort or pain. In clinical practice, urinary symptoms are the major concerns that prompt patients to seek treatment.

Complete resection of the affected mucosa via transurethral resection (TUR) or fulguration and close follow-up have been widely adopted as a preventive strategy because of the perceived risk of bladder cancer development from KSM. However, a number of studies indicated that the risk of malignant transformation of KSM may be exaggerated. Stack et al found a similar rate of TP53 mutation in KSM patients and healthy subjects (16.7% vs 14.3%), which is significantly lower than that of transitional cell carcinoma patients (39.9%). Despite frequent simultaneous presence of KSM and squamous cell carcinoma of the urinary bladder, the absolute risk for progression to carcinoma in the absence of dysplasia cannot be established. Therefore, KSM is increasingly considered to be distinct from leukoplakia in other localizations, including the mouth, the larynx, and the genital region.

Nevertheless, it remains imperative to determine whether the complete conservative resection alleviates KSM-associated symptoms. Without relief of KSM-associated symptoms, it remains questionable to conduct complete conservative resection for reasons other than elimination of an unsubstantiated risk of malignant transformation.

Several previous studies have indicated that local ablative therapy by endoscopic approach could ease urinary symptoms. Steven et al successfully treated KSM in a woman with a 4-year history of severe LUTS and recurrent urinary tract infection by TUR. Costantini et al reported that transurethral fulguration by side-firing laser led to at least 75% improvement in urinary symptoms in 68% of the 28 patients with refractory urethral syndrome and squamous metaplasia of the bladder neck region. Rofeim et al reported that the ablation of Nd:YAG laser for Hunner’s ulcers improved the urinary symptoms and pain symptom in all 24 patients with interstitial cystitis. TUR of the prostate has been recommended by various guidelines for easing symptoms, such as severe hematuria and LUTS, and improving quality of life (QoL). However, no major guidelines recommended TUR procedures for symptomatic relief in metastatic urinary bladder.

In the current retrospective study, we reviewed the outcome, particularly relief of KSM-associated urinary symptoms, of symptomatic KSM patients who underwent transurethral bipolar plasma resection (bi-TUR).

2 | METHODS

2.1 | Patients

The study was approved by the institutional review board of the First Hospital of Yueyang City. Informed patient consent was not required due to the retrospective nature of the study. All subjects provided written consent to receive bi-TUR.

This retrospective study enrolled patients with symptomatic KSM who underwent bi-TUR between 1 January 2013 and 31 March 2016 at the First Hospital of Yueyang City, Yueyang, Hunan Province, China. Major exclusion criteria were asymptomatic KSM, acute bacterial upper or lower urinary tract infection, suspected neurogenic bladder, and mental illness. Patients with incomplete follow-up information were also excluded.

2.2 | Data retrieval

We searched the hospital’s digital medical records management database using the keywords “squamous metaplasia of urinary bladder” or “keratinizing squamous metaplasia” or “vesical leukoplakia”. Two study coordinators independently reviewed each patient’s medical record. Retrieved data included demographics, clinical presentation, International Prostate Symptom Score (IPSS), QoL due to urinary symptoms, pain score, laboratory and radiological data, histopathological report, and perioperative outcome. The IPSS score ranged from 0 to 35. A score of 0-7 was defined as mildly symptomatic, 8-19 as moderately symptomatic, and 20-35 as severely symptomatic. Pain was assessed using a Numeric Rating Scale-11 (NRS-11). The results of cystoscopic and/or urological system ultrasound surveillance after treatment were also retrieved.

2.3 | Surgical procedure

Surgery was performed by Dr W and Dr T with 10 years of experience in TUR. TUR was performed using total intravenous anesthesia by using an Olympus 26-F resectoscope and Olympus ESG-400 generator (Olympus Surgical Technologies Europe, Hamburg, Germany) at 100 W for cutting and 80 W for coagulation. Normal saline was used for irrigation. When the resectoscope was inserted into the bladder, an initial cystoscopic assessment was performed to define the lesion morphology, margin, ureteral orifices, and the bladder neck. The end portion of the resectoscope sheath was placed on the bladder neck. The resection started at the lateral border of the lesion. The depth of resection should reach the healthy tissue. At the end of the procedure, a Foley catheter was inserted. Irrigation was not routinely required.

2.4 | Follow-up

The final follow-up time was November 2018. Follow-up was conducted via telephone interview, regular mail, or clinic visit. Patients were evaluated for IPSS, QoL, and NRS-11 scores. The patients were asked whether they still had blood in the urine.

2.5 | Assessments

Efficacy was assessed using the IPSS to determine changes from baseline in LUTS. Self-reported QoL by the QoL score from the last
question of the IPSS questionnaire was also evaluated at the final follow-up. A QoL score of 0-2 represented improvement, a score of 3 indicated no improvement, and a score of 4-6 suggested deterioration.

2.6 | Statistical analyses

All statistical analysis was conducted using SPSS for Windows, version 19.0 (SPSS Inc., Chicago, Illinois). Categorical variables were reported as numbers and percentages. The distributions of the continuous variables were tested using the Kolmogorov-Smirnov test. Most variables were nonnormally distributed. Therefore, the data were analyzed using nonparametric methods, and continuous variables were reported by their median with the interquartile range (IQR). The nonparameter test was analyzed with the Mann-Whitney test. Pearson Chi-square test was used to compare the categorical data. Statistical significance was set at $P < .05$.

3 | RESULTS

3.1 | Patient demographic and baseline characteristics

The study flowchart is shown in Figure 1. Totally 257 patients were diagnosed with vesical leukoplakia, including 256 women and 1 man. A total of 165 patients met the exclusion criteria and were not included in the current analysis. Finally, 92 female patients were included in the current retrospective analysis. The demographic and baseline characteristics of the study population are summarized in Table 1. LUTS were the most common symptoms that affected patients. But no obstructive symptoms were reported. Most of the patients received medical therapy for symptom control at least 2 weeks before operation, but the efficacy was not satisfactory or failed. No patients complained of severe symptomatic interference. Gross bloody urine was reported in six patients. A total of 40 patients complained of nonspecific pain in the bladder area or hypogastrium. A total of 51.1% of the patients had two or more symptoms concurrently.

Cystoscopic examination showed that the lesions in all patients were limited and located at 6 o’clock of the bladder neck and trigone (Figure 2). Concurrent cystitis glandularis was identified in 16 patients (17.4%).

3.2 | Operative characteristics of the study population

The median TUR operative time was 10 minutes (IQR 5, 10). The catheter dwelling time was 5 days (IQR 4, 6). The length of hospital stay was 5 days (IQR 5, 6). Transient hematuria was seen in four patients (4.3%) and severe hematuria that required hospitalization and irrigation in two patients (2.2%). One patient underwent reoperation to stop bleeding due to clot retention.

3.3 | The outcome of follow-up

The median follow-up duration was 51 months (IQR 42, 59). A total of 68 cystoscopies were performed in 50 patients. The regular yearly urinary ultrasound surveillance was done in 85 patients. Four patients (4.3%) presented recurrence, including one patient at 2 years and three patients at 3 years post surgery; it was detected by cystoscopy with biopsy, and the patients underwent reoperation. No malignant disease was found during the course of follow-up. There were significant improvements in LUTS from baseline IPSS after TUR ($P < .001$; Table 2). The percentage of the patients with moderate-severe LUTS went down from 52.2% to 18.5%. The median NRS-11 pain score was 3 (IQR 2, 3) at baseline and was reduced to 0 (IQR 0, 1) at the last visit. A total of 21 patients (52.5%) out of 40 patients reported that the pain symptoms disappeared completely. No patients reported blood in the urine at the final follow-up.
Improvement of self-reported QoL was significant ($P < .001$; Table 2). On the final follow-up, 57.6% of patients reported an improvement (QoL score 0-2 points), 26.1% of patients reported no improvement (QoL score 3 points), and 16.3% reported deterioration (QoL score 4-6 points).

### DISCUSSION

KSM has been considered a rare condition of the urinary bladder. The reported incidence is 1:10 000 of hospital admissions.\cite{13} However, according to two studies in our center, the hospital diagnosis rate of vesical leukoplakia was 8.7% and 7.3% in 2005 and in 2006,\cite{14,15} respectively, suggesting that the disease may not be as rare as others have shown, and urologists may actually have a greater chance of encountering KSM patients. In 2002, the International Consultation on the Diagnosis of Non-Invasive Urothelial Neoplasms designated KSM as a presumed preneoplastic condition. When KSM is extensive or associated with dysplasia, the condition should be upgraded and considered preinvasive.\cite{16} For these reasons, complete removal of the local lesion by various endoscopic approaches and subsequent endoscopic follow-up has been recommended by many authors. However, up to now, there are insufficient data to prove the presumption. An official treatment strategy on the condition has not been released. In our study, all lesions of the patients were limited under cystoscopy, and biopsies revealed keratinizing stratified squamous epithelium.

### TABLE 1
Patient demographic and baseline characteristics (n = 92)

| Variables                          | n (%) |
|-----------------------------------|-------|
| Age (y), median (IQR)             | 42 (36, 49) |
| Menstrual status                  |       |
| Premenopause                      | 57 (62.0) |
| Postmenopause                     | 35 (38.0) |
| Symptom duration (mo), median (IQR)| 12 (2.25, 54) |
| Treatment                         |       |
| Antibiotics                       | 89 (96.7) |
| Tamsulosin                        | 90 (97.8) |
| Symptoms                          |       |
| LUTS                              | 72 (78.3) |
| Storing                           | 65 (90.3) |
| Postnicturition                   | 7 (9.7) |
| IPSS score, median (IQR)          |       |
| 1-7                               | 44 (47.8) |
| 8-19                              | 48 (52.2) |
| Pain                              | 40 (43.5) |
| Pain score, median (IQR)          |       |
| 1-3                               | 34 (85) |
| 4-6                               | 6 (15) |
| Hematuria                         | 6 (6.5) |
| QoL score, median (IQR)           | 4 (3, 5) |

| Histopathology                    |       |
| Squamous metaplasia               | 76 (82.6) |
| Squamous metaplasia and cystitis glandularis | 16 (17.4) |

Abbreviations: IPSS, International Prostate Symptom Score; IQR, interquartile range; LUTS, lower urinary tract symptoms; QoL, quality of life.

*Unless otherwise specified.

### TABLE 2
Results for efficacy variables at baseline and follow-up (n = 92)

| Variables                          | Baseline, n (%) | Last visit, n (%) | P      |
|-----------------------------------|-----------------|-------------------|--------|
| LUTS                              |                 |                   |        |
| IPSS score, median (IQR)          | 8 (3, 12)       | 3 (1, 6)          | <.001  |
| non                               | 20 (21.7%)      | 24 (26.1%)        |        |
| 1-7                               | 24 (26.1%)      | 51 (55.4%)        | <.001  |
| ≥8                                | 48 (52.2%)      | 17 (18.5%)        |        |
| Pain                              |                 |                   |        |
| Pain score, median (IQR)          | 3 (2, 3)        | 0 (0, 1)          | <.001  |
| non                               | 0 (0%)          | 21 (52.5%)        |        |
| 1-3                               | 34 (85%)        | 18 (45%)          | <.001  |
| ≥4                                | 6 (15%)         | 1 (2.5%)          |        |
| Hematuria                         | 6               | 0                 |        |
| QoL score, median (IQR)           | 4 (3, 5)        | 2 (2, 3)          | <.001  |

Abbreviations: IPSS, International Prostate Symptom Score; IQR, interquartile range; LUTS, lower urinary tract symptoms; QoL, quality of life.
without atypia or dysplasia. These might partly explain the absence of malignant transformation during follow-up.

Patients with KSM usually present with various urinary symptoms. Some studies showed that the urinary symptoms, especially LUTS, impaired the QoL of patients and increased the tendency toward anxiety and depression. Therefore, an appropriate and effective treatment for symptom relief should be given. Because the etiology of KSM is unclear, currently, no effective medical therapy is available. Antibiotics, the most common therapy used in clinical practice, may help symptomatic remission, but the efficacy is not durable. Alpha blockers or anticholinergics are effective for treating LUTS associated with benign prostatic hyperplasia, but they cannot play a similar role in treating women with LUTS. New treatments are being explored. Benelli et al successfully treated a KSM patient with severe LUTS by repeated TUR combined with intravesical instillation of hyaluronic acid. Guo et al found increased epidermal growth factor receptor (EGFR) expression in bladder KSM lesions, suggesting that EGFR may be a candidate treatment target.

Although the fundamental aim of conservative TUR is to eradicate the risk of bladder squamous cancer development, the role of relieving urinary symptoms has also been observed. Benelli et al not only noted the regression of whitish plaque but also found resolution of severe LUTS by repeated TUR. A retrospective study further demonstrated the efficacy of laser surgery in relieving urinary symptoms by destroying bladder metaplasia lesion, with 68% of the 28 patients achieving at least 75% improvement in urinary symptoms at a mean follow-up duration of 49 months. The efficacy of TUR or similar techniques in relieving urinary symptoms has also been observed. Benelli et al not only noted the regression of whitish plaque but also found resolution of severe LUTS by repeated TUR. A retrospective study further demonstrated the efficacy of laser surgery in relieving urinary symptoms by destroying bladder metaplasia lesion, with 68% of the 28 patients achieving at least 75% improvement in urinary symptoms at a mean follow-up duration of 49 months. The efficacy of TUR or similar techniques in relieving LUTS was also demonstrated by other investigators. These authors believe that the aggressive treatment strategy offers a good option for patient refractory to medical therapy. Possible mechanisms may include the following: (a) Local ablation treatment could destroy intracellular reservoirs of bacteria in the trigone area, which could help reduce inflammation. Local laser therapy was found to improve the microbiological and clinical outcomes of chronic periodontitis patients. (b) Clinical observation showed that when the plaques were peeled off, the underlying tissue bled easily. Thus, when the plaques and the underlying tissue are removed, the regenerated normal urothelium will not bleed. (c) In KSM, the bladder is deprived of the protective layer of glycosaminoglycans covering the urothelium, which leads to the syndrome of leaking epithelium that allows penetration of allergens, chemical irritants, medicines, toxins, and potassium ions into the bladder tissue, consequently resulting in painful bladder syndrome. The reconstructed urothelium would resist the stimulating factors in urine, consequently improving painful bladder syndrome and urethral syndrome.

Our results demonstrated that bi-TUR therapy could control hematuria symptoms, greatly improve pain symptoms, significantly reduce the severity of LUTS, and ultimately improve QoL. At a median follow-up of 51 months, 57.6% of the patients reported an improvement in QoL; this success rate was lower than that in the studies by Costantini et al and Hussain et al (57.6% vs 68% and 72%, respectively). The possible reasons include: (a) The assessment tools for clinical outcome were different. In the study by Costantini et al, the Urogenital Distress Inventory (UDI)-6 questionnaire was adopted. Improvement was defined as at least 75% reduction on the UDI-6 questionnaire. In the study by Hussain et al, patients with zero total antibiotic course and/or positive urine culture over the follow-up period after fulguration of trigonitis were defined as cured. (b) A different energy platform and treatment mode was used. Costantini adopted laser energy and Hussain used fulguration mode for surgery. In our study, we adopted the bipolar plasma energy platform and low cutting mode for therapy. Costantini et al found that a trend toward improvements emerged as the joule levels rose.

Limitations of our study include its retrospective nature, relatively small sample size, lack of a controlled group, and short-term follow-up. We only compared the clinical outcomes between baseline and final follow-up. A dynamic observation of symptoms after bi-TUR was lacking; thus, our study could not accurately describe the impact of treatment on clinical symptoms and QoL of the patients. In our study, most patients received follow-up urinary ultrasound; the data of cystoscopy follow-up was limited. Therefore, it is impossible to accurately assess the recurrence and malignancy of the disease.

Totally, the results of the retrospective study demonstrated that bi-TUR therapy significantly relieved urinary symptoms in women with KSM. Improvement of QoL was acceptable with a success rate of 57.6%. Considering the very low complication rate, bi-TUR may be a treatment option for patients who are resistant to medical therapy. Furthermore, well-designed studies are required to assess the effectiveness of TUR for KSM.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Huan Wang, Tie Chong, and Xiu-Ying Tang were responsible for the conceptualization and Huan Wang and Tie Chong for the design of this study. Data acquisition was carried out by Huan Wang and Wen-Bo Zhen. Huan Wang also searched the literature. The clinical studies were conducted by Huan Wang and Xiu-Ying Tang. Huan Wang and Tie Chong both analyzed the data, and Huan Wang carried out the statistical analysis. Huan Wang prepared the manuscript and, Huan Wang and Tie Chong edited and reviewed the manuscript.

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