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INVITED REVIEW

Bladder neck stenosis after transurethral prostate surgery: a systematic review and meta-analysis

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Abstract

Purpose Bladder neck stenosis (BNS) is a long-term complication of surgical procedures for benign prostatic hyperplasia (BPH). We performed a systematic literature review and a meta-analysis of the incidence of BNS after transurethral procedures for BPH.

Methods We performed a systemic literature review using MEDLINE, EMBASE, and Cochrane Central Controlled Register of Trials. We accepted only randomized trials comparing transurethral resection of the prostate (TURP) vs. other transurethral surgery for BPH that were grouped in Ablation vs. Enucleation modalities. The incidences of BNS were pooled using the Cochran–Mantel–Haenszel Method with the random effect model and expressed as Risk Ratios, 95% Confidence Intervals, and p values. Study heterogeneity was assessed utilizing the I^2 value.

Results 72 studies were identified for meta-analysis, 46 comparing TURP vs. Ablation and 26 TURP vs. Enucleation. The pooled incidence of BNS was 1.3% after TURP, 0.66% after enucleation and 1.2% after Ablation. The incidence of BNS was higher after TURP than after Enucleation but the difference was not statistically significant (RR 1.75 95% CI 0.81–3.79, $p=0.16$). There was no significant heterogeneity among the studies (I^2 0%, Chi^2 4.11, $p=0.90$). The incidence of BNS was higher after TURP than after Ablation, but the difference was not statistically significant (RR 1.31, 95% CI 0.82–2.11, $p=0.26$) with no significant heterogeneity (I^2 0%, Chi^2 21.1, $p=0.51$).

Conclusion Our study showed no difference in the rate of BNS incidence among randomized trials comparing TURP vs. Ablation vs. Enucleation and can be used as a reference to counsel patients undergoing BPH surgery.

Keywords Benign prostatic hyperplasia · Urinary bladder neck obstruction · Postoperative complications · Transurethral resection of prostate · Prostatectomy · Transurethral · Laser therapy

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Introduction

Monopolar transurethral resection of the prostate (M-TURP) was introduced in the late 1930s and is still considered as the current standard/first surgical choice in patients with a prostate volume 30–80 ml [1]. New energy sources/modalities, mainly bipolar and laser energies, have been introduced in the last 3 decades to decrease early morbidity of M-TURP. Indeed, Holmium laser enucleation of the prostate (HoLEP), Thulium laser enucleation of the prostate (ThuLEP), Green-Light laser photovaporization of the prostate (PVP), and bipolar TURP (B-TURP) are associated with a shorter hospital stay and fewer early complications compared to M-TURP [2–4].

Long-term complications, such as urethral stricture and bladder neck stenosis (BNS), have been reported with a similar rate after currently available endoscopic BPH surgical procedures [5]. BNS has also been described after open, laparoscopic and robotic-assisted simple prostatectomy with an incidence up to 6%, with laparoscopic and robotic-assisted techniques having the lowest rate [6, 7]. Urologists are frequently facing patients asking for less invasive surgical procedures. Simultaneously, patients are nowadays involved in choosing their BPH surgery and should be warned about postoperative complications. However, data are lacking about the difference of BNS incidence among transurethral procedures (Ablation vs. Resection vs. Enucleation).

The present study aims to perform a systematic literature review and a meta-analysis of the incidence of BNS after transurethral procedures for BPH in randomized clinical trials.

Methods

Aim of the review and literature search

We aimed to perform a systematic review to assess the incidence of BNS after endoscopic surgical treatment of BPH. The primary outcome was to assess whether BNS incidence was different among different techniques. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework.

A comprehensive literature search was performed on September 22, 2020, using MEDLINE, EMBASE, and Cochrane Central Controlled Register of Trials (CENTRAL). Medical Subject Heading (MeSH) terms and keywords such as "Benign Prostatic Hypertrophy", "Bladder Outlet Obstruction", "Transuretheral Resection of Prostate", "Enucleation of the prostate" and "Vaporization of the prostate" were used with no date limits imposed. The search was limited to those in English. Animal and pediatric studies were also excluded. The search strategy is presented in Online Appendix. Additional articles were sought from the reference lists of the included articles.

The review protocol was registered in PROSPERO with the registration number CRD42020223521.

Selection criteria

The PICOS (Patient Intervention Comparison Outcome Study type) model was used to frame and answer the clinical question. P: men with surgical indication for BPH; Intervention: transurethral procedures; Comparison: monopolar/bipolar TURP; Outcome: incidence of BNS; Study type: randomized clinical trials. The incidence of BNS was calculated by comparing the results of the studies that used different surgical techniques. Surgical techniques were allocated in two groups regardless of energy and according to the transurethral procedure that was performed. The group of Ablation procedures included photo-vaporization (PVP), laser vaporization and bipolar/monopolar vaporization. The Enucleation group included Holmium (HoLEP), Thulium (ThuLEP), Diode (DiLEP), Bipolar (BTUEP), and monopolar (MTUEP) techniques. The transurethral resection group consisted of monopolar and bipolar resection procedures.

Study screening and selection

All retrieved records were screened through Covidence Systematic Review Management® by two independent authors. Discrepancies were solved by a third senior author. Studies were included based on PICOS eligibility criteria. Only randomized studies were accepted. Non-randomized studies, retrospective studies, case reports, meeting abstracts, editorials, and letters to editors were excluded. The full text of the screened papers was selected if found relevant to the topic of this review. The research was further implemented by the manual search based on the references of the full-text relevant papers. Discrepancies were solved by a third author. Only the paper with the longest follow-up of the same study population was included.

Data synthesis and statistical analysis

We aimed to perform a meta-analysis comparing the presence of BNS among different techniques of transurethral interventions at the last available follow-up. Meta-analyses were only performed when three or more studies were reporting the same outcome. The incidences of BNS were pooled using the Cochran–Mantel–Haenszel Method with the random effect model and expressed as Risk Ratios (RR), 95% Confidence Intervals, and p values. A sub-analysis was performed to explore whether the incidence of BNS was different after monopolar and bipolar TURP. A further sub-analysis was accomplished to assess the influence of study follow-up on BNS incidence. Risk ratios of less than one (1) indicate the intervention decreases the risk of BNS. Analyses were two-tailed, with a significance set at $p < 0.05$ and a 95% confidence interval. Study heterogeneity was assessed utilizing the I^2 value. Substantial heterogeneity was defined as an I^2 value > 50% or a Chi^2 p value < 0.10. Meta-analysis was performed using Review Manager (RevMan) 5.4 software by Cochrane Collaboration. The quality assessment of the included studies was performed using the Cochrane Risk of Bias tool [8].

Pooled analysis was performed using OpenMeta[Analyst] software (http://www.cebm.brown.edu/openmeta/#).

Results

The literature search retrieved 4998 papers. 2008 duplicated papers were removed. A further 2548 records were excluded amongst the title and abstract screening. The full texts of the remaining 442 studies were screened and 351 papers were excluded. The remaining 91 papers were further assessed to exclude studies with the same population and different follow-up. Finally, 72 studies were identified for meta-analysis. As a consequence of the lack of RCTs comparing ablation to enucleation, a meta-analysis was not performed between the two groups. Figure 1 shows the PRISMA flow diagram.

Incidence of BNS

The pooled incidence of BNS in patients who underwent TURP, enucleation, and ablation are reported in Supplementary Figs. 3, 4, and 5, respectively. The incidence ranged from 0.5 to 15.4% (pooled rate 1.3%) in TURP, and it was 0.5 to 3.6% (pooled rate 0.66%) and 0.4 to 8.7% (pooled rate 1.2%) in enucleation and ablation, respectively. The incidence of BNS after M-TURP ranged from 0.5 to 15.4% (pooled rate 1.4%) (Supplementary Fig. 6). The incidence of BNS after B-TURP ranged from 0.4 to 5.1% (pooled rate 0.1%) (Supplementary Fig. 7).

Enucleation vs. TURP

Twenty-six RCTs compared Enucleation vs. TURP [9–34]. Studies characteristics are summarized in Supplementary Table 1. Among 3462 patients included, 19 and nine suffered from BNS in TURP and Enucleation group respectively. The incidence of BNS was higher after TURP than after Enucleation but the difference was not statistically significant (RR 1.75 95% CI 0.81–3.79, $p = 0.16$). There was no significant heterogeneity among the studies (I^2 0%, Chi^2 4.11, $p = 0.90$) (Fig. 2a). Supplementary Figure 1 shows the risk of bias assessment for included studies. Sub-analysis confirmed that the incidence of BNS was similar between M-TURP and Enucleation (RR 1.12 95% CI 0.39–3.21, $p = 0.84$) and higher after B-TURP compared to Enucleation but the difference did not reach significance (RR 2.93 95% CI 0.94–9.06, $p = 0.06$). Test for subgroup difference showed no significant difference ($p = 0.22$). Sub-analysis showed that the RR of BNS was highest after TURP in studies with follow-up longer than 36 months (Fig. 2b), but the difference was not significant probably due to the low number (350) of included patients (RR 3.85 95% CI 0.43–34.29, $p = 0.23$).

Ablation vs. TURP

Forty-six RCTs compared ablation vs. TURP [35–80]. Studies characteristics are summarized in Supplementary Table 2. Among the 4702 patients included, 52 and 34 patients suffered from BNS in TURP and Ablation group respectively. The incidence of BNS was higher after TURP than after Ablation, but again the difference was not statistically significant (RR 1.31, 95% CI 0.82–2.11, $p = 0.26$), with no significant heterogeneity (I^2 0%, Chi^2 21.1, $p = 0.51$) (Fig. 3a). Supplementary Figure 2 shows the risk of bias assessment for included studies. Sub-analysis confirmed that the incidence of BNS was higher after both M-TURP and B-TURP compared to Ablation but the difference was not statistically significant (monopolar TURP RR 1.33 95% CI 0.82–2.17, $p = 0.24$; bipolar TURP RR 2.19 95% CI 0.53–9.12, $p = 0.28$). Test for subgroup differences showed no significant difference ($p = 0.52$). Sub-analysis showed that the RR of BNS was highest after TURP in studies with follow-up between 13 and 24 months (RR 2.44 95% CI 0.57–10.46, $p = 0.23$) (Fig. 3b). Conversely, the RR was higher after Ablation in studies with follow-up between 25 and 36 months (RR 0.74 95% CI 0.27–2.00, $p = 0.55$).

Discussion

Pharmacological failure and severe lower urinary tract symptoms represent the most common indication of surgical treatment of clinical BPH [1]. Bipolar energy and lasers are currently used in enucleation and vaporization techniques to challenge monopolar TURP as the gold standard treatment in prostate volume up to 80 ml. Nevertheless, any surgery that improves symptoms must be balanced against potential complications. Among late complications, BNS can be a bothersome and recurrent disease, leading to urinary retention and multiple repeated invasive procedures that affect the quality of life and defeat the very purpose of the original surgery [5].

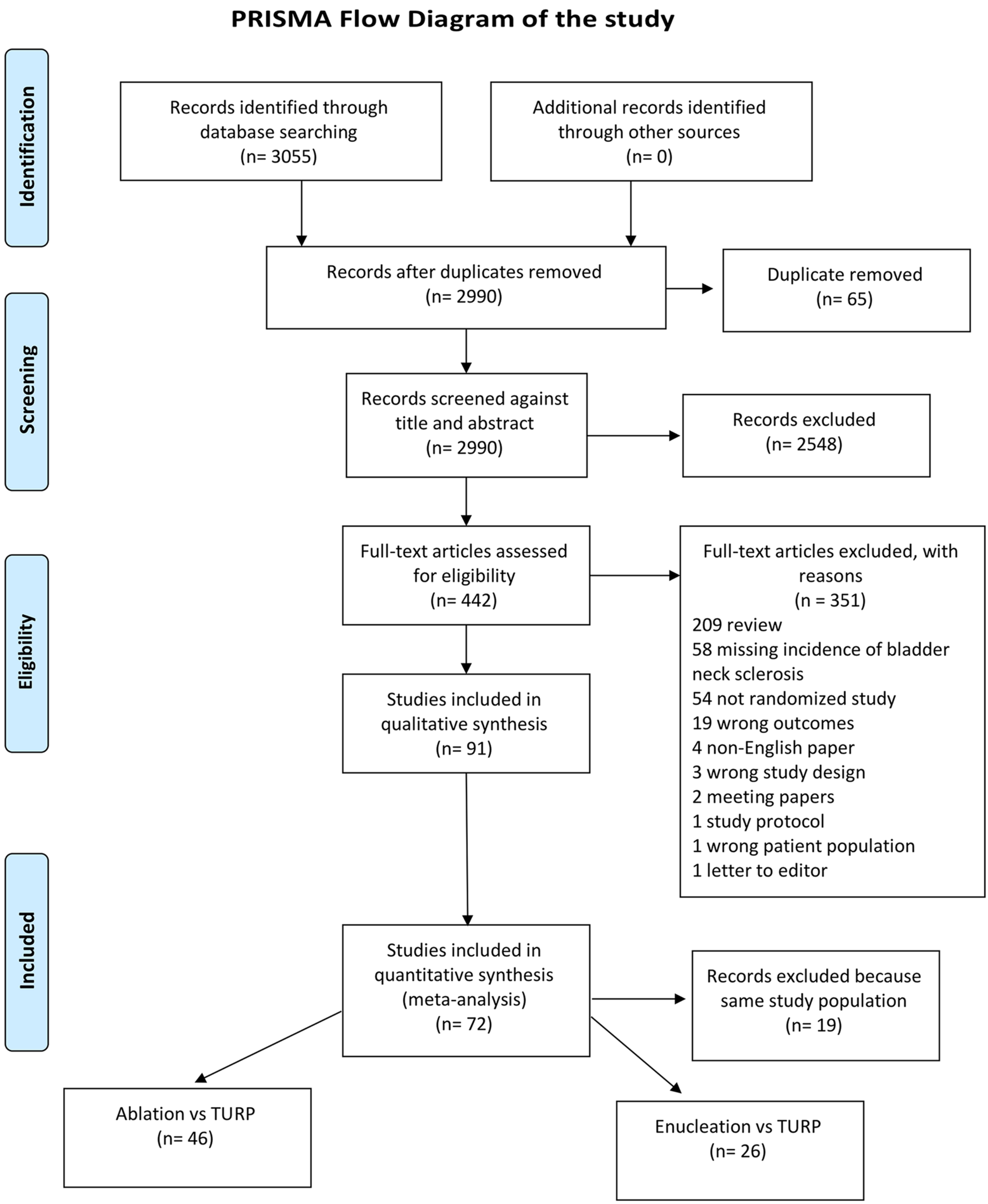

Fig. 1 PRISMA flow diagram of the study

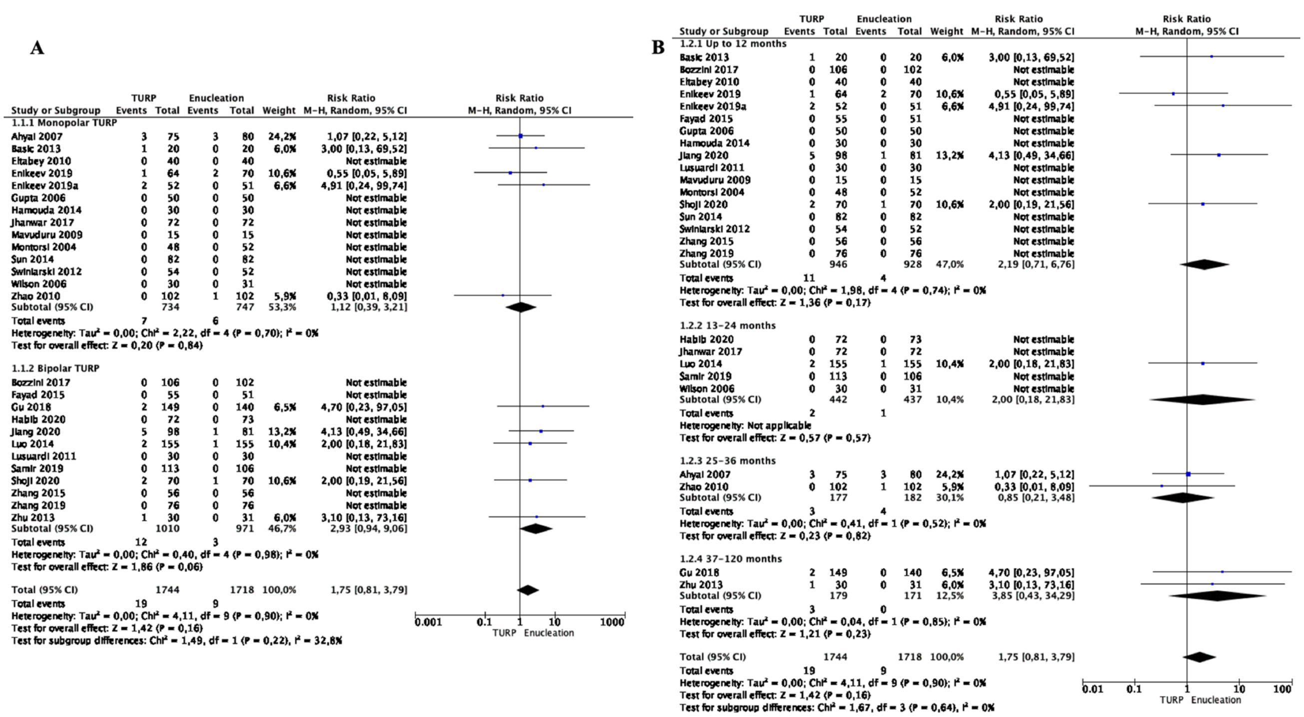

Fig. 2 **a** Meta-analysis of included studies TURP vs. enucleation; **b** meta-analysis of included studies TURP vs. enucleation according to study follow-up

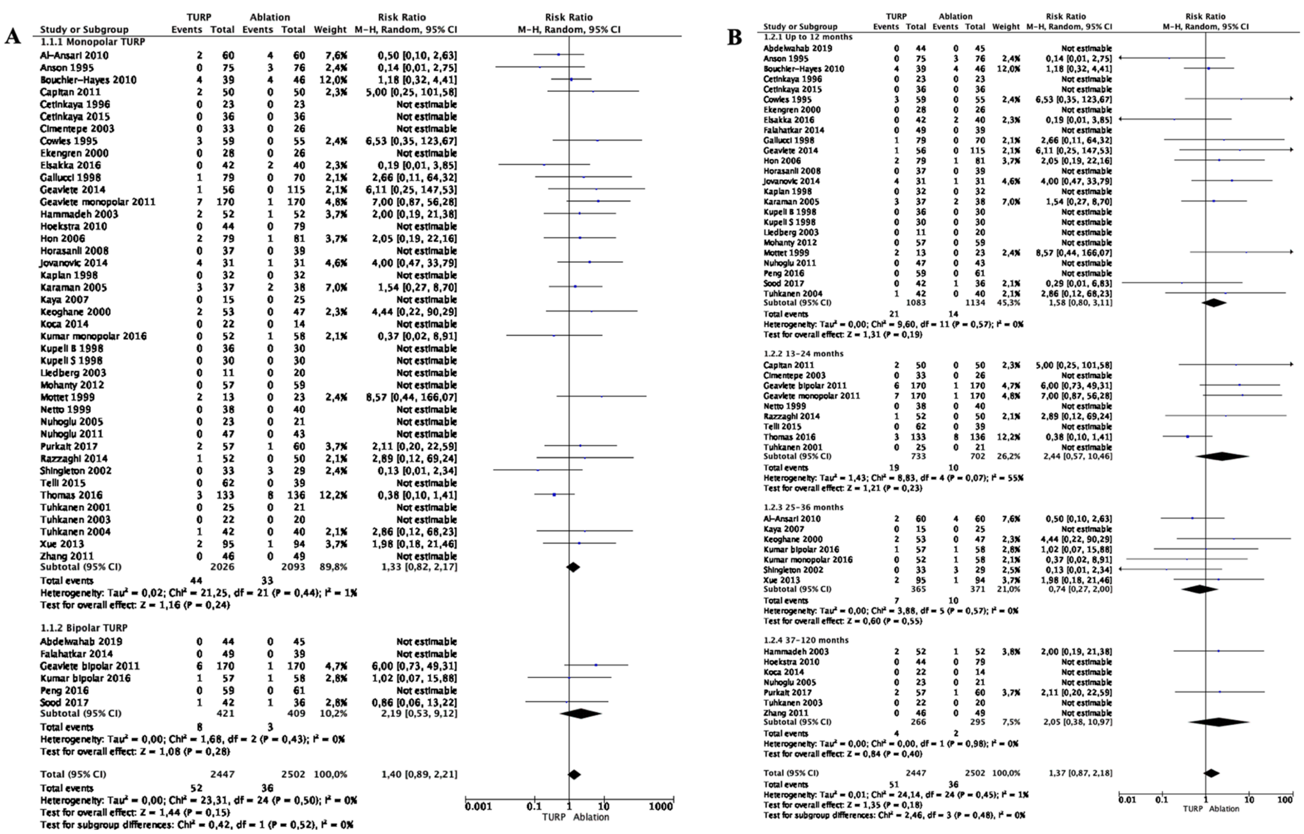

Fig. 3 **a** Meta-analysis of included studies TURP vs. ablation; **b** meta-analysis of included studies TURP vs. ablation according to study follow-up

The present review showed that the incidence of BNS after endoscopic surgery for BPH was low (1.3, 0.8, and 1.2% after TURP, Enucleation, and Ablation, respectively). However, the meta-analysis highlighted that the risk of BNS was higher after TURP than after Enucleation (RR 1.47 95% CI 0.71–3.05, $p=0.30$) and Ablation (RR 1.31, 95% CI 0.82–2.11, $p=0.26$), even if the difference did not reach statistical significance.

Our study shows that the pooled rate of BNS after transurethral Enucleation was very low at 0.8%. Despite the moderate sample size in the included trials, the rate was comparable with the largest case series. In two HoLEP series, each including more than 1000 cases, the authors reported a BNS rate of 1.1–1.5% and showed that BNS was significantly associated with smaller size glands and noted up to 5-year follow-up [81, 82]. Ahyai et al. showed in the largest randomized study comparing HoLEP vs. M-TURP (200 patients) no difference of BNS incidence at 36-month follow-up (3.1% in HoLEP and 3.3% in M-TURP, *p* 1.0) [12]. Conversely, Gu et al. also found a lower rate of BNS incidence in 280 patients at 72-month follow-up between HoLEP (0%) and B-TURP (1.34%) [27]. Three studies comparing B-TUEP vs. TURP showed a rate of BNS up to 1% in enucleation groups [15, 21, 29]. This result was in line with a large series of 1100 patients who underwent B-TUEP in a single center (0.9%) [83]. Shoji et al. also showed a rate of 1.4% of BNS after ThuLEP that was lower compared to B-TURP (2.9%), but again the difference was not statistically significant (*p* 0.561).

The pooled rate of BNS after Ablation was slightly higher (1.2%) than in Enucleation procedures. From the overall included papers, 15 studies compared Green-Light laser PVP to M-TURP. In all studies, the incidence of BNS was low and mostly occurred late after surgery [47, 55, 57–59, 61, 65, 66, 69, 73, 75–79]. Eight trials reported long-term follow-up results (at least 24 months) [47, 58, 61, 66, 69, 76, 77, 79]. Two studies showed a higher rate of BNS in the PVP group [47, 58] and five studies in the TURP group [61, 66, 69, 76, 77] but the difference was not statically significant. Kumar et al. showed only one case in both groups [79]. Despite the limited number of studies with a low number of included patients and high heterogeneity, the incidence of BNS among other laser ablation techniques appears low. Regarding neodymium:yttrium–aluminum-garnet laser ablation, Anson et al. showed a rate of 3.9% at 12-year follow-up (no case in the TURP group) [35]. Conversely, Tuhkanen et al. reported only one case in the TURP group at 4-year follow-up [52]. Several studies compared monopolar and bipolar vaporization with TURP [37–41, 43, 44, 49, 53, 54, 62, 63, 67, 68, 70, 74, 80], but most of them were small series with short follow-up. Hammadeh et al. showed in 104 patients a rate of BNS of 1.9% after M-vaporization and 3.8% after M-TURP at 5-year follow-up (*p* 0.19) [49]. Geavlete et al. showed a lower incidence of BNS after B-vaporization (0.6%) than after M-TURP (4.1%) and B-TURP (3.5%) in 510 patients at 18-month, but again the difference was not statistically significant (*p* 0.047) [62]. Finally, Razzaghi et al. showed no BNS case after Diode laser vaporization and only one case after TURP (1.9%) at 24-month follow-up [71].

Smaller prostate volume, larger instrument sheath, larger resecting loop, low resection speed, extensive resection of the bladder neck, diabetes, smoking habits, cardiovascular disease, repeat catheterization, traction of the balloon, and postoperative urinary infections have been correlated with an increased risk of BNS onset after transurethral surgery [5].

Surgical procedures and energy sources could also be considered theoretical risk factors. Although no difference in BNS rate between Enucleation and monopolar/bipolar TURP was demonstrated in our study, the lower pooled incidence of BNS after Enucleation could be explained by the lower rate of the amount of heat transmitted to the bladder neck, and without excessive coagulation needed to control bleeders. Indeed, the potential damage to underlying tissue could be further minimized because Holmium and Thulium lasers are highly absorbable in water and have a penetration depth of only 0.4 and 0.2 mm, respectively [3]. The minimal disturbance to the bladder neck by laser enucleation was demonstrated in a recent study. Sun et al. highlighted in a randomized trial in men with prostate size ≤ 30 g a significantly lower rate of BNS after ThuLEP compared with Thulium laser resection (1.8% vs. 13.6%, $p=0.045$) [84]. Bladder neck incision at the end of enucleation or ablation and minimizing energy at bladder neck level have been proposed as prophylactic maneuvers to minimize the risk of BNS [81, 82, 85].

A better bladder neck restoration might also be supported by the lower incidence of BNS after robotic-assisted simple prostatectomy. Lee et al. showed that at a mean of 31 months after robotic-assisted simple prostatectomy no patients out of 150 developed BNS [86]. The 360° urethra-vesical anastomosis could enhance bladder neck healing, minimizing the risk of scar formation. Indeed, a higher and early incidence of BNS has been reported after open simple prostatectomy, probably associated with a greater chance of scar formation due to the simple approximation of the bladder neck mucosa to the prostatic capsule or re-established urothelial continuity at the trigone [6].

The recurrence of BNS is unfortunately not that uncommon. Patients suffering from recurrent BNS are challenging because they experience repeated treatment failures. Studies regarding the therapy of recurrent BNS after transurethral surgery are lacking and of low quality. Most of the series reported concomitant data of patients suffering BNS after radical prostatectomy. Dilatation, endoscopic bladder neck incision/resection, and YV-reconstruction of the bladder neck have been reported as treatments with discordant outcomes [5]. Transurethral dilatation is a palliative treatment to maintain patency surges in men who cannot or do not wish to undergo other surgical interventions. However, BNS dilatation showed a statistically significant increase in difficulty and decrease in quality of life and there was a trend toward patients with BNS to experience more pain compared to patients with anterior urethral stricture [87]. Transurethral incision of the bladder neck is the commonest performed procedure for refractory cases, but the optimal surgical technique (cold knife vs. diathermy vs. laser) is still debatable. Ramirez et al. showed that a standardized approach, consisting of a single deep lateral incision at 9 o'clock position down through muscle fibers at bladder neck had a 72% success rate at the first attempt in a series of 50 men (39 of them had failed previous BNC treatment). Half of the patients who failed the first session were resolved in a subsequent surgery [88].

The etiology of BNS recurrence is ambiguous, with scar hypertrophy as one of the hypotheses to justify this unfavorable post-operatory evolution, due to a prolonged inflammatory phase. Thus, in analogy to skin keloids, intralesional injection of Mitomycin C has been used in an attempt to reduce scar formation due to its anti-fibroblast properties and decreased collagen deposition. In a short follow-up small series of ten patients with post-TURP refractory BNCs (> 3 times) circumferential bladder neck resection with an electrocautery loop, up to peri-vesical fat, followed by MMC (2 mg diluted in 10 ml of distilled water) injection into the resected bladder neck at 10 sites, showed an 80% successful rate [89]. On the other hand, a series with 55 patients reported that the efficacy of intralesional injection of Mitomycin C after transurethral incision of the bladder neck was lower than previously shown, with an overall success rate of 75% with multiple attempts, but it was associated with a 7% rate of serious adverse events, including the need of cystectomy [90]. Small series have also shown that intralesional triamcinolone acetonide, a long-acting glucocorticoid with anti-inflammatory function, injected after circumferential transurethral bipolar resection of the scar tissue with up to 8 points of injection also showed 92.3% success rate in patients who had failed multiple prior endoscopic treatments [90].

Bladder neck reconstruction is often used as a last resort after several failed endoscopic treatments, since it is a complex surgery, traditionally through an open approach, and requires an experienced reconstructive surgeon familiar with both abdominal and perineal approaches. The YV-reconstruction of the bladder neck represents one of the most widely used techniques and has been recently revisited and improved to enhance vascularity and mobility of the utilized flaps, being called the T-plasty, with QOL improvement in 90% of the patients and no de novo stress urinary incontinence [91]. The minimally invasive approach has also been demonstrated as an available and effective option for refractory bladder neck stenosis, by pure or robotic-assisted laparoscopy [92, 93].

Conclusion

TURP remains the current commonest choice in patients with a prostate volume 30–80 ml requiring surgery. However, new transurethral procedures are challenging its role as the gold standard. BNS is one of the most relevant long-term complications of transurethral surgery for BPH. Our study showed no difference in the rate of BNS incidence among randomized trials comparing TURP vs. Ablation vs. and TURP vs. Enucleation and can be used as a reference to counsel patients undergoing BPH surgery properly, elucidating the potential risk of BNS and explaining the need of adequate follow-up to identify this complication.

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Author contributions DC: project development, data management, statistics, data analysis, graphics illustration, manuscript writing and editing; JYCT: project development, data management, data analysis, manuscript editing; TRWH and ABG: manuscript editing, supervision; MLW: project development, data management, manuscript writing; ER, GMP, MG, VG, and BKCC: data management, manuscript writing; VWSC: data management, data analysis.

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Data availability Data available on request from the authors.

Declarations

Conflict of interest D. Castellani, M. L. Wroclawski, G.M. Pirola, V. Gauhar, E. Rubilotta, V. W-S Chan, B. K-C Cheng, M. Gubbiotti, A. B. Galosi, and J. Y-C. Teoh have no conflicts of interest to declare. T. R. W. Herrmann is company consultant for Karl Storz.

Human and animal rights Neither human participants nor animals were involved in this study.

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