Holmium laser enucleation of the prostate (HoLEP): size-independent gold standard for surgical management of benign prostatic hyperplasia

Akhil K. Das, MD, Timothy M. Han, BA, Thomas J. Hardacker, MD
Department of Urology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

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Introduction: *Holmium laser enucleation of the prostate (HoLEP) has become an increasingly common surgical management option for treatment of symptomatic benign prostatic hyperplasia (BPH). Transurethral resection of the prostate (TURP) has long been considered the gold standard, contemporary literature and newer guidelines indicate that HoLEP has become the new size-independent endoscopic gold standard for surgical BPH treatment.*
Materials and methods: *We provide a review and update on current HoLEP surgical techniques, outcomes, safety, and durability according to the growing body of literature.*
Results: *The current body of literature and guidelines indicate HoLEP as a safe and effective surgical treatment for symptomatic BPH regardless of prostate size. Durable long term subjective and objective outcomes have been demonstrated in previous studies, extending beyond 10 years.*
Conclusions: *HoLEP continues to demonstrate durable long term efficacy for treating patients suffering from lower urinary tract symptoms (LUTS) due to BPH. The American Urological Association (AUA) guidelines recommend its use as a size-independent endoscopic treatment option. HoLEP has proven itself to be the new gold standard in surgical treatment for LUTS secondary to BPH with the ability to endoscopically treat prostates independent of size, with durable long term outcomes.*

Key Words: HoLEP, BPH, LUTS

Introduction

Benign prostatic hyperplasia (BPH) represents the most common benign neoplasm in American men, with almost 3 in 4 affected by the seventh decade of life.[1] Proliferation of prostatic glandular epithelium, smooth muscle and connective tissue results in prostatic urethral compression, manifesting as bladder outlet obstruction (BOO) and lower urinary tract obstructive symptoms (LUTS).[2] Historically, surgical management of BPH has been transurethral resection of the prostate (TURP) and has served as the gold standard to which all other treatments are compared.[3] Monopolar TURP does carry the risk of TUR syndrome, which occurs between 0.78% and 1.4% of cases,[4] and results in neurologic disturbance, pulmonary edema, cardiovascular compromise, and potentially death secondary to dilutional hyponatremia.[5] TURP can also have increased bleeding risk in those on anticoagulation and can be challenging in men with larger prostates. In the current current American Urological Association (AUA) guidelines for the surgical management of BPH, TURP is one of the options for prostates less than 80 grams (g).

For larger prostates (> 80 g), open simple prostatectomy (OSP) has traditionally been the main surgical treatment option, though laser enucleation has become widely adopted as well. The holmium laser has been employed to treat BPH after its successful use in treating urinary calculi.[6] This laser enables the surgeon to enucleate the transition zone of the prostate from the surgical capsule by taking advantage of existing anatomic planes. In doing so, significantly improving total tissue removal compared to TURP and is less invasive than OSP while maintaining equivalent outcomes.

Address correspondence to Dr. Akhil Das, Department of Urology, Thomas Jefferson University, 1025 Walnut Street, College Building, Suite 1112, Philadelphia, PA 19107 USA

Analysis of these treatment modalities has shown HoLEP to have improved subjective and objective outcomes, including AUA Symptom Score (AUA-SS), postoperative Q_{max} and retreatment rates, when compared to TURP and OSP.[7] Additionally, HoLEP results in reduced immediate complications, decreased length of hospital stay (LOS), shorter catherization times, and decreased blood loss when compared to TURP[8] and OSP.[9] According to current AUA guidelines, laser enucleation techniques are the only recommended size-independent endoscopic surgical option for symptomatic BPH.[3] This review will detail surgical strategies and techniques, outcomes, safety, and long term durability of the HoLEP procedure.

Equipment and technique

The standard HoLEP technique has been previously described[10] and is performed using a high-power 100-120 W holmium laser (Lumenis, Yokneam, Israel) with an end-firing 550-micron laser fiber. Newer laser systems, with two pedals, offer the ability to alternate between treatment settings – commonly 2.0 J with a frequency of 40-50 Hz and wide pulse width – and hemostasis settings – typically 1.5 J and 30 Hz. The procedure is performed using a 26-Fr continuous flow endoscope with a laser bridge. The laser fiber is delivered through the working channel within a 7 Fr laser catheter, which provides stabilization of the fiber throughout the procedure. The inflow port is connected to two separate 3 liter normal saline irrigation bags, which are left wide open, and the outflow port is left to gravity drainage.

The classic, and most commonly used, HoLEP technique is performed by enucleating the median and lateral lobes of the prostate and releasing them into the bladder. Incisions are made at the 5- and 7-o'clock location at the bladder neck and are carried down to the fibers of the prostatic capsule. These incisions are then extended distally and joined proximal to the verumontanum. Starting at this distal location, the median lobe is dissected off of the capsule until it can be released into the bladder. This process can be aided by using the end of the scope to lift the prostatic adenoma while using the laser fiber to develop the dissection plane at the level of the capsule. A similar approach is utilized for the lateral lobes, which are enucleated separately. An additional 12-o'clock incision is made at the bladder neck and again carried distally to the level of the verumontanum, with care to avoid damage to the external urethral sphincter. This incision is again carried down to the level of the prostatic capsule and using similar technique, the lobe is gradually dissected free, as the surgeon works to connect the 12-o'clock incision with the 5-o'clock incision. Once all lobes are enucleated, hemostasis can be achieved by activating the laser on bleeding tissue, but from a further distance than usual. This technique serves to "de-focus" the laser energy and results in tissue blanching and coagulation.

Once all three lobes are free-floating within the bladder, the endoscope is exchanged for an offset nephroscope with a straight working channel through which a soft tissue morcellator is placed. It is important to maintain a full bladder during this process, as decompression can lead to bleeding and decreased visualization. A second irrigation channel is placed in order to optimize visualization during morcellation, with the morcellator serving as outflow suction. Suction on the morcellator is activated, which draws the prostatic adenoma onto the blades. Once the adenoma is visualized to be safely away from bladder mucosa, the blades are activated and prostatic tissue is extracted. Under usual circumstances, the surgeon is able to completely morcellate all adenoma tissue, however, there are instances in which this cannot be completed, and remaining tissue must be extracted by other means (i.e. resectoscope or foreign body grasper). After ensuring all tissue has been removed from the bladder, a 24-Fr three-way Foley catheter is placed and continuous bladder irrigation is initiated.

The newer techniques and equipment HoLEP may help improve OR time, shorten the learning curve, and reduce the incidence of transient stress incontinence. Newer HoLEP surgical techniques include the two-lobe and complete en-bloc enucleation of the prostate.[12,13] In a randomized control trial comparing two-lobe technique to the standard three-lobe technique, Xu et al demonstrated reduced incidence of retrograde ejaculation and urinary incontinence.[11] Similarly, studies comparing efficacy and safety of traditional HoLEP and en bloc technique have shown potential advantages toward the latter technique, including decreased enucleation time and total operative time owing to faster identification of the surgical capsule,[13,14] lower risk of major complications,[15] and improvements in quality of life.[15] A study comparing traditional three-lobe, two-lobe, and en bloc techniques done by Tokatli et al, found decreased enucleation time with the two-lobe technique, and also higher rates of transient urinary incontinence in the en bloc group.[16]

Varying laser settings have also been studied with results demonstrating that low-powered HoLEP (LP-HoLEP) can be performed feasibly, safely, and effectively.[17,18] A randomized trial by Elshal et al comparing lower power (LP)-HoLEP (2 J, 25 Hz) to

standard HoLEP (2 J, 50 Hz) found no difference in enucleation efficiency, postoperative dysuria and sexual function or objective flow rates between the two techniques.[19] As low-power holmium lasers are widespread given their use in treating urinary calculi, this could aid in adoption of the HoLEP technique.

Another promising change in operative efficiency has come from novel improvements in morcellator technologies. Currently, three main prostate morcellators exist: VersaCut (Versapulse; Lumenis Inc., Santa Clara, CA, USA), Piranha (Richard Wolf Inc., Knittlingen, Germany), and DrillCut (Karl Storz Inc., Tuttlingen, Germany). VersaCut was the first morcellator used for HoLEP and utilizes reciprocating non-toothed blades controlled by a foot pedal and continuous suction. The Piranha and DrillCut morcellators use oscillating toothed blades which rotate at variable rates with intermittent suction. Studies have compared the morcellator technologies with seemingly variable conclusions. El Tayeb et al performed a prospective randomized trial comparing the Piranha to the VersaCut, which revealed that despite the Piranha having a statistically significant increased cost ($p < 0.001$) and a more complicated design (less user-friendly for operating room staff), 75% of urology faculty, fellows, and residents preferred it over the VersaCut, reporting more efficient tissue removal.[20] Rivera et al examined cost comparisons between VersaCut and Piranha and found that both morcellation efficiency ($p < 0.01$) and expense of operating room time ($p < 0.005$) significantly favored the Piranha, even when controlling for disposable costs ($p < 0.05$).[21] Another retrospective study done by McAdams et al found that the Piranha's oscillating morcellation efficiency was nearly double that of VersaCut (8.6 g/min versus 3.8 g/min, $p < 0.0001$) with no apparent learning curve.[22] In contrast, Maheshwari et al revealed in their study that while VersaCut demonstrated significantly higher morcellation efficiency, the safety profile of the Piranha was significantly better.[23] Hodhod et al demonstrated that the DrillCut morcellator had superior ex vivo morcellation power but modest aspiration speed in comparison to other morcellators.[24] In a different study, Ibrahim et al conducted a prospective, randomized controlled trial comparing the DrillCut to the VersaCut, revealing that the DrillCut was associated with significantly lower morcellation rate ($p = 0.03$) and significantly higher cost of disposables ($p < 0.01$).[25]

Lastly, the recent advancements in laser technology in the form of a larger vapor bubble per pulse have shown potential usefulness in quicker dissection of adenoma off the capsule with better hemostasis. This technology is currently being evaluated at several centers to see if there is a true reduction in enucleation time with improved coagulation compared to standard holmium lasers.

Efficacy, outcomes, and durability

HoLEP has been extensively studied and many large trials have examined efficacy and outcomes. To our knowledge, Tan et al performed the first randomized trial comparing HoLEP to TURP for the treatment of BOO secondary to BPH.[26] Their study demonstrated that HoLEP was superior to TURP with more prostate tissue removed (40.4 versus 24.7 grams), shorter mean catheter time (17.7 versus 44.9 hours), shorter hospital stay (27.6 versus 49.9 hours), and greater relief of obstruction at 6 month follow up as assessed by pressure flow studies, though at the cost of increased operative time for HoLEP (62.1 versus 33.1 minutes). Long term follow up data at 7 years showed that HoLEP was at least equivalent to TURP with no significant differences Q_{max}, AUA symptom score (AUA-SS), quality of life (QoL) score, BPH Impact Index (BPHII), International Index of Erectile Function (IIEF), International Continence Society Short Form Male questionnaire (ICSmaleSF) Voiding Score, or ICS Male Incontinence Score (IS) after 1 year.[27] No patients who underwent HoLEP required re-operation, while three (17.6%) of those who underwent TURP required further intervention.[27] Kuntz et al found in a prospectively randomized comparison of HoLEP and TURP done for BOO in patients with prostates less than 100 g that while having longer operative times, HoLEP had comparatively shorter catheter time, LOS, and blood loss.[28] Ahyai et al reported 3-year follow up data, showing AUA-SS and PVR were better in the HoLEP grouped compared to TURP.[29] Q_{max} and reoperation rates were similar between the two groups. These results strongly suggest HoLEP to be a true alternative with unique advantages over TURP. Meta-analyses of other trials comparing HoLEP to TURP also found comparable symptom improvement[30] or superior results seen in patients who underwent HoLEP, again demonstrating its advantage over TURP with regard to blood loss, catheterization time, and hospital stay.[30,31] Yin et al found in their meta-analysis that while TURP demonstrated significantly shorter operative times ($p = 0.001$) and lower incidence of postoperative dysuria ($p = 0.003$) compared to HoLEP, Q_{max} and International Prostate symptom score (IPSS) were significantly improved in the HoLEP group ($p < 0.0001$ and $p = 0.01$, respectively) at 12 months postoperatively.[31] In extensive analysis, HoLEP has been found to be at least as effective as the prior gold standard, TURP, for treatment of BPH, with unique advantages.

A multitude of data exist comparing HoLEP to more invasive procedures such as open simple prostatectomy (OSP) or robot-assisted simple prostatectomy (RSP). Kuntz et al reported 5-year follow up results on their randomized controlled trial comparing HoLEP versus OSP for prostates > 100 grams and demonstrated similar improvements in AUA-SS, Q_{max}, and PVR between the two groups.[32] Both groups also demonstrated similarly low reoperation rates (5% in HoLEP, 6.9% in OSP [p = 1.0]). A separate randomized control trial performed by Naspro et al compared HoLEP and OSP in prostates > 70 grams with 2-year follow up data.[33] Their study revealed findings favoring HoLEP, including decreased catheterization time ($p < 0.001$), shorter hospital stays ($p < 0.001$), and decreased blood loss with lower transfusion rates ($p < 0.001$).[33] The study also found similar improvements from baseline in urodynamic parameters, and comparable late complication rates between the two groups, though OSP was found to have decreased operative time. These studies suggest that HoLEP is a minimally invasive alternative to OSP with at least similar efficacy in large prostates. With regard to RSP, Zhang et al performed a study comparing perioperative outcomes between 32 RSP patients and 600 HoLEP patients at two separate academic institutions.[34] Results showed that HoLEP demonstrated reduced mean operative times ($p < 0.001$), decreased blood loss with lower transfusion rates, shorter hospital stay, and decreased catheterization time, with no difference in Clavien 3+ complication rates. This suggests that in expert hands, HoLEP appears to have a favorable perioperative profile compared to RSP, though long term follow up data are not yet available.

Ahyai et al contends that prior studies finding increased operative time for HoLEP, as compared to TURP and OSP likely had some confounding variables, including limited surgeon experience with HoLEP, unavailability of tissue morcellators, and the fact that significantly more tissue was being treated during HoLEP than with other modalities.[35] The study compared 100 TURP and 60 OSP cases from previous randomized controlled trials with a matched pair analysis of 1000 HoLEP cases. These were matched based on documented resected prostate tissue, and resection speed in grams per minute was calculated. The study revealed that resection speed and operative time for HoLEP were significantly faster than TURP ($p < 0.01$) and similar to those of simple OSP ($p \geq 0.21$).

In addition to comparative studies comparing HoLEP to other surgical BPH management options, many large-volume studies with long term data exist. Krambeck et al performed a retrospective analysis of 1065 HoLEPs at a single institution, which showed that HoLEP effectively improved both AUA-SS and Q_{max}; mean AUA-SS decreased from 20.3 preoperatively to 5.3 at 12-month follow up, while Q_{max} increased from 8.4 mL/sec preoperatively to 22.7 mL/sec at 12-month follow up.[36] Elmansy et al retrospectively analyzed 949 patients who underwent HoLEP and had durable improvement in both objective and subjective outcomes at 62-month follow up.[37] To our knowledge, the longest follow up study was performed by Ibrahim et al, and consisted of 1476 patients over an 18-year period who underwent HoLEP at a single institution with over 9 years of follow up data.[38] These patients were found to have significant improvements in mean IPSS ($p < 0.001$) and QoL ($p < 0.001$) compared to preoperative values with only 21 patients requiring reoperation (1.4%). Furthermore, in the 132 patients who could be followed more than 10 years, Q_{max} ($p < 0.001$) and PVR ($p < 0.001$) were significantly improved.

The current AUA guidelines for surgical management of BPH recommend HoLEP and ThuLEP (thulium laser enucleation of the prostate) as the only size-independent treatment options.[3] HoLEP has been more rigorously scrutinized, with more publications, trials, is performed at more institutions, and has been around longer than ThuLEP. Humphreys et al retrospectively analyzed 507 patients who underwent HoLEP and evaluated both objective and subjective measures stratified by prostate size (< 75 g, 75-125 g, > 125 g).[39] No significant differences were found between the three cohorts with regard to hospitalization, catheterization time, AUA-SS, average Q_{max}, average PSA, and complications (i.e. transient stress incontinence, transient dysuria, blood transfusion requirement, strictures). Similar studies have been performed in patients with large prostates > 175 grams[40] and ≥ 200 grams,[41] demonstrating that HoLEP is a safe and effective procedure with satisfactory outcomes and low morbidity, independent of prostate size.

Safety, complications, and adverse effects

HoLEP has demonstrated its safety advantages over TURP and OSP, including decreased blood loss and lower transfusion rates.[8,9,28,30,31,33] The unique properties of the holmium laser allow it to coagulate tissue as it cuts, significantly improving hemostasis during HoLEP. The relatively short wavelength of the holmium laser allows for rapid tissue vaporization, while a shallow depth of penetration and coagulation (0.4 and 0.3 mm, respectively) minimizes damage to surrounding tissue. Additionally, the pulsed laser energy of the holmium laser enables efficient cutting and coagulation of vessels, compared to other laser

energies. Due to these unique properties, HoLEP may be safely utilized in patients with bleeding disorders or those on anticoagulation.[42,43] El Tayeb et al performed a study which compared 116 HoLEP patients who required anticoagulation (AC) or antiplatelet (AP) therapy to 1558 HoLEP patients who were not on AC/AP therapy.[44] The study showed that other than prolonged hospitalization ($p < 0.001$) and duration of continuous bladder irrigation ($p < 0.001$), the use of intermittent or continuous AC/AP therapy did not adversely affect outcomes. With regard to antiplatelet therapy, Sun et al performed a large retrospective study of 1124 HoLEP patients comparing patients who were receiving dual antiplatelet therapy (DAPT), continuous single antiplatelet (AP) therapy, single AP therapy but intermittent during preoperative time, and no AP therapy.[45] Similar complication 30-day complication rates were found ($p = 0.678$) between all groups, with all patients demonstrating improved IPSS, QoL scores, and PVR at 12-month follow up. This literature along with current AUA guidelines recommend that HoLEP is a safe and attractive option for use in patients who are at higher risk of bleeding, such as those on anticoagulation.[3]

In addition to excellent hemostatic properties, previously described size-independent treatment efficacy, HoLEP has also shown an age-independent treatment efficacy and safety profile. Mmeje et al retrospectively analyzed and compared outcomes and morbidity in 311 HoLEP patients aged 50-59, 60-69, 70-79, and ≥ 80 years, with functional outcomes assessed using IPSS, Q_{max}, PVR, and urinary continence.[46] No significant differences were observed between groups with regard to morbidity rates, hospitalization time, 1-year functional outcomes, incidence of Clavien 3+ complications, and change in serum hemoglobin levels.

Intraoperative and postoperative complications from HoLEP are rare, with Krambeck et al describing 24 incidents (2.3%) in a study of 1065 HoLEPs described above.[36] These complications included clot retention (7 patients), significant hematuria prolonging hospitalization (5 patients), open cystotomy to remove adenoma (3 patients), myocardial infarction (3 patients), and atrial fibrillation requiring cardioversion, morcellator bladder injury, cerebral vascular accident, and sepsis (1 patient, respectively). Urethral stricture requiring office dilation ranged from up to 1.3% at short/intermediate term follow up to 0% at long term follow up, while bladder neck contracture rates ranged from 0.8 to 6% over the same follow up period. At the most recent follow up in their study, 3 patients (0.3%) were in urinary retention and significant stress and urge incontinence was noted in 9 (0.8%) and 6 (0.6%) patients, respectively. Similarly, Elmansy et al reported low complication rates, and rates of persistent stress and urge incontinence of 1 and 0.5% in their 10-year follow up data of 949 HoLEP patients.[37] Additionally, 0.8% of patients developed bladder neck contracture, and 1.6% of patients developed urethral stricture with only 0.7% of patients requiring reoperation due to residual adenoma.[37] In the 18-year follow up study described above, Ibrahim et al also reported low complication rates with perioperative blood transfusion required in 0.8% of patients, and postoperative urethral stricture and bladder neck contracture development in 21 (1.4%) and 30 patients (2.1%), respectively.[38] Notably, only 21 patients (1.4%) required repeat HoLEP. With durable long term data and multiple studies, the literature strongly indicates HoLEP as a safe procedure with low complication and treatment failure rates.

Despite its long term durable treatment efficacy and safety profile, HoLEP does carry the risk of ejaculatory dysfunction and altered orgasm perception.[47] Placer et al reported loss of antegrade ejaculation in 70.3% of 202 sexually active HoLEP patients, while 21% reported a reduction in semen quantity.[48] However, rates of sexual side effects appear comparable between HoLEP and TURP/OSP.[33,49,50] Furthermore, Klett et al reported in a retrospective study with 3-year follow up data in 393 HoLEP patients that there was a significant subjective improvement in IPSS compared to baseline ($p = 0.0001$) with no significant change from baseline in mean IIEF-5 scores at 3, 6, 12, 24, and 36 months.[51] Additionally, attempts have been made to maintain ejaculatory function with HoLEP, with Kim et al demonstrating an overall success rate of ejaculation preservation in 46.2% of their patients who received an ejaculatory hood sparing technique.[52] The results of these studies highlight the importance of proper patient counseling prior to HoLEP regarding sexual side effects, while also providing data on promising future directions with regards to optimization of surgical technique.

Patient preference and learning curve

While HoLEP has its distinct advantages and side effect profile, it can be difficult to assess patients' perspectives and satisfaction across the multiple treatment modalities for symptomatic BPH. Abdul-Muhsin et al utilized an independent third-party survey sent to all patients who underwent any surgical treatment for BPH over a 6-year period to help address this question.[53] There was a response rate of 55.6% (479 respondents), including patients who received HoLEP (n = 214), TURP (n = 210), holmium laser ablation of the prostate (n = 21), photoselective vaporization

(n = 18), transurethral incision of the prostate (n = 9), and open simple prostatectomy (n = 7). For the tested individual domains, significant differences were noted in urinary intermittency ($p < 0.001$), weak stream ($p = 0.003$), straining ($p < 0.001$), and QoL ($p = 0.001$), in favor of HoLEP. Additionally, HoLEP demonstrated a significant advantage in voiding ($p = 0.02$) and QoL domains ($p = 0.03$) using ICSmaleSF, as well as the lowest rates of patient regret.

Despite endorsement in the literature and AUA guidelines, wide adoption of HoLEP and implementation in the urology community has been somewhat limited. This is most likely secondary to the steep learning curve of the HoLEP procedure. Relatively few US urologists receive HoLEP training during residency and learning the technique afterward can be challenging. Robert et al conducted a prospective, multicenter observational study involving surgeons experienced in TURP and OSP, but with no previous HoLEP experience.[54] Nearly half of the centers ultimately chose to either abandon the HoLEP technique before the end of the study or to not continue performing HoLEP at the conclusion. In a systematic review assessing the HoLEP learning curve, Kampantais et al showed that HoLEP has an acceptable learning curve with a proposed number of 25-50 cases.[55] A structured mentorship program and the use of simulation can greatly reduce the number of cases needed. A separate systematic review focusing on the complications of the HoLEP learning curve demonstrated that complication rates are similar or lower to those reported by traditional techniques.[56]

Conclusions

Overall, HoLEP has proven to be an extremely effective, safe, and durable treatment for patients suffering from LUTS due to BPH. The AUA guidelines highlight this by recommending HoLEP as a size-independent treatment option for those who are candidates for surgical treatment. The literature shows HoLEP to be an equivalent if not superior surgical solution to TURP and OSP with a growing body of research comparing HoLEP favorably to other techniques such as RSP. While there are some limitations to this technique, including high rates of retrograde ejaculation and a steep learning curve, HoLEP has a large body of literature demonstrating its efficacy, long term durability, and favorable risk profile. HoLEP offers a surgical management option for patients who may not be optimal candidates for other procedures based on prostate size, age, or bleeding risk. Given its widespread utility and durable outcomes, HoLEP is quickly becoming the new gold standard in the treatment of surgical BPH. □

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