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Invited Review

Evolution of Aquablation®—From innovation to establishment

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ABSTRACT

Technological progress is continuously improving medical care. The urological profession is well-known for further development of technical innovations and quick transfer into daily practice. Robot-assisted surgery, for example, has been part of the clinical routine in modern urological clinics for many years. In the endourological field, the implementation and further evolution of laser-based procedures have dominated research in the last decade. Recently, in 2015, the presentation of a new robot-assisted technique of waterjet-based ablation of prostate tissue raised attention in the society—the Aquablation® therapy. Aquablation therapy has been investigated within several randomized and controlled clinical trials, and—with growing experience—the technique has been modified over recent years to improve the safety of the procedure. Due to the clinical outcome, the number of hospitals performing Aquablation therapy is increasing continuously. This article provides an overview of the technique, its modifications, and the current status of evidence.

Key words: Ablation Techniques; lower urinary tract symptoms; prostatic hyperplasia; treatment outcome.

Introduction

Benign prostatic hyperplasia (BPH) is the most common benign urological disease in men with onset around the age of 40. Its incidence is age related: by 60 years of age, the prevalence is over 50% and even affects about 90% of those over 85 years of age.[1] The overgrowth of benign prostatic tissue can lead to quality-of-life-impairing lower urinary tract symptoms (LUTSs) such as weakened urinary stream, urgency, frequent urination, bladder voiding dysfunction, or nocturia. If this condition is left untreated, complications such as acute urinary retention, urinary tract infections, chronic urinary retention, irreversible damage to the detrusor, and renal insufficiency may occur.[2] Initial therapeutic management includes watchful waiting or the use of drugs, most notably selective alpha1-blockers, in larger prostates also in combination with 5-alpha-reductase inhibitors, or phosphodiesterase type 5 inhibitors. This medical therapy may lead to limited or short-term improvement, especially in men with moderate to severe symptoms. In other cases, pharmacological therapy is discontinued due to side effects, requiring surgical therapy. In addition to the historical reference standard TUR P for small to medium glands and open simple prostatectomy for large glands, modern ablative and nonablative surgical approaches have evolved in recent decades. While TUR P is recommended as the current standard for prostate volumes up to 80 mL in size, it carries risks such as bleeding, bladder neck sclerosis, incontinence, erectile dysfunction, or retrograde ejaculation.[3] For prostate volumes >80 mL, holmium laser enucleation of the prostate (HoLEP) is the preferred treatment option, which demonstrated higher intraoperative safety and hemostasis with comparable impact on erection and ejaculation.[4–6] However, a major issue is the challenging learning curve[7] and side effects concerning ejaculatory and continence function. As new approaches evolve, Aquablation (AquaBeam System, PROCEPT BioRobotics, Inc., USA) has been included in guidelines as

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an innovative tool in the treatment of BPH following the approval by the FDA in December 2017. Aquablation is a minimally invasive, high-velocity water jet technology for robotically assisted and real-time ultrasound-guided removal of obstructive prostatic tissue.

Clinical and Research Consequences

This article provides an overview of the history and existing studies of the Aquablation therapy. As a basis for the work, the focus has been placed particularly on prospective randomized studies, reviews, and case reports, which were selected according to their clinical relevance. Recently, systematic reviews for Aquablation therapy have been published.[8,9] However, this work is intended to represent a chronological course of the technique's evolution. The primary objective is the comparison with the established surgical techniques TUR-prostate, transurethral laser enucleation, and simple prostatectomy. This paper focuses on functional outcomes and potential complications regarding continence, ejaculatory, and erectile function. In addition, further development and modifications of the technique are highlighted, particularly with regard to the hemostasis technique. Based on this work, the reader should be able to critically appraise the Aquablation therapy and its limitations.

How It All Started: Small to Medium Prostates

Faber et al.[10] applied this new technique in 2015 in a study of eight male beagles via a previously created perineal urethrostomy. In 2016, the results of the first prospective, nonrandomized, single-center study of 15 men undergoing Aquablation were published by Gilling et al.[11] The mean prostate size of these patients was 54 mL, ranging from 27 to 85 mL. This first-in-man study proved the feasibility and safety of Aquablation with comparable improvement in symptoms and objective measurement parameters compared with other BPH surgical interventions. This trend was confirmed in another study by Gilling et al.[12] in 2018, which provided the first randomized comparison of Aquablation and TUR P in men with LUTS due to BPH. WATER (Waterjet Ablation Therapy for Endoscopic Resection of Prostate Tissue) is a double-blind, multicenter clinical trial that compared the safety and efficacy of Aquablation and TUR P. A total of 181 patients with moderate to severe LUTS due to BPH and a prostate size of 30-80 mL (mean 53 mL) were enrolled. The mean operative time was similar in the Aquablation and TUR P groups, while the resection time itself was significantly lower in the Aquablation arm (4 vs. 27 minutes). When comparing the improvement of International Prostate Symptom Score (IPSS) at 6 months as the primary efficacy end point, Aquablation therapy was shown to be noninferior meeting the endpoint objective. The studies primary safety hypothesis with a safety endpoint determined as Clavien Dindo persistent grade 1 or grade 2, or higher operative complications was met demonstrating superiority for Aquablation therapy. In a subgroup of larger prostates between 50 and 80 mL, Aquablation was shown to be superior to TUR P with respect to the primary efficacy as well as the safety endpoint. Interestingly, Gilling et al.[12] found a lower risk of sexual dysfunction following Aquablation. Among sexually active men, anejaculation was less frequent after Aquablation than after TUR-P (10% vs. 36%).

In a following preplanned subgroup analysis, Plante et al.[13] confirmed superior symptom score improvements in men with larger prostates following the Aquablation therapy. Larger changes in IPSS were observed in men with obstructive anatomic conditions (i.e., larger prostates >50 mL, larger middle lobes, and severe obstructive middle lobes) or more severely compromised urodynamic measurements (i.e., lower Q_{max} and elevated baseline post-voiding volume), suggesting that robotic-assisted waterjet removal of particularly obstructive prostate tissue appears to be more effective than TUR P. The reduced rate of anejaculation was also reconfirmed. In 2019, Misrai et al.[14] published a French prospective clinical trial, called FRANCAIS WATER, which included a total of 30 men with a prostate size between 45 and 69 mL treated by three different surgeons with no prior experience in Aquablation. This study confirmed the safety, reproducibility, and efficacy of Aquablation therapy of small- to medium-sized prostates with similar functional improvements as in the previously mentioned work. The opportunity of antegrade ejaculation preservation was again emphasized, as a lower anejaculation rate (26.7%) was demonstrated compared with published TUR P data.[15]

New Challenge: Large Prostates ≥80 mL

Surgical therapy for BPH has undergone many innovative changes over the past decade, and new techniques continue to

Main Points

- Aquablation therapy, first described in 2015, is an emerging minimally invasive and robotically assisted procedure for the treatment of benign prostatic hyperplasia.
- The efficacy and safety results of the WATER trial (prostates up to 80 mL) have been confirmed by several other prospective studies and "real life" data.
- Concerns regarding bleeding complications have been largely resolved by further development of the hemostasis technique.
- So far, it has not been clarified whether Aquablation therapy is not inferior to the current standard of minimally invasive treatment of large prostates >80 mL—transurethral laser enucleation.

be explored, which are mainly determined by the prostate volume. Small prostate glands with a size <80 mL can be treated by numerous procedures. According to guideline recommendations, the current reference standard is TUR P. The development of laser-assisted transurethral and other innovative techniques (e.g. REZUM, UROLIFT) have supplemented the surgical spectrum. In contrast, The therapy of large prostate glands >80 mL is much more challenging especially considering the operating time, bleeding risks, duration of catheterization, and hospitalization. Open or laparoscopic/robotic-assisted simple prostatectomy, photoselective vaporization, HoLEP, or thulium laser enucleation/vapoenucleation of the prostate are the most commonly used procedures above this prostate size. In experienced centers, laser enucleation is the surgical treatment of choice for men with prostates >80 mL. Surgical outcome and perioperative morbidity after laser enucleation, especially with increasing prostate size, are highly dependent on the surgeon's experience and endourologic skills. This is also reflected in the relatively steep learning curve, which is why alternative feasible and easily reproducible procedures are being sought.[7,16]

The results of the aforementioned studies investigating the impact of Aquablation in small- to medium-sized prostates <80 mL were promising and even superior to TUR P in terms of sexual side effects. To evaluate the safety and efficacy of Aquablation in larger prostates, the WATER II study was conducted in 2017, a prospective multicenter clinical trial in which Aquablation was performed on 101 men with moderate to severe BPH symptoms and large-volume 80-150 mL prostates. In April 2020, Desai et al.[17] presented the 2-year-results. Aquablation therapy was shown to be a safe and effective procedure even for larger prostates with the advantage of an easy reproducibility, as most surgeons in the study had little or even no experience with Aquablation. This study demonstrated symptom reductions and significant urodynamic improvements: the IPSS showed a 17.4-point improvement, the maximum urinary flow rate increased from 8.7 to 18.2 mL s^{-1}, and postvoid residual urinary volume decreased from 131 mL at baseline to 45 mL at 2 years. Two subjects underwent retreatment with HoLEP and TUR P, respectively, due to recurrent BPH symptoms. Antegrade ejaculation was found to be preserved in 81% of the subjects, again proving superiority to other methods. Following the Aquablation therapy, a relatively high transfusion rate was noticed. However, this study was conducted entirely without the use of cautery for hemostasis. Bleeding-related events occurred in 14 patients (13.9%), of which eight (7.9%) occurred prior to discharge and six (5.9%) occurred within 1 month of discharge. Overall, 10 (10%) subjects required blood transfusion post-Aquablation. Five subjects needed to return to the operating theater for cystoscopic fulguration.[18] Bach et al.[19] reported data from a single center in real practice where men with a wide range of prostate volumes of 20-154 mL were treated. Their data were consistent with the results of WATER II shown previously and demonstrated the efficacy and safety of Aquablation even in larger prostates. Recently, Gross et al[20] reported two cases of rectal perforation after Aquablation® therapy of prostates >80 mL within their first 50 cases. The authors concluded that rectal manipulation with the Transrectal ultrasound (TRUS) probe mounted on the mobile arm should be limited due to the decreased haptic feedback. In review of the currently published literature, these complications have been limited to single cases and seem to be related to surgeons' performance, rather than to the method.

Evolution of Hemostasis

All variants of surgical therapy for BPH require an effective intraoperative and postoperative bleeding management to avoid anemia and blood transfusion. TUR P is a highly effective treatment of smaller glands <80 mL with a relatively low transfusion rate of 1-3%.[21] In contrast, larger prostates are more challenging, and their resection requires correspondingly more time. Once resection time exceeds 90 minutes, the transfusion rate increases to 7.3%.[22] In clinics with limited endourological experience, open simple prostatectomy is commonly performed for larger prostates. Due to the more invasive nature of this procedure, transfusion rates range from 7 to 14%.[23–25] In contrast, published data on laser enucleation indicate a relatively low transfusion rate of 4%.[26]

Since the introduction of Aquabeam in 2015, different techniques of hemostasis have been performed over the different trials. In the WATER study, hemostasis was performed by focal nonresective electrocautery or low-pressure inflation of a foley balloon catheter in the prostatic fossa. Here, one of the 116 subjects in the Aquablation therapy arm required postoperative blood transfusion due to bleeding. In direct comparison, no transfusion was necessary in the TUR P arm (2:1 ratio, Aquablation therapy: TUR P). Nevertheless, the transfusion rate was <1%, which was lower than in the aforementioned data of TUR P.[21] In 2019, Bach et al.[19] demonstrated a relatively low transfusion rate of 2.5% analyzing the center's first 118 consecutive cases (nonrandomized, all commers) with a mean prostate size of 64.3 mL (range 20-154 mL). Hemostasis was achieved here in 96.6% completely athermal by postoperative bladder neck traction via the inflated transurethral catheter.

In WATER II (prostate volume 80-150 mL), robust traction of the Foley balloon catheter was applied through a special catheter tension device (CTD) without prior electrocautery. This

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approach showed a relatively high transfusion rate of 10%. Addressing this issue, Elterman et al.[27] recently compared different hemostasis techniques in terms of transfusion rate in a pooled data analysis (n:801). Robust traction using the special CTD was compared with standard traction (tying the catheter to the leg or gauze knot synched up to the meatus). Here, an advantage was shown for standard traction for prostate size above 48 mL. For large prostate volumes of 78-280 mL, this effect was pronounced (7.8% vs. 1.8%). In addition, the subgroup of cases in which bladder neck cauterization was combined with standard traction showed a low transfusion rate of 1.9% across all prostate sizes. The authors concluded that athermal hemostasis is feasible, but focal bladder neck cauterization may improve hemostasis, especially for large prostates. Based on these results, the combined approach using the bladder neck spot cautery and standard traction represents clinical practice.

Continence Function

As incontinence is associated with a significant impairment of the quality of life, the preservation of continence function should be a priority of any prostate surgery. TUR P is considered as the reference procedure with low incontinence rates. Rassweiler et al.[3] reported persistent incontinence in 0.5% of the cases. In contrast, HoLEP can be associated with a relatively high postoperative incontinence rate ranging from 1.5 to 42.7%.[28–31] Cho et al.[30] showed that the incontinence rate decreases from 16.2% at 2 weeks postoperatively to 5% at 3 months and 1.1% at 12 months postoperatively, highlighting the temporary character of post-procedure incontinence and tolerable incontinence rates in long time follow-up. In contrast, Sapetti et al.[31] demonstrated that 32.7% of patients were still incontinent at 6 months follow-up (postoperative 42.7%). As the most invasive procedure for the treatment of large prostate volumes, incontinence rates of 5.4-9.4% were reported for simple prostatectomy.[32,33]

Postoperative incontinence associated with Aquablation therapy is low in contrast. Accordingly, no incontinence occurred in any of the patients in FRANCAIS WATER trial.[14] Data analysis of the WATER trial grouped incontinence (leakage) with other urinary symptoms such as urgency, difficulty, and frequency (Clavien Dindo 1 and 2 events). These occurred at 3-month follow-up in six patients (5.1%) in the Aquablation therapy arm. A comparable rate was recorded in the TUR P arm (three patients, 4.6%, nonsignificant difference).[12] In WATER II (large prostate volumes 80-150 mL), incontinence was found in 5% of cases at the 1-month follow-up and in 1% at the 24-month follow-up.[18] Consistently, Bach et al.[34] demonstrated a 1% incontinence rate analyzing the "all comers" pooled data of five sites (n: 178).

One possible explanation for the low incontinence complications is the placement of the handpiece under visualization in front of the external sphincter during the planning phase of the Aquablation therapy. Accidental damage to the sphincter is, thus, very unlikely, as the application of the waterjet is limited to this level.

Ejaculatory Function

Retrograde ejaculation or anejaculation is a common side effect of the various ablative therapies for BPH and is likely caused by heat-related damage to the ejaculatory ducts and extensive apical resection.[15] While the rate of retrograde ejaculation after TUR P is described as over 60%, rates between 70 and 80% are found after HoLEP.[35] For men seeking ejaculation preservation, Aquablation therapy appears to be the primary ablative procedure of choice based on the results of the initial studies. In WATER (prostate volume 30-80 mL), anejaculation was less frequent after Aquablation than after TUR-P (10% vs. 36%). In the subgroup analysis of larger prostates (prostate volume 50-80 mL), an even lower rate of anejaculation was found (2% vs. 41%).[13] However, the advantage of ejaculatory preservation in larger prostate glands could not be confirmed in WATER II. In their cohort, 81% of sexually active men maintained their ejaculatory function.[18] In contrast, a higher rate of anejaculation (27%) was found in FRANCAISE WATER (prostate volume 45-69 mL), although this was still below common rates after TUR P or HoLEP.[14] The authors hypothesized a low rate of retrograde ejaculation due to the optimized apical contour planning through precise robotically assisted and real-time ultrasound-guided resection that avoids damage to the ejaculatory ducts around the verumontanum. Interestingly, a case–control study using data from the WATER, WATER II, and WATER FRANCAISE demonstrated that posterior depth of contour plan below the peak verumontanum and damage to the ejaculatory ducts is correlated with a higher rate of ejaculatory dysfunction.[36] Based on these data, more conservative Aquablation therapy, particularly in the region of the verumontarum, might lead to further improvement in ejaculatory function in future series.

Erectile Function

While disorders of ejaculatory function are generally considered as common adverse events of BPH surgery, the literature is inconsistent regarding the impact on erectile function. Thermal damage of the neurovascular bundles is suggested as a potential cause of postoperative erectile dysfunction. While Taher et al.[37] showed a 13-14% risk of erectile dysfunction after TUR P, Briganti et al.[5] demonstrated in a prospective randomized setting that pre- and postoperative erectile function in terms of intercourse satisfaction, sexual desire, and overall satisfaction did not worsen after TUR P or HoLEP. The analysis revealed a deterioration of the International Index of

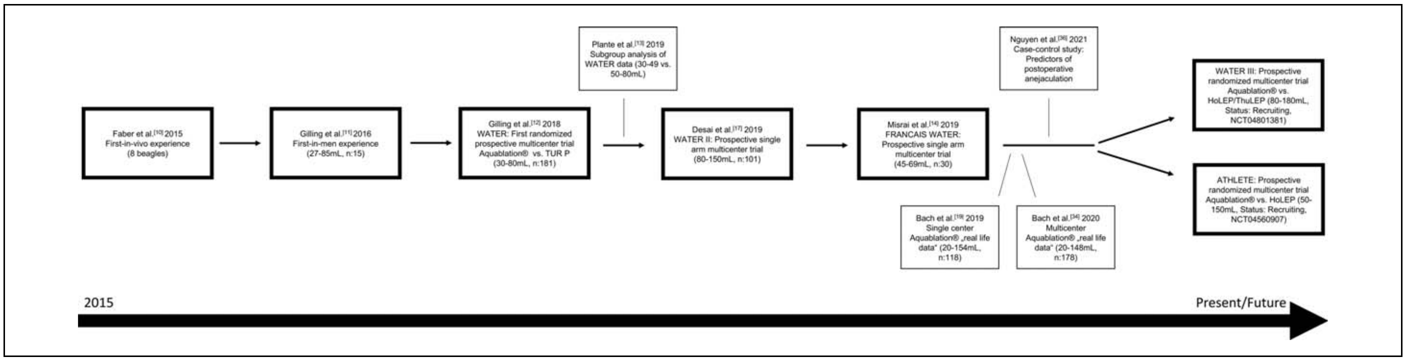

Figure 1. Evolution of evidence: Milestones of Aquablation® therapy

Erectile Function (IIEF) orgasmic function domain with no significant differences between TUR P and HoLEP. The authors related this finding to the high prevalence of ejaculatory dysfunction postoperatively. In contrast, they showed even a positive correlation of erectile function score and IPSS improvement postoperatively, suggesting a positive influence of LUTS improvement on sexual function.

Numerous studies addressed the erectile function monitored by questionnaires such as IIEF-5/SHIM or IIEF-15 for Aquablation therapy. In the first prospective single-arm study in 2017, Gilling et al.[38] already showed that erectile function (measured with IIEF-15) did not deteriorate postoperatively. The domain "satisfaction during sexual intercourse" even improved significantly.[38] These results could be confirmed in WATER. Here, a significantly higher postoperative score of the domain "overall satisfaction" was found compared to TUR P.[12] Bach et al.[34] reconfirmed these results in their "all comers" data by showing stable IIEF-15 subdomains through the 12 months follow-up; only one patient (1%) reported erectile dysfunction indicated by a one-point drop in the IIEF5/SHIM score.

The athermal approach may be beneficial in terms of protection of the nervous structures in the prostatic capsule and, thus, could be the reason for the favorable maintenance of erectile function.

Conclusion

Over the last 5 years, Aquablation therapy has been investigated in numerous studies. The evidence for small and medium prostate sizes up to 80 mL is excellent. The results of the randomized, controlled, and double-blinded WATER trial have been reproduced by several single-arm studies and "real life" data analyses. Regarding larger prostate volumes, initial concerns in terms of higher risk of bleeding and transfusion were resolved by the modification of the hemostasis technique. However, Aquablation therapy is still a young procedure that will have to face further challenges in the future. Although treatments of very large prostates up to 280 mL have been described, larger series with follow-up studies are needed to evaluate the procedure in this indication.[27] Other challenges include extreme anatomic variants such as very large middle lobes with severe intravesical protrusion. So far it has not been clarified whether Aquablation therapy is noninferior to the current standard of minimal invasive treatment of large prostates >80 mL—the transurethral laser enucleation. This issue is currently addressed in the randomized, controlled multicenter study—WATER III: a randomized, controlled trial of Aquablation vs. transurethral laser enucleation of large prostates (80-180 mL) in BPH (NCT04801381 and DRKS00023668) and the randomized, controlled trial—ATHLETE: Aquablation vs. HoLEP in the treatment of BPH in medium to large size prostates (NCT04560907). Furthermore, the long-term data from the aforementioned prospective studies need to be tracked to further analyze this modern and exciting procedure.

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Conflict of Interest: Thorsten Bach: Honoraria for lectures, Advisory Board participation, trial participation (WATER III); Stefan Hauser: Advisory Board participation, trial participation (WATER III); Manuel Ritter: trial participation (WATER III); Johannes Stein: trial participation (WATER III); Alexander Cox: trial participation (WATER III).

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