TITLE: GreenLight™ Laser for Benign Prostatic Hypertrophy: A Clinical and Cost-Effectiveness Review

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CONTEXT AND POLICY ISSUES:

Benign prostatic hyperplasia (BPH) is a non-cancerous enlargement of the prostate that commonly occurs in older men. The minimally invasive approach of transurethral resection of the prostate (TURP) is the gold-standard treatment for BPH. While effective, TURP is associated with a number of complications including increased bleeding and sexual dysfunction. Therefore, there is an interest in a number of emerging minimally invasive therapies as alternative treatment options.

Recent advancements in laser technology have led to the introduction of photoselective vaporization of the prostate (PVP) using the GreenLight™ potassium-titanyl-phosphate (KTP) laser. PVP uses the KTP laser to remove obstructive prostatic tissue. The laser energy is selectively absorbed by hemoglobin in the prostate tissue and results in tissue destruction. The GreenLight™ PVP laser system has gone through several evolutions from the original 80-watt laser, to the most recent 120-watt GreenLight HPS™ system.

With the increasing use of GreenLight™ to treat BPH, there is a need to review the evidence regarding its use. This report will review evidence for the clinical and cost-effectiveness of GreenLight™ laser therapy for the treatment of BPH.

RESEARCH QUESTIONS:

1. What is the evidence for the clinical benefit and harm of GreenLight™ laser for the treatment of patients with benign prostatic hypertrophy?

2. What is the cost-effectiveness of GreenLight™ laser for the treatment of patients with benign prostatic hypertrophy compared to transurethral resection?
METHODS:

This report is an update to a previous HTIS report (#I0356) on the clinical and cost-effectiveness of GreenLight™ laser therapy for the treatment of BPH. The intent of the previous report was to provide a reference list of the best available evidence; this report provides a critical appraisal of the published literature. Due to the availability of more rigorous evidence from health technology assessments (HTAs), systematic reviews, randomized controlled trials (RCTs) and controlled clinical trials (CCTs), observational studies were not included in this report.

A limited literature search was conducted on key health technology assessment resources, including PubMed, OVID Embase, The Cochrane Library (Issue 3, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. Results include articles published between 2003 and September 2008, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, HTAs, systematic reviews, and meta-analyses are presented first. These are followed by RCTs, CCTs, and economic evaluations.

SUMMARY OF FINDINGS:

The literature search identified one health technology assessment, three systematic reviews, four economic evaluations, three RCTs, and three CCTs. Two of the systematic reviews on treatments for BPH that were identified did not find any literature pertaining to GreenLight™ laser and are therefore not discussed further. The studies reviewed herein evaluated the 80-watt GreenLight™ laser.

Health technology assessments

A health technology assessment prepared for the Ontario Health Technology Assessment Commission (OHTAC) evaluated an array of energy delivery systems, including the 80-watt KTP GreenLight™ laser for the treatment of BPH. Their inclusion criteria were RCTs comparing GreenLight™ laser to the gold-standard treatment TURP. No RCTs were identified through their literature search to allow comparison of safety and efficacy of this technique with TURP. The authors identified a prospective cohort study that demonstrated outcomes similar to TURP. The authors also noted that GreenLight™ laser treatment of BPH requires a shorter duration of catheterization and can be performed in an out-patient setting making PVP with GreenLight™ laser a cost-effective procedure. OHTAC recommended that given the increased used of PVP clinically, a registry study should be conducted to determine the long-term clinical effectiveness and complication rates for this technology.

Systematic reviews and meta-analyses

A systematic review by Stafinski et al. (2008) evaluated the safety (adverse events and complications) and effectiveness of PVP with GreenLight™ laser as measured by maximum or peak urinary flow rate, post-void residual volume, and International Prostate Symptom Score (IPSS) pre- and post-treatment. An analysis of the cost-effectiveness of PVP with GreenLight™ laser compared with TURP was also made. Inclusion criteria for this systematic review were those studies (RCTs, CCTs, and observational studies) in which participants with BPH were treated with the GreenLight™ system. A direct comparison to TURP was not necessary for
inclusion. Patients that had received a diagnosis of prostate cancer or were treated with another PVP system other than GreenLight™ were excluded as were those that had been treated with a KTP laser of less than 80-watt. Fourteen studies met the selection criteria: 12 case series, one RCT, and one cohort study. A total of 1,376 GreenLight™ PVP procedures were evaluated. Participants ranged in age from 44 to 95 years. Thirteen of the 14 studies followed participants for six to 12 months and only one study followed patients beyond one year after receiving treatment and reported outcomes at 24 months. Although only one RCT was included in this systematic review, findings were consistent across most studies. PVP and TURP had similar safety profiles although participants receiving PVP were less likely to develop clot retention. The authors concluded that the general risk of experiencing a complication was comparable between groups; however PVP had favourable outcomes in terms of length of patient hospitalization and catheterization time. Four economic studies of PVP were available for evaluation in this systematic review: two peer-reviewed studies, one conference abstract, and one government report. The authors concluded based on disposables, capital equipment, and hospitalization costs, that PVP was less costly per case than TURP. Limitations include lack of RCTs on topic and lack of data beyond 2 years following treatment.

Randomized controlled trials

A RCT by Horasanli et al. (2008)¹⁰ compared the short-term outcomes of treating BPH with PVP or TURP. Seventy-six participants with enlarged prostates (between 70 mL and 100 mL) and with an IPSS greater than seven (IPSS = 0-7 mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic) were randomly assigned to receive either PVP with a GreenLight™ 80 watt KTP laser (n=39; mean age of 69.2 years) or TURP (n=37; mean age of 68.3 years). Peri-operative analysis revealed that operating room time was significantly greater in the PVP group (87 ± 18.3 min versus 51 ± 17.2 min); however, time to catheter removal (1.7 ± 0.8 days versus 3.9 ± 1.2 days) and length of hospital stay (2 ± 0.7 versus 4.8 ± 1.2 days) were significantly shorter in the PVP group. Functionally, TURP-treated patients performed significantly better than patients in the PVP group in terms of maximum urinary flow rate, post-void residual volume, IPSS, and erectile function scoring. Peri-operative and post-operative complications were variable, but significantly fewer patients in the PVP group required blood transfusions (zero versus three patients in the TURP group). Acute urinary retention early after catheter removal occurred in six patients in the PVP group and one in the TURP group. Seven patients in the PVP group required re-intervention because of insufficient healing, whereas no patients in the TURP group required re-intervention. The authors concluded that PVP using the GreenLight™ laser system for the management of larger prostates (greater than or equal to 70 mL) may not be recommended and should be reserved as an alternative to TURP when it is contraindicated. The authors also stated that since their study was the first RCT to compare PVP to TURP in larger prostates, additional similar studies but with larger numbers of patients are warranted. A comment on this RCT by Horasanli et al. appeared in a subsequent journal issue.¹¹ Malek disagreed with the description of ‘large volume prostate’ offered by Horasanli et al. and noted that the 17.9% reoperation rate for patients that were treated with PVP was “unprecedentedly high” and was presumably due to “poor vaporization technique”. Malek also remarked that the results from the RCT by Horasanli et al. contradicted two other published studies assessing PVP in similar-sized or larger prostates; indeed one of these studies was not cited by Horasanli et al.

Alivizatos et al. (2008)¹² conducted a RCT comparing the effectiveness and the safety of PVP using the GreenLight™ laser system to open prostatectomy (OP) for the surgical treatment of large prostatic adenomas. Patients (n=125) were randomly assigned to receive either PVP (n=65) or OP (n=60) and were assessed at one, three, six, and 12 months post-operatively. The
mean age of patients receiving PVP was 74 years and 67.5 years for OP. Peri-operative and early post-operative data were collected. Clinical end-points evaluated were IPSS and peak urinary flow rate. Patients receiving PVP had a shorter hospital stay than those undergoing OP (48 hours versus 144 hours, respectively) and a shorter time to catheter removal (24 hours versus 120 hours). The operation time for PVP was greater than that of OP (80 hours versus 50 hours). Both groups had significant improvements in functional outcomes. There was no difference in IPSS between groups across all time points evaluated. Patients in the OP group had higher IPSS-quality of life scores at six and 12 months post-operatively than patients in the PVP group. No differences in peak urinary flow rate and post-void residual volume was observed. Prostate volume was significantly lower in the OP group than in the PVP group at three months of follow-up and remained lower throughout the course of the study. The authors concluded that over a 12 month period, use of the 80-watt GreenLight™ laser to ablate larger prostates was an effective treatment; however, they did suggest that this procedure should be evaluated in additional larger RCTs.

Bouchier-Hayes et al. (2006) reported early results from their RCT comparing PVP using the GreenLight™ laser system to TURP. A total of 120 patients were to be included in the trial (at the time of publication, 95 patients had been randomized). In the present study, the authors reported on 76 patients all of whom have had at least six weeks of follow-up post-operatively. The authors noted that all 76 patients were evaluable at six weeks, 68 at three months, 57 at six months, and 44 at 12 months. Three patients dropped out after randomization, but were included in the statistical analysis. Evaluations of maximum flow rate, post-residual volume, and IPSS were made at one, three, six, and 12 months following treatment. Assessments of irrigation use, length of catheterization time, length of hospital stay, blood loss, cost, and operative time were also performed. The mean age in the TURP group was 66.23 years and 65.23 years in the PVP group. The mean prostate volume was greater in the PVP group (42.44 cc) versus the TURP group (33.22 cc), although this difference was not statistically significant. Outcome data on flow rate, IPSS, as well as quality of life scores, and “bother” score (this score is based on what the patient believes would be his ability to tolerate his current level of symptoms for the rest of his life) are reported; however, baseline scores were not reported. In addition, it is unclear from the publication which evaluation time point the outcome data reported represents or if in fact it is an average of all time points. Both groups had an increase in mean flow rate, decreased IPSS, and had equivalent improvements in post-void residual volume, quality of life scores, and bother scores. The mean length of catheterization time was shorter in PVP-treated patients (12.2 hours versus 44.5 hours in the TURP group). Similarly, the mean length of hospital stay for PVP-treated patients was shorter than patients receiving TURP (1.08 days versus 3.4 days, respectively). The authors also reported that the costs for the PVP group were AU$3,368 per case and AU$4,291.68 for each TURP case. Costs were 22% less for the PVP group.

The same lead author as above, published an update to their RCT in 2007. In this report, the authors stated that 120 patients are to be randomized to receive either PVP or TURP and stated that data will be reported on 87 patients; however, data are provided in the report tables for a total of 110 patients (n=50 TURP patients and n=60 for PVP patients). Although they had stated they would evaluate the patients at one, three, six and 12 months, they report data from 6 weeks (84 patients), three months (90), six months (72), and 12 months (59). There are inconsistencies with the data reported in the abstract and the results sections of the article, and therefore, only data from the tables in the results section are discussed. Similarly to their first reports, significant improvements in maximum urinary flow rate, IPSS, quality of life, and bother scores were observed in patients receiving either TURP or PVP. There was no significant difference between TURP and PVP for any of these outcomes. PVP-treated patients had a
significantly shorter time of catheterization, hospital stay, less blood loss, and cost-per case (which was reported to be identical to the previous report, 22% less for a PVP case).

**Controlled clinical trials**

A non-randomized two-centre study was conducted by Ruszat et al. (2008)\(^{15}\) to evaluate the clinical efficacy and the rate of complications of PVP using the 80-watt KTP GreenLight™ laser compared with TURP. The study evaluated a total of 396 patients (PVP, \(n=269\); TURP, \(n=127\)) with BPH. Follow-up time was 24 months. The mean age of patients in the PVP group was 72 ± 9.7 years and 68 ± 8.7 years in the TURP group. Patients in the PVP group were significantly older than patients in the TURP group and as such, some of the results were age-stratified. Results showed that the rate of complications including intraoperative bleeding, blood transfusions, perforation, and clot retention was significantly lower in PVP-treated patients. Length of hospital stay was significantly shorter in the PVP group for patients under 70 years (3.0 days versus 4.7 days for TURP patients) and for patients 70-80 years of age (4.0 days versus 5.0 days for TURP). TURP-treated patients (all age groups) showed increased improvement in peak urinary flow over PVP-treated patients. IPSS and post-void residual volumes between the PVP group and TURP group were not significantly different. Prostate volume was reduced by 63% in the TURP group and 44% after PVP treatment. Despite the increased age of patients receiving PVP, the authors concluded that PVP was advantageous in terms of peri-operative safety and provided similar functional outcomes as TURP. The authors also stated that a longer follow-up is required to determine the long-term efficacy of GreenLight™ PVP.

A non-randomized study by Tasci et al. (2008)\(^{16}\) compared PVP to TURP for the treatment of BPH. In their preliminary report, 81 patients with pre-operative prostate volumes between 70 mL and 150 mL received either PVP (\(n=40\)) or TURP (\(n=41\)). The mean age of patients in the PVP group was 71.9 ± 5.9 years and 70.1 ± 5.4 years in the TURP group. Evaluation of IPSS, quality of life, prostate volume, peak urinary flow rate, and post-void residual volume were made at one, three, six, 12, and 24 month follow-up time points. At 24 months, IPSS scores between PVP and TURP were not significantly different (3.7 versus 3.9), quality of life scores were identical (1.2), and no significant difference in maximum urinary flow rate was observed between groups (19.4 mL/sec versus 17.1 mL/sec). Patients treated with TURP had lower post-void residual volume than PVP (16.7 mL versus 19.0 mL). Operative time was significantly longer for PVP procedures than TURP (126.2 ± 17.4 min versus 77.9 ± 8.3 min); however catheterization time (27.9 ± 3.6 hours versus 74.0 ± 4.4 hours) and length of hospital stay (40.7 ± 8.5 hours versus 91.3 ± 7.4 hours) were both shorter in the PVP group. Three patients who received PVP and one patient who received TURP required re-operation. The authors concluded that both PVP and TURP were safe for the treatment of large prostates and that the two procedures have similar complication rates and functional outcomes. The authors also stated that PVP is advantageous over TURP because it requires a shorter hospital stay and has a shorter length of catheterization time. A follow-up study by the same investigators was published in the same year. Tugcu et al. (2008)\(^{17}\) reported on their non-randomized study of 210 patients receiving either PVP (\(n=112\)) or TURP (\(n=98\)). Assessments of operative time, hospitalization time, length of catheterization, IPSS, quality of life, maximum urinary flow rate, and post-void residual volume were reported. Mean operative time was higher in the PVP group than the TURP group (55.5 ± 21.8 min versus 46.0 ± 8.7 min); however length of catheterization and hospital stay were shorter in the PVP group. At the longest follow-up point (24 months) there were no significant differences between PVP and TURP groups, in terms of IPSS, quality of life, maximum urinary flow rate, and post-void residual volume. The authors came to the same conclusions regarding the efficacy of GreenLight™ PVP as in their preliminary report.
Bachmann *et al.* (2005) conducted a non-randomized two-centre study of 101 patients receiving either PVP (n=64) or TURP (n=37). The mean age of patients in the PVP group was 71.0 ± 9.3 years and 68.7 ± 7.9 years in the TURP group. Evaluation of IPSS, peak urinary flow rate, and post-void residual volume was made at six months. Operative time was shorter in the TURP group (49.4 ± 16.0 min versus 59.6 ± 24.4 min), whereas length of catheterization time was shorter in the PVP group (1.8 ± 1.8 days versus 3.0 ± 1.5 days). At six months, no differences between groups were observed in IPSS, peak urinary flow rate, and post-void residual volume. The authors concluded that PVP with the GreenLight™ laser system was safe and effective and early functional outcomes at six months following PVP or TURP treatment are comparable.

**Economic evaluations**

A review of cost-implementation of various treatments for BPH including PVP with 80-watt GreenLight™ laser by Alivizatos and Skolarikos (2007) suggested that preliminary cost studies on minimally invasive treatments for BPH favoured GreenLight™ laser over TURP. They found that PVP with GreenLight™ laser often could be performed as day-cases especially when small or mid-sized prostates are being treated, thereby reducing in-hospitals costs. The authors noted that additional long-term prospective studies comparing GreenLight™ laser to TURP are necessary to conclude on cost-effectiveness. Alivizatos and Skolarikos also stated that it will be difficult to determine the cost-effectiveness of PVP GreenLight™ laser because much depends on the reimbursement schemes in specific countries.

A report by Stovsky *et al.* (2007) estimated the costs of procedures for BPH including PVP with GreenLight™ PVP and TURP. The authors reported the 24-month total procedural costs for PVP to be US$3,589 and US$4,927 for TURP. An earlier report by Stovsky *et al.* (2006) developed a Markov model to calculate the expected cost per patient who received PVP after six months (US$3,020), 12 months (US$3,214), and 24 months (US$3,589) of follow-up and TURP after six months (US$4,030), 12 months (US$4,331), and 24 months (US$6,179) of follow-up.

A report by Agribas *et al.* (2005) conducted a study to compare the costs of available treatment technologies for BPH including PVP and TURP. The costs were calculated based on invoice costs occurred by patients under-going either treatment procedure. Costs per PVP patient were US$1,662 and US$902 per TURP patient.

**Limitations**

Several reports suggested that use of the 80-watt GreenLight™ laser for PVP is increasingly being used to treat BPH. Despite the widespread use, only recently have RCTs been conducted on this procedure. Follow-up duration was typically one year or less with the exception of one non-randomized study that had a follow-up duration of 24 months. Several recent systematic reviews were unable to assess fully the efficacy of the GreenLight™ laser due to the lack of available RCTs. In addition, because of the evolution of KTP laser systems, only a few studies assessed the most-commonly used 80-watt GreenLight™ system. Our search identified three RCTs that were performed and compared directly PVP with GreenLight™ laser to TURP. The reporting manner of one of the RCTs was difficult to interpret and made our analysis of their data challenging. Several of the studies were conducted by the same group of investigators. It was noted in several reports that this procedure had a ‘learning curve’ and caution should be taken when offering this service. It was also noted that PVP should be provided by a physician who has a level of comfort with this procedure to mitigate any potential risks.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Based on the available literature, the 80-watt GreenLight™ laser for PVP in the treatment of BPH has comparable functional outcomes as TURP. PVP may require a shorter hospital stay thereby decreasing costs associated with treatment. PVP also may require a shorter time of catheterization which could shorten hospital stay and decrease risk of urinary tract infections. In addition, PVP is associated with fewer complications than TURP. Our literature search identified only three RCTs comparing PVP with TURP. In 2005, the National Institute for Health and Clinical Excellence (NICE) in the UK deemed the evidence available at that time regarding GreenLight™ laser for PVP to be adequate to support its use; however, the guidance stated that clinicians offering this procedure should have specialized training with this technique. The lack of high quality evidence for the use of PVP for the treatment of BPH perhaps should be considered as should clinical expertise when deciding which treatment is most appropriate for patients. In addition, a recent 120-watt GreenLight HPS™ laser for PVP has become available. Limited information is available about this new model but suggests that laser PVP is under evolution and further trials are likely expected.

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