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Transurethral high-energy water vapour therapy for benign prostate hyperplasia

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Methods

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Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered temporary.

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Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Name of the technology / procedure: **Transurethral high-energy water vapour therapy for benign prostate hyperplasia**

Target population

The transurethral high-energy water vapour therapy is proposed to treat patients with benign prostate hyperplasia (BPH) [Rezum website].

Description of the procedure and technology

Transurethral resection of the prostate (TURP) is recognised as the gold standard surgical treatment for symptomatic BPH [Campos Pinheiro L, 2012]. Modern TURP is safe and efficient for relieving moderate to intense lower urinary tract symptoms (LUTS): mortality is very low (0.1%), 5- and 10-year reoperation rate is 5.8% and 6% respectively [Wasson JH, 2000], the IPSS (International Prostatic Symptoms Score) decreases by 70-50%, and uroflowmetry (Qmax) increases of 125% [Thomas AW, 2005]. However, up to 20% of patients submitted to TURP are not satisfied with their outcome [Mishriki SF, 2008] and complications and side effects may arise, like need of blood transfusion (2.9%), serious transurethral resection syndrome (1.4%), urinary retention (5.8%), urinary tract infection (3.6%), retrograde ejaculation (more than 75%) and sexual dysfunction with impotence (12%) [Campos Pinheiro L, 2012].
Trying to overcome the complications and side effects related to TURP, a plethora of minimally-invasive procedures have been developed in the last two decades to treat BPH by transurethral access, like the transurethral incision of the prostate (TUIP), the transurethral electrovaporisation (TUVP), the visual laser ablation (VLAP), the transurethral microwave therapy (TUMT), the transurethral needle ablation (TUNA), the holmium laser enucleation of the prostate (HoLEP), and the photoselective vaporisation of the prostate (PVP) [Lee SW, 2013].
Water vapour localised injections have been recently proposed to quickly treat BPH in outpatient or office-based setting [Dixon CM, 2012c]. The therapy uses sterile vapour to deliver thermal energy to the gland and damage the hyperplastic tissue. This HS report focuses on the systems able to provide transurethral high-energy water vapour therapy to BPH patients.

Clinical importance and burden of disease

Although several epidemiological studies have been conducted over the past 20 years, the prevalence of BPH remains difficult to determine. In the absence of a clinically standardised definition, epidemiological data of BPH in the literature are quite variable, because they are strongly influenced by the variables used to define the disease and by considerable heterogeneity in the sampling methods. Generally the variables considered include: prostate enlargement, the presence of LUTS, the reduction in urinary flow, urodynamic obstruction or hyperplasia diagnosed histologically. There is also a lack of homogeneity between studies in the way BPH is evaluated, clinically and through the method of administration of questionnaires to study

populations [De La Rosette J, 2006]. BPH is, however, a process closely related to aging [Chute CG, 1993] whose clinical manifestations are represented by symptoms referable to LUTS that negatively impact on the quality of life of patients [Donovan JL, 1997].
The prevalence of BPH ranges around values between 17% and 37%, depending on the age group. Data from USA are quite similar to data collected across Europe [AUA, 2010]. An analysis by age groups conducted in Italy in 2009 showed an increasing trend with increasing age, with a decrease in the over 85: 0.6% (35-44 years); 4.7 (45-54 years); 20.3 (55-64 years); 37.5 (65-74 years); 42.9 (75-84 years); and 37.5 (≥85 years) [SIMG, 2010]. A study of European mortality rate of BPH conducted on the WHO mortality database indicates that at the end of the nineties was 0.35/100,000 inhabitants [Levi F, 2003].
Treatment options have different levels of evidence and therefore different levels of recommendation. Medical management can be based on alpha-1-adrenergic antagonists, 5-alpha-reductase inhibitors, antimuscarinics, herbal therapies, phosphodiesterase-5 inhibitors in monotherapy or combination. Surgical options are several, ranging from open prostatectomy to less invasive approaches like TURP [AURO 2012].
Given the high prevalence, low mortality and low progression, BPH and LUTS represent a socio-economic problem as they strongly affect the quality of life of patients [Coyne KS, Wein AJ, 2009; Coyne KS, Kaplan SA, 2009] and impact on the health care system in a considerable way. In Italy, the economic impact of BPH is relevant and tends to increase with the aging of the population (the population of over 65 years has increased from four million in 2000 to about five and a half million in 2012) [ISTAT 2013].
If proved safe and effective, new minimally-invasive treatments, aimed to reduce procedure time, complications, and side effects associated to the current treatments of BPH, may lead to sensible gains in terms of patient's benefits and costs reduction.

Products, manufacturers, distributors and approval

We identified only one system intended to treat BPH by transurethral high-energy water vapour therapy: the Rezum system (manufactured by NxThera, Inc.). The Rezum system received the CE mark in 2013; the clinical use of the Rezum system in the USA is limited to investigational purposes, according to the FDA regulation [Rezum website].
The Rezum system is composed by a sterile water container, a vaporiser, a vapour delivery system and a display [Dixon C, 2013c]. During the procedure, water vapour is released, for a few seconds, directly into the hyperplastic tissue by a narrow sheath similar to a rigid cystoscope, inserted transurethrally. The thermal energy released to the tissues denatures the cell membranes, causing cell death, collapse of the vasculature and denervation of the alpha adrenergic nerves and receptors in the treatment zone. Over time, the denatured tissue should be absorbed by the body's immune system response, determining the reduction in hyperplastic tissue volume and allowing the urethra to expand and restore urine flow [Rezum website]. The complete procedure takes a few minutes.

Product name [Manufacturer]	Distributor	CE Mark	RDM	FDA
Rezūm System [NxThera, Inc.]	None for Italy	☑	☐	☐

Setting

The transurethral high-energy water vapour therapy by the Rezum system can be provided in an outpatient or in-hospital setting [Rezum website].

☐ Home	☑ Hospital	☑ Outpatient
☐ Accident and Emergency	☑ Other: Day-surgery	

Roll out in Italy

According to the manufacturer's press releases, targeted, early commercialisation of the Rezum system will start in 2014 in selected European countries [Rezum website]. No details about the launch on the Italian market are available.

☑ Pre-marketing	☐ On the market for 1-6 months	☐ On the market for 7-12 months
☐ On the market for more than 12 months	☐ Not identified	

Comparators

Transurethral high-energy water vapour therapy is proposed to treat patients with BPH thus the main comparator is the TURP, currently considered the gold standard treatment [Lee SW, 2013].
Given the variability in the evidence base, other minimally-invasive surgical approaches, including TUVP, TUIP, VLAP, TUMT, TUNA, HoLEP, and PVP, as well as *Botulinum* toxin injections and urethral stenting, should be considered as "competitors" of the technology and not proper comparators.

Effectiveness and safety

We carried out searches on the EuroScan database (12th November 2013) looking for reports on the transurethral high-energy water vapour therapy for BPH. The search gave no results.
We searched the major databases, MEDLINE (29th October 2013), Embase (29th October 2013), and the Cochrane Library (29th October 2013), looking for studies, published from 2008, in Italian or English, reporting on effectiveness and safety of transurethral high-energy water vapour therapy for BPH in all kinds of patients (humans). Among the resulting 19 citations we selected 6 citations for full-text analysis. All the 6 citations were conference abstracts (Table 1); no full-text studies were identified.
One abstract [Larson TR, 2010] reports the proof-of-concept of the Rezum treatment on a group of patients that received the vapour injections prior to prostatectomy or in an office procedure. Reductions in the IPSS were reported at one week and at one month of follow-up.

The remaining five abstracts were published between 2012 and 2013 by the same group of authors [Dixon CM, 2012a; Dixon CM, 2012b; Dixon CM, 2012c; Dixon CM, 2013a; Dixon CM, 2013b] and are funded by the manufacturer RxThera. The three abstracts published in 2012 [Dixon CM, 2012a; Dixon CM, 2012b; Dixon CM, 2012c] were mainly aimed at assessing the patient tolerability and reporting treatment effects. The two abstracts published in 2013 [Dixon CM, 2013a; Dixon CM, 2013b] refer to the same cohort of 30 patients and report improvements in IPSS, quality of life (QOL); maximal urine flow rate (Qmax) and postvoid residual urine measurement (PVR) at up to 6 months of follow-up.
We searched in the clinicaltrial.gov database (12th November 2013) using "rezum" and "transurethral high-energy water vapour therapy" as combination of keywords and identified one registered study (NCT01912339). The study is currently recruiting participants to evaluate the safety and efficacy of the Rezum system and assess its effect on urinary symptoms secondary to BPH. This study is a US multicenter, prospective, controlled, randomised single-blinded clinical trial started in July 2013 and aimed to enroll 195 subjects (males, 50 years and older). Subjects will be first randomised in a 2:1 proportion in favor of the Treatment Arm (Rezum). Subjects in the Control arm (rigid cystoscopy) will be allowed to crossover to have the Rezum treatment after the 3-month follow-up examination. Completion is expected in June 2019.

Potential benefits to patients

The Rezum system aims at reducing procedure time, procedural discomfort, and post-procedure complications associated with medications and other treatments [Rezum website].

☐ Mortality reduction or increased survival	☑ Reduction of the morbidity	☑ Improved quality of life (patient/users)
☐ Improved patient monitoring	☐ Other:	☐ Not identified

Cost of the technology / procedure

As the manufacturer NxThera decided not to provide any further information about the technology over what is already reported on the website and by press release, no considerations about the costs can be made. The transurethral high-energy water vapour therapy delivered by the Rezum system is meant as a substitute of the standard surgical treatment (TURP), so any cost analysis should consider the new costs versus the current ones.

☐ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☐ Increased costs due to the required investments
☐ New costs	☐ Other:	☑ Not identified

Potential structural and organisational impact

Structural impact

There are no relevant issues from a structural point of view and Rezum system's dimensions are compatible with general operational activities.

☐ Increase in requirement of instruments	☑ Always be used	☐ Can be used only under specific circumstances
☐ Decrease in requirement of instruments	☐ Other:	☐ Not identified

Organisational impact

Using data and information available, no considerations can be made about the organisational aspects of the Rezum therapy in term of skills required, training, learning curve of the operators.

☐ Increase in the number of procedures	☐ Re-organisation required	☐ Training required for users
☐ Reduction in the number of procedures	☐ Other:	☑ Not identified

Conclusions

Transurethral high-energy water vapour therapy for BPH is still in its infancy. Potentially, the treatment can be beneficial (in terms of IPSS, QOL, Qmax, and PVR) and no treatment-related severe adverse events have been reported. However, few patients have been treated worldwide and the only data available (non-comparative) come from conference abstracts published by the same group of authors. No final statements can be made in this situation and the introduction of the technology in a clinical context should be managed only within evidence-generation frameworks.

Future prospects

Data collection for the only clinical trial on the Rezum system (NCT01912339) will be completed on December 2018. NxThera announced the application of the Rezum system platform in a variety of other endourology conditions, including prostate cancer and kidney cancer [Rezum website]. In the meanwhile, new data about other minimally-invasive transurethral procedures will be available and new minimally-invasive procedures will be proposed for BPH [Lusuardi L, 2013]. The technology could be considered for a future re-assessment.

Table 1: Description of the abstracts reporting transurethral high-energy water vapour therapy for BPH.

Ref. [study design]	Description of the study	Number of patients	Reported results (by the study authors)
Larson, 2010 [Case series]	Two groups of patients received the vapour injections prior to prostatectomy (n=9) or in an office procedure (n=9). The treatment effect was assessed by pathological examination in the prostatectomy group, and by Gadolinium-enhanced MRI in the others.	18	- The Rezum procedure was well tolerated by all the patients; - Reductions in the IPSS were observed at 1 week and at 1 month of follow-up.
Dixon, 2012a [Case series]	A group of patients with clinical BPH was treated using the Rezum system. Gadolinium-enhanced MRI's were conducted at 1 week to assess areas of cell death. Early post-treatment clinical parameters were assessed.	18	- All patients tolerated the procedure with minimal discomfort; - Mean prostate volume* was 44 cc (range 24–108 cc); - MRI confirmed no injury outside of the prostate.
Dixon, 2012b [Case series]	Three men undergoing open prostatectomy for clinical BPH were concomitantly treated using the Rezum system. After extirpation, the adenoma was subjected to pathological examination.	3	- No gross thermal injuries on the periphery of the prostate were observed intraoperatively; - Histology confirmed the cell death in the treated area.
Dixon, 2012c [Single case]	One patient with clinical BPH was treated using the Rezum system. Endoscopic view, generator screen and transrectal ultrasonography were recorded simultaneously. MRI was performed 1 week and 1 month after treatment.	1	- MRI confirmed the treatment effect in the transition zone.
Dixon, 2013a [Case series]	A group of men was treated using the Rezum system according two different protocols. Gadolinium-enhanced MRI's were conducted at 1 week, 1, 3 and 6 months to assess the location of thermal lesions and perform volume measurements for total prostate, transition zone and thermal lesions.	30	- Mean thermal lesion volume at 1 week (n = 30) was 10 cc (range 7–35 cc) and decreased by 93% at 3 months (n = 28) and 97% at 6 months (n = 28). - Mean total prostate volume at 1 week (n = 30) was 75 cc (range 29–169 cc) and decreased by 26% at 3 months (n = 28) and 33% at 6 months (n = 28).
Dixon, 2013b [Case series]	A group of men was treated using the Rezum system according two different protocols. Standard outcome measures including, IPSS, QOL, Qmax and PVR were used. Safety was assessed by serial MRI's with 3D rendering and standard adverse event reporting.	30	- Mean baseline IPSS (n = 30) improved from 23 (range 15–35) to: 19 at one week (n = 30), 13 at one month (n = 30), 8.5 at three months (n = 24), and 8.5 at six months (n = 24); - Mean baseline QOL (n = 30) improved from 4.3 to: 2.9, at one week (n = 30), 2.3, at one month (n = 30), 1.4 at three months (n = 24), and 1.5 at six months (n = 24). - Mean baseline Qmax (n = 30) improved from 8.4 cc/sec to: 10 cc/sec at one month (n = 29), 12.8 cc/sec at three months (n = 26), 12.1 cc/sec at six months (n = 24); - Mean baseline PVR (n = 28) remained stable at 1 week (72 cc) and improved to 45 cc at six months (n = 24); - Transient retention, mild dysuria and haematuria were reported. - No treatment-related severe adverse events occurred.

Key: Ref. = reference; MRI = magnetic resonance imaging; IPSS = international prostatic symptoms score; QOL = quality of life; Qmax = maximal flow rate; PVR = postvoid residual.

* Mean prostate volume measured by transrectal ultrasound (TRUS).

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Evidence searches

Searches of the databases were carried out on 29th October 2013 using the following keywords to indicate:

- ***the technology of interest:*** *water vapour; steam; water vaporization.*
- ***the pathology of reference:*** *benign prostatic hyperplasia.*

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Glossary

BPH: Benign prostatic hyperplasia.

CRD: Centre for Reviews and Dissemination.

DRG: Diagnosis-Related Groups.

FDA: Food and Drug Administration.

HoLEP: Holmium laser enucleation of the prostate.

IPSS: International Prostatic Symptoms Score.

ISS: Istituto Superiore di Sanità (Italian National Health Institute).

ISTAT: Italian National Institute of Statistics.

LUTS: Lower urinary tract symptoms.

PVP: Photoselective vaporisation of the prostate.

PVR: Postvoid residual urine measurement.

Qmax: Maximal urine flow rate (uroflowmetry).

QOL: Quality of life index.

RDM: Medical device Repertory (http://www.salute.gov.it/dispositivi/paginainternasf.jsp?id=499&menu=repertorio).

TUIP: Transurethral incision of the prostate.

TUMT: Transurethral microwave therapy.

TUNA: Transurethral needle ablation.

TURP: Transurethral resection of the prostate.

TUVP: Transurethral electrovaporisation of the prostate.

VLAP: Visual laser ablation of the prostate.

WHO: World Health Organization.