Rapid assessment van enkele nieuwe behandelingen voor prostaatkanker en goedaardige prostaathypertrofie

KCE reports 89A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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VOORWOORD

Een groot deel van de mannelijke bevolking krijgt te maken met een prostaataandoening. Enerzijds is er prostaatkanker, de derde meest voorkomende doodsoorzaak door kanker, na long- en colorectale kanker. Anderzijds is er goedaardige prostaatvergroting. Al is deze laatste aandoening niet levensbedreigend, ze leidt wel tot grote morbiditeit. Zowat de helft van de mannen ouder dan 60 jaar heeft te maken met een goedaardige prostaatvergroting en ongeveer de helft van deze mannen ondervinden hinder van deze vergroting. Naarmate de leeftijd stijgt, neemt de kans op prostaatvergroting toe en stijgt ook de kans op symptomen.

In 2006 bracht het KCE een rapport uit over PSA testing voor prostaatkankerscreening. In dit rapport gaat onze aandacht opnieuw uit naar dit klinisch domein. Ditmaal treedt niet de diagnose, maar wel de behandeling op de voorgrond. Zoals men kan lezen in dit rapport werd het KCE uitgenodigd zich te buigen over enkele nieuwe operatietechnieken die meer en meer toegepast worden zowel voor prostaatkanker als voor goedaardige prostaathyperplasie.

De overheidsinstanties wensten te weten of deze nieuwe technieken voldoende veilig zijn voor de patiënt, of ze ten minste even doeltreffend zijn als de traditionele technieken en of de kostprijs in verhouding staat met de eventuele voordelen die deze technieken met zich meebrengen.

Deze vragen zijn inderdaad essentieel om zich uit te spreken over een eventuele terugbetaling van deze nieuwe technieken. Het KCE tracht de gestelde vragen zo goed mogelijk te verhelderen via een HTA (Health Technology Assessment) aanpak die reeds in vele voorgaande rapporten werd toegepast. We hopen dat deze studie zal bijdragen tot de besluitvorming in dit domein.

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Samenvatting

DEEL I: HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) BEHANDELING VOOR PROSTAATKANKER

INLEIDING

Prostaatkanker is de meest voorkomende kanker bij mannen. Volgens Belgische cijfers is hij verantwoordelijk voor ongeveer 29% van alle nieuwe kankerdiagnoses bij mannen. Jaarlijks zijn dit ongeveer 9 600 gevallen van prostaatkanker. Ondanks dat het de meest frequent gediagnosticeerde kanker bij mannen is, is hij niet de meest levensbedreigende. Als doodsoorzaak staat hij op de derde plaats van de kankers en bovendien treedt de dood in dat geval ook vrij laat op, meestal na de leeftijd van 75 jaar.

Voor gelokaliseerde prostaattumoren met een gunstige of intermediaire prognose is de optimale behandeling nog niet gekend. Radicale behandeling wordt bij voorkeur gebruikt bij patiënten met een levensverwachting van meer dan tien jaar (een leeftijdsbeperking van 70 jaar wordt voorgesteld). De standaard radicale behandelingen van gelokaliseerde prostaatkanker zijn radicale prostatectomie (verwijdering van de prostaat en vesiculae seminalis) enerzijds en radiotherapie (uitwendig of inwendig) anderzijds. Vooral omdat er geen vergelijkende studies werden uitgevoerd, zijn er geen definitieve argumenten waarom men de ene behandeling boven de andere zou verkiezen. Ondanks uitstekende overlevingspercentages worden zowel prostatectomie als radiotherapie geassocieerd met een heleboel complicaties, zoals bloedverlies met complicaties die gepaard gaan met de transfusie, erectiele disfunctie, incontinentie en een verstoorde werking van de darmen. Omwille van deze complicaties werden alternatieve behandelingen ontwikkeld, waaronder high-intensity focused ultrasound (HIFU) en cryotherapie. Cryotherapie wordt niet gebruikt in België.

HIFU-therapie, die in het midden van de jaren 90 werd ontwikkeld, wordt transrectaal toegediend en vernietigt de diepgelegen prostaattumorcellen door het weefsel via hoogfrequente geluidsgolven op te warmen terwijl de nabijgelegen gezonde weefsels gespaard blijven. Vaak wordt meer dan een sessie uitgevoerd. De therapie gebeurt zowel in ambulante als in gehospitaliseerde setting. HIFU wordt meestal voorafgegaan door een transurethrale resectie van de prostaat (TURP).

INTERNATIONALE MARKTGOEDKEURING VAN HIFU

Op dit moment zijn twee apparaten op de Europese markt beschikbaar met CE-keurmerk. Ablatherm is het meest gebruikte apparaat in Europa. Voor beide apparaten, Ablatherm en Sonablate, is een Premarket Approval (PMA) procedure lopende bij het FDA (Food and Drug Administration). Om deze PMA te verkrijgen, is voor beide apparaten een Fase III klinische studie gestart voor de behandeling van laagrisico, gelokaliseerde prostaatkanker, in vergelijking met cryotherapie en brachytherapie.

KLINISCHE DOELTREFFENDHEID VAN HIFU

Alle tot dusver gepubliceerde studies over HIFU-behandeling voor gelokaliseerde prostaatkanker (T1-T2 NxM0) zijn patiëntenseries ("case series"), die vatbaar zijn voor selectie-vertekening en die slechts surrogate eindpunten meten gedurende een korte follow-up periode. Via een substantiële daling in serum PSA (prostate specific antigen) enerzijds en negatieve biopsieën anderzijds, toonden enkele studies aan dat HIFU een impact heeft op de ontwikkeling van prostaatkanker. Deze studies hadden een relatief korte follow-up periode van minder dan 5 jaar en er werden ook verschillende definities voor biochemische ziektevrije overleving (PSA) gebruikt. Langere follow-up studies, die HIFU vergelijken met de standaardbehandelingen, blijven cruciaal om te concluderen of HIFU een genezing op lange termijn voor de kanker biedt en of het een impact heeft op het specifieke overlijdenspercentage.

HIFU wordt ook gebruikt voor een bewezen lokaal recidive van prostaatkanker na faling van uitwendige bestraling of brachytherapie. Aangezien er over dit specifieke gebruik maar weinig studies zijn en aangezien de klinische situatie van de patiënten bovendien erg variabel is, kunnen geen conclusies worden getrokken over de klinische doeltreffendheid van HIFU in deze specifieke patiëntenpopulatie.

ECONOMISCHE EVALUATIE VAN HIFU

In een Franse kostenstudie werd berekend dat de volledige behandeling (inclusief hospitalisatie) met Ablatherm meer kost dan externe radiotherapie, maar minder dan radicale prostatectomie en brachytherapie.

Aangezien er geen bewijs van een voldoende kwaliteit is aangaande de voordelen (maar ook niet aangaande de nadelen) van HIFU-behandeling voor prostaatkanker, kunnen geen conclusies worden getrokken over de kosten-effectiviteit van de behandeling.

BELGISCHE SITUATIE

RIZIV data tonen aan dat er jaarlijks ongeveer 3 500 radicale prostatectomieën voor prostaatkanker zijn, waaronder 2200 klassieke en 1 300 endoscopische. Data tonen ook dat er jaarlijks ongeveer 770 prostaat brachytherapieën zijn. Voor externe radiotherapie en "watchful waiting" en "active surveillance" zijn er geen data beschikbaar.

Momenteel wordt de HIFU-behandeling voor prostaatkanker in 4 Belgische centra aangeboden. In totaal ondergingen meer dan 730 patiënten (waaronder ongeveer 150 buitenlandse) deze nieuwe behandeling, dit vanaf eind 2000 tot midden 2008. Wanneer we de buitenlandse patiënten buiten beschouwing laten, is dit ongeveer 0,8% van alle nieuwe prostaatkankerpatiënten in die periode. De kosten van de behandeling worden momenteel gedeeltelijk gedragen door de patiënt (zijn privéverzekering), het ziekenhuis en het RIZIV. Het bedrag dat de patiënt uit eigen zak betaalt varieert van ziekenhuis tot ziekenhuis (van € 0 tot € 3 000).

CONCLUSIE EN BELEIDSAANBEVELINGEN

- Ondanks het feit dat de optimale behandeling van gelokaliseerde laagrisico prostaatkanker nog niet gekend is, werd de primaire tumorbehandeling ervan grotendeels beschreven in evidence-based richtlijnen. De richtlijnen van NICE zijn duidelijk: "Bij mannen met een gelokaliseerde laagrisico prostaatkanker mag niet routinematig een radicale therapie worden voorgesteld. Rekening houdend met hun levensverwachting en persoonlijke voorkeur, dienen de opties "oplettend afwachten" ("watchful waiting") of "actief toezicht" ("active surveillance") te worden voorgesteld. […] Voor mannen met een gemiddelde risicostatus van de ziekte dient ook "actief toezicht" als optie te worden overwogen." (vertaald citaat)
- Voor de behandeling met HIFU is er echter op dit moment nog geen bewijs van voldoende kwaliteit. Alle gepubliceerde studies zijn patiëntenseries. De technologie werd ook nog niet voor klinisch gebruik goedgekeurd door de FDA in de Verenigde Staten. Op basis van deze elementen kan terugbetaling van deze therapie in België voor primaire tumorbehandeling nog niet worden aanbevolen.
- Aangezien slechts weinig studies gepubliceerd zijn over HIFU als secundaire therapie na faling van radiotherapie, is het onmogelijk om wetenschappelijke conclusies te trekken over dit specifieke gebruik. Voor deze kleine patiëntengroep is hormoontherapie echter vaak het enige alternatief ten aanzien van HIFU. Gezien de nevenwerkingen en de hoge kostprijs van hormoontherapie kan een terugbetaling van HIFU voor deze zeldzame gevallen, na goedkeuring van de ziekenfondsen en in het kader van studies, worden aanbevolen.
- Zodra meer en betere gegevens over de doeltreffendheid van HIFU beschikbaar zijn, kunnen deze aanbevelingen worden herzien.

DEEL II: PHOTOSELECTIVE VAPORIZATION OF THE PROSTATE (PVP) EN HOLMIUM LASER VOOR GOEDAARDIGE PROSTAATHYPERTROFIE

INLEIDING

Benigne prostaathypertrofie (BPH) is een goedaardige vergroting van de prostaat waaraan ongeveer 50% van de mannen boven 60 jaar lijdt. De prevalentie van hinderlijke symptomen die gepaard gaan met BPH neemt toe met de leeftijd. De symptomen worden onderverdeeld in opslag- (irritatieve) symptomen enerzijds en ledigings- (obstructieve) symptomen anderzijds. Obstructieve symptomen omvatten onderbreking, zwakke straal en onvolledige lediging. Bij irritatieve symptomen gaat het om verhoogde frequentie, nachtelijk urineren en dysurie (vermindering van urineproductie). Irritatieve symptomen hebben meestal te maken met de toenemende instabiliteit van de blaaswand die verdikt is door musculaire hypertrofie. Bij een ongecompliceerde BPH, zonder Lower Urinary Tract Symptoms (LUTS) (ook wel plasproblemen genoemd), is geen behandeling vereist. In andere gevallen zijn er een aantal behandelingsopties. Naast een operatieve behandeling, kan overwogen worden om oplettend af te wachten ("watchful waiting") of om een medicamenteuze behandeling te starten. Sommige geneesmiddelen verminderen het prostaatvolume en het risico van urineretentie en dus ook de nood aan een chirurgische ingreep. Het is belangrijk dat de patiënt participeert in de therapeutische beslissing. Een patiënt kan de meest effectieve therapie verkiezen, maar kan ook de voorkeur geven aan een minder effectieve therapie indien die minder risico's en/of kosten met zich meebrengt.

Sinds de jaren 1940 is TURP (transurethrale resectie van de prostaat) de meest effectieve chirurgische behandeling voor BPH. Open prostatectomie blijft een gepaste behandelingsoptie voor patiënten met een grote prostaat of met bijkomende blaaspathologie. Ondanks dat TURP een zeer doeltreffende behandeling is, kampt ze ook met enkele nadelen. De behandeling heeft een relatief hoog morbiditeitscijfer en een mortaliteitspercentage van 0.2 tot 2.5 % (0.2% in België). In de voorbije decennia ontstonden een reeks minimaal invasieve alternatieven voor de gouden standaard TURP. Van de nieuwe lasertechnieken voor operatieve behandeling van BPH, worden PVP (met de kalium-titanyl-fosfaat (KTP)-laser) en holmium lasers meer en meer gebruikt door de internationale urologische gemeenschap.

INTERNATIONALE MARKTGOEDKEURING VAN PVP EN HOLMIUM LASER

De GreenLight PVP en twee holmium lasers (Trimedyne 80 watt holmium laser en Lumenis (Coherent) 60-100 watt) kregen 510(k)-goedkeuring van de FDA voor de behandeling van BPH. De procedure voor deze 510(k)-goedkeuring (of "premarket nofitication") omvat het aantonen van de substantiële equivalentie aan een apparaat dat reeds op de markt is. Deze procedure is over het algemeen minder strikt dan de premarket approval (PMA). Er werden geen studies voor BPH geïdentificeerd die deze 510(k)-procedures ondersteunen.

In Europa kregen de PVP en holmium lasers het CE-keurmerk.

KLINISCHE DOELTREFFENDHEID VAN PVP

In de gepubliceerde (R)CT's is het aantal behandelde patiënten relatief klein (150 patiënten) en de follow-up periode erg kort (1 jaar). Deze studies wijzen er op dat PVP kan leiden tot minder bloedverlies in vergelijking met TURP. Er is geen significant verschil in seksueel functioneren na PVP of TURP, maar de studies zijn nog te kort om conclusies te trekken. Bij PVP kan de duur van de katheterisatie en de hospitalisatie aanzienlijk korter zijn, maar deze resultaten moeten ook door grotere en geblindeerde studies worden bevestigd.

Wanneer we de niet-gecontroleerde observationele studies bekijken, zijn er een aantal die een langere follow-up periode hebben (tot 5 jaar), maar de patiëntenpopulatie is te klein voor betrouwbaar bewijs.

Om de incidentie van bijwerkingen op lange termijn correct te kunnen evalueren, zijn gecontroleerde studies op langere termijn noodzakelijk.

Er is dus slechts beperkt bewijs over de veiligheid en doeltreffendheid van PVP.

KLINISCHE DOELTREFFENDHEID VAN HOLMIUM LASER

Voor de holmium laser enucleatie van de prostaat (HoLEP) Er is slechts beperkt bewijs over de veiligheid en doeltreffendheid. Het aantal patiënten dat opgenomen is in gerandomiseerde studies is klein (300 patiënten) en de follow-up periode is kort (2 jaar). Eén studie toonde aanzienlijk minder bloedverlies onmiddellijk na de chirurgische ingreep bij HoLEP dan bij TURP. De studies tonen geen significant verschil in seksueel functioneren tussen HoLEP en TURP, maar de studies zijn nog te kort om conclusies te trekken.

ECONOMISCHE EVALUATIE VAN PVP EN HOLMIUM LASER

Kleine studies op korte termijn wijzen er op dat PVP en HoLEP verschillende economische voordelen kunnen bieden zoals een kortere hospitalisatie en een kortere duur van katheterisatie, in vergelijking met de standaard behandeling. Er zijn echter nog geen follow-up gegevens op langere termijn beschikbaar uit gerandomiseerde studies en daarom kan nog niet worden geconcludeerd dat deze nieuwe technieken ook kostenbesparend zullen zijn op lange termijn. Door het ontbreken van langetermijn RCT's, is er geen goede documentatie beschikbaar over therapeutische falingen. Omdat deze falingen eventueel kunnen leiden tot aanzienlijke gezondheidsuitgaven, kan nog geen betrouwbare conclusie worden gemaakt over de kosten-effectiviteit van deze nieuwe technologieën in vergelijking met de standaard behandeling.

BELGISCHE SITUATIE

In 2006 werden meer dan 10 000 klassieke TURP's en meer dan 1 500 open prostatectomieën uitgevoerd in België. In de 116 ziekenhuizen die de procedure aanboden, werden gemiddeld 90 TURP's en 16 open prostatectomieën uitgevoerd. In de periode van 1995 tot 2006 daalde het aantal TURP's met 9%. In dezelfde periode daalde het aantal open prostatectomieën voor BPH met 23%.

Vijf ziekenhuizen bieden momenteel PVP-therapie aan in klinische routine. Een groter aantal ziekenhuizen heeft PVP in test case geëvalueerd, maar hebben het gebruik ervan niet verdergezet. Geschat wordt dat in totaal ondertussen rond 300 PVP-procedures werden uitgevoerd (met inbegrip van de testen) in de periode 2004 tot midden 2008. Voor deze nieuwe procedure factureren de ziekenhuizen meestal een klassieke TURP aan het RIZIV. Daarenboven betaalt de patiënt (of zijn privéverzekering) meestal de prijs van de laser fiber uit eigen zak (ongeveer € 1 500).

Holmium laser behandeling wordt momenteel niet aangeboden voor BPH in België.

ORGANISATORISCHE KWESTIES

Naast het feit dat meestal goede resultaten worden geboekt met de standaard TURP-procedure, heeft TURP ook het voordeel dat het aan de universiteiten wordt aangeleerd en dat het traditioneel wijdverbreid is binnen de urologische gemeenschap. Naast het nadeel van het ontbreken van langetermijnresultaten, hebben de nieuwe onderzochte technieken ook het nadeel van de investeringskosten en het feit dat de urologen nog steeds een heel leerproces moeten doormaken vooraleer zij de procedure op een veilige en efficiënte manier kunnen uitvoeren. Beide nieuwe technieken hebben een aanzienlijke leercurve, die wordt geschat op 15 tot 30 procedures.

CONCLUSIE EN BELEIDSAANBEVELINGEN

- Gezien de onzekerheden over de doeltreffendheid en kostenbesparing van de nieuwe therapieën moet TURP op dit moment de standaard behandeling blijven. Gezien de beperkte bewijzen die de technieken tot dusver ondersteunen, is het gerechtvaardigd een beslissing over de terugbetaling uit te stellen totdat meer gegevens beschikbaar zijn.
- Verder onderzoek is aangewezen om de onzekerheid over de doeltreffendheid en kosten van PVP en holmium in vergelijking met standaard behandeling te reduceren. Zowel klinische als kostengegevens dienen te worden geregistreerd. De globale evaluatieperiode dient minimum 5 jaar te zijn om het percentage heringrepen voor de verschillende technieken te beoordelen. Op basis van deze gegevens zou in de toekomst een beter gefundeerde beslissing kunnen worden genomen over eventuele terugbetaling van PVP en/of holmium laser behandeling.
- Gezien de leercurve en het beperkte bewijs van veiligheid en doeltreffendheid, moet de patiënt duidelijk geïnformeerd worden over de risico's en onzekerheden van de nieuwe behandelingen indien deze worden overwogen.
- Zodra meer en betere gegevens over de doeltreffendheid van de technologieën beschikbaar zijn, kunnen deze aanbevelingen worden herzien.

Scientific Summary

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LIST OF ABBREVIATIONS

AUA	American urological association
BDFS	Biochemical disease-free survival
BOO	Bladder outlet obstruction
BPH	Benign prostate hypertrophy/hyperplasia
CPG	Clinical practice guideline
HIFU	High intensity focused ultrasound
IDE	Investigational device exemption
HoLAP	Holmium laser ablation of the prostate
HoLEP	Holmium laser enucleation of the prostate
HoLRP	Holmium laser resection of the prostate
KTP	Potassium titanyl phosphate
LUTS	Lower urinary tract symptoms
MeSH	Medical subject heading
NIHDI	National institute for health and disability Insurance (RIZIV/INAMI)
OP	Open prostatectomy
PSA	Prostate specific antigen
PVP	Photoselective vaporisation of the prostate
QALYs	Quality-adjusted life years
TUIP	Transurethral incision of the prostate
TUNA	Transurethral needle ablation
TURP	Transurethral resection of Prostate
IPSS	International prostate symptom score

GLOSSARY

Active surveillance	Active surveillance is a treatment option for early localised prostate cancer in which the cancer is closely followed to determine its biological aggressiveness, based on PSA testing, digital rectal examination (DRE) and repeat biopsy. If significant disease progression occurs, there is a possibility of offering curative treatment.
Benign prostatic hyperplasia/hypertrophy (BPH)	Non-cancerous enlargement of the prostate over time
Brachytherapy	Internal radiotherapy
Gleason score	A system of grading prostate cancer tissue based on how it looks under a microscope. Gleason scores range from 2 to 10 and indicate how likely it is that a tumor will spread. A low Gleason score means the cancer tissue is similar to normal prostate tissue and the tumor is less likely to spread; a high Gleason score means the cancer tissue is very different from normal and the tumor is more likely to spread.
Lower Urinary Tract Symptoms (LUTS)	Based on IPSS. Three categories: – no or mild LUTS: IPSS 0-7 – moderate LUTS: IPSS 8-19 – severe LUTS: IPSS >19
Open prostatectomy	The removal of some (or all) of the prostate as surgical treatment for BPH. This procedure is used for patients with concomitant bladder pathology or with large prostate (80 to 100 ml).
Prostate Specific Antigen (PSA)	A protein produced by the prostate gland which tends to be higher in men with prostate cancer
Radical prostatectomy	The removal of all of the prostate and seminal vesicles as surgical treatment for prostate cancer
TNM classification	T - Primary Tumour T1, T2, T3, T4. Increasing size and/or local extent of the primary tumour N - Regional Lymph Nodes N0. No regional lymph node metastasis N1. Regional lymph node metastasis M - Distant Metastasis M0. No distant metastasis M1. Distant metastasis
Trans-Urethral Resection of the Prostate (TURP)	Procedure in which a thin tube-like telescope is passed up along the urethra to remove pieces of the enlarged prostate gland as standard surgical treatment for BPH.
Urethra	The tube leading from the bladder through which urine passes to the outside of the body
Urinary incontinence	Inability to hold the urine
Urinary retention	Inability to urinate or empty a full bladder
Urinary tract infection	Infection of the urine in the bladder

Watchful waiting	In the case of prostate cancer, watchful waiting is an alternative to radical treatments, either for older men, where the cancer may grow so slowly that it may not affect the person's quality of life, or for those whose health may not allow them to undergo radiotherapy or surgery. It involves regular tests, once or twice a year for PSA and DRE (digital rectal examination). More active treatments, such as hormone therapy, can then be considered depending on a rise in PSA levels. The difference with active surveillance is that with watchful waiting, the treatment, when it happens, is intended to *control* the cancer, whereas with active surveillance, treatment will still be intended to be *curative*. In the case of BPH, watchful waiting means that medical or surgical treatment is deferred. It involves regular examination and monitoring of the men's condition to see if the symptoms are improving or getting worse.

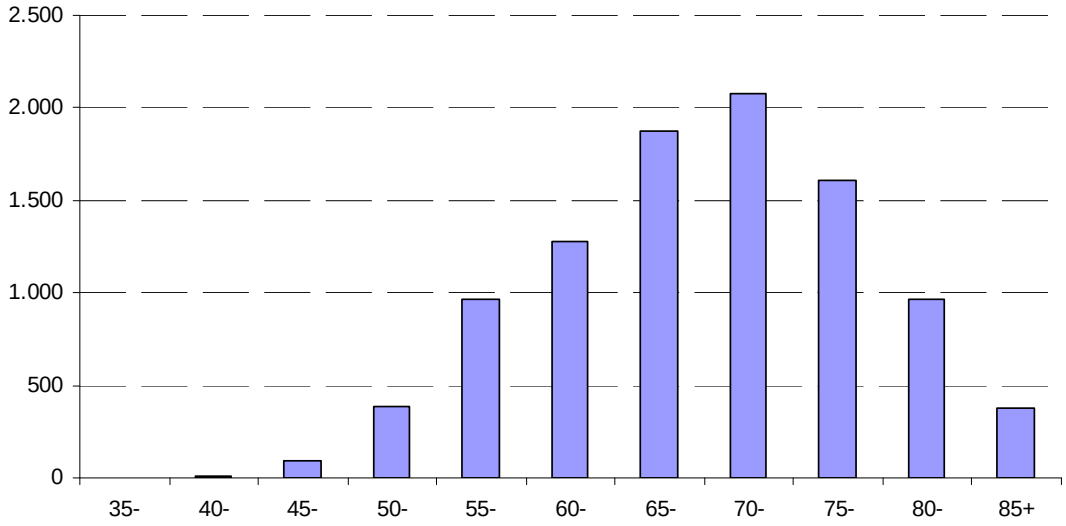
1 RAPID ASSESSMENT OF HIFU FOR PROSTATE CANCER

1.1 INTRODUCTION

Epidemiology of prostate cancer

Prostate cancer is the most common cancer in men. In 2004, it accounted for 29% of all new male diagnoses of cancer in Belgium. Prostate cancer risk is strongly related to age. Very few cases were registered in men under 50 years (1%). Around 52% of cases occurred in men over 70 years of age. Figure 1 shows the number of cases in 2004 by age of diagnosis as reported by the National Cancer Registry. The total annual incidence in Belgium was 9 628 cases.

Figure 1: Incidence of invasive prostate tumours per age group in 2004 in Belgium



Source: based on data from the National Cancer Registry (www.kankerregister.org)

Mortality of prostate cancer

Although prostate cancer it is the most frequently diagnosed cancer in men, it is only the third most common cause of death by cancer in Belgium. The cumulative mortality for men under 75 years remained about 1.1% between 1990 and 1997. In other words, out of 100 Belgians who reached or should have reached the age of 75, 64 have a latent prostate carcinoma, 2 to 6 have been diagnosed with prostate cancer, and one has died of prostate cancer. [1]

If a man dies of prostate cancer, it occurs fairly late in life: mostly after the age of 75. This fact puts the relative importance of prostate cancer as a cause of death into perspective [1].

The risk factors for localized prostate cancer prognosis are defined in 1992 by the American Joint Committee on Cancer (AJCC). They defined three categories: low risk (PSA <10ng/ml and Gleason score <=6 and T1c or T2a), intermediate risk (PSA 10-20ng/ml or Gleason score 7 or T2b/c) and high risk cancers (PSA >20ng/ml or Gleason score >= 8).

Standard treatment options for prostate cancer

The optimal treatment of localised stages remains unknown. Radical treatments are reserved for patients whose life expectancy is greater than ten years (an age limit of 70 years is suggested). The standard radical treatments of localised prostate cancer are radical prostatectomy and radiotherapy (external and internal). Besides the immediate radical treatments, there is also the possibility of deferred treatment, notably active surveillance (i.e. observation with selective delayed curative intervention) and watchful waiting (i.e. observation with palliative treatment for symptomatic cancer progression). There is no definitive argument for the superiority of one treatment above another mainly because comparative trials are lacking.(Hummel, 2003 #102)(NICE, 2008 #112)

Limitations of standard treatments and new treatment options

Radical prostatectomy and radiotherapy are associated with a range of complications and morbidity, such as blood loss with transfusion related complications (for radical prostatectomy), bowel dysfunctions (for radiotherapy) and erectile dysfunction and stress incontinence (for both treatments). Hummel et al. estimated the incidence of late side effects, occurring a year or more after radical treatments based on existing trials, meta-analyses and case series. For radical prostatectomy, impotence rates were estimated to vary from 44% to 60% and urinary symptoms from 5% to 25%. For external radiotherapy, impotence rates were estimated from 29% to 36%, urinary symptoms from 9% to 23% and bowel symptoms from 8% to 26%.(Hummel, 2003 #102)

Due to those complications, alternative treatments were developed. Among these are cryotherapy and HIFU treatment. In the US, cryotherapy is used for localized prostate cancer patients with disease severity ranging from low, intermediate to high risk and for patients who have had previous radiotherapy treatment that has failed. Cryotherapy is not frequently used in Europe and to our knowledge it is not available in Belgium.

HIFU treatment

HIFU treatment is a new treatment form for prostate cancer management. It uses high-intensity focused ultrasound and is developed from the middle of the years 90 onwards. This HIFU therapy is generally transrectally administered and destroys the deep-seated target prostate cells by coagulating the tissue while sparing the adjacent healthy tissues. High intensity ultrasound beams focus the target tumor achieving a temperature of 80-100 °C in the tumorous cells. A cooling balloon surrounding the probe protects the rectal mucosa. Local, regional or general anaesthesia is administered to the patient. Often more than one session is performed, either as a day "surgery", an outpatient or inpatient procedure. HIFU is usually preceded by a TURP (transurethral resection of the prostate) to reduce side effects. The commercial name for HIFU is Ablatherm® (produced by EDAP-Technomed®) or Sonablate 500® (produced by Focus Surgery®). Ninety per cent of the trials published were performed with the Ablatherm device for which several product improvements were introduced after the first reports.

Background of this rapid assessment

The topic of this rapid assessment was introduced by the Belgian NIHDI (National Institute for Health and Disability Insurance) in order to assess the necessity of reimbursing the use of this device based on a clinical and cost effectiveness analysis for prostate cancer. Applications for reimbursement of HIFU with Sonablate 500® and Ablatherm® were introduced at the TRI-CTI (Technische Raad implantaten - Conseil Technique des implants).

Currently there are two companies that produce HIFU units for patient use: Focus Surgery Inc (based in the United States) producing Sonablate® and EDAP Technomed (based in France) producing Ablatherm®. In this chapter, an overview is given of the regulatory status of the products of both manufacturers.

1.2 REGULATORY STATUS OF HIFU TREATMENT

1.2.1 Sonablate® by Focus Surgery

The United States

In the United States, the Sonablate® 500 has not yet received approval for clinical use by the FDA. The Food and Drug Administration (FDA) has granted the Sonablate® 500 an Investigational Device Exemption (IDE), which allows the device to be used in a Phase III clinical multi-center study, to collect safety and efficacy data for final FDA approval.

In this phase III clinical study Sonablate® 500 is used for the treatment of low risk, localized (T1c/T2a) prostate cancer[a]. The study enrols 466 subjects at 24 institutions and has started in April 2007[b]. The control for the study will be brachytherapy. The Sonablate® 500 was developed by Focus Surgery, Inc and is manufactured by Misonix, Inc. Misonix Inc who also holds distribution rights in Europe. Takai Hospital Supply Ltd. and THS International distribute the Sonablate® 500 in Southeast Asia and the Middle East.

Europe and Japan

The Sonablate® 500 has received the CE Mark for the treatment of prostate diseases in Europe. The device also has obtained the MHW approval in Japan.

1.2.2 Ablatherm® by EDAP-Technomed

The United States

Ablatherm is not approved by the FDA for clinical use yet. EDAP-Technomed received an IDE in 1999 and there is currently a Phase III clinical trial ongoing for primary untreated prostate cancer.[c] This study is a non-inferiority study of the Ablatherm as compared to cryotherapy for the treatment of low risk, localized prostate cancer.

Europe, Russia, Canada and South Korea

Ablatherm has the CE Mark in the European Union and is also approved in Russia, Canada and South Korea[d]. Ablatherm is the most common technology used in Europe contrary to Sonablate which is actually only used in Southeast Asia and the Middle East. Consequently, we decided to focus our study on Ablatherm.

- **Both Sonablate® and Ablatherm® have not received approval for clinical use by the FDA. For both devices a Phase III clinical trial is currently ongoing, comparing HIFU with cryotherapy and brachytherapy.**

a Source : http://www.focus-surgery.com/Trials.htm
b Source : http://clinicaltrials.gov/ct2/show/NCT00485381?spons=%22Focus+Surgery%22&spons_ex=Y&rank=2
c See : http://clinicaltrials.gov/ct/show/NCT00295802?order=2
d Source : www.edap-hifu.com/fr/medecins/hifu/3a_traitement_presentation.htm

1.3 CLINICAL EFFECTIVENESS OF HIFU THERAPY

1.3.1 Research questions

The clinical part addresses the following clinical questions:

1. What is the evidence on clinical effectiveness and safety of the HIFU therapy for prostate cancer?
2. What are the patient outcomes (a.o. quality of life)?
3. Is there any benefit compared to the standard therapies?

1.3.2 Literature review

Methodology

The literature review complies with the search process (standard search) in use at the Belgian Health Care Knowledge Centre (KCE) for health technology assessment review. First, relevant HTA reports were sought. Secondly, as the treatment of localized prostate cancer remains controversial, a search was done for guidelines focusing on prostate cancer and mentioning treatment with HIFU. Thirdly, based on quality appraisal criteria, those HTA reports and guidelines with the highest level of evidence were selected.

Afterwards, the evidence – identified through those reviews – was updated by searching Medline and the Cochrane Database of Systematic Reviews from the search date of the review to February 2008. A combination of appropriate MeSH terms and free text words was used (see table 2).

The identified studies were selected based on title and abstract. Finally, an additional hand-search of grey literature was also conducted using the Google search engine.

Sources

The HTA database of the Centre for Reviews and Dissemination (CRD) and the websites of INAHTA agencies were sought for HTA reports.

The following databases or web sites were sought for guidelines: National Guideline Clearinghouse (NGC), National Institute for Health and Clinical Excellence (NICE), New Zealand Guidelines Group (NZGG), Scottish Intercollegiate Guidelines Network (SIGN) and National Comprehensive Cancer Network (NCCN).

In- and exclusion criteria

For all eligible studies, the full-text was retrieved. In case no full-text was available in English, Dutch, German or French, the study was not taken into account. Studies for which only an abstract exists (and no full article) and studies focusing on Sonablate were not included. A date restriction (2002 – 2008) was used for the initial search. Studies with fewer than 50 patients were excluded.

Initial search results

The following HTA reports, guidelines and systematic reviews were identified:

- 3 HTA reports from: National Horizon Scanning Centre (NHSC)[2], NICE 2004{National Institute for Clinical Excellence, 2005 #107} and College Voor Zorgverzekeringen (CVZ)[3]
- 2 Guidelines on prostate cancer treatment mentioning HIFU: European Association of Urology (EAU)[4] and NICE 2008[5]
- 2 SR's: Hummel 2003[6] and Rebillard 2003[7].

Critical appraisal of initial search results

The critical appraisal was first done for the retained HTA reports using the INAHTA HTA checklist. The reports published by NICE and CVZ were retained (see results in Appendix from Chapter 1.2, table 31). The AGREE instrument was used for the critical appraisal of guidelines.

The guideline published by NICE on prostate cancer in 2008 was critically appraised and a high quality score was assigned to it (see results in table 32 in appendix)[5]. However, the search strategy of this CPG included a filter for systematic reviews and RCTs and therefore did not retain all observational studies (the following 10 case series were retained for the Ablatherm device: Beerlage et al. 1999; Chaussy & Thüroff 2003; Gelet et al. 1999; Gelet et al. 2000; Poissonnier et al. 2003; Thüroff et al. 2003; Ficarra et al. 2006; Ganzer et al. 2007; Lee et al. 2006; Poissonnier et al. 2007).

A lower score was assigned to the guideline of the EAU as details on the critical appraisal of references were lacking.

For the critical appraisal of the reviews, the Cochrane checklist was used (see results in table 33). The review from Hummel received a high score; this review is also included in the evidence report from NICE (2005). The review from Rebillard (2003) was considered for critical appraisal and received a lower score as it does not contain a critical appraisal of the included articles.[7]

As the NICE 2004 review(National Institute for Clinical Excellence, 2004 #107) on HIFU provided the most recent exhaustive evidence review, this report was taken as a basis for our literature search.

Search for additional evidence to update NICE 2004(National Institute for Clinical Excellence, 2004 #107)

The evidence identified through the review of NICE 2004 on HIFU for Prostate Cancer was updated by searching Medline and the Cochrane Database of Systematic Reviews from the search date of the HTA onwards (from February 2004 to the 14th of February 2008). In addition, the reference lists of the selected HTA reports and guidelines were searched for any missing relevant publications. Recent publications on the same topic were also identified using the "cited-by" tool of Medline. No record was found with the same MeSH terms in the entire Cochrane Library. External experts participating to the meeting at the KCE also provided two additional papers. Reference lists of four recent reviews from Aus[8], Murat[9], Rebillard (2008)[10] and Tsakiris[11] were also checked to detect any missing articles.

For each of the study centers, only the most recent publication with the largest patient population was retained as multiple studies appeared to be reporting on the same patient population.

Eventually the results from NICE 2004 were updated with more recent publications from Blana et al. 2006(Blana, 2006 #131), Lee et al. 2006(Lee, 2006 #29), Poisonnier et al. 2007(Poissonnier, 2007 #15) and Blana et al. 2007 (Blana, 2007 #5).

Search terms for Medline

The following search strategy was adapted to each database (see Table 1).

Table 1: Medline search terms for HIFU (prostate cancer)

PROSTATE CANCER/
high intensity focused ultrasound.mp.
HIFU.mp
prostate and cancer.mp

1.3.3 Indications and contra-indications for HIFU therapy

HIFU is notably applied as a minimally invasive therapy in the treatment of localized prostate cancer (T1-T2 Nx Mo), mostly low and intermediate risk (see risk factors classification on 1.1). HIFU has also been used for locally proven recurrence of prostate cancer after primary treatment failures.

Some relative or absolute contraindications need to be considered before offering HIFU therapy to a patient. The gland volume is a major relative limitation and should not be over 40 mL. In case of suspicion of urethral obstruction, a TURP will be done prior to the HIFU procedure.

1.3.4 HIFU therapy as primary therapy

Most activities and research on HIFU therapy for cancer are conducted in Europe at three centres, namely; Edouard Herriot Hospital in Lyon (France), St Joseph Hospital in Regensburg (Germany) and Klinikum München-Harlaching (Germany). They all use the device Ablatherm developed by EDAP-Technomed (Vaux en Velin, France).

All studies found are prospective or retrospective case-series; none of the studies included a control group or patients treated by another technology. Outcomes presented in those series were overall survival, biochemical failure and disease-free survival rate. Overall survival at relatively short term (<5years) was not considered as a relevant outcome for localised prostate cancer as the mortality due to those cancers appears late after diagnosis.[12] Different definitions were used for biochemical failure and disease-free survival.

It is difficult to find the overall number of patients treated because some reports are based on multicenter studies and patient data may be used twice by different authors.[8, 10]

Table 2: Outcome results and complication rates for HIFU treatment (with the Ablatherm device) in first-line treatment of localized prostate cancer

Centre(s) and most recent publication	No. of patients	Mean pre-HIFU PSA (ng/ml)	Mean follow-up (months)	Biochemical disease-free survival rate (criteria)	Impotence (%)	Urinary incontinence (%) (any degree)	Urinary retention (%)	UTI (%)	Stenosis (%)
Harlaching München, Montsouris Paris, St Josef Regensburg, Saint-Louis Paris, Univ. Hospital Nijmegen, Edouard Herriot Lyon: Thüroff et al. 2003 (Thuroff, 2003 #19)	402[a]	10.9	13.6	-	-	14.6	8.6	13.8	3.6
St Josef Regensburg, Edouard Herriot Lyon, Harlaching München: Blana et al. 2007 (Blana, 2007 #59)	140[a]	7.0	76.8	58% with hormonal therapy at 5 yrs 63% without hormonal therapy at 5 yrs (negative biopsies and PSA nadir + 2 ng/ml and no salvage therapy start)	43.2	5.7	-	7.1	-
Univ. Hospital Nijmegen: Beerlage et al. 1999 (Beerlage, 1999 #42)	111[b]: 49 selective HIFU (A), 62 global HIFU (B)	-	12	-	A: 0 B: 100	8	-	-	1
Harlaching München: Chaussy and Thüroff 2003 [13] [c]	271[a]: 96 HIFU (A) 175 HIFU + TURP (B)	A: 8.6 B: 8.0	A: 18.7 B:10.9	A: approx 80% at 100 wks B: approx 84% at 180 wks (ASTRO criteria[d])	A: 40 B: 31.8	A: 15.40 B: 6.90	-	A: 47.90 B: 11.40	-
Edouard Herriot Lyon: Poissonnier et al. 2007 (Poissonnier, 2007 #14) [e]	227[a]	6.99	27	66% at 5 yrs (negative biopsy and PSA < 1 ng/ml)	35.8	13	9	2	12
St Josef Regensburg: Blana et al. 2006 [14] [f]	223[b]: 223 : 1st HIFU (A) 49 : 2nd HIFU (B)[j]	-	-	-	A : 49.8 B: 55.1	A: 7.6 B: 12.2	-	A : 0.4 B : 4.1	A :19.7 B: 14.3
Samsung Medical Center Seoul: Lee et al. 2006 [15]	58[b]	10.9	14	81% for T1 and 51% for T2 at 18 months (negative biopsy and ASTRO criteria[d])	-	16	3.5	-	-

[a] Exclusively first-line treatments.
[b] Not specified whether second-line treatments were excluded.
[c] Study likely includes patient population of Chaussy and Thüroff 2000 (Chaussy, 2000 #21) (n=65), Chaussy and Thüroff 2000(Chaussy, 2000 #140), Thüroff and Chaussy 2000 (Thuroff, 2000 #141) and Chaussy and Thüroff 2001(Chaussy, 2001 #20) (n=184). Patients may also be included in Thüroff et al. 2003(Thuroff, 2003 #19).
[d] The 1997 ASTRO consensus definition of biochemical failure as a surrogate endpoint for recurrence after radiotherapy is three consecutive rises in PSA (American Society for Therapeutic Radiology and Oncology)(European Association Of Urology, 2008 #133) . In 2006, the criteria were redefined as follows: "PSA increase is >=2 ng/mL higher than the PSA nadir value independent of the serum concentration of the nadir"(Roach, 2006 #142)
[e] Study likely includes patient population of Gelet et al., 1996(Gelet, 1996 #143) (n = 14), Gelet et al., 1999(Gelet, 1999 #144) (n = 50), Gelet et al., 2000(Gelet, 2000 #145) (n = 82), Poissonnier et al. 2003(Poissonnier, 2003 #146) (n=120) and Gelet et al. 2003(Gelet, 2003 #147) (n T1-T2=120). Part of the patient population may also be included in Thüroff et al. 2003(Thuroff, 2003 #19).
[f] Study likely includes patient population of Blana et al. 2004(Blana, 2004 #129).
[g] Cumulative rates are shown for both groups.

In the studies (table 2), various definitions are used for disease-free survival after HIFU treatment and the resulting rates range considerably.

Aus[8] concludes that there are not enough data available to support the use of HIFU as an alternative to the established therapies.[8]

Murat[9] also concludes that it is difficult to assess the potential role of HIFU therapy as no long-term data are available.[9]

The 2008 review from Rebillard[10] concludes that long–term follow up studies are needed for further evaluation of cancer specific and overall survival rates.[10]

1.3.5 HIFU therapy as salvage therapy

Only a limited number of studies are published on HIFU as salvage therapy. All of them are case series with short follow-up. The first results were published by Gelet et al. 2004. 71 patients were treated with HIFU after local recurrence of prostate cancer after external radiotherapy. Mean follow-up was 14.8 months. 80% of the patients had negative biopsies after HIFU treatment.(Gelet, 2004 #139)

Murat et al. 2008 studied the effect of HIFU used as salvage therapy after external beam radiation (EBRT) on 167 patients. The latest results, of May 2008, showed that local control was achieved in 73% of the patients (negative biopsy results) but follow-up remains short (mean 18 months).[16]

Chaussy et al. 2006 studied the effect of HIFU after surgical and pharmacological hormonal treatment (100 patients), radical prostatectomy (36 patients) and external radiotherapy (29 patients). A biopsy-proven tumor-free state was achieved in 60-74% of patients, depending on the primary treatment.

Other curative salvage treatment options include salvage radiotherapy, after radical prostatectomy failure, and salvage prostatectomy, cryosurgery and brachytherapy after radiotherapy failure.[416] Both radical prostatectomy and radiotherapy deal however with considerable side effects. The experience with salvage brachytherapy and cryosurgery is furthermore very limited[16] and cryosurgery is only to a limited extent available in mainland Europe.

1.3.6 Complications

Table 2 shows the complications as reported in the selected studies. The results however are difficult to compare as different definitions of complications were used and as the population is heterogeneous in terms of antibiotic use, coexisting pathologies, synchronous TURP and previous specific status.

In addition, the time effect with the continuous evolution of technology results in different-generation HIFU devices in the various reported series. This also occurs within the same series, in which two different-generation devices sometimes have been used.

The main complications are erectile impotence (ranging from 0 to 100%), urinary retention (ranging from 3.5 to 9%), urinary tract infection (UTI) (ranging from 0.4 to 47.9%), postoperative urethral stenosis (ranging from 1 to 19.7%) and some degree of urinary incontinence (ranging from 5.7 to 16%).

1.3.7 Patient's benefit

Standard therapies for localised prostate cancer are not free of significant complications and risks. Furthermore some patients are not suitable for major surgical procedures or cannot tolerate radiation therapy. HIFU appears to be an alternative that is as minimally invasive as possible. Poissonnier (Lyon) described the standardized HIFU treatment procedure as follows: hospitalization the day before treatment for rectal preparation, a single session treatment combining TURP and HIFU with a safety margin for treatment of the prostate apex and discharge from hospital at day 4 without urinary catheter.[17] This length of stay however still needs to be compared with the length of stay in case of other standard treatments in randomized studies.

1.3.8 Ongoing research in United States

As mentioned in the introduction, EDAP TMS SA started a non-randomized controlled study (with cryotherapy as comparator[e]) at 22/02/2006. This study is currently recruiting participants (>60 years) suffering from low risk (T1a,b c or T2a, PSA= or < 10ng/ml, Gleason score= or<6) localized (N0 M0) prostate cancer in order to determine the equivalence of the HIFU treatment performed with the Ablatherm device, as compared to cryotherapy[f]. Primary outcome measures are PSA nadir and PSA stability according to ASTRO criteria (24 months follow up without a positive biopsy). Secondary outcomes measures are: disease specific survival and overall survival, Quality of Life and changes in baseline IPSS.

1.3.9 Discussion

The results of the clinical effectiveness review should be viewed in the context of the quality of the available evidence. All published studies are case series, open to patient selection bias and measuring surrogate end-points with short-term follow-up.[6] Studies demonstrated that at relatively short follow-up (< 5year), HIFU affects the development of the prostate cancer as shown by both a substantial decrease in serum PSA and negative biopsies but no data were available on long term (10 year) overall survival or on long term disease specific survival. Furthermore, various criteria and follow-up periods for BDFS were used and the resulting rates varied widely.

Longer follow-up remains crucial to determine whether HIFU provides a long-term cure of the cancer and influences specific death rate of the cancer.[8] Efficacy results obtained with HIFU treatment must furthermore be compared with those obtained by actual "gold standards" treatments for prostate cancer. HIFU therapy is typically used and recommended for those patients with localized prostate cancer with clinical stage T_{1-2} N_{x-0} M_0, who are not suitable for a radical prostatectomy (eg., more than 70 years of age, life expectancy less than 10 years or major comorbidities precluding surgery) or who refuse to undergo surgery. For a large part of these patients, however, deferred treatment (active surveillance or watchful waiting) is recommended as standard treatment in the guidelines published by the European Association of Urology (EAU)(European Association Of Urology, 2008 #133) and the National Institute for Clinical Excellence (NICE)(NICE, 2008 #112). For the patients with well and moderately differentiated tumours T_{1-2b}, with less than 10 years life expectancy or who do not accept treatment-related complications, the EAU recommends deferred treatment as standard treatment. The guideline from NICE also recommends not routinely offering immediate radical therapy to men with localised low-risk prostate cancer. They should be offered watchful waiting or active surveillance, depending on their life expectancy and values. For men with intermediate-risk disease, active surveillance should be discussed as an option, besides radical prostatectomy or radiotherapy (internal or external). For men with high-risk localized prostate cancer, radical therapy is recommended. For low and intermediate risk cancers, results should thus be compared to results of deferred treatment and immediate curative treatment. The study of Albertsen et al. (2005)(Albertsen, 2005 #30) showed a very low cancer-specific death rate within the first 15 years in low-and intermediate risk groups when treated conservatively (with observation or immediate or delayed androgen withdrawal therapy). For high risk cancers, HIFU results need to be compared to immediate radical treatments. For patients over 70 years, the standard radical treatment is external radiotherapy, as radical prostatectomy is a major operation.

Besides as primary treatment, HIFU has also been used for locally proven recurrence of prostate cancer after external radiation or brachytherapy failures. However, it is impossible to draw firm conclusions on this specific use. There are few reports and patient clinical situations are highly variable. Other curative salvage treatment options include salvage radiotherapy, after radical prostatectomy failure, and salvage prostatectomy, brachytherapy and cryosurgery after radiotherapy failure.[416] Both radical prostatectomy and radiotherapy however deal with considerable side effects.

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[e] cryotherapy is currently not used in Belgium

[f] htttp://clinicaltrials.gov/ct2/Ablatherm

The experience with salvage brachytherapy and cryosurgery is furthermore very limited (Murat, 2008 #20) and cryosurgery is only to a limited extent available in mainland Europe. Hormonal treatment therefore remains the main alternative to HIFU for this specific patient group.

Key Messages

- **HIFU is applied as a minimally invasive therapy for low risk localized prostate cancer (T1-T2 NxMo) and for locally proven recurrence mainly after radiation or brachytherapy failures.**
- **All published studies are case-series and they are not comparing HIFU with standard therapy. (level of evidence 3)**
- **In the US, EDAP and Focus Surgery (the two companies producing HIFU) have started a phase III study in order to establish the non inferiority of HIFU treatment as compared to cryotherapy and brachytherapy.**
- **Biochemical disease-free survival for localized prostate cancer treated with HIFU ranges from to 84% at 22 months, to 58% at 72 months. Long-term data (cancer specific and overall mortality rate) are needed to establish evidence on efficacy and comparative studies are required to compare the results with standard treatments.**
- **In second-line treatment, other curative salvage treatment options deal with considerable side effects or are still in experimental phase. Hormonal treatment is therefore the main alternative to HIFU for salvage therapy,**

1.4 ECONOMIC EVALUATION OF HIFU

1.4.1 Cost of HIFU equipment and disposables

According to information from a Belgian expert, the Ablatherm device costs around €550 000 (excl. VAT). Annual maintenance costs around €45 000 (excl. VAT). The cost per treatment of the equipment depends heavily on the number of patients treated yearly. (E.g. when a 7 year lifetime of the device is considered and 50 patients are treated per year, then the cost of the equipment is around €2 480 per treatment (excl. VAT) or €3 000 incl. VAT. When the number of patients is 100 per year, then the cost of the equipment per treatment is halved to €1 240 (excl. VAT) or €1 500 (incl. VAT).

According to information from the EDAP annual report 2007, the average unit sales price of new Ablatherm devices was €444 000 in 2007 (excl. VAT). Besides selling devices, EDAP also provides Ablatherm devices to hospitals for free for a limited period. In this case, the hospitals pay the company on the basis of the number of individual treatments rather than paying the device. With this business model, the hospital does not need to make an initial investment until the increase in patient demand justifies the purchase of an Ablatherm. In 2006 the average price per treatment was €2 990 (VAT excl.) (€2,8 million revenues for 936 RPPs (revenues per procedure)).

On top of the equipment cost, there is the cost of the disposables. According to information from a Belgian expert, the Ablapack (containing the disposables needed for one treatment) costs around €550.

1.4.2 Total cost of HIFU treatment

In the CEDIT 2004[18] report, the total cost of treatment was calculated based on data from a number of French hospitals and compared to the cost of other treatments for localized prostate cancer. The total cost of treatment with Ablatherm was calculated at €4 720 to €6 450. The reported average length of stay was 5 days.

The operative phase represented more than 60% of the total costs, the pre-operative phase between 5 and 10% and the post-operative phase (surveillance consultations for 12 months) between 20 and 30%. The total treatment cost was considered comparable to other treatments for localised prostate cancer. The hospital cost for prostatectomy the first year was 6 900€, for brachytherapy €7 200 and for the first year external radiotherapy €3 200.

1.4.3 Cost-effectiveness of HIFU

As there is no evidence yet on benefits (nor on harms) of HIFU treatment, obviously no high-quality full economic evaluation can be performed yet. Besides a preliminary analysis of the National Collaborating Centre for Cancer (NCC-C) of 2008, performed for NICE, no other full economic evaluation studies were found in the economic literature search. An overview of the different steps of the literature search is detailed in appendix. The NCC-C study is briefly described in the section below.

1.4.3.1 NCC-C for NICE 2008[19]

The primary aim of the economic part of this study was to perform an economic evaluation of watchful waiting versus radical prostatectomy.

As there is a lack of comparative data on outcomes with other treatment options (including HIFU), the secondary objective of the study was to estimate how much more effective these other therapies would need to be, compared to watchful waiting, to be considered cost-effective at a willingness-to-pay of £30 000 per additional QALY. The original intention was to do this analysis in relation to radical prostatectomy. However, as watchful waiting appeared to be the dominant therapy in the first analysis, watchful waiting was taken as comparator. Besides HIFU, also external beam, brachytherapy, cryotherapy and IMRT were considered. As the latter therapies are not evaluated in this report, only the results for HIFU are presented here.

Radical prostatectomy versus watchful waiting

The evaluation of radical prostatectomy versus watchful waiting was done based on the 10 year RCT published by Bill-Axelson et al. (2005). A Markov model was built dividing a patients' possible prognosis into a series of discrete health states. Each cycle (a year), within the 20-year horizon of the analysis, patients had an annual probability of 1) continuing to have localised disease/be cured; 2) developing metastatic disease, 3) dying from natural causes or 4) dying from prostate cancer. All patients who developed metastatic disease were assumed to receive hormonal therapy until death. All patients were assumed to receive two PSA tests per year on outpatient basis.

Costs and benefits were assigned to each health state. Transition probabilities defined the movement of an individual between the health states over the cycle length. The costs and benefits of comparative watchful waiting versus radical prostatectomy were then estimated on the basis of the length of time individuals spent in each health state.

Based on Steineck et al., the following assumptions were included for the side effects. 35% more people receiving radical prostatectomy experienced erectile dysfunction and 28% more people experienced urinary leakage compared to watchful waiting. It was also assumed that 16% more people in the watchful waiting arm had urinary obstruction compared to those receiving radical prostatectomy.

In table 4, an overview is given of the assumed utilities with the different health states.

Table 3: Utilities

Utility/Disutility	EQ-5D	Based on
Utility of person with localised disease	0.78	Equal to utility of the general population, male, 65 years
Utility of person with metastatic disease	0.42	Cowen et al. (1999)
Disutility for impotence	-0.09	Cowen et al. (1999)
Disutility for urinary obstruction/leakage	-0.21	Cowen et al. (1999)

Source: NCC-C for NICE 2008

The costs were considered from a NHS perspective and included the cost of the initial treatment, a 2-yearly PSA testing for all patients, the cost of complications and the cost of hormonal therapy for patients that developed metastatic disease until death. See Table 4 for an overview of costs of treatments and PSA testing.

Table 4: Costs of treatment and PSA testing

	Cost estimate	Source
Radical prostatectomy	£5 603	Calvert et al. (2003)
Hormonal therapy (annual)	£2 612	Hummel et al. (2003)
TURP	£2 009	NHS unit costs
Urinary incontinence	£115 (per annum)	Turner et al.
Twice yearly PSA test	£154	Calvert et al. (2003)
HIFU	£7 500	EDAP-TMS

Source: NCC-C for NICE 2008

The baseline results (costs, life years and QALYs) are summarized in Table 5. As watchful waiting appeared to result in more QALYs and less costs, radical prostatectomy was dominated by watchful waiting.

Table 5: Baseline results of watchful waiting compared to radical prostatectomy

	Cost	LY	QALYs
Watchful waiting	£6 185	9.69	6.63
Radical prostatectomy	£10 619	10.19	6.36

Source: NCC-C for NICE 2008

HIFU versus watchful waiting

In order to estimate how much more effective HIFU would need to be compared to watchful waiting, in order to be cost-effective at a willingness-to-pay of £30 000 per additional QALY, a threshold analysis over a 20 year period was performed.

The analysis estimated that a QALY increase of 0.20 was required in order for HIFU to be cost-effective compared to watchful waiting. A QALY increase of 0.20 means a gain of 2.4 months in perfect health. The results are shown in Table 6. Further clinical studies will now be required to see whether HIFU meets these effectiveness requirements.

Table 6: Results from the threshold analysis over a 20 year period compared to watchful waiting

	Expected full cost of treatment option	Required QALY increase	Equivalent health gain in months[a]
HIFU	£12 188	0.20	2.4

[a] Number of extra months of perfect health required over a 20 year period for HIFU to be considered cost-effective. This was calculated as follows: 1 day of perfect health = 1/365 = 0.002739 QALYs. 0.20 QALYs/0.002739 QALYs = 73 days = approximately 2.4 months

- **A French cost study has shown that the total treatment with Ablatherm costs more than external radiotherapy, but less than radical prostatectomy and internal radiotherapy.**
- **Given the lack of data on clinical effectiveness for HIFU at long term, no conclusions can be drawn yet on the cost-effectiveness of this treatment.**

1.5 BELGIAN SITUATION

In this chapter we aim to give a brief overview of the Belgian situation on the conventional treatments for prostate cancer on one hand and on HIFU on the other hand. How many patients are treated with radical prostatectomy, external radiotherapy, brachytherapy and HIFU? In order to answer this question, different sources were explored. As no accurate data was available on external radiotherapy for prostate cancer, an estimate was made for this treatment option. Furthermore, this chapter covers the financing of HIFU in Belgium (patient/hospital/NIHDI).

1.5.1 Overview of conventional treatments for prostate cancer in Belgium

1.5.1.1 Radical prostatectomy in Belgium

Data on radical prostatectomy is available from the NIHDI. The billing code for the radical prostatectomy procedure has a reimbursement value of €927.01 in 2008 (and €797.71 in 2006). In 2006, 3 547 treatments were charged in Belgium for a total NIHDI expenditure of €2 953 000 (see Figure 2). This code covers both classical as endoscopic radical prostatectomy.

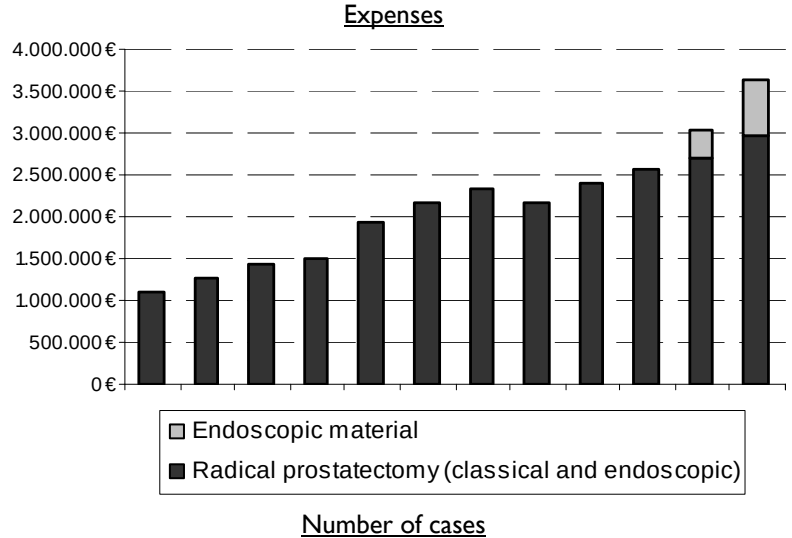
Besides the procedure code, there is also a material code for endoscopic radical prostatectomies: 694610-694621. This code exists since April 2005 and covers the disposables and implantable material. In 2006, 1 343 times the material code was invoiced (see also Figure 2). The reimbursement value is €510.93 since July 2006.

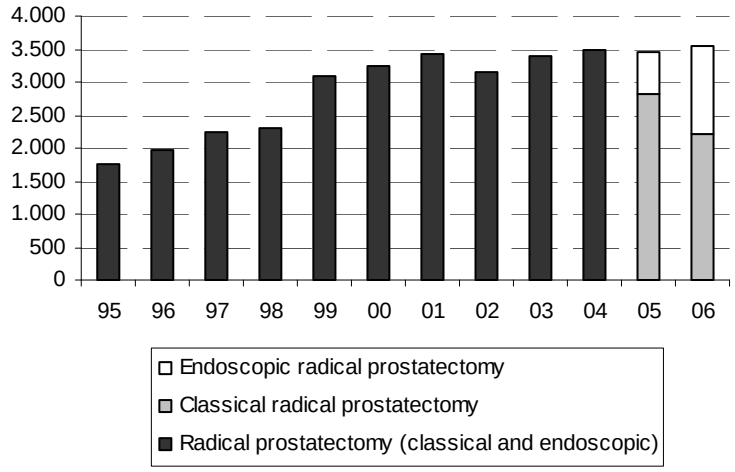
In total thus 2204 classical and 1 343 endoscopic radical prostatectomies were performed in 2006.

Table 7: NIHDI billing codes for radical prostatectomy

Code	Dutch label	French label	Value
261796-261800	Totale prostatectomie inclusief exeresis van het vesiculair blok met urethro-vesicaal hechten	Prostatectomie totale, y compris l'exérèse du bloc vésiculaire avec suture urétro-vésicale	K 450 Reimbursement : €927.01 Out-of-pocket patient : €0
694610-694621	Geheel van gebruiksmateriaal en van implanteerbaar materiaal gebruikt tijdens de verstrekking 261796 - 261800 via endoscopische weg	Ensemble du matériel de consommation et du matériel implantable utilisé lors de la prestation 261796 - 261800, par voie endoscopique	U 645 Reimbursement : €510.93 Out-of-pocket patient : €170.30

Figure 2: Radical prostatectomies: NIHDI expenses and number of cases





Source: NIHDI 1995-2006 reimbursement year data

1.5.1.2 External radiotherapy for prostate cancer in Belgium

In the KCE report on IMRT (2007)[20]), an estimate was made of the number of treatment courses of external beam radiotherapy for prostate cancer in 2006. This estimate was based on the "optimal" radiotherapy uptake rate for prostate cancer from a publication of CCORE (2003) on one hand and on actual Belgian radiotherapy uptake rates across all cancers, on the other hand.

The CCORE publication set the "optimal", i.e. evidence-based, radiotherapy uptake rates through a systematic review for a comprehensive range of cancers with a view to facilitating further planning efforts for external radiotherapy infrastructure needs. The publication reported this "optimal" radiotherapy uptake rate for prostate cancer at 60%. Adding 25% of cancer patients requiring re-treatment through external radiation, an optimal level of 75 treatment courses per one hundred prostate cancers was calculated. However, as the radiotherapy uptake across all cancers in Belgium was lower than the optimal overall uptake rate from CCORE, notably 26% lower, a downward correction factor of 0.74 was used to calculate an estimate more in line with the Belgian situation. The final estimated radiotherapy treatment course rate for prostate cancer was calculated at 56% (=75%*0.74). Given the prostate cancer incidence of 9 626 in 2006, the estimated number of prostate cancer radiotherapy treatment courses in Belgium was around 5 400.

In order to estimate the number of first radiotherapy treatment courses for this report, we need to deduct the retreatments from this figure (25%), which results in around 4 300 patients starting a radiotherapy treatment for prostate cancer in 2006.

1.5.1.3 Brachytherapy for prostate cancer in Belgium

According to the KCE report on Radioisotopes reimbursement (2008)[21], there were 765 reimbursed prostate brachytherapies in 2005. This figure was deducted from the number of seeds reimbursed.

- **The prostate cancer incidence in Belgium is 9 626 patients (2006 data).**
- **Data from the NIHDI show that there are yearly around 3 550 radical prostatectomy treatments, amongst which 2204 classical and 1 343 endoscopic. Data also show that there are yearly around 770 prostate brachytherapies for prostate cancer. For prostate external radiotherapy, no data is available, but according to non-data-based estimates, around 4 300 patients start prostate radiotherapy (2006 estimate).**

1.5.2 Overview of HIFU in Belgium

1.5.2.1 Belgian hospitals performing HIFU therapy

According to information from the websites of the companies producing HIFU equipment, there are currently four Belgian hospitals performing HIFU therapy for prostate cancer.

Table 8: Belgian hospitals performing HIFU therapy

Institut Jules Bordet, Bruxelles	Ablatherm
Algemeen Ziekenhuis Middelheim, Antwerpen	Ablatherm
Clinique universitaire (UCL) de Mont-Godinne	Ablatherm
Universitair Ziekenhuis Leuven	Ablatherm + Sonablate

Source: http://www.hifu-planet.com/2_English/lieu.html (consulted in April 2008) for Ablatherm and http://www.misonix.com/medical/Intl/IntlProductInfo/Oncology for Sonablate

1.5.2.2 Number of patients treated with HIFU in Belgium[g]

At ZNA Middelheim Antwerp, more than 650 patients (amongst which about 150 foreign patients) have been treated with HIFU since October 2000. At UCL de Mont-Godinne, around 50 patients have been treated from September 2004. At UZLeuven, 27 patients have been treated (18 primary prostate cancer, 8 radiotherapy failures and 1 radical prostatectomy failure). Taking into account that also a number of patients have been treated in Jules Bordet, it can be concluded that in total more than 730 patients were treated from October 2000 to July 2008. Excluding the foreign patients, the figure equals around 0.8% of all new prostate cancer patients in this period.

1.5.2.3 Financing of HIFU treatment

As already mentioned, the NIHDI does not have a specific nomenclature code for the HIFU intervention. Different NIHDI facturation practices may exist at the hospitals. Generally, a TURP, preceding the HIFU treatment, is invoiced. No total prostatectomy is invoiced.

The out-of-pocket payments for HIFU treatment for the patient or his private insurance also variy from hospital to hospital.

At academic hospitals, or general hospitals with academic character, no extra honoraria fees can be billed for new medical techniques to patients in a common room, as is determined in the Royal Decree of 25 april 2002 on the "Budget van financiële middelen" / "Budget des moyens financiers" [h], in order to be entitled to the B7 financing. Only an extra fee can be charged for the consumables.

At one of these hospitals, the consumables are charged to the patient (or his private insurance) at a price of around €720. At another hospital, the treatment cost is fully born by the hospital. Only a supplement for transrectal echography and anesthesia are charged and when the patients are treated with a TURP first, also a TURP is charged.

At a general hospital, extra honoraria can be billed for new medical techniques. The general hospital communicated a price of around €3 000 fully paid by either the patient or his private insurance. According to the hospital, in 50% to 75% of the patients, the private insurance intervenes.

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g Data of July 2008

h Art. N12. Bijlage 12. 1. Nieuwe medische technieken. Om recht te hebben op de B7A financiering, dienen universitaire ziekenhuizen: [7° (voor het geheel van het ziekenhuis de tarieven van het nationaal akkoord artsenverzekeringsinstellingen toepassen voor de patiënten opgenomen in een dubbele en gemeenschappelijke kamer. Ingeval waar er geen akkoord is, zijn de tarieven die gebruikt worden als basis voor de berekening van de tussenkomst van de verplichte verzekering voor geneeskundige verzorging en uitkeringen, de maximale tarieven dewelke kunnen toegepast worden. Het bewijs moet geleverd worden via een attest ondertekend door de beheerder en de voorzitter van de medische raad. <KB 2006-11-10/43, art. 24, 016; Inwerkingtreding : 01-07-2007>]

- **Currently, HIFU treatment for prostate cancer is performed at 4 centers.**
- **In total, more than 730 patients in total have been treated with HIFU in Belgium (from October 2000 to mid 2008), amongst which around 150 foreign patients. Excluding the foreign patients, this is around 0.8% of all new prostate cancer patients in that period.**
- **The cost of treatment is currently born partly by the patient (or his private insurance), the hospital and the NIHDI. The out-of-pocket payment for the patient (or his private insurance) varies from €0 to €3 000.**

1.6 INTERNATIONAL REIMBURSEMENT POLICIES

Different reimbursement policies are observed internationally. Despite a lack of evidence on impact on survival and quality of life, NHS provides a reimbursement based on procedure safety. The National insurances in Canada, France and the Netherlands, however, do currently not reimburse HIFU treatment for prostate cancer. Also some private insurances, such as CIGNA[i], do not reimburse the treatment.[3]

1.7 CONCLUSION

The choice of treatment of prostate cancer remains difficult. Best treatment depends on the stage, the risk factors and the patient's health status and life expectancy.

The guidance from NICE is clear: "Men with localised low-risk prostate cancer should not routinely be offered immediate radical therapy. They should be offered watchful waiting or active surveillance, depending on their life expectancy and values. Active surveillance with delayed intervention should also be discussed as an option with men who have intermediate-risk disease."[5]

Adolfsson cited seven studies reporting disease specific survival rate at 10yr situated between 75% and 87% for T1-2, grades 1-3, localized and well or moderately differentiated prostate cancers.[22] Furthermore, the guideline published by the EAU recommends watchful waiting as standard treatment for well and moderately differentiated tumours T1-T2b (low and intermediate risk) and < 10-year life expectancy. Watchful waiting is also recommended for asymptomatic patients who do not accept treatment-related complications.[4]

Nevertheless, some authors disagree with those recommendations as the patient may prefer a more active therapy than watchful waiting or active surveillance. HIFU therapy is typically used for those patients who are older than 70 years or not suitable for surgery.[9] Besides HIFU, however, also other treatment options exist for this patient group. It is therefore necessary to inform the patient as objectively as possible about the advantages and disadvantages of all the treatments options. So, the choice between deferred treatment and an immediate active treatment should be left to the patient.

It is currently impossible to give a firm answer to the final question: are the advantages of HIFU sufficient to counterbalance the complications and uncertainty of results at long term, compared to standard treatment options? Therefore, the reimbursement of this therapy for primary treatment of localized prostate cancer is currently not recommended.

Besides as primary treatment, HIFU is also used for locally proven recurrence of prostate cancer after radiotherapy failure. Other curative salvage treatment options deal with considerable side effects or are still in experimental phase. Hormonal treatment is therefore the main alternative to HIFU. Therefore, for this restricted subpopulation of patients conditional reimbursement can be considered within the context of clinical studies.

[i] CIGNA Corporation is a Philadelphia-based health service company. The Philadelphia headquarters are located in Two Liberty Place.

2 RAPID ASSESSMENT OF PHOTOSELECTIVE VAPORIZATION OF THE PROSTATE (PVP) AND HOLMIUM LASER FOR BENIGN PROSTATE HYPERTROPHY

2.1 INTRODUCTION

This topic was introduced by the NIHDI as it received an application for reimbursement for Greenlight PVP at the TRI-CTI (Technische Raad implantaten - Conseil Technique des implants). The number of BPH treatments in Belgium was around 14 100 in the year 2006 (including TURP, open prostatectomy and resection of bladder neck/urethral posterior valves). For TURP treatments alone, in total nearly € 30 million was paid by national health authorities for hospitalization, pharmaceuticals and honoraria in 2005.

2.1.1 Definition, epidemiology and symptoms of BPH

Definition

Benign prostatic hypertrophy (BPH) is a nonmalignant enlargement of the prostate due to excessive growth of the glandular and stromal elements. It is a common condition in men older than 40 years of all races and cultures.[23]

Epidemiology

Benign prostatic hyperplasia affects about 50% of men aged 60 years and over. The enlargement is a normal consequence of aging as has been shown by autopsy studies of histological prevalence of 82% in men aged 71-80.[24] Similar to the histological prevalence, the prevalence of bothersome symptoms also increases with age. Approximately half of all men who have a histological diagnosis have moderate to severe symptoms.[25]

Symptoms

Symptoms of BPH (lower urinary tract symptoms or LUTS) combine both storage (irritative) and voiding (obstructive) symptoms. Obstructive symptoms include hesitancy, a weak urinary stream and incomplete voiding. Irritative symptoms are mainly due to the increasing instability of the hypertrophied bladder. They include frequency, nocturia and dysuria.

2.1.2 Non-operative versus operative treatment

In case of uncomplicated BPH without LUTS no treatment is required. In other cases, there are a number of different treatment options. Besides operative treatment, also watchful waiting and pharmaceutical therapy can be considered, as the natural development of BPH shows usually a slow progression. The used pharmaceuticals are alpha-adrenoceptor antagonists (alpha-blockers) and 5-alpha-reductase inhibitors or a combination of both. The inhibitors of the 5-alpha-reductase reduce the prostatic volume, therefore they reduce the risk of urinary retention and surgical need.[i] The effect of alpha-blockers is limited to reducing the symptoms.

It is important that the patient participates in the treatment decision. The impact of LUTS on his quality of life (the degree to which he is actually bothered by LUTS) varies regardless of the level of symptom severity as defined based on clinical parameters. A patient with mild symptoms or mild to severe symptoms that are not bothersome will still prefer watchful waiting. A patient with moderate to severe symptoms that are bothersome, however, can have a wide range of preferences. The patient may prefer the most effective therapy, but also a less effective therapy if it also has less risk or cost.[25]

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i The effect of 5-ARIs was studied in the PLESS and COMBAT trials

2.1.3 Standard operative therapy: TURP

The aim of surgical treatment for BPH is to reduce the bulk of the prostate in order to relieve the static obstruction that the gland's enlargement has caused.

Until the 1930s, open prostatectomy (OP) was the only available surgical treatment for BPH.[26] During an open operation, the pieces of the prostate blocking the urethra were removed either through an incision in the bladder (suprapubically) or through an incision in the anterior part of the capsule of the prostate (retropubically).[27] This open prostatectomy was highly invasive, with overall morbidity rates as high as 36% and a mortality rate of 1.4%.[28]. This operation is now recommended only for patients with large prostates (> 50 grams) or who need treatment on bladder pathologies at the same time.[27,28]

Since the 1940s, the less invasive 'transurethral resection of the prostate' (TURP) has been the most used surgical treatment for BPH. TURP turned out to be almost as efficient as open prostatectomy in relieving the symptoms of BPH, to have a lower morbidity and to be less costly.[27] TURP involves cutting the prostatic tissue into small chips, through electroresection.[29] The resection is done with a telescope, called the resectoscope, which has a built-in wire loop to which a low current is applied. Simultaneous irrigation with an iso-osmotic non-conducting fluid is done to maintain visibility.[27,30]

Limitations of TURP

Despite being a very effective treatment, and therefore considered as the "gold standard", TURP deals with some disadvantages.

First of all, there is a high morbidity rate. 15% to 20% of patients develop a significant complication following TURP and a second intervention is necessary in 10% to 15% of patients within ten years. The post-operative complications can include urinary tract infection, erectile dysfunction, retrograde ejaculation (in at least two-thirds of patients), transurethral (TUR) syndrome, urinary incontinence, bladder neck contracture and urethral stricture, as well as intra- and postoperative haemorrhage that may necessitate transfusions (8.4% in Belgium in 2000)[31]. Secondly, TURP has a mortality rate of 0.2–2.5%. (0.2% for younger men (aged less than 70) to 2.5% for older men (aged over 85).[32,33,34] In Belgium, mortality rate was 0.2% in 2000[31].

Bipolar TURP

Until recently, the use of monopolar current was the only method available for TURP. With the recent development of the bipolar TURP, using bipolar electrosurgery, coagulation takes place at a much lower peak voltage of 65–120V compared with monopolar systems of 500–800V depending on the system used. This lower peak volume of energy would cause fewer irritative symptoms post-resection than standard monopolar TUR systems. The effectiveness and cost of this new type of TURP is yet to be assessed.

2.1.4 Alternative/new operative treatments

In past decades, a range of minimally invasive alternatives to the gold standard TURP emerged. Most of these alternatives destroy and remove the prostate cells that obstruct the urethra by applying heat. Heat can be applied in different ways, through high intensity ultrasound, microwave or electrical energy. Another way heat is applied is through laser energy, delivered through thin optic fibres.[35]

2.1.4.1 *Laser energy treatments*

In search of shorter hospital stays and decreased morbidity while maintaining the efficacy and durability of TURP, a variety of endoscopic laser techniques, to remove obstructing prostatic tissue, have evolved over the past 10-15 years. The main ones are:

- Nd:YAG: the neodymium yttrium aluminium garnet laser
- Ho:YAG: the holmium yttrium aluminium garnet laser
- KTP: the frequency-doubled Nd:YAG-potassium-titanyl-phosphate laser
- the diode.

See Table 9 for an overview of the different laser treatments.[35]

The laser techniques allow for coagulation, vaporisation or resection/enucleation, depending on the wavelength and power and type of emission.[36] The laser energy can be delivered through a bare fibre (end-firing), a right-angled fibre (side-firing), contact tips or an interstitial fibre.[37,38]

Table 9: Overview of various laser prostatectomy techniques

	Technique	Laser used
TULIP	Coagulation (non-contact)	Nd: YAG
VLAP	Coagulation (non-contact)	Nd: YAG side-firing
ILC	Coagulation (contact)	Nd: YAG diode contact tip
CLV	Vaporisation (contact)	Nd: YAG contact tip
PVP	Vaporisation	Nd:YAG laser passed through KTP potassium titanyl phosphate (KTP) crystal
CELAP HoLAP	Laser ablation	Diode Ho: YAG+Nd:YAG side-firing
HoLRP HoLEP	Laser excision	Ho:YAG end-firing

Source: Partly based on ASERNIP-S (2003)[35]
Note : TULIP: Transurethral Ultrasound-guided Laser-induced Prostatectomy ; VLAP : Visual Laser Ablation of the Prostate ; ILC: Interstitial Laser coagulation of the Prostate; CLV: Contact Laser Vaporisation of the Prostate; CELAP: Combination Endoscopic Laser Ablation of the Prostate; HoLAP: Holmium Laser Ablation of the Prostate; HoLRP: Holmium Laser Resection of the Prostate; HoLEP: Holmium Laser Enucleation of the Prostate. PVP: Photoselective Vaporization of the Prostate

The ideal type of laser for treatment of BPH is the one that has a high degree of incisional, vaporising properties allowing complete removal of prostatic tissue, and has the ability to coagulate blood vessels in the prostatic fossa with a small penetrating ability.[36]

Several coagulative laser techniques, such as TULIP (Transurethral Ultrasound-guided Laser-induced Prostatectomy), VLAP (Visual Laser Ablation of the Prostate) and TUILC (Transurethral Interstitial Laser Coagulation) have lost popularity because of the need for long catheterization time (and therefore more complications), the unpredictable results and high re-operation rates.[36,39, 40, 41]

Contrary to the coagulative laser techniques, the high-powered KTP and holmium lasers are used more and more nowadays.[36] Therefore, this report reviews the literature concerning these two types of laser treatments.

Holmium laser techniques

The holmium:YAG (Ho:YAG) laser can be used either as an ablation tool or as an incisional and dissecting tool allowing resection or enucleation of whole lobes of the prostate, mimicking the action of the index finger in open prostatectomy (Wilson, L. C. and Gilling, P. J. , 2005).

Holmium laser ablation of the prostate (HoLAP) and holmium laser enucleation of the prostate (HoLEP) are two options that effectively treat obstructive prostates with little blood loss. Use of the holmium:YAG laser in the treatment of BPH has changed significantly over the past five years.

As techniques have been refined and equipment improved, the spectrum of treatment has progressed from simple vaporization of tissue (HoLAP) to the complete removal (HoLRP), or enucleation (HoLEP), of intact lobes of prostatic mass.

- HoLAP: holmium laser ablation of the prostate

HoLAP involves techniques using holmium laser to vaporize obstructive prostatic tissue. Patients who undergo HoLAP usually do not require overnight hospitalization and in most cases, the catheter is removed the same day or the morning following the procedure. Ablation usually is performed when the prostate is smaller than 60 cc (cubic centimeters).

- HoLRP: holmium laser resection of the prostate.

A resectoscope with a fibre loop on the end is passed up the urethra to the opening of the bladder. A bilateral bladder neck incision is made to define the margins of resection. The median and lateral lobes are then individually undermined and peeled off the prostate capsule in a retrograde direction until only a bridge of tissue remains at the bladder neck. Laser energy cuts away the smaller pieces of prostate tissue, prior to their release into the bladder. These are then removed by the resectoscope.[42;43;44;35]). According to external experts of the project, HoLRP is not yet used in Belgium.

- HoLEP: holmium laser enucleation of the prostate.

HoLEP is the most recent development in the evolution of holmium laser prostatectomy. HoLEP enables dissection of large pieces of prostate (the intact median and lateral lobes). Once enucleation of the prostatic lobes is achieved, the lobes are mechanically mashed with a morcellator which is applied either transurethrally or suprapubically. The pieces are consequently taken out via the resectoscope.[44] An advantage of this method is that it permits to retrieve sufficient tissue for the detection of undiagnosed prostate cancer. An inconvenient is that the holmium technique requires substantial skill in endoscopic techniques as well as precise knowledge of the anatomy and morphology of the bladder neck and prostatic urethra. The performance of 20 to 30 procedures on prostate adenomas weighing less than 50 gm should be achieved before proficiency can be expected and larger prostatic enucleations are attempted.[45] Enucleation is usually performed when the prostate is larger than 60 cc.

As HoLAP and HoLRP have been superseded by HoLEP[46], the latter treatment will be the major focus in the holmium laser review.

PVP (photoselective vaporization of the prostate)

PVP is generally administered with a GreenLight laser. The GreenLight laser surgical system delivers laser light pulses via a specially designed fiber optic device inserted through a standard cystoscope. The laser light pulses are then directed toward the enlarged prostate tissues. The green-laser quickly and accurately vaporizes the prostatic obstruction. The PVP technique utilizes the beam from an Nd:YAG laser passed through a KTP potassium titanyl phosphate (KTP) crystal. The light beam is at a wavelength of 532 nm, half of the 1064nm wavelength of the Nd:YAG laser. At this wavelength, the beam is within the green-light spectrum. This wavelength is preferentially taken up by the red heme moiety of haemoglobin, but is not absorbed by water.[47] The absorption length in prostate tissue is only 1-3 mm and the high-energy density causes rapid photo-thermal vaporisation of intracellular water, known as photoselective vaporisation.[48] The procedure is performed with saline irrigation and the catheter is left in situ at the end of the operation.[36]

KTP vaporization of the prostate may be beneficial because the wavelength of current laser models is close to peak absorption of haemoglobin and allows excellent haemostasis and the new generation lasers produce only a 1-2mm coagulation zone for safe vaporization.[49] The disadvantage of the technique is that it does not provide tissue for histological examination.[46]

2.1.4.2 *Alternative therapies not using laser technique*

TUMT (Transurethral microwave thermotherapy)

In this procedure, a catheter is placed transurethrally into the prostatic fossa, and a microwave antenna is used to heat the prostatic tissue to a minimum 45°C. As such, coagulation necrosis of the prostatic tissue is achieved.[46] This technique only requires local or no anaesthesia reduces risk of bleeding and eliminates risk of TUR syndrome due to absorption of irrigant solution. However, TUMT has lost its popularity because of post treatment catheterization for several weeks and poor long-term results compared with TURP. The technology currently has low utilization and has therefore not been included in this assessment.

TUNA (Transurethral needle ablation)

Transurethral needle ablation (TUNA) uses radiofrequency waves to heat prostatic tissue. Two small needles are placed inside the prostate lobes by piercing the urethra under endoscopic visual control. Between the 2 electrodes, the radiofrequency energy is applied, causing significant temperature rise (about 100°C). This heat leads to coagulative necrosis of prostatic tissue. Tissue necrosis from ablation occurs at the time of the procedure, but tissue absorption occurs over the 8 weeks after the procedure. Therefore patients often notice little improvement in voiding symptoms for the first 2 to 3 weeks until necrotic tissue absorption begins.[46] TUNA can be performed as an outpatient procedure with local anaesthesia.

As this technique is currently (not anymore) in use in Belgium, it has not been included in this assessment.

HIFU (High Intensity Focused Ultrasound)

Besides for prostate cancer, HIFU was also introduced as a minimally invasive treatment for patients with BPH.[50;46] HIFU is the only technique permitting contact- and irradiation-free in-depth tissue ablation.[50;46] Due to very high energy, HIFU can precisely reach a target with a very short emission time. An ultrasound beam is brought to a tight focus at a distance from its source. If sufficient energy is concentrated within the focus, the cells lying within this focal volume are killed, whereas those lying elsewhere are spared. A probe is introduced into the rectum and the covering sheet is inflated with 50 to 70 ml of degassed water to ensure air-free contact with the rectal wall. A urethral catheter is inserted during the imaging phase in order to assist the identification of the bladder neck, prosthetic urethra and veromontanum. HIFU is well tolerated but requires general anaesthesia or heavy intravenous sedation.[46]

As this technique is currently not in use in Belgium for this indication, it has not been included in this assessment.

WIT (Water Induced Thermotherapy)

In WIT, also called balloon thermoablation or liquid ablation, heated water is circulated through a balloon that spans the prostatic urethra. There is a console heating system that heats and maintains water temperature at a chosen temperature between 60 or 70 degrees Celsius, and a peristaltic pump that continuously circulates the water.

Usually, WIT protocols use water heated to 60 or 62 degrees Celsius. The circulating water inflates the balloon and conductively heats the prostate tissue, thereby causing coagulation necrosis. During WIT, urethral and rectal temperatures are monitored using temperature sensors. Because the treatment balloon length and catheter length are available in nine lengths, WIT can be used to treat prostates of varying sizes.[51, 52]

WIT can be performed on an outpatient basis with local analgesia (lidocaine gel). In clinical studies, long catheterization times (weeks) or placement of temporary urethral stents were necessary. WIT is not considered an alternative to TURP in patients who can undergo TURP. Rather, it is an option for patients at high risk for surgical complications, such as cardiopulmonary problems, or for patients who may require a less invasive treatment.[51,52]

Other surgical non-laser techniques

Other techniques, such as transrectal hyperthermy (TRH), transurethral thermotherapy (TUT) and balloon dilatation have not been investigated as they are outdated methods.[53]

- **Several coagulative laser techniques for operative treatment of BPH, such as TULIP, VLAP and TUILC have lost popularity because of the need for long catheterization time (and therefore more complications), the unpredictable results and high re-operation rates. A variety of non-laser surgical treatments for BPH (TUNA, TUMT, HIFU,…) have also been abandoned and are currently not used in Belgium.**
- **To date, amongst the new laser techniques, PVP and holmium lasers are more and more used in the urologic community worldwide. Therefore, this rapid assessment is focused on the PVP and holmium laser (HoLEP).**
- **PVP is currently used at a number of Belgian hospitals.**

2.2 REGULATORY STATUS OF PVP AND HOLMIUM LASER

2.2.1 Regulatory status of PVP

The laser procedure (product name: GreenLight PVP) received FDA clearance in May 2001[k]. The device is also CE approved in Europe.

2.2.2 Regulatory status of holmium laser

Two holmium lasers are 510(k) cleared for treatment of BPH by the FDA: Trimedyne's 80 watt holmium laser and Lumenis (Coherent) 60-100 watt holmium laser.

The Lumenis holmium laser received FDA 510(k) clearance for surgical ablation and vaporization in 1990. From 2001, additional indications included holmium laser resection, enucleation and ablation of the prostate.

In Europe, the holmium laser is CE approved.

2.3 CLINICAL EFFECTIVENESS

2.3.1 Research questions

The clinical part addresses the following clinical questions on the two selected "minimal invasive techniques": PVP and holmium laser (HoLEP).

1. What is the evidence on clinical effectiveness and safety of those techniques in BPH?
2. What are the patient outcomes after these interventions (a.o. quality of life)?
3. Is there any benefit from these compared to the standard therapies?

2.3.2 Literature review

2.3.2.1 Methodology, sources, in- and exclusion criteria.

For the applied methodology, the explored sources and the in- and exclusion criteria, we refer to the section on the literature review of HIFU. The methodology applied was similar to the one applied for the HIFU search, except that no guidelines have been searched for BPH.

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k Source: http://www.prostatelaser.com.my/faq.htm#q3 consulted in June 2008

2.3.2.2 *Systematic search*

Results for HTA reports

The following HTA reports were identified.

For PVP:

- National Health Service (NHS) R&D Health Technology Assessment[54]
- L. Boltzmann Institut (report published in German, Wien 2007)[55],
- CADTH published in 2006 an Interventional Procedure Guidance. [56]

For PVP and holmium:

- the Ontario Health Technology Advisory Committee [46]
- German report unpublished (IQWIG)

For holmium:

- Interventional procedure overview of holmium laser prostatectomy (NICE 2003)

Critical appraisal of HTA reports

For the critical appraisal of the HTA reports, the INAHTA HTA checklist was used (see results in Appendix from Chapter 2.3 in table 40).

PVP

Two reports, published by the National Health Service (NHS) R&D Health Technology Assessment[54] and L. Boltzmann Institut (report published in German, Wien 2007)[55], were critically appraised and received a high quality score.

The Canadian Agency for Drugs and Technologies in Health (CADTH) published in 2006 an Interventional Procedure Guidance. [56] In this report, however, there was no statement on conflicts of interest, nor on external review. The description of the selected studies was also very short.

PVP and holmium

The report of the Ontario Health Technology Advisory Committee) [46] was critically appraised. The report fulfilled all criteria of the INAHTA HTA checklist.

The "Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen" (IQWiG) placed on the Web a draft from "Nichtmedicamentöse lokale Verfahren zur Behandlung der BPH " (report in process written in German) in order to receive comments. [53] This very extensive report was critically appraised and also fulfilled all criteria of the INAHTA checklist.

Holmium

The report published by the NHS: "International Procedure Guidance 17" [57] received a high quality score.

Search for additional evidence to update HTA reports

For each clinical question, the evidence identified through the qualitative HTA reviews, was updated by searching Medline and the Cochrane Database of Systematic Reviews from the last search date of the HTAs on. A combination of appropriate MeSH terms and free text words was used (see Table 10).

In addition, the reference lists of the selected HTA reports were searched for any missing relevant publications.

PVP

One RCT on PVP was identified (Fowler 2005). Furthermore, the study of Ruszat [58] about safety in patients on ongoing oral anticoagulation was found and the Bouchier-Hayes study from 2007, an update from the 2006 study. The following article was excluded: Hwang (abstract in English but full report in Korean).

Holmium

1 systematic review on holmium was identified (Tooher 2003). For the critical appraisal of the systematic review of Tooher[35] on holmium, the Cochrane checklist was used (see results in table 42). The review obtained a high score.

Search terms for updating

For Medline the MeSH terms described in table 11 were used.

Table 10: Medline search terms for updating

	MEDLINE Search Strategy
PVP	((photo-selective or photoselective) adj vapo?ri#ation).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
	(Potassium titanyl phosphate or KTP).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
Holmium	(((Holmium or YAG) adj4 la#er adj6 prostat$) or holrp or holap or holep).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

Results

The final selected studies to update the selected HTA reports are:

- Ruszat [58]
- Bouchier-Hayes [59]

In appendix, a flowchart gives an overview of the full search and sifting process.

2.3.3 Clinical effectiveness of PVP therapy

2.3.3.1 Selected HTA reports

The reports that were used as a basis for this report (see annex table 40) are listed in Table 12. It concerns The Interventional procedures Guidance 120 published by NICE in 2005, one HTA report published by the Ontario Advisory Board Committee in 2006 [46] and two reports in German [55,53].

Table 11: Summary of HTA reports selected

CPG ID	Search date	Recommendation and comments	Supporting evidence	Level of evidence
NICE 2005 Guidance 120	October 2004	Current evidence on safety and efficacy appears adequate to support the use of this procedure. Data on long term efficacy are limited (follow-up at one year).	Malek 2000 Hai 2003 Carter 1999	Low (prospective cohort study)
Ontario HTA Advisory Committee 2006	June 21, 2006	PVP is clinically as effective as TURP for the relief of urinary symptoms (on 6-month follow-up). Time to catheter removal was significantly shorter in patients undergoing PVP than TURP.	Shingleton 2002	Low (prospective cohort study)
Ludwig Boltzmann Institut Wien 2007	Not mentioned	Lack of follow-up data. Conclusions from Bouchier Hayes too optimistic. A much larger observational study is required to assess the incidence of adverse events at long term.	Bouchier-Hayes 2006 Fowler 2005 NICE 2004 Gupta N 2006 Wilson 2006 Bachmann A 2005 Malek 2000	Moderate (study in process, too short follow-up)
IQWiG	May 2005	The three studies were not retained after critical appraisal. Too short follow up.	Bouchier-Hayes 2006 Bachmann A 2005, Hwang 2005 (abstract only)	Moderate

2.3.3.2 *Efficacy*

Efficacy outcome measures evaluate the efficacy of the treatment in relieving the symptoms or sequelae of BPH. Symptom scores are instruments that provide an objective assessment of subjective phenomena. The current international standard, used worldwide, is the AUA Symptom Index/International Prostate Symptom Score (IPSS; see appendix of chapter 2.3). The Q max (maximal flow rate in ml/s) is an easy, feasible and reproducible test widespread used as quantitative measure.

Table 12: Prospective control studies

Study ID	Population and intervention	Symptom scores	Peak flow rate	Complications	Study type
Shingleton 2002	100 patients , 50 patients underwent TURP, 50 received PVP (60 Watt)	Follow up at 36 to 72 months: mean symptoms score not statistically significant 7.7±5.6 between TURP and 9.9±6.7 for PVP	Follow up at 36 to 72 months: mean peak flow rate not statistically significant (12.8±5.6 for TURP and 12.3±5.3 for PVP)	Morbidity and complication rates are similar between the two groups	RCT
Bachmann 2005,	101 patients , 37 patients underwent TURP, 64 received PVP	Follow up at 6 months: IPSS change not statistically significant between TURP (72%) and PVP (71%)	Follow up at 6 months: improvement of Qmax not statistically significant between TURP (176%) and 162% for PVP	Excellent intraoperative safety Serum Hb significantly (p=0.027) lower after TURP than after PVP	Prospective non randomised trial
Bouchier-Hayes, 2007	110 patients , 50 patients received TURP, 60 received PVP (80 watt)	Follow up at 12 months on 87 patients, IPSS reduction not statistically significant between TURP (56.5%) and PVP (54.08%)	Follow up at 12 months: increase of Qmax not statistically significant between TURP (149%) and PVP (167%)	PVP is associated with significantly less blood loss (g/dl) (0.43±0.77) than TURP (1.52±1.48)	RCT Insufficient numbers Interim data

All control studies demonstrated that TURP and PVP are equivalently effective in improving the symptoms of benign prostatic enlargement.[59-61] However, the follow-up is short and too few patients (no more than 150 patients on each arm) were included. Consequently, the statistical power of those studies remains questionable. HTA reports concluded that data on long term efficacy are limited and that larger observational studies are required to asses the incidence of adverse events at long term.[46, 55] Furthermore, IQWiG did not include the study of Bachmann as there were no prognostic factors in the study and as only intermediate data were presented. IQWiG did not include the study of Bouchier-Hayes either as the study also presented intermediate data only. IQWiG asked the authors of both studies for further data but did not yet receive an answer at the time of publication of their report. Taking into account that samples are too small and that follow-up remains relatively short, PVP seems to be as clinically effective as TURP.

2.3.3.3 *Safety*

In all controlled studies, morbidity and complication rates were similar between TURP and PVP groups.[60, 61] In particular, blood loss requiring transfusion is one of the most common problems following prostate surgery. Three studies demonstrated less blood loss immediately after surgery. In Bachmann series, serum haemoglobin was significantly (p = 0.027) lower after TURP (12.9 ± 1.5) than after PVP (13.7 ± 2.0). (The drop in serum haemoglobin was not mentioned in the study.)

In Bouchier-Hayes series, the blood loss (0.43±-0.77 g/dl) for PVP was significantly (p< 0.05) lower than for TURP (1.52±1.48 g/dl). It must be noted that in this study, platelet inhibitor therapy was stopped 10 days preoperatively. In a recent study (2007), Ruszat reported that PVP was performed by 116 men on ongoing oral anticoagulation or antiplatelet therapy, with 31% (n = 36) receiving coumarin derivatives; 61% (n = 71), aspirin; and 8% (n = 9), clopidogrel. Retrospectively, no more bleeding complications necessitating blood transfusions were observed for those patients than for the control group (patients without anticoagulation).[58] TURP performed by patients on ongoing oral anticoagulation may require blood transfusions.[62] However, there is a need for large controlled trials directly comparing PVP and TURP.

2.3.3.4 Patient outcomes

Sexual problems are the most common problems for patients after prostate interventions. Shingleton and Bachman reported a similar rate of sexual problems (erectile dysfunction, retrograde ejaculation or decreased ejaculate) after TURP or PVP. Bouchier-Hayes also noted that there was no significant difference in sexual function after TURP or PVP. However, series remain short and it is difficult to conclude based on current data.

2.3.3.5 Benefits

Most benefits are obtained by a diminution of the length of catheterisation and length of stay. Bachman reported a significant difference (p< 0.001) between number of days with catheter: 1.8 (±1.8) for PVP versus 3.0 (±1.5) for TURP and a significant difference (p< 0.001) between number of hospital days: 5.5 (±2.7) for PVP versus 7.1 (±1.8) for TURP. Bouchier-Hayes also reported a significant difference (p< 0.0005) between length of catheterization time (in hours): 13.1 (±8.2) for PVP versus 44.72 (±37) for TURP and a significant difference (p< 0.00000001) between number of hospital days: 1.1 (±0.28) for PVP versus 3.57 (±1.5) for TURP. Those results also must be confirmed by blinded RCTs as the treatment decision may influence the length of stay.

2.3.3.6 Observational studies

As already mentioned, no long term data were found based on RCTs. Using the "cited-by" tool of Medline, a non-exhaustive search for observational studies with longer follow-up was done. A recent observational study from Malek et al. (2005)[63] was identified. In this study, long-term observation (up to 5 years) of 94 patients treated with PVP found no incidences of significant postoperative haematuria, despite the fact that half the patients were taking antiplatelet medications. Six patients (6%) experienced mild, sterile dysuria that resolved within 2 to 3 weeks without treatment. The investigators noted several delayed complications including: transient self-limiting gross haematuria (3%), soft vesicle neck contracture (2%) and epididymitis (1%). No patients had urinary incontinence or newly developed impotence. In addition, no patient required reoperation, including those who declined to return for long-term follow-up. Retrograde ejaculation was noted in 9/37 (24%) sexually active patients at 1 year, 8/31 (26%) at 2 years, 5/21 (24%) at 3 years and 0/9 (0%) at 5 years (Malek et al. 2005).

- **The number of patients treated in controlled trials is low (150 patients) and follow-up short (1 year). Taking this into account, there exits only limited evidence on safety and efficacy to support the use of PVP.**
- **Studies indicated that blood loss may be lower after PVP compared with TURP.**
- **There was no significant difference in sexual function after TURP or PVP, but series remain too short to conclude.**
- **PVP may significantly reduce length of catheterization and hospital stay, but those results must also be confirmed by larger and blinded studies, as the treatment decision may influence the length of stay.**
- **Looking at non-controlled observational studies, there are a few with longer follow-up (up to 5 years), however, the patient population is too small for firm evidence. Longer term controlled studies are required to assess the incidence of adverse events at long term.**

2.3.4 Clinical effectiveness of holmium laser (HoLEP)

2.3.4.1 Efficacy

The reports that were used as a basis for this report are listed in Table 14. It concerns the Interventional Procedure Guidance (nr 17) published by NICE[57] and the two already cited reports about minimal invasive techniques[46, 53].

Table 13: Summary of HTA reports selected on HoLEP

CPG ID	Search date	Recommendation and comments	Supporting evidence	Level of evidence
NICE 2003 Guidance 17	October 2002	HoLEP is at least as effective as TURP in improving bladder neck obstruction, symptom scores and quality of life.	Tooher 2002 Gilling 1998 Kitigawa 1998 Kuntz 2002	Moderate (RCT's of poor quality)
Ontario HTA Advisory Committe 2006	June 21, 2006	The results of RCTs on HoLEP versus TURP with 1-year follow-up showed excellent clinical outcomes in regard to the urinary symptom score and peak urinary flow.	Kuntz 2004a Kuntz. 2004b Rigatti 2006 Gupta 2006 (3-arm study; TUVRP vs HoLEP vs TURP) Montorsi 2004 Tan. 2003 (HoLEP vs open Prostatectomy)	Moderate (1 year follow up)
IQWiG	Online published on 02.06.2008	Study results in respect of symptoms were heterogeneous without any straightforward explanation for this heterogeneity	Kuntz 2004a Kuntz. 2004b Briganti 2006 Gupta 2006 (3-arm study; TUVRP vs HoLEP vs TURP) Naspro 2006 Sasonia 2006 Wilson 2006	Moderate (inconsistency)

Tooher performed in 2003 the first systematic review based on five RCT's. Although four out of five RCT's were considered of poor quality, he concludes that HoLEP was at least as efficacious as TURP in the short term (12 months).[35] The Ontario Health Technology Advisory Committee (OHTAC) published a meta-analysis on the Web in august 2006. This meta-analysis pooled data published by Tan[45], Gupta 2006, (3-arm study; TUVRP vs HoLEP vs TURP)[64], Kuntz 2004[65] and Rigatti 2006[66]. Results may be assessed for 233 patients treated by HoLEP versus 228 patients treated by TURP.

At one year follow-up, the weighted mean difference was – 0.78 (95% CI –1.39 to – 0.16, P = .01) for IPSS and 1.75 (95% CI 0.31 to 3.19; P = .02) for Qmax, both in favour of HoLEP, but this analysis did not allow to draw conclusions for longer follow-up.

The most recent meta-analysis was performed by IQWiG. They pooled data published by Gupta (2006)[64], Kuntz 2004[67,65], Briganti 2006, Naspro 2006[68] and Wilson 2006[69]. Briganti, Rigatti and Naspro are co-workers in Milan. Briganti and Rigatti reported on patients treated from January 2002 to January 2003 while Naspro reported on patients treated from March 2003 to December 2004. Tan and Wilson are co-workers in Tauranga, New Zealand, but they both reported on the same cases series. Results were analysed for 301 patients treated by HoLEP versus 295 patients treated by TURP, at one year follow-up. The weighted mean difference for IPSS is – 0.16 (95% CI –0.47 to 0.15, P = .004) in favour of HoLEP. For longer follow-up (24 months), results were analysed for 105 patients treated by HoLEP versus 103 patients treated by TURP, and the weighted mean difference for IPSS is 0.11 (95% CI –0.16 to 0.38, P = .0791) in favour of TURP. IQWiG concluded that the study results in respect of symptoms were heterogeneous without any straightforward explanation for this heterogeneity.

2.3.4.2 Safety

The meta-analysis published by OHTAC[46] mentioned that none of the patients treated by HoLEP required blood transfusion versus 5 patients on those treated by TURP (2.2%). Data on blood transfusion were not reported by all studies in the meta analysis and therefore this percentage must be taken cautiously. In Kuntz's series haemoglobin loss was significantly (p=0.001) lower -1.3 ± 1.0 [0–3.9] (gm/dl) for HoLEP than for TURP: -1.8 ±1.4 [0–7.8]. [65]

2.3.4.3 Patient outcomes

Kuntz reported sexual outcomes.[65] Ten patients (11.2%) developed impotence and 66 (74%) developed retrograde ejaculation in the HoLEP arm, versus 9 patients (10.5%) for impotence and 61 (70.3%) for retrograde ejaculation in the TURP arm. Briganti reported that the retrograde ejaculation caused by TURP and HoLEP significantly lowered the orgasmic function domain with no differences between techniques.[70] Naspro also demonstrated that sexual complications were comparable in both groups.[68] Finally, IQWiG concluded that there is insufficient evidence for an advantage in terms of QoL, but that there is also insufficient evidence to conclude that the treatments are of equal value, as none of the studies was conceived as an equivalence or non-inferiority trial.

2.3.4.4 Benefit

Most benefit is obtained by a diminution of the length of catheterisation and of length of hospital stay. All studies reported a significant difference (p< 0.001) between number of days with catheter 1 day or less for HoLEP versus 3 to 7 for TURP. A similar significant difference (p< 0.001) was shown for the number of hospital days 1 day for HoLEP versus 3 to 7 for TURP or open prostatectomy. Those diminutions may be a consequence of decreased bleeding in HoLEP cases.[65] On the other hand, studies reported a longer operating time for HoLEP than for TURP. OHTAC mentioned that the pooled mean operating time was 23 min longer in the HoLEP arm. This prolonged time may be due to the use of a morcellator and depends on the size of the prostate.[46]

- **Taking into account that the patient population is small (300 patients), follow-up short (2 years) and some results heterogeneous, limited evidence on safety and efficacy is available to support the use of HoLEP.**
- **One study demonstrated a significantly lower blood loss immediately after surgery for the use of HoLEP compared with TURP.**
- **There were no significant differences in sexual function between HoLEP and TURP, but series remain too short to conclude.**
- **Current evidence indicates that HoLEP may significantly reduce length of catheterization and hospital stay, but the studied patient population is small.**

2.4 ECONOMIC EVALUATION OF PVP AND HOLMIUM LASER

2.4.1 Cost of PVP and holmium laser

This section provides an overview of cost elements as found in a number of scientific articles. In order to get a full cost picture of the new laser therapies, a number of components need to be taken into account. First of all, there is the procedure cost which includes the initial investment, the operation time and associated human resources cost, the disposable materials and the cost of blood transfusions. Second, there is the hospitalization cost, which depends on the length of stay, the postoperative nursing requirements and irrigation and catheterization needs. Besides the procedure and hospital costs, also follow-up costs (costs occurring after hospital discharge) and costs of adverse events and retreatment need to be taken into account for a full economic evaluation compared to conventional therapy.

In the following cost data overview, the focus is put on the most transferable, least country-specific, cost information. It concerns the investment and disposables cost, and resource use data (operation time, length of hospitalisation), based on international literature. Detailed international data on unit costs (cost of a surgeon, cost of a hospital day), however, has been omitted here, as these costs are considered too country-specific to be extrapolated to the Belgian situation.

2.4.1.1 Cost data on PVP

A number of studies have addressed the cost of PVP. In Switzerland, a cost analysis showed comparable costs during hospital stay for TURP and PVP (Ruszat, 2006). The Australian cost analysis of Bouchier-Hayes (2007) showed lower costs during hospital stay for PVP compared to TURP. The American study of Stovsky (2006) also reported lower costs for PVP than for TURP, not only taking into account costs during hospital stay, but also follow-up care, adverse events and retreatment. An overview of the overall costs is given in Table 14.

Table 14: Overview of data on overall costs for PVP

Source	Costs included	TURP	PVP
Ruszat 2006	Costs of initial procedure (operation room, surgeons and anaesthesiologists, disoposables) and postoperative nursing	CHF 8 131	CHF 8 238
Stovsky 2006	Costs of initial procedure, adverse events, re-treatment and routine follow-up care at 24 months time horizon	US$ 4 927	US$ 3 589
Bouchier-Hayes 2007	Cost of initial procedure and hospitalization ($p<0.005$)	AU$ 4 292	AU$ 3 368

In Table 16, some literature data is given on three main resource use parameters, notably operation time, length of stay and length of catheterization. In all presented studies, there is a clear decrease in length of stay and length of catheterization. It is not clear whether the operation time is shorter or longer for PVP.

In Table 17, some data are presented on the investment, maintenance and disposables cost for PVP. The data are based on literature on one hand, and on data from Hospithera, Belgian distributor of Greenlight technology, on the other hand. This distributor provided cost data for both the Greenlight PVP (80 watt) and the new, higher power (120 watt) Greenlight HPS. According to the distributor, the newer version (HPS) is recommended. Their price data is shown in US dollars, as the device is imported from the US. Further, Table 17 shows that cost of disposables is higher for PVP. The cost of the surgical set-up also seems higher for TURP (at least in the study of Ruszat (2006)).

Table 15: Overview of data on resource use for the initial procedure and hospitalization for PVP

	Source	TURP	PVP	P value
Operation time (min.)	Ruszat 2006 [71]	66 (N=28)	54 (N=77)	0.011
	Bachmann 2005 [61]	49.4 ± 16.0	59.6 ± 24.4	0.047
Length of stay (days)	Bouchier-Hayes 2007 [59]	3.57 ± 1.5	1.1 ± 0.28	<0.00000001
	Ruszat 2006 [71]	6.5	5.2	<0.001
	Bachmann 2005 [61]	7.1 ± 1.8	5.5 ± 2.7	<0.001
Length of catheterization (hrs)	Bouchier-Hayes 2007 [59]	44.72 ± 37	13.1 ±8.2	<0.005
	Ruszat 2006 [71]	74.4 (N=28)	45.6 (N=77)	<0.001
	Bachmann 2005 [61]	72 ± 36	43,2 ± 43.2	<0.001

Please note that not all resource use parameters are included in this table, such as the number and volume of blood transfusions, as no comparative data was found on it.

Table 16: Overview of data on investment and disposables cost for PVP

	Source	TURP	PVP
Device cost (VAT excl.)	MAS 2006	CAN$ 135 000	CAN$ 100 000
	Bachmann 2005 [72]		€ 100 000- € 120 000
	Hospithera 2008	Bipolar TURP: €35 000-45 000	HPS: US$ 198 000 PVP: US$ 162 000
Lifetime of device	Hospithera 2008	Usually 3 to 5 yrs (fast model rotation)	10 yrs
Yearly maintenance cost (VAT excl.)	Hospithera 2008	minimal	€ 5 000
Cost of operation room (device and maintenance cost)	Ruszat 2006 [71]	CHF 1 639	CHF 1 226
Costs for disposables (per procedure)	Ruszat 2006 [71] All disposables including laser fibre	CHF 222	CHF 1 775
	Bachmann 2005 [72] Laser fibre only		€ 1 000 to € 1 200
	Hospithera 2008 Laser fibre only		US$ 1 500

- **Taking into account that only a limited number of comparative cost studies are available and that they are not blinded, cost data indicate that PVP has a shorter length of stay and length of catheterization than classical TURP. Overall, cost studies show lower to slightly higher costs for PVP compared to TURP.**
- **As long term studies are still lacking, the long term costs cannot be assessed yet.**

2.4.1.2 *Cost data on HoLEP*

The Italian study of Salonia et al. indicates a lower overall treatment and hospitalization cost for HoLEP than for OP for larger prostates (see Table 18). In this study, costs associated with HoLEP are 18% lower than with OP.

Table 17: Data on overall costs for HoLEP

Source	Costs included	HoLEP	OP
Salonia 2006	Costs of initial procedure, hospital stay and unplanned events during hospital stay. Medical salary costs not included.	€2 356.5	€2 868.9

In Table 19, an overview is given of some more data on the resource use for HoLEP as found in the literature. In general, the data show longer operative time for HoLEP than for TURP or OP and a shorter length of hospitalization and length of catheterization for HoLEP.

Table 18: Overview of data on resource use for the initial procedure and hospitalization for HoLEP

	Source	HoLEP	TURP	OP	P value
Operative time (min.)	Kuntz et al. 2004 [c]	94.6	73.8		<0.0001
	Montorsi et al. 2004 [d]	74	57		<0.05
	Salonia et al. 2006 [a]	73.4		57.7	0.002
	Kuntz et al. 2002 [g]	135.9		90.6	<0.0001
Laser energy time (min.)	Tan & Gilling 2003 [b]	66.4			
Morcellation time (min.)	Tan & Gilling 2003 [b]	16.1			
Autologous blood transfusion volume (mL)	Salonia et al. 2006 [a]	48.5		133.3	0.07
Homologous blood transfusion volume (mL)	Salonia et al. 2006 [a]	24.5		120.0	0.04
Postoperative holding area (hrs)	Salonia et al. 2006[a]	0.25		0.416	
Length of hospitalization (hrs)	Kuntz et al. 2004[c]	53.3	85.8		<0.0001
	Montorsi et al.[d]	59	85.8		<0.001
	Salonia et al. 2006[a]	64.6		131.0	<0.0001
	Kuntz et al. 2002 g	69.6		251.0	<0.0001
	Moody & Lingeman 2001[e]	50.4		146.4	
	Larner et al. 2003[f]	5.03			
	Tan & Gilling 2003[b]	28.4			
Length of catheterization (hrs)	Kuntz et al. 2004[c]	27.6	43.4		<0.0001
	Montorsi et al. 2004[d]	31	57.78		<0.001
	Kuntz et al. 2002 [g]	30.8		194.4	<0.0001
	Salonia et al. 2006 [a]	35.3		106.3	<0.0001
	Larner et al. 2003 [f]	48			
	Tan & Gilling 2003[b]	19.7			

[a] 29 patients treated with OP, 34 patients with HoLEP. Prostate 70 to 220g.
[b] 43 patients treated with HoLEP. Prostate >100g.
[c] 100 patients treated with HoLEP, 100 with TURP. Prostate <100g.
[d] 52 patients treated with HoLEP, 48 patients treated with TURP.
[e] 10 patients with HoLEP and 10 with OP
[f] 38 patients treated with HoLEP.
[g] 60 patients treated with HoLEP, 60 with OP. Prostate >100g.
Note: where cells are left blank, no information is available.

Furthermore, some literature data on the cost of the investment and disposables is presented In Table 20.

Table 19: Overview of data on investment and disposables cost for HoLEP

	Source	Holmium	OP
Device cost (VAT excluded)	Tan 2003b [73]	100 watt laser: US$140 000	
	Lumenis	100 watt laser: € 137 900 Morcellator: €17 000	No device needed, only surgical materials
Lifetime of device (and morcellator)	Lumenis	10 – 15 yrs	not applicable
Fiber	Lumenis	Reusable fiber for HoLEP: €450 (reusable for 10 – 20 procedures)	not applicable
Yearly maintenance cost	Lumenis	€1 000 (preventive maintenance)	not applicable
Operating room surgical setup/disposables/fibers	Salonia et al. 2006	€ 690.5 (HoLEP)	€ 382.3

- **Taking into account that only few full comparative cost studies are available and that they are based on a small population and not blinded, cost data indicate that HoLEP has a shorter length of hospitalization and length of catheterization than TURP.**
- **As long term studies are still lacking, the long term costs cannot be assessed yet.**

2.4.2 Review of cost-effectiveness studies on PVP

2.4.2.1 Introduction

As for both PVP and HoLEP laser treatment, the number of patients treated in controlled trials is low and follow-up short (1-2 years), no high-quality cost-effectiveness study can be performed yet. Nevertheless, a literature search was done in search of preliminary cost-effectiveness results. An overview of these results is provided in this chapter.

2.4.2.2 Selection criteria

All references obtained from the literature searches (see further in sections 2.4.2.3 and 2.4.3.1) were assessed based on title, abstract and keywords. When no abstract was available or the reference was unclear or ambiguous, consideration of the reference was made on the basis of full-text assessment. Reference lists of retrieved papers were checked for additional relevant references. Papers fulfilling several selection criteria were included in the economic review. Only full economic evaluations that compare two or more alternatives and consider both costs and consequences, including cost-effectiveness, cost-utility, cost-benefit and cost-minimisation analyses, were eligible.

2.4.2.3 Review of economic literature on PVP

Literature search strategy on PVP for BPH

HTA INSTITUTES REPORTS

As a first step, the HTA sources were searched (the CRD-HTA database and the websites of INAHTA members). 9 reports after 2000 were identified: Ludwig Boltzmann Institut (2007)[55], MAS (2006)[46], IQWiG (2007)[53], IECS (2007)[74], CADTH (2006)[75], AHRQ (2004)[52], NICE (2005)[54] and 2 reports from Hayes (2002 and 2006). All the reports were consulted, except for the Hayes reports (since they were not available for purchase anymore as they were published more than 2 years ago). The search was performed on 22 April 2008.

ELECTRONIC DATABASES

None of the consulted HTA institutes' reports covered a full review of the economic literature which could serve as a basis for further review. Therefore, as a second step, other databases were also searched to find the most recent qualitative review – if any - and to find primary studies to update this review.

The CRD-NHS EED database was searched on 29 April 2008. The databases Medline, Embase, and Econlit were searched on 7 May 2008. Studies were searched from the year 2000 onwards.

Overview of full economic evaluations

No complete reviews were identified. Two original full economic evaluations were identified: Stovsky 2006 and Bouchier-Hayes (2007)[l]. First, a brief overview is given of these studies. Afterwards, the limitations of the studies are discussed.

Stovsky 2006

METHODOLOGY

In the study of Stovsky (2006), a decision analytic Markov model was used to compare the clinical outcomes and cost characteristics of PVP, microwave thermotherapy, transurethral needle ablation, interstitial laser coagulation and TURP. In the model, hypothetical cohorts of 10 000 patients were entered. The patients in these hypothetical cohorts were followed for 2 years, on a monthly basis. In month 1, the patient incurred the cost of the procedural intervention. Each month the patient was exposed to the risk of adverse events related to the intervention and to the risk of requiring re-treatment. In the model, adverse events and retreatment could only occur once per patient. In each month, the monthly scores for American Urological Association/International Prostate Symptom Score (AUASS/IPSS), maximum flow rates (Qmax) and quality of life (QoL) scores were calculated per patient. The QoL score was based on the disease specific QoL question in the AUASS/IPSS questionnaire with answers on a 6-point scale. With the model a projection was made of the total expected costs related to the interventions from the Medicare perspective and their clinical outcomes, during a 2 year horizon.

OUTCOMES

Clinical outcomes were measured by AUASS/IPSS, Qmax and QoL. Changes in the scores for TURP were obtained from the data set of the AUA Clinical Guidelines for the Management of BPH[25]. For PVP, a literature review and analysis of clinical trials was performed by the authors, in line with the AUA guidelines methodology. The following studies on PVP were taken into account: Bachmann et al. (2005)[72;61], Carter et al. (1999)[76], Hai and Malek (2003)[77], Malek et al. (2005)[63], Miki et al. (1997)[78], Reich et al. (2005)[79], Sulser et al. (2004)[80] and Te et al. (2004)[81]. The changes in outcomes were measured from the baseline values to the values at 6, 12 and 24 months after treatment (see Table 21).

l The report Bouchier-Hayes et al. (2006) is not mentioned here as it contains the first results of Bouchier-Hayes (2007)

Table 20: Clinical outcomes

Time Horizon	% decrease from baseline	
	PVP	**TURP**
AUASS/IPSS		
6 Mos	73	67
12 Mos	74	67
24 Mos	76	66
Qmax		
6 Mos	188	124
12 Mos	199	125
24 Mos	221	117
QoL		
6 Mos	81	76
12 Mos	82	76
24 Mos	83	73

Note: AUASS/IPSS and QoL are inversely related to improvement in symptoms and quality of life and, therefore, decrease in AUASS/IPSS and QoL indicates fewer symptoms and better quality of life, respectively

The baseline values were assumed to be identical across the procedural interventions. They were calculated at 22 for AUASS/IPSS, 8.5 for Qmax and 4.5 for QoL. AUASS/IPSS and QoL scores are inversely related to improvement in symptoms and quality of life and, therefore, a decrease in AUASS/IPSS and QoL score indicates fewer symptoms and better quality of life, respectively.

PROBABILITIES

Probabilities of adverse events of TURP were based on the American Urological Association (AUA) Clinical Guidelines for the Management of BPH[m]. Probabilities of adverse events of PVP, as they were not included in the guidelines, were based on a literature search and review done by the authors according to the approach described in the AUA guidelines methodology. Compared with TURP, PVP seemed to have lower risk for reoperation, urinary tract infection, impotence or erectile dysfunction, dysuria, bladder neck stenosis/stricture and hematuria. PVP had equal incontinence rates and higher urinary retention risk (see Table 22).

COSTS

The model included the costs of initial treatment, follow-up care, adverse events and retreatment.

The costs of initial treatment were taken from the perspective of Medicare. These costs were obtained by summing up physician and facility payments from the 2005 Medicare fee schedules. As Medicare payments for BPH procedures depend on the setting in which the procedure is performed, it was assumed that for PVP treatment, all procedures were performed in a hospital outpatient setting, whereas for TURP treatment, all procedures were in a hospital inpatient setting. The costs of initial treatment were $2 852 for PVP and $3 748 for TURP.

Table 21: Costs of initial treatment and follow-up care

	Costs of initial treatment (2005 $)	**Costs of follow-up care per month (2005 $)**
PVP	2 852	22
TURP	3 748	22

The costs of adverse events are based on Medicare data, reflecting actual services provided to patients. Using the Medicare 5% institutional and physician/supplier files from 1999 to 2001, physician/supplier claims that indicated a diagnosis of BPH and a procedure for BPH, were analysed.

[m] Management of BPH (2003). American Urological Association. Available at http://www.auanet.org/duidelines/bph.cfm.

For each patient a history of medical services was constructed for up to 1 year following the date of the procedure. The cost of adverse events was calculated independently from the type of the initial procedure. See Table 22 for an overview of costs and probabilities of adverse events.

Table 22: Costs and probabilities of adverse events

Adverse event	Cost of managing adverse event	Probability of adverse event for PVP (%)	Probability of adverse event for TURP (%)
Reoperation	3 889	1	5
Incontinence	286	3	3
Urinary tract infection	314	5	6
Impotence/erectile dysfunction	282	0	10
Dysuria/irritative voiding	183	9	15
Bladder neck stenosis/stricture	534	3	7
Urinary retention	294	6	5
Hematuria	313	5	6

Costs of follow-up care were estimated at $22 per month for both treatment options (see Table 21). This amount was calculated based on the same 1999-2001 patient data from Medicare 5% institutional and physician/supplier files. All claims with a diagnosis of BPH and indicating that the service was related to BPH but not to an adverse event, were taken into account. These monthly costs were assumed to occur for the full 24 months period.

RESULTS

PVP resulted in larger beneficial changes in I-PSS, Qmax and QoL scores at all time points evaluated, compared to TURP. The largest difference between PVP and TURP was observed for Qmax (percentage decrease from baseline at 24 months: 221 versus 117%). The expected cost per patient at all three time points was lowest for PVP (see Table 23). The cost savings of PVP came from the low rates of adverse events and retreatment. Most costs at all time periods (at 6, 12 and 24 months) were due to the initial procedural intervention, while only 6–30% of the total cost was related to treatment of adverse events or to retreatment. Sensitivity analysis of the model showed that the re-treatment rate for the PVP procedure should be 17% to make the cost of PVP equal to the cost of TURP. According to the authors, this rate is however more than three times greater than the PVP retreatment rate reported in the literature (Reich (2005)[79]). The model also showed that even with rates of adverse effects for the PVP laser at the maximum observed values, the expected total cost of the method at 12 and 24 months would still be less than that of all other treatment modalities.

Table 23: Expected cost per patient (US$)

	Time horizon		
	6 Months	12 Months	24 Months
PVP	3 020	3 214	3 589
TURP	4 030	4 331	4 927

Bouchier-Hayes et al. 2007[59]

METHODOLOGY

A series of 120 patients was randomized to undergo TURP or PVP. Evaluation of clinical outcomes was repeated at 1, 3, 6 and 12 months after treatment. They included IPSS reduction, Qmax, QoL score, bother score and BSFQ (baseline sexual function questionnaire) score). Irrigation use, length of catheterization (LOC), length of hospital stay (LOS), postvoiding residual volume, sexual function, blood loss, cost and operative time were also assessed.

OUTCOMES

For the reported outcomes, see section 2.3.3.2.

COSTS

Costs were calculated from the hospital perspective. Only costs during hospital stay were taken into account. An average cost per case of AU$4 292 and AU$3 368 was reported for TURP and PVP respectively (see Table 24). These calculations were made on the basis of a sample of 5 random cases from each arm. The costing manager of the hospital assessed the inpatient cost to the hospital including drugs, nursing care, operating theatre time for the total length of stay. For the cost of the fibre also AU$1 000 per patient was added. A capital cost was considered of AU$147 per PVP case and AU$14.70 per TURP case. Capital costs were assessed assuming 163 procedures per year (which equalled the number of TURPs performed in the hospital in the year prior to the start of the study). The considered lifetime of the equipment, however, is not known. Professional fees were not included. Costs of adverse events occurring after hospital discharge were not included either.

Table 24 also shows that the length of catheterization, length of stay and haemoglobin decrease were significantly lower for PVP.

Table 24: Average cost results of PVP versus TURP

	TURP	PVP	P
LOC (hr)	44.72	13.1	<0.0005
LOS (days)	3.57	1.1	<0.00000001
Hemoglobin decrease (g/dL)	1.52	0.43	<0.05
Cost per case (AU$)	4 292	3 368	<0.005

RESULTS

The trial showed equivalent improvements in flow rates and IPSS scores for PVP and TURP at 1 year follow-up. The trial demonstrated a reduced length of stay, length of catheterization and less adverse events for PVP at 1 year follow-up. The costs were also 22% less in the PVP group.

Discussion of the studies

First of all, as also described in the studies, there are important limitations to the outcome data of the studies. In both studies, the data on clinical effectiveness of PVP, compared to TURP, are based on results from trials with a small patient population, sometimes observational and nonrandomized studies, with short follow-up so far. The results can not yet be extrapolated to large populations and the durability of the PVP procedure has yet to be assessed. For cost-effectiveness analysis, both the short- and long-term treatment effects should be taken into account to reflect the differences between PVP and TURP (or other standard treatment).

Secondly, there are also important limitations to the cost side of these studies. In both studies the considered length of stay is short compared to other studies (Stovsky assumed that all PVP procedures are performed in a hospital outpatient setting and Bouchier-Hayes reported an average length of stay of 1.1 days). This short length of stay remains to be confirmed by larger and blinded studies, as some other (small) studies report considerably longer lengths of stay. The studies of Bachman (2005)[61] and Ruszat (2006) (add reference) notably report average lengths of stays of respectively 5.5 and 5.2 days and the studies Dincel et al. 2004[82] and Reich et al. 2005[79] did not show a shorter hospitalization time for PVP than for TURP. Furthermore, once more effectiveness data is gathered and probabilities of adverse events after hospital discharge, are better known in the long run, then also these costs need to be taken into account. These were only taken into account for a 1-year period in the study of Stovsky and were not at all included in the study of Bouchier-Hayes.

Finally, as the cost calculations are done in Ireland and the US, they can give an indication on the costs, but as such they are not applicable to the Belgian situation.

2.4.2.4 *Conclusion on cost-effectiveness of PVP*

PVP may provide several benefits such as reducing length of hospital stay, length of catheterization and blood loss and may therefore result in potential cost savings compared to TURP. However, as long as its long-term effectiveness is not yet proven, results of cost-effectiveness studies remain highly uncertain. Therefore, the treatment deserves further attention and research should be done to gather long-term clinical evidence and cost data on a large scale. PVP should be further compared to TURP, pharmaceutical therapy and other forms of minimally invasive treatments such as holmium laser prostatectomy.

2.4.3 Review of cost-effectiveness studies on HoLEP for BPH

2.4.3.1 *Literature search strategy and search results*

HTA institutes reports

As a first step, the HTA sources were searched (the CRD-HTA database and websites of INAHTA members). 6 reports were identified from the following institutes: ASERNIP-S (2003)[35], MAS (2006)[46], IQWiG (2007)[53], AHRQ (2004)[52] and 2 reports from Hayes (2002 and 2006). All the reports were consulted, except for the Hayes reports, as they were not available for purchase anymore as they were published more than 2 years ago. The ASERNIP-S (2003)[35] report contained a part on cost-effectiveness with a systematic literature search until 10/08/2002 for Medline and Embase and until 16/08/2002 for CRD-NHS EED and CRD-HTA (amongst the search in other databases). In the report only one full economic evaluation was identified, the cost-minimization study of Gilling et al. 1999 (republished with more cost data in Fraundorfer 2001).

Electronic databases

As a second step, the other databases (CRD-NHS EED, Embase, Medline and Econlit) were consulted for additional primary economic evaluations. Studies were searched from 2000 onwards. See appendix for more details on the search.

2.4.3.2 *Overview of full economic evaluations*

Two full economic evaluations were identified on holmium laser therapy: Fraundorfer (2001)[83] and Salonia et al (2006)[84]. However, as the study of Fraundorfer dealt with HoLRP, and as both costs and clinical outcomes are not directly comparable to HoLEP, this study was not included here. The study of Salonia comparing HoLEP with open prostatectomy for large prostate (OP) is presented in the appendix of chapter 2.4. No studies were identified comparing with TURP.

2.4.3.3 *Conclusion on cost-effectiveness of holmium*

Small short-term cost studies showed a potential economic benefit due to the significantly shorter length of hospital stay and catheterization of HoLEP compared to TURP. However, no full economic evaluations were identified comparing HoLEP with TURP. As large, blinded and long term clinical studies are still missing, no conclusion can be drawn yet with regard to the cost-effectiveness of this new technology compared to TURP.

- **A small number of short-term studies indicate that PVP and HoLEP may provide a number benefits such as reduced hospital stay, catheterization time and blood loss and therefore have the potential to be cost saving and/or lead to QoL improvement compared to TURP and OP.**
- **Important long-term outcome and cost data, however, are still lacking and treatment failures in the long term are not well documented. As treatment failures may eventually translate into considerable health care expenditures, no firm conclusion can be drawn yet that PVP or HoLEP are cost-effective treatments compared to TURP and OP.**
- **Longer-term blinded research should be done to gather both outcome and cost data on a large scale.**

2.5 BELGIAN SITUATION

In this chapter, a brief overview is given of the use of the classical treatments and the new surgical technique, PVP, for BPH in Belgium. Which techniques are currently applied in Belgium and for how many patients? What is the average length of stay for TURP and for PVP in Belgium? How is the new technique financed: hospital versus patient versus the National Institute for Health and Disability Insurance (NIHDI)? For a more extensive overview on the medical practice of TURP in Belgium, we refer to the study of the Belgian NIHDI of 2003, "Onderzoek van medische praktijk en conformiteit bij transurethrale resectie van de prostaat/Examen des pratiques médicales et de leurs conformités dans le cadre de la résection transurétrale de la prostate"[31].

2.5.1 Overview of classical surgical treatments for BPH in Belgium

2.5.1.1 Number of BPH surgical treatments (based on NIHDI nomenclature data)

The billing codes applicable for the treatment of BPH are listed in Table 25. The codes for OP (260632/43) and TURP (261553/64) have a value of €389.35 in 2008. The code for resection of bladder neck or urethral posterior valves, in practice also covering TUIP (transurethral incision of the prostate) procedures, has a reimbursement value of €207.65 in 2008.

Besides the procedure codes, there is also a material code for the loop used in the TURP procedure. This code is also used for loops in other treatments (such as cystoscopies and resection of bladder tumour).

Table 25: NIHDI billing codes for treatment of BPH

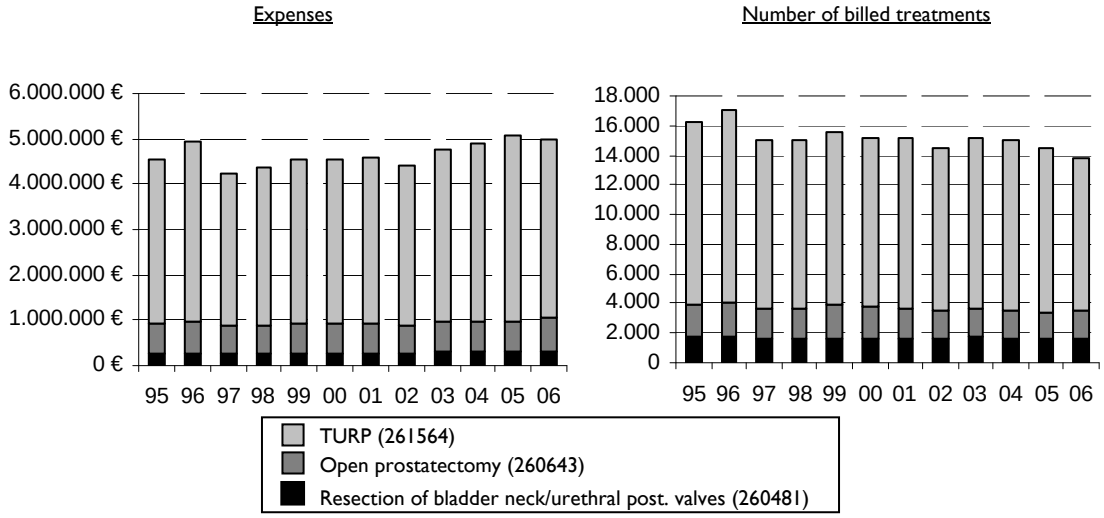
NIHDI code	Label (Dutch)	Label (French)	Value
260632-260643	Prostatectomie	Prostatectomie	K225 Reimbursement value: €389.35 Out-of-pocket patient: €0
261553-261564	Endoscopische resectie van de prostaat, inclusief cystoscopie	Résection endoscopique de la prostate, y compris la cystoscopie	
260470-260481	Endoscopische resectie van blaashals of van achterste urethrakleppen, inclusief cystoscopie	Résection endoscopique du col de la vessie ou de valves urétrales postérieures, y compris la cystoscopie	K120 Reimbursement value : €207.65 Out-of-pocket patient : €0
699510-699521	Lus voor het endoscopisch verwijderen van obstructief weefsel en tumoren van de urogenitale tractus, gebruikt bij de verstrekkingen 260315-260326, 260470-260481, 261391-261402 of 261553-261564	Anse pour l'ablation endoscopique de tissu obstructif et de tumeurs du tractus urogénital, utilisée lors des prestations 260315-260326, 260470-260481, 261391-261402 ou 261553-261564	U40 Reimbursement value : €12.68 Out-of-pocket patient : €29.56

In 2006, 10 330 TURP cases were billed in in-hospital setting (261564) (and 100 in ambulatory setting (261553)). For open prostatectomy (for which the primary indication is BPH), 1 864 cases were billed in in-hospital setting (NIHDI 260643) (and 1 in ambulatory setting (NIHDI 260632)).

Furthermore, 1 657 cases of endoscopic resections of bladder neck or urethral posterior valves were billed in in-hospital setting (NIHDI 260481) (and 148 in ambulatory setting (NIHDI 260470). Besides TUIP for BPH treatment, it is possible that this code is also used for other indications and for women. In Figure 3, an overview is given of the evolution of the expenses and the number of cases of the different surgical treatments for BPH in the last years.

The number of billed TURPs decreased by 9% from the year 1995 to 2006. The number of open prostatectomies decreased by 23% in the same period.

Figure 3: NIHDI expenses and number of treatments on the 3 in-hospital billing codes for surgical BPH treatment by reimbursement year



Source: NIHDI 1995-2006. Note that the 260481 code may not have been exclusively used for BPH, but also for other indications and for women.

2.5.1.2 *Total public expenditures on TURP (based on coupled MCD-MFD data from TCT[n])*

In Table 26, a number of data on APr-DRG 482 (TURP) for 2005 are presented. In 91.5% of the TURP cases, the severity of illness was minor to moderate. The overall average age of the patients was 72. For the hospitalization of minor cases, on average €1 298 was paid by the national health authorities (total per diem payments). For moderate cases, €1 789 was paid. For pharmaceuticals, on average €174 and €233 per case was paid for respectively minor and moderate cases. For honoraria, the average payments were respectively €987 and €1 150. In total, nearly € 30 million was paid in 2005 for hospitalization, pharmaceuticals and honoraria of all TURP patients.

Table 26: 2005 data on public health expenditures on APr-DRG 482 (Transurethral prostatectomy)

Severity of illness	N° of stays	% of stays	Avg. age	Avg. total per diem payment	Avg. total for pharmaceutical payments per stay	Avg. total for honoraria per stay	Total exp. (per diem + pharm. + hon.) for all stays
Minor	5 361	56.1	70	1 297,66	173,45	987,01	13.177.981,32
Moderate	3 384	35.4	73	1 789,33	233,06	1 150,02	10.735.435,44
Major	687	7.2	77	3 991,55	476,51	1 770,51	4.285.897,59
Extreme	131	1.4	79	7 469,42	1251,02	3 527,15	1.604.434,29
Total	9 563	100.0	72	1 738,61	231,08	1 135,77	29.803.748,64

Source: Technische Cel/Cellule Technique

A check was done to see which diagnoses are reported in this APr-DRG 482. The results of this check are in Table 28. The six most common diagnoses in 2004 in this Apr-DRG were searched. Five out of the six most common diagnoses were BPH (notably the codes 6000, 6001, 6002, 6009 and 78820). These codes were reported in 79% of all stays. One code, however, was for prostate cancer (code 185). This code was reported in 15% of all stays. The diagnoses of the remainder of the stays (<6% of all stays) were not further investigated. These data thus show that at least 79% of the data reported in the APr-DRG 482 represent TURPs for BPH.

[n] Minimal Clinical Data-Minimal Financial Data from the Technische Cel-Cellule Technique

Table 27: Selection APrDRG 482 in registration year 2004. Frequency table of main diagnosis of the hospital stay

Main diagnosis	N° Stays	% of stays	Label (in Dutch)
6000	4 078	40,48%	Hypertrofie (benigne) van prostaat
6002	2 122	21,06%	Benigne gelokaliseerde hyperplasie van prostaat
185	1 526	15,15%	Maligne neoplasma van de prostaat
6009	1 032	10,24%	Prostaat'hyperplasie, niet gespecificeerd
6001	685	6,80%	Nodulaire prostaat
78820	80	0,79%	Urineretentie, niet-gespecificeerd
Other	552	5,48%	
Total	10 075	100%	

2.5.1.3 Length of stay for TURP in Belgium

Table 28 shows that the average length of stay across all cases in APr-DRG 482 was 7 days in 2005. For the minor cases, the average length of stay was 5 days, for the moderate cases 7 days.

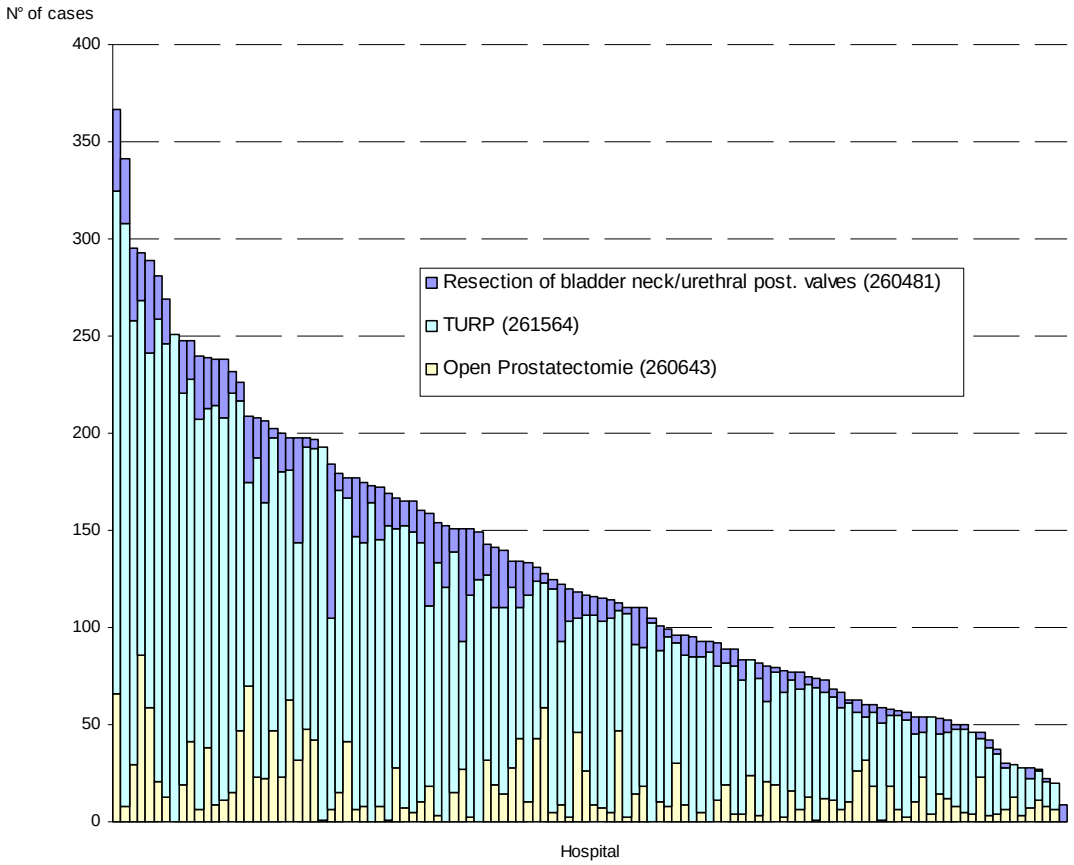
Table 28: 2005 data on length of stay for APr-DRG 482 (TURP)

Severity of illness	% of stays	Avg. length of stay (days)
Minor	56.1	5
Moderate	35.4	7
Major	7.2	16
Extreme	1.4	33
Total	100.0	7

2.5.1.4 Number of surgical treatments for BPH per hospital

116 hospitals perform the TURP and open prostatectomy procedures. In 2006, they performed on average 90 TURPs, 16 open prostatectomies and 16 resections of bladder neck/urethral posterior valves. Figure 4 depicts the number of BPH treatments per hospital in 2005.

Figure 4: Cases of TURPs, OPs and Resections of bladder neck or urethral posterior valves by hospital in 2005



Source: NIHDI data 2005

- **Nearly € 30 million was paid for hospitalization, pharmaceuticals and honoraria of all TURP patients in 2005.**
- **In 2006, in total around 14 100 treatment cases for TURP, open prostatectomies and resections of bladder neck/urethral posterior valves, were billed,**
- **The number of TURPs decreased by 9% from the year 1995 to 2006. In the same period, the number of open prostatectomies decreased by 23%.**
- **The average length of stay for minor and moderate TURP was 5 and 7 days respectively in 2005.**
- **In 2005, on average, 90 TURPs and 16 open prostatectomies were performed per hospital.**

2.5.2 PVP and holmium laser technology diffusion in Belgium

PVP

There are currently 5 Belgian hospitals using this technology (either Greenlight PVP or the newer version, Greenlight HPS): 4 academic and 1 general hospital. They are listed in Table 29. According to Hospithera, the use of the Greenlight PVP will gradually fade out and be replaced by the Greenlight HPS.

Table 29: Belgian hospitals performing PVP

UZA Edegem	PVP
UZ Gasthuisberg, Leuven	HPS
Cliniques Universitaires de Bruxelles - Hôpital Erasme	HPS
AZ Maria Middelares, Gent	HPS
CHU Ambroise Paré, Mons	PVP

Source: Communication from Hospithera

In the past, the PVP procedure was also performed at VZW Monica Deurne, but the involved urologist recently moved his activities to another hospital abroad. Besides these hospitals, a large number of hospitals have also used PVP in test case, amongst which hospitals in Kortrijk, Zoersel, Vilvoorde, Uccle, Hasselt, Gent, Deurne, Leuven, Brussels and Liège. At one of the test case sites, 2 out of around 20 patients became incontinent and needed to be re-operated at a university hospital.

According to an estimate from Hospithera, from September 2004 to mid 2008, in total around 300 fibers have been used in Belgium and thus around 300 procedures have been performed. The fibers used in the test cases are included.

Holmium

According to the expert group, there are currently no centres in Belgium performing holmium therapy for BPH.

2.5.3 Current financing of PVP in Belgium

The financing of the PVP treatment was asked at one hospital. The act TURP (261564) is billed to the NIHDI. Above the usual out-of-pocket payments for a TURP, the patient (or his private insurance), pays the price of the fiber of about €1 500. This information is also in line with the information we obtained from the distributor. As the length of stay can be significantly reduced (according to the expert group a 1-night stay is possible), the PVP procedure may be financially attractive from hospital point of view.

- **Five hospitals are currently performing PVP therapy. Some hospitals have tested and stopped PVP.**
- **According to information from Hospithera, around 300 patients have been treated with PVP from September 2004 until mid 2008 (test cases included). This is on estimate about 0.7% of all TURPs in that period.**
- **According to experience in Belgium, in many cases of PVP treatment, a one-night stay is possible.**
- **Holmium laser therapy for BPH is not yet performed in Belgium.**

2.6 ORGANIZATIONAL AND PATIENT ISSUES

Learning process

Besides the fact that generally good results are obtained with the standard TURP procedure, TURP also has the advantage that it is taught at universities and that it is traditionally widespread throughout the urological community. Besides the disadvantage of a lack of long term results, the newer investigated techniques also have the disadvantage of the investment cost and the fact that the urologists still have to go through a learning process before they are able to perform the procedure safely and effectively. As currently no –or only very limited- tutoring is available, learning the procedure is left to the initiative of interested urologists themselves. Especially the HoLEP procedure appears to require considerable surgical skill. The HoLEP is essentially an endoscopic Millin's prostatectomy and the average urologist, it seems, may struggle to match the outstanding results of Gilling and other investigators without a considerable learning curve.[85] For HoLEP, we find an estimated learning curve of 20-30 procedures to become familiar with the technique[46,86;44; 87]. From this perspective, the PVP procedure may offer some advantages, as it is based on a manual technique very similar to the TURP, associating the best haemostatic and resection properties of laser and electrocautery, without the hazards of morcellation. Still, in contrast to TURP, the amount of vaporized tissue is unknown with the PVP procedure. In the literature, an estimated learning curve for PVP of 15-20 procedures was found[46].

The skill of a surgeon to work with a certain technique depends on good training, experience and regular practice. Some surgeons prefer familiar techniques; other surgeons are comfortable with a wide variety of approaches.

Communication of safety towards patient

So far, limited evidence on safety and efficacy supports the use of PVP, holmium and HIFU. Therefore, clear information on the risks and uncertainties should be provided to the patient.

2.7 CONCLUSION

Despite being a very effective treatment, and therefore considered as the "gold standard", TURP deals with some disadvantages. In search of a decreased morbidity and a shorter hospital stay, a range of minimally invasive alternatives to TURP were developed during the past decades. The techniques discussed in this report are PVP and holmium Laser (with the focus on HoLEP). Holmium laser treatment has not yet been introduced in Belgium, whereas the PVP technique was evaluated at several Belgian sites and a request for reimbursement was submitted to the NIHDI.

For PVP, the number of patients treated in controlled trials is low (150 patients) and follow-up short (1 year). The results suggest a reduction in length of hospital stay (in Belgium, in many cases a one-night stay is possible), length of catheterization and blood loss after PVP. Compared with TURP these advantages may reduce patient discomfort and result in cost savings. There was no significant difference in sexual function after TURP or PVP, but series remain too short to conclude.

The frequency of a second intervention after PVP is currently not known. After TURP, a second intervention is necessary in 10% to 15% of cases. Looking at non-controlled observational studies, there are a few with longer follow-up (up to 5 years), however, the patient population is too small for firm evidence. Longer term controlled studies are required to assess the incidence of adverse events at long term.

In Belgium, around 300 patients have been treated with PVP until now (test cases included) and five hospitals are currently performing PVP therapy in clinical routine. A larger number of hospitals have evaluated PVP but have not continued performing this therapy in clinical routine. A learning curve of 15 to 20 procedures per surgeon is estimated during which adverse events may be seen more frequently. In addition to the uncertainties on long term results, there is also the high investment cost of the device and the ability (or difficulty) of surgeons (and other clinical staff) to build and maintain skills in multiple techniques that have probably hampered a more widespread distribution.

There is a need for additional comparison of PVP and holmium laser with TURP, pharmaceutical therapy and other forms of minimally invasive treatments. Similar conclusions were formulated in a recent systematic review and meta-analysis.[88] We concur with Lourenco et al. that the evidence supporting alternative techniques is still limited, and that TURP should currently remain the standard approach.

3 APPENDICES

APPENDIX TO CHAPTER 1.2: CLINICAL LITERATURE REVIEW ON HIFU FOR PROSTATE CANCER

Table 30: Critical appraisal of the HTA reports with the INAHTA HTA Checklist (HIFU)

Item	NHSC 2002 [2]	Nice 2005 {National Institute for Clinical Excellence, 2005 #107}	CVZ 2007[3]
Preliminary			
1. Appropriate contact details for further information?	yes	yes	yes
2. Authors identified?	Name of Committee	Name of Committee	yes
3. Statement regarding conflict of interest?	no	no	no
4. Statement on whether report externally reviewed?	yes	yes	no
5. Short summary in non-technical language?	no	yes	no
Why?			Focused on reimbursement
6. Reference to the question that is addressed and context of the assessment?	yes	yes	yes
7. Scope of the assessment specified?	yes	yes	yes
8. Description of the health technology?	yes	yes	no
How?			
9. Details on sources of information?	yes	yes	yes
10. Information on selection of material for assessment?	no	yes	yes
11. Information on basis for interpretation of selected data?	partly	yes	yes
What?	One reference		Critical apraisal
12. Results of assessment clearly presented?	yes	yes	yes
13. Interpretation of the assessment results included?	Partly	yes	yes
What then?	no evidence level		
14. Findings of the assessment discussed?	short	yes	yes
15. Medico-legal implications considered?	partly	Inform consent but no medico-legal implications	yes
16. Conclusions from assessment clearly stated?	Partly, short	yes	yes
17. Suggestions for further action?	no	yes	no
Conclusion	Not included	Included	Included

Table 31: Critical appraisal of the guidelines with the agree instrument

Based on http://www.agreetrust.org/docs/AGREE_Instrument_English.pdf	EAU [4]	NICE [5]
SCOPE AND PURPOSE 1. The overall objective(s) of the guideline is(are) specifically described. 2. The clinical question(s) covered by the guideline is(are) specifically described. 3. The patients to whom the guideline is meant to apply are specifically described.	good	good
STAKEHOLDER INVOLVEMENT 4. The guideline development group includes individuals from all the relevant professional groups. 5. The patients' views and preferences have been sought. 6. The target users of the guideline are clearly defined. 7. The guideline has been piloted among target users.	low	good
RIGOUR OF DEVELOPMENT 8. Systematic methods were used to search for evidence. 9. The criteria for selecting the evidence are clearly described. 10. The methods used for formulating the recommendations are clearly described. 11. The health benefits, side effects and risks have been considered in formulating the recommendations. 12. There is an explicit link between the recommendations and the supporting evidence. 13. The guideline has been externally reviewed by experts prior to its publication. 14. A procedure for updating the guideline is provided.	Unclear (critical appraisal of articles not retrievable on website)	good
CLARITY AND PRESENTATION 15. The recommendations are specific and unambiguous. 16. The different options for management of the condition are clearly presented. 17. Key recommendations are easily identifiable 18. The guideline is supported with tools for application.	good	good
APPLICABILITY 19. The potential organisational barriers in applying the recommendations have been discussed. 20. The potential cost implications of applying the recommendations have been considered. 21. The guideline presents key review criteria for monitoring and/or audit purposes.	Not mentioned	good
EDITORIAL INDEPENDENCE 22. The guideline is editorially independent from the funding body. 23. Conflicts of interest of guideline development members have been recorded.	Conflicts of interest not mentioned	yes
Overall assessment: Would you recommend these guidelines for use in practice? Strongly recommend Recommend (with provisos or alterations) Would not recommend Unsure	Recommend cautiously	Strongly recommended

Table 32: Critical appraisal of the systematic reviews with the Dutch Cochrane Collaboration checklist

Dutch Cochrane collaboration Formulier Vc	**Rebillard[7]**	**Hummel[6]**
Vraagstelling adequaat geformuleerd	yes	yes
Zoek actie adequaat uitgevoerd	yes	yes
Adequate selectie van artikels	unclear	yes
Adequate kwaliteitsbeoordeling van artikels	no	yes
Adequate beschrijving data extractie	-	-
Belankrijste kenmerken oorspronkelijk onderzoeken beschreven	yes	yes
Adequaat omgegaan met klinische en statistische heterogeneiteit	-	-
Statistiche pooling correct uitgevoer	-	-
Conclusion	Not included	included

EVIDENCE TABLES

Reference	Included studies	Conclusion	Level of Evidence
Nice 2005 Interventional procedures programme	Hummel 2003 (systematic review) Beerlage 1999 Chaussy and Thüroff 2000 Thüroff 2003 Chaussy and Thüroff 2003 Gelet 2001 Blana 2004	Only case-series studies, no RCT were found Current primary treatments for localised prostate cancer include 'watchful waiting', radiotherapy and radical prostatectomy. Current evidence on the safety and efficacy of high-intensity focused ultrasound (HIFU), as measured by reduction in prostate-specific antigen (PSA) levels and biopsy findings, appears sufficient. The effects of HIFU for prostate cancer on quality of life and long-term survival remain uncertain.	Low
NICE 2008 Guideline	Beerlage 1999 Chaussy and Thüroff 2003 Thüroff 2003 Gelet 1999 Gelet 2000 Poissonnier 2003 Ficarra et al. 2006 Ganzer et al. 2007 Lee et al. 2006 Poissonnier et al. 2007	All the included studies were case series Follow-up in these series was short (one study more than two years) Toxicities associated : sexual dysfunction, stress incontinence, urethral strictures and urinary tract infection HIFU is not recommended for men with localised or locally advanced prostate cancer other than in the context of controlled clinical trials.	Low
Rebillard 2003	Chaussy 2001 Chaussy 2003 Connort 2001-02 Thüroff 2003 Gelet 2001 Gelet 2003 Poissonnier 2003 Blana 2004 Vallancien 2003 Posters : D'Hondt 2003 Conti 2002	HIFU treatment is a valuable alternative option for low or intermediate risk cancer, in men with a life expectancy between 5 and 15 years. HIFU preliminary results are similar to those reported for the other therapeutic options	Out
Hummel 2003	Beerlage 1999 Chaussy and Thüroff 2000 Thüroff 2003 Gelet 1999 Gelet 1996 Gelet 2000 Gelet 2001 Kile 2000	Eight case-series (level 5) were included Insufficient evidence to draw conclusions regarding effectiveness Most studies report HIFU as a salvage procedure	Low

Table 33: Description of studies on HIFU for prostate cancer

Reference	Location	Population	Intervention	Design	Results
Beerlage 1999	Lyon	9 patients with a T1-2 N0, M0 PCa	HIFU primary study	Retrospective study	complete necrosis in the treated area in 7 of 9 patients.
Thüroff, Chaussy, Vallancien, Wieland, Kiel, le Duc, Desgrandchamps, de la Rosette, Gelet, 2003	Multicentr Lyon Regensburg München Paris (Montsouris) Paris (Saint Louis) Nijmegen	Patients (N = 402) with localized (stage T(1-2)N(0-x)M mean age was 69.3 mean follow-up duration was 407 days	mean of 1.4 HIFU sessions	Prospective study	negative biopsy rate observed in the T1-2 primary-care population was 87..2%, , 92.1% in low-risk patients
Chaussy and Thüroff 2003		65 patients (MO) not suitable candidates for radical prostatectomy		Feasability study	Mean follow-up was 10 months (1-18 months) DFSR : 82% at 10 months (ASTRO)
Lee 2006	Korea	58 patients	Ablatherm HIFU device with or without transurethral resection of the prostate (TURP)	Retrospective study	Mean follow-up was 14 months (6-21 months) DFSR : 69% at 14 months (ASTRO +biopsies)
Blana, Murat, Thuroff, Wieland , Chaussy , Gelet 2007	Lyon[a] Regensburg München	140 patients, patients with low- or intermediate-risk localised prostate cancer with a mean (SD) age 69.1 yr, Mean (SD) follow-up was 6.4 yr			Control prostate biopsies were negative in 86.4% of patients. Actuarial disease-free SR at 5 and 7 yr were 66% and 59%, respectively
Poissonnier 2007	Lyon [a] All patients from April 1994 to July 2003	T1-2 localized prostate cancers, prostate specific antigen (PSA) <or=15 ng/ml, Gleason score <or=7, prostate volume <or=40 cc and no previous radical treatment for prostate cancer		Retrospective study (partially prospective)	Mean follow-up was 27+/-20 months (12-121 months) Actuarial disease-free survival rate (DFSR) at 5-year was 66%, if initial PSA <or=4 ng/ml DFSR = 90% if initial PSA>4<10, DFSR = 57% if initial PSA>10<15, DFSR = 61%

[a] It is not clear whether the same patients are included. A mail was sent to the authors for further precision, but no answer was received before the date of publication of this study.

APPENDIX TO CHAPTER 1.3: ECONOMIC LITERATURE REVIEW ON HIFU FOR PROSTATE CANCER

OVERVIEW OF SEARCH FOR COST-EFFECTIVENESS STUDIES

HTA institutes reports

As a first step the CRD-HTA database was searched for existing HTA reports. The search was completed with a manual search on the websites of all the members of INAHTA (International Network of Agencies for Health Technology Assessment). In total 8 HTA reports were found covering HIFU for prostate cancer: NCCC for NICE (2008)[19], Hummel (2003)[6], ASERNIP-S (2006)[35], NHSC (2002)[89], CVZ (2007)[3], CEDIT (2004)[18], ANEAS/HAS (2001)[90], NICE (2004) {National Institute for Clinical Excellence, 2005 #107}. All reports covered efficacy or effectiveness of HIFU for prostate cancer. Only the most recent report, notably the NICE (2008) report, covered the cost-effectiveness of HIFU, amongst other therapies for prostate cancer. In this report, a systematic literature review was done for cost-effectiveness studies with a last update in July 2007. Therefore our further search in the electronic databases was confined to the period July 2007-2008.

Table 34: Details of the literature search on economic evaluation of HIFU in the CRD-HTA database

Database	Date	Search term	Results
CRD-HTA	22 April 2008	prostate cancer, hifu, high intensity focused ultrasound; limit to yr=2000-2008	127

Electronic databases

As a second step, the following databases were searched: Medline, Embase, the NHS-EED database from the Centre for Reviews and Dissemniation (CRD) and Econlit. No other full economic evaluation was identified besides the NICE report of 2008. Figure 5 shows an overview of the found and selected references and the reasons for exclusion.

Table 35: Details of the literature search on economic evaluation of HIFU in the CRD-NHS EED database (performed on 22 May 2008)

Database	Date	Search term	Results
CRD-NHS EED	22 April 2008	MeSH Prostatic Neoplasms EXPLODE 1 2 3 4 RESTRICT PD 01/07/2007 22/05/2008	18

Table 36: Details of the literature search on economic evaluation of HIFU in Embase (performed on 22 May 2008)

No.	Query	Results
#1	'socioeconomics'/exp	107,196
#2	'cost benefit analysis'/exp	47,28
#3	'cost effectiveness analysis'/exp	54,835
#4	'cost of illness'/exp	8,673
#5	'cost control'/exp	32,468
#6	'economic aspect'/exp	757,03
#7	'financial management'/exp	188,043
#8	'health care cost'/exp	129,255
#9	'health care financing'/exp	9,162
#10	'health economics'/exp	412,571
#11	'hospital cost'/exp	17,598
#12	'finance'/exp	7,971
#13	'funding'/exp	3,007
#14	financial	112,64
#15	'cost minimization analysis'/exp	1,338
#16	'prostatic neoplasms'/exp	80,703

#17	'prostate cancer'/exp	61,658
#18	'prostatic intraepithelial neoplasia'/exp	789
#19	pin	9,549
#20	cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplas* OR intraepithelial* OR adeno*	2,709,864
#21	prostat* AND #20	96,882
#22	'high intensity focused ultrasound'/exp	515
#23	hifu	462
#24	'high intensity' OR 'high-intensity'	9,636
#25	ultrasound	164,306
#26	#24 AND #25	1,235
#27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	769,765
#28	#16 OR #17 OR #18 OR #19 OR #21	105,578
#29	#22 OR #23 OR #26	1,263
#30	#27 AND #28 AND #29	14
#31	#27 AND #28 AND #29 AND [embase]/lim AND [2007-2008]/py	5

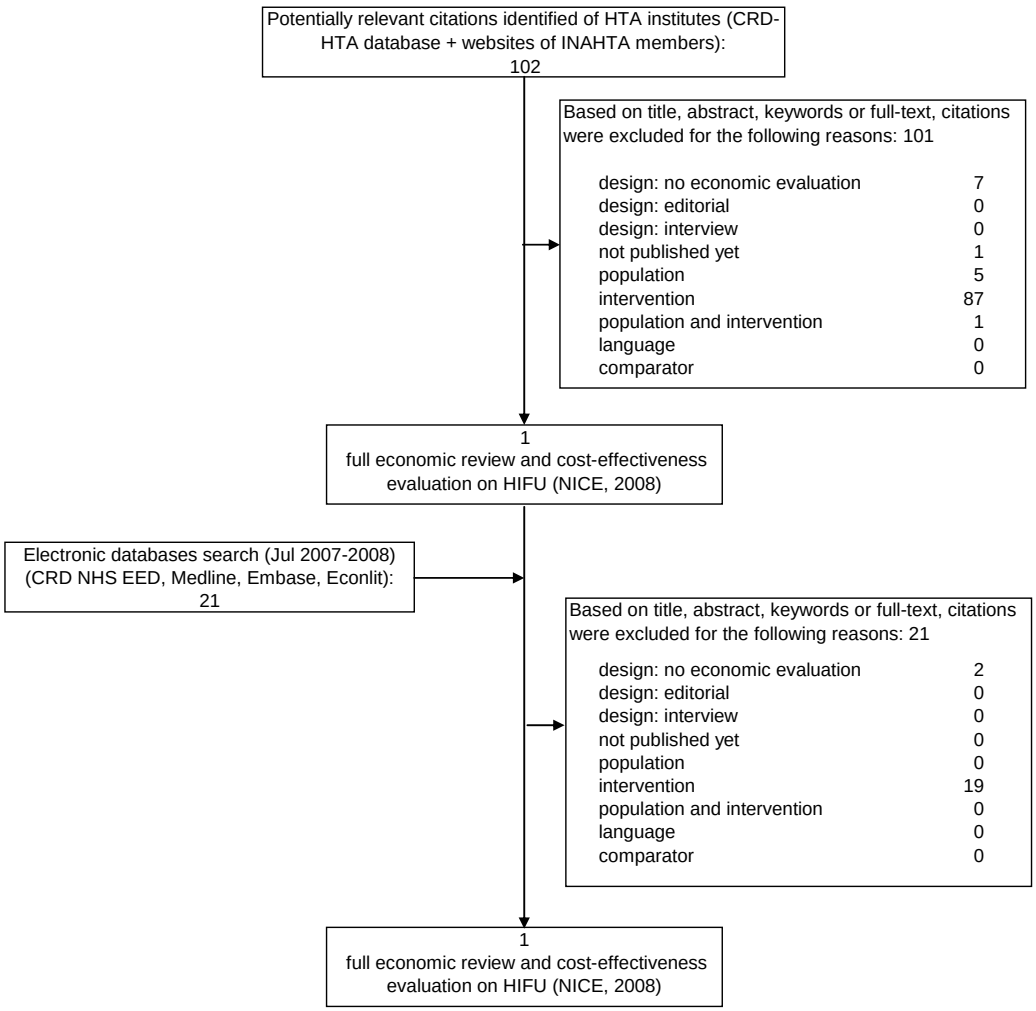
Table 37: Details of the literature search for economic evaluation of HIFU in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1950 to Present> (performed on 22 May 2008)

1	economics/	25705
2	exp "costs and cost analysis"/	137757
3	exp "Economics, Hospital"/	15527
4	economics, medical/	7012
5	economics, nursing/	3839
6	economics, pharmaceutical/	1915
7	(econom$ or cost$ or pric$).tw.	315319
8	(value adj1 money).tw.	14
9	budget$.tw.	12230
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	416740
11	letter.pt.	646091
12	editorial.pt.	232183
13	historical article.pt.	251140
14	11 or 12 or 13	1119100
15	10 not 14	395464
16	animals/	4267616
17	human/	10410719
18	16 not (16 and 17)	3216446
19	15 not 18	370352
20	exp "prostatic neoplasms"/	60963
21	Prostatic Intraepithelial Neoplasia/	826
22	pin.tw.	7182
23	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial$ or adeno$)).tw.	62498
24	20 or 21 or 22 or 23	81256
25	"ultrasound, High-Intensity Focused, Transrectal"/	138
26	(high intensity adj2 ultraso$).tw.	812
27	HIFU.tw.	452
28	25 or 26 or 27	912
29	24 and 28	213
30	19 and 29	9
31	limit 30 to yr="2007 - 2008"	4

Table 38: Details of the literature search on economic evaluation of HIFU in Econlit (performed on 9 May 2008)

Database	Date	Search term	Results
Econlit	9 May 2008	high intensity focused ultrasound.mp. [mp=heading words, abstract, title, country as subject]	0
		hifu.mp. [mp=heading words, abstract, title, country as subject]	0

Figure 5: Overview of identification and selection of studies

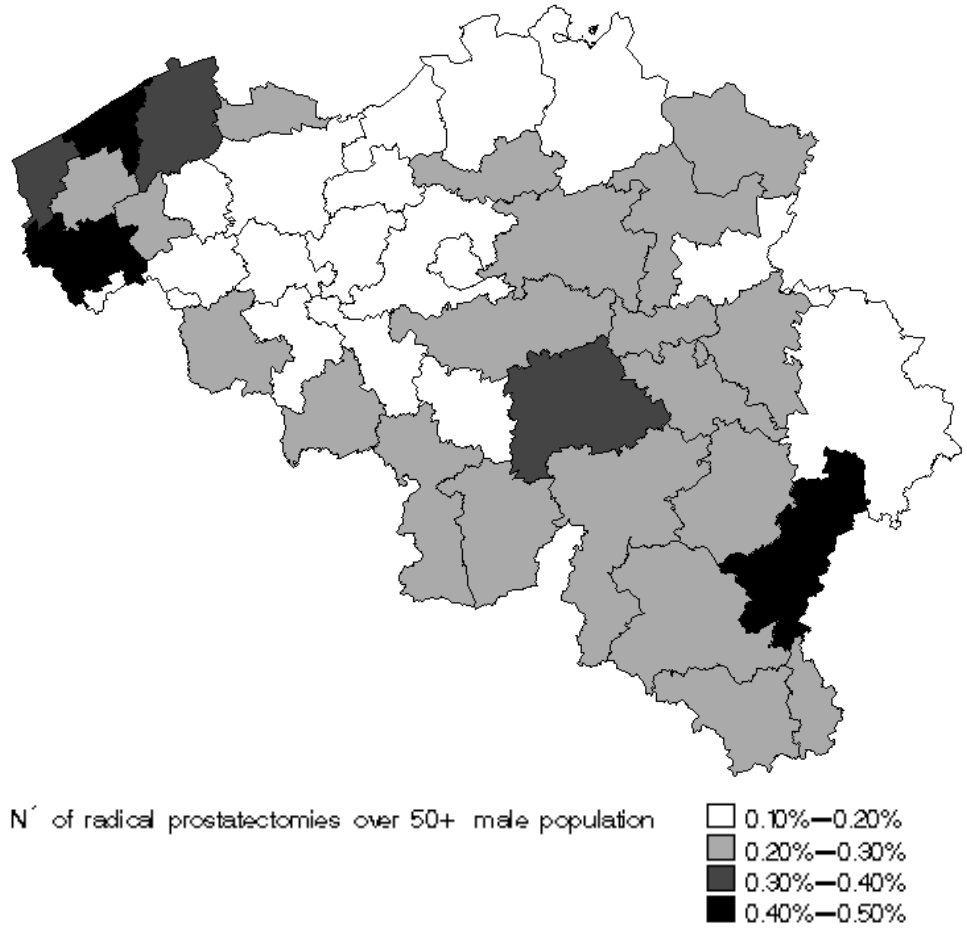


APPENDIX TO CHAPTER 1.4: HIFU FOR PROSTATE CANCER: BELGIAN SITUATION

GEOGRAPHICAL VARIATION OF RADICAL PROSTATECTOMIES

Figure 6 shows the variation by district for the number of radical prostatectomies on the male 50+ population in the year 2006. The ratio is highest in the districts Ieper, Oostende and Bastogne (higher than 0.40%). The weighted average for Belgium overall is 0.208%. The data are based on the domicile of the patient.

Figure 6: Number of radical prostatectomies (NIHDI 261800) on the male 50+ population in 2006



Source: NIHDI

APPENDIX TO CHAPTER 2.3: CLINICAL LITERATURE REVIEW ON PVP AND HOLMIUM FOR BPH

Table 39: Critical appraisal of the HTA reports with the INAHTA HTA Checklist (PVP alone)

Item	NHS 2005 (PVP)	CADTH 2006 (PVP)	L. Boltzman Institut 2007 (PVP)
Preliminary			
1. Appropriate contact details for further information?	yes	yes	yes
2. Authors identified?	yes	Name of Committee	yes
3. Statement regarding conflict of interest?	yes	no	no
4. Statement on whether report externally reviewed?	yes	no	yes
5. Short summary in non-technical language?	no	no	yes
Why?			
6. Reference to the question that is addressed and context of the assessment?	yes	yes	yes
7. Scope of the assessment specified?	yes	yes	yes
8. Description of the health technology?	yes	yes	yes
How?	good	good	
9. Details on sources of information?	yes	yes	Yes (in other document)
10. Information on selection of material for assessment ?	yes	no	yes
11. Information on basis for interpretation of selected data?	yes	yes	yes
What?			
12. Results of assessment clearly presented?	yes	yes	yes
13. Interpretation of the assessment results included?	yes	yes	yes
What then?			
14. Findings of the assessment discussed?	yes	yes	yes
15. Medico-legal implications considered?	no	No	yes
16. Conclusions from assessment clearly stated?	yes	yes	yes
17. Suggestions for further action?	yes	yes	partly
Conclusion	Included	Not included	Included

Table 40: Critical appraisal of the HTA reports with the INAHTA Checklist (PVP and /or Holmium)

Item	NHS 2003	Ontario (PVP and Holmium)	IQWiG (PVP and Holmium)
Preliminary			
1. Appropriate contact details for further information?	yes	yes	yes
2. Authors identified?	yes	Name of Committee	Name of Committee
3. Statement regarding conflict of interest?	yes	no	no
4. Statement on whether report externally reviewed?	yes	yes	yes
5. Short summary in non-technical language?	no	yes	not yet (unpublished report)
Why?			
6. Reference to the question that is addressed and context of the assessment?	yes	yes	yes
7. Scope of the assessment specified?	yes	yes	yes
8. Description of the health technology?	yes	yes	yes
How?	good	Precise	
9. Details on sources of information?	yes	Yes	Yes +++
10. Information on selection of material for assessment ?	yes	yes	yes
11. Information on basis for interpretation of selected data?	yes	yes	yes
What?		Detailed information	
12. Results of assessment clearly presented?	yes	yes	yes
13. Interpretation of the assessment results included?	yes	yes	yes
What then?			
14. Findings of the assessment discussed?	yes	yes	yes
15. Medico-legal implications considered?	no	yes	No
16. Conclusions from assessment clearly stated?	yes	yes	yes
17. Suggestions for further action?	yes	yes	yes
Conclusion	Included	Included	Included

Table 41: Critical appraisal of the systematic reviews with the Dutch Cochrane Collaboration checklist

Dutch Cochrane collaboration Formulier Vc	Tooher [91]
Vraagstelling adequaat geformuleerd	yes
Zoek actie adequaat uitgevoerd	yes
Adequate selectie van artikels	yes
Adequate kwaliteitsbeoordeling van artikels	yes
Adequate beschrijving data extractie	yes
Belangrijkste kenmerken oorspronkelijk onderzoeken beschreven	yes
Adequaat omgegaan met klinische en statistische heterogeneiteit	yes
Statistiche pooling correct uitgevoer	yes
Conclusion	Included

Table 42: HTA and SR description for PVP (BPH)

Reference	Included studies	Conclusion	Evidence level
NICE 2005 Interventional procedures Guidance 120	Malek 2000 Hai 2003 Carter 1999 At Mayo Clinic	High powered (60-80 W) KTP laser energy Current evidence on safety and efficacy appears adequate to support the use of this procedure . Data on long term efficacy are limited (follow-up at one year)	Low
Canadian Agency for Drugs and Technologies in Health 2006	Observational studies : Sandhu J 2004 Malek R 2000 Te 2004 Hai Sulser 2004 Riech 2005 Volkan T 2005 Bachmann A 2005 Fu W 2005 Malek R 2005 Sandhu J 2005 Sarica K 2005 Fu W 2006 Te A 2006 Comparative trial (not randomized): Bachmann 2005	Patients population may overlap Main follow-up : 1 year Main outcomes : IPSS High rate of loss to follow up Conclusion : Studies suggest that PVP performs well in the short term RCT's and longer follow-up are needed to confirm the results Performance of PVP is relative to other interventions	Low (publication not included
Ontario Health Technology Advisory Committee 2006	Bachmann 2005 Shingleton 2002	Based on a prospective cohort study, PVP is clinically as effective as TURP for the relief of urinary symptoms caused by BPH (based on 6-month follow-up data). Time to catheter removal was significantly shorter in patients undergoing PVP than TURP. Operating room time was significantly longer in PVP procedure than TURP. PVP has the potential to reduce health care expenses due to shorter hospital stay.	Moderate
Ludwig Boltzmann Institut Wien 2007	Bouchier-Hayes 2006 Fowler 2005 NICE 2004 Gupta N 2006 Wilson 2006 Bachmann A 2005 Malek 2000 Ontario	Lack of follow up data Conclusions from Bouchier Hayes to optimistic A much larger observational study is required to asses the incidence of adverse event at long term	Moderate
Institut für Qualität un Wirrtschaftlichkeit im Gesundheitswesen IQWiG 2007	Bouchier-Hayes 2006 Bachmann A 2005 Hwang 2005	To short follow up	Moderate

Table 43: HTA, guidelines and SR description for Holmium (BPH)

Reference	Included studies	Conclusion	Evidence level
NICE 2003 Interventional procedures Guidance 17	Tooher 2002 Gilling 1998 Kitigawa 1998 Kuntz 2002	Studies are characterized by follow-up periods and small sample sizes. Compared to TURP, HoLEP appears to result in less blood loss, and shorter catheterisation times. No other conclusions about safety could be made, and no differences in patient outcomes were detected between the two procedures.	Moderate (one RCT but comparator not TURP , others are NR CT)
Ontario Health Technology Advisory Committee	Rigatti et al. 2006 Gupta et al. 2006 (3-arm study; TUVRP vs HoLEP vs TURP) Kuntz et al. 2004 (same as Kuntz et al. 2002) Montorsi et al. 2004 Tan et al. 2003	The learning curve associated with this procedure and a lack of structured training programs have interfered with widespread acceptance of this technology. (44) A novice has to undertake 10 to 30 cases in a properly structured training environment in order to achieve outcomes similar to those published in the literature.	Moderate
Institut für Qualität un Wirrtschaftlichkeit im Gesundheitswesen IQWiG 2007	Kuntz 2004a Kuntz. 2004b Briganti 2006 Gupta 2006 (3-arm study; TUVRP vs HoLEP vs TURP) Naspro 2006 Sasonia 2006 Wilson 2006	HoLEP Study results in respect of symptoms were heterogeneous without any straightforward explanation for this heterogeneity	Moderate (inconsistency)

INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)o

ORIGINAL DESCRIPTION OF THE IPSS SCORING SYSTEM

To calculate your voiding symptom severity, make a response (by clicking on one response box) for each of the 7 questions below. After responding to all 7 questions, click on "Calculate." Note the total symptom score and read the commentary at bottom.

During the last month or so how often have you...					
Not at all	Less than 1 time in 5	Less than 1/2 the time	About 1/2 the time	More than 1/2 the time	Almost always
1. had a sensation of not emptying your bladder completely after urinating?					
0	1	2	3	4	5
2. had to urinate again less than two hours after you have urinated?					
0	1	2	3	4	5
3. how often have you stopped and started, serveral times when you urinated?					
0	1	2	3	4	5
4. found it difficult to postpone urination?					
0	1	2	3	4	5
5. had a weak urinary stream?					
0	1	2	3	4	5
6. had to push or stain to urinate?					
0	1	2	3	4	5
During the last month...					
None	1 time	2 times	3 times	4 times	5 times or more
7. how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?					
0	1	2	3	4	5

° http://www.usrf.org/questionnaires/AUA_SymptomScore.html

APPENDIX TO CHAPTER 2.4: ECONOMIC LITERATURE REVIEW ON PVP AND HOLMIUM FOR BPH

SEARCH STRATEGY FOR COST-EFFECTIVENESS STUDIES

For the economic evaluation of PVP and Holmium laser techniques, the websites of HTA institutes (Table 55) and following databases were searched: Medline, Embase, Centre for Reviews and Dissemination (CRD) databases (NHS Economic Evaluation Database (NHS EED), and Health Technology Assessments (HTA)) and Econlit. The following tables provide an overview of the search details.

Table 44: Details of the literature search for economic evaluation of PVP and Holmium in CRD-HTA and CRD-NHS EED databases

Database	Date	Search term	Results
CRD-HTA	22 April 2008	MeSH Prostatic Hyperplasia EXPLODE 1 Limit to yr=2000-2008	28
CRD-NHS EED	29 April 2008	MeSH Prostatic Hyperplasia EXPLODE 1 Limit to yr=2000-2008	55

Table 45: Details of the literature search for economic evaluation of PVP in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1950 to Present> (performed on 7 May 2008)

No.	Query	Results
#1	economics/	25700
#2	exp "Costs and cost analysis"/	137518
#3	exp "Economics, Hospital"/	15494
#4	economics, medical/	7008
#5	economics, nursing/	3838
#6	economics, pharmaceutical/	1907
#7	(econom$ or cost$ or pric$).tw.	313565
#8	(value adj1 money).tw.	14
#9	budget$.tw.	12178
#10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	414834
#11	letter.pt.	643725
#12	editorial.pt.	230868
#13	historical article.pt.	250834
#14	11 or 12 or 13	1115132
#15	10 not 14	393618
#16	animals/	4261935
#17	human/	10393783
#18	16 not (16 and 17)	3212927
#19	15 not 18	368570
#20	exp "Prostatic hyperplasia"/	15038
#21	(benign prostat$ hyperplasia or benign prostat$ hypertrophy).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	9389
#22	20 or 21	17425
#23	(potassium or titanyl or phosphate or KTP or photoselective or vaporization or laser or greenlight).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	469733
#24	19 and 22 and 23	86
#25	limit 24 to (yr="2000-2008")	37

Table 46: Details of the literature search on economic evaluation of PVP in Embase (performed on 7 May 2008)

No.	Query	Results
#1	'socioeconomics'/exp	106870
#2	'cost benefit analysis'/exp	47169
#3	'cost effectiveness analysis'/exp	54649
#4	'cost of illness'/exp	8632
#5	'cost control'/exp	32410
#6	'economic aspect'/exp	755349
#7	'financial management'/exp	187617
#8	'health care cost'/exp	128915
#9	'health care financing'/exp	9148
#10	'health economics'/exp	411609
#11	'hospital cost'/exp	17569
#12	'finance'/exp	7968
#13	'funding'/exp	2928
#14	financial	112439
#15	'cost minimization analysis'/exp	1324
#16	'prostate hypertrophy'/exp	19288
#17	(benign prostat* hyperplasia):ta,ab,ti,df,dn	9153
#18	'lasers'/exp	51842
#19	potassium titanyl phosphate':ta,ab,ti,df,dn	210
#20	ktp:ta,ab,ti,df,dn	654
#21	photoselective laser vaporization':ta,ab,ti,df,dn	9
#22	greenlight:ta,ab,ti,df,dn	42
#23	'laser prostatectomy'/exp	9
#24	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15) AND (#18 OR #19 OR #20 OR #21 OR #22 OR #23) AND (#16 OR #17)	44
#25	limit #24 to yr="2000-2008"	29

Table 47: Details of the literature search on economic evaluation of PVP and Holmium in Econlit (performed on 9 May 2008)

1	MeSH Prostatic Hyperplasia EXPLODE 1 Limit to yr=2000-2008	55
1	holmium.mp. [mp=heading words, abstract, title, country as subject]	0
2	benign prostatic hyperplasia.mp. [mp=heading words, abstract, title, country as subject]	7
4	photoselective vaporisation.mp. [mp=heading words, abstract, title, country as subject]	0
7	benign prostatic hypertrophy.mp. [mp=heading words, abstract, title, country as subject]	0
8	KTP.mp. [mp=heading words, abstract, title, country as subject]	0

Table 48: Details of the literature search on economic evaluation of Holmium in Embase (performed on 19 May 2008)

No.	Query Results	Results
#1.	'socioeconomics'/exp	107,085
#2.	'cost benefit analysis'/exp	47,253
#3.	'cost effectiveness analysis'/exp	54,79
#4.	'cost of illness'/exp	8,662
#5.	'cost control'/exp	32,452
#6.	'economic aspect'/exp	756,579
#7.	'financial management'/exp	187,955
#8.	'health care cost'/exp	129,165
#9.	'health care financing'/exp	9,157
#10.	'health economics'/exp	412,324
#11.	'hospital cost'/exp	17,589
#12.	'finance'/exp	7,97
#13.	'funding'/exp	2,988
#14.	financial	112,594

#15.	'cost minimization analysis'/exp	1,334
#16.	'prostate hypertrophy'/exp	19,313
#17.	benign:ta,ab,ti,df,dn AND prostat*:ta,ab,ti,df,dn AND hyperplasia:ta,ab,ti,df,dn	9,166
#18.	benign:ta,ab,ti,df,dn AND prostat*:ta,ab,ti,df,dn AND (hyperplasia:ta,ab,ti,df,dn OR hypertrophy:ta, ab,ti,df,dn)	11,209
#23.	'holmium *4 laser *6 prostat*':ta,ab,ti,df,dn OR ' yag *4 laser *6 prostat*':ta,ab,ti,df,dn OR holrp: ta,ab,ti,df,dn OR holap:ta,ab,ti,df,dn OR holep:ta ,ab,ti,df,dn	91
#24.	'holmium laser'/exp	997
#25.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	769,236
#26.	#16 OR #17 OR #18	21,119
#27.	#23 OR #24	1,017
#28.	#25 AND #26 AND #27	21
#29.	limit #28 to yr="2002-2008"	18

Table 49: Details of the literature search on economic evaluation of Holmium in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1950 to Present> ((performed on 4 June 2008)

1	economics/ (25707)
2	exp "costs and cost analysis"/ (137921)
3	exp "economics, hospital"/ (15538)
4	economics, medical/ (7013)
5	economics, nursing/ (3839)
6	economics, pharmaceutical/ (1917)
7	(econom$ or cost$ or pric$).tw. (316562)
8	(value adj1 money).tw. (14)
9	budget$.tw. (12268)
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (418080)
11	letter.pt. (648126)
12	editorial.pt. (233347)
13	historical article.pt. (251349)
14	11 or 12 or 13 (1122490)
15	10 not 14 (396758)
16	animals/ (4272426)
17	human/ (10423883)
18	16 not (16 and 17) (3219533)
19	15 not 18 (371569)
20	exp "prostatic hyperplasia"/ (15081)
21	(benign prostat$ hyperplasia or benign prostat$ hypertrophy).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (9476)
22	20 or 21 (17530)
23	((holmium or YAG) adj4 la#er adj6 prostat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (174)
24	(holrp or holap or holep).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (86)
25	23 or 24 (184)
26	19 and 22 and 25 (7)
27	from 26 keep 1-7 (7)
28	limit 27 to (yr="2000-2008") (5)

Figure 7: Overview of identification and selection of studies for PVP

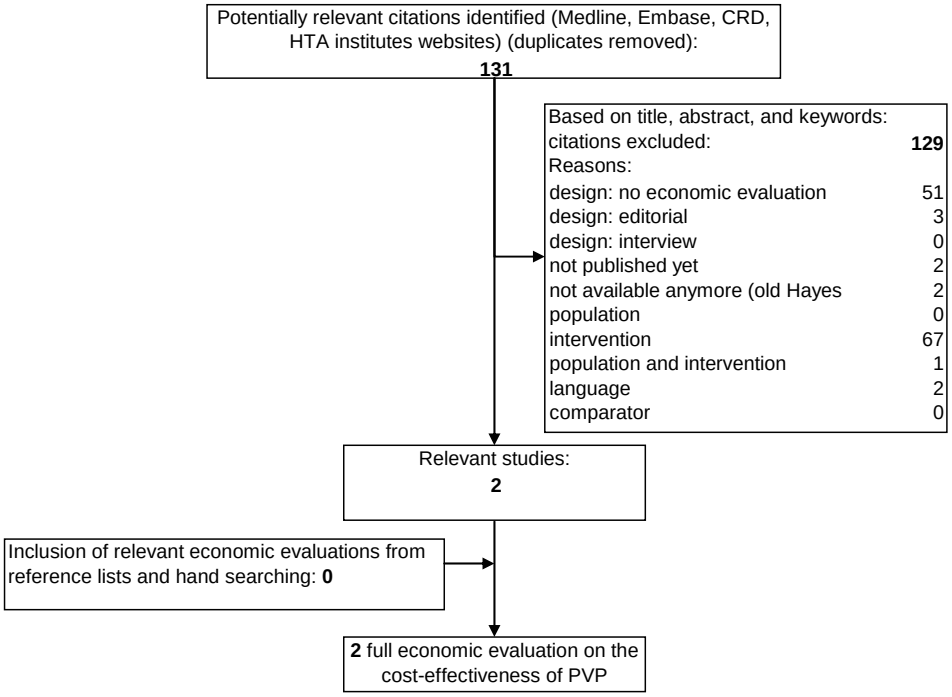
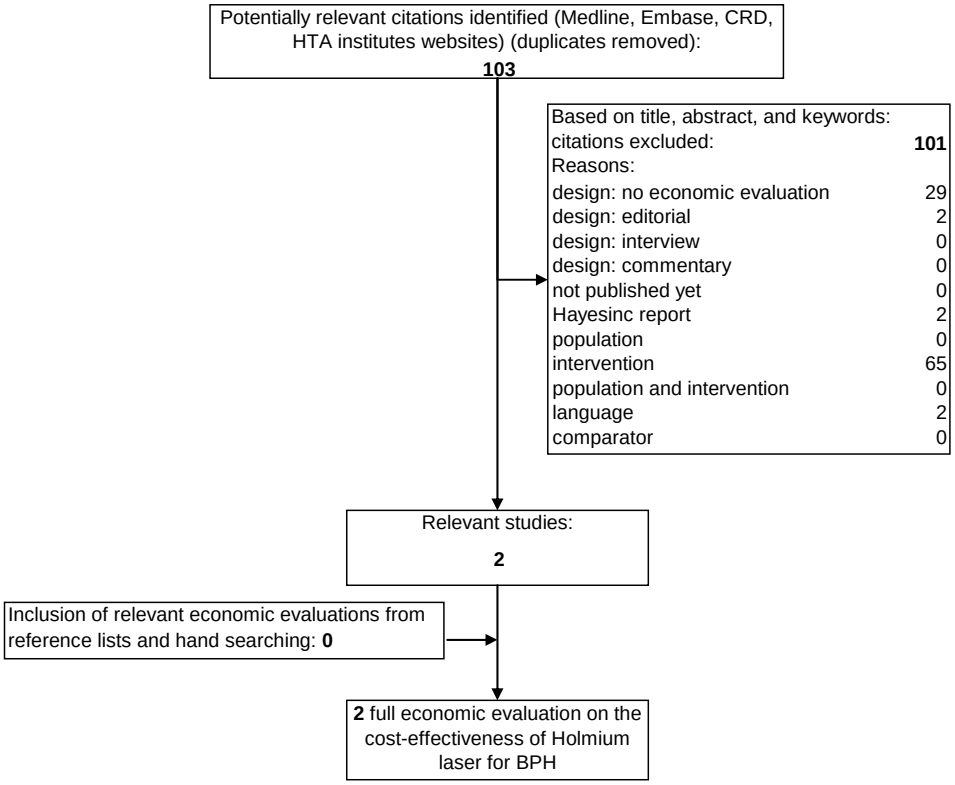


Figure 8: Overview of identification and selection of studies for Holmium



ECONOMIC EVALUATION STUDY OF SALONIA (2006) COMPARING HOLEP WITH OPEN PROSTATECTOMY[84]

Methodology

The study of Salonia et al. (2006)[84] comparing the cost of HoLEP and open prostatectomy, can also be regarded as a full economic evaluation, in that it also refers to existing literature regarding the equivalence in clinical outcomes of HoLEP and OP at 12 months of follow-up. The study can thus be read as a cost-minimization analysis.

63 patients with symptomatic BPH in a large prostate (70 to 220g) and documented BOO (bladder outlet obstruction) were randomized to surgical treatment with OP (n=29) or HoLEP (n=34). Cost data were recorded prospectively. The study took place in Italy.

Costs

The following cost data were taken into account: premedication and prophylaxis, anaesthesia (disposables/drugs/sedation), operating room surgical setup/disposables/fibers, irrigation fluid, autologous and homologous blood transfusion, operating room time, postoperative holding area, perioperative analgesic solution, hospital stay and unplanned events during hospital stay. See Table 50 for an overview of costs. The costs for unplanned events included the extra costs during hospital stay for extra analgesic solution and any drugs used to treat acute severe hypotension or bradycardia, recatheterization, clot irrigation, and urinary tract infection. Costs for unplanned events after the hospital stay were not considered. The medical salary costs (urologist and anaesthesiologist) were not considered either as they were already included in the monthly salaries.

Table 50: Cost comparison between HoLEP and OP

	OP (n=29)	HoLEP (n=34)	P value*
Premedication and prophylaxis	€ 6.0	€ 6.0	
Anaesthesia (disposables/drugs/sedation)	€ 47.2	€ 48.8	
Operating room surgical setup/disposables/fibers	€382.3	€690.5	
Irrigation fluid	€100.0	€ 57.5	
Autologous blood transfusion (€75/U)	€ 75.0	€ 75.0	
Homologous blood transfusion (150/U)	€ 66.7	€ 11.4	
Baseline Hb	14.0 g/dL	14.7 g/dL	0.72
Postoperative Hb	10.9 g/dL	12.5 g/dL	0.0009
Autologous blood transfusion	133.3mL	48.5 mL	0.07
Homologous blood transfusion	120.0 mL	24.5 mL	0.04
Patients requiring autologous blood transfusion	8/29	4/34	X^2=1.61; df =1; P=0.20†
Patients requiring homologous blood transfusion	7/29	2/34	X^2=2.88; df=1; P=0.09†
Operating room time (€480/hr)	€461.3	€590.5	
Operative time (min)	57.5 min.	73.4 min.	0.002
Enucleated weight (g)	62.6 g.	56.2 g.	0.58
Postoperative holding area (€480/hr)	€200	€120	
Perioperative analgesic solution	€1.8	€1.8	
Hospital stay (€280/day)	€1530.0	€755.2	
Catheterization time (hr)	106.3 hr	35.3 hr	<0.0001
Hospital stay (hr)	131.0 hr	64.6 hr	<0.0001
Unplanned events	€0.4	€1.6	
Total cost	€2868.9	€2356.5	

* Two-tailed Student's t test, except when noted differently

† Chi-square test

Clinical outcomes

No clinical outcomes such as Qmax, AUA score or IPSS were collected post-operatively. Instead, the authors referred to a number of studies that demonstrated that HoLEP is as effective and safe as OP in treating patients with BOO resulting from large prostates. The authors referred to Tan et al. (2003)[45], Gilling et al. (2000)[92], Kuntz and Lehrich (2002)[86] and Naspro et al. (2005)[93]. They also refer to a number of studies indicating that HoLRP and, therefore, according to the authors, also HoLEP, are as effective as TURP at 12 months of follow-up. The authors referred to Tooher et al. (2004)[91] and Gilling et al. (1999)[94] for HoLRP, and to Tan et al. (2003)[45], Tooher et al. (2004)[91] and Montorsi et al. (2004)[95] for HoLEP.

Results

The authors concluded that HoLEP is cost-saving compared to OP, and as literature indicated equivalent effectiveness, thus cost-effective compared to OP. Although the cost for the operating surgical setup, the disposables and the fibers used was higher for the laser group compared to open surgery group (€690 vs €382), the significantly lower cost of hospital stay following laser prostatectomy (€755.2 vs €1530) outweighed in the final result.

Discussion of the study

What concerns the clinical outcomes, the authors of Salonia et al. refer to a number of studies indicating equivalent clinical effectiveness of HoLEP and OP. However, the evidence provided in these studies is based on small samples and they do not provide any information on long term effectiveness yet. Furthermore, besides referring to studies on HoLEP, Salonia et al. also referred to studies on HoLRP to underpin the equivalence of HoLEP to OP. Still, it is very questionable whether the results from HoLRP can be extrapolated to HoLEP as it concerns two different techniques. Therefore, as firm evidence on long term clinical effectiveness of HoLEP for BPH is still lacking, the results of this cost-effectiveness study remain highly uncertain.

The focus of this study, however, was on the cost calculation. The recorded costs included all costs during the hospital stay, both the costs of the initial procedure and of unplanned events. No costs after hospital discharge were recorded. Once more effectiveness data is gathered and probabilities of adverse events are better known, it is required to include the costs of the unplanned events after hospital discharge as well, comprising the doctor visits and hospital readmissions due to complications.

Despite the shortcomings of the study, that are mostly linked to the lack of firm RCT data, the study indicated clearly that the new technology has the potential to be cost-saving compared to OP. This difference was largely driven by the shorter hospital stay. Salonia reported mean hospital stays of 64.6 hours for HoLEP versus 131.0 hours for OP. These results are in line with the results from other studies. Moody and Lingeman (2001)[96] reported on average 50.4 hours for HoLEP and 146.4 hours for OP (on a series of two times 10 patients). Kuntz et al. (2002)[86] reported a hospital stay of 48 hours for HoLEP and 240 hours for OP and Tan and Gilling (2003)[73] reported even a mean hospital stay of 28.4 hours for HoLEP.

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Wettelijk depot : D/2008/10.273/61

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
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5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
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9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
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