TransUrethral Needle Ablation (TUNA) for the treatment of benign prostatic hyperplasia

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Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which services should attract funding under Medicare.

This report was prepared for the Medical Services Advisory Committee by Kirsten Howard, Epidemiologist, and Sally Wortley, Research Assistant, from The NHMRC Clinical Trials Centre, University of Sydney, with recommendations made by the MSAC Supporting Committee for transurethral needle ablation. The report was endorsed by the Commonwealth Minister for Health and Ageing on 17 May 2002.

Publication approval number: 3094

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

Contents

Tables

Figures

Executive summary

The procedure

TransUrethral Needle Ablation (TUNA) is one of several new minimally invasive thermal technologies for transurethral treatment of the prostate in symptomatic benign prostatic hyperplasia. It is designed to provide selective thermal ablation of the interstitial prostatic tissue.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the NHMRC Clinical Trials Centre, University of Sydney, was engaged to conduct a systematic review of literature on TUNA. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of transurethral needle ablation

The evidence for the efficacy and safety of TUNA is based on one published, although, relatively small, randomised controlled trial (level II evidence) comparing TUNA to transurethral resection of the prostate (TURP), two prospective non-randomised studies, and a number of uncontrolled case series reports. The two non-randomised studies compared TUNA to other minimally invasive procedures such as visual laser ablation and transurethral microwave thermotherapy. However, no studies reporting on pharmaceutical interventions in comparison to TUNA were identified.

Clinical need

Benign prostatic hyperplasia (BPH) is the most common disease seen in the prostate. Symptomatic BPH is estimated to have a prevalence of around 40 per cent for men in their seventies. Severity of symptoms varies widely and may fluctuate or gradually progress over time. Episodes of acute urinary retention may eventuate. Left untreated, BPH may also result in upper urinary tract changes.

Surgical options include open prostatectomy, TURP, and transurethral incision of the prostate (TUIP). Pharmacological interventions include 5-alpha-reductase inhibitors and alpha-1 adrenergic blockers. The former is designed to shrink the prostate, whereas the latter relaxes the smooth muscle in the prostate and around the bladder neck.

TUNA belongs to a group of less invasive procedures designed to reduce symptoms of urinary obstruction.

Safety

TUNA appears to be a relatively safe procedure. Data from the randomised trial suggest that TUNA has fewer post-operative complications such as bleeding than does TURP. Non-randomised evidence suggests that apart from urinary retention, which appears more common with the TUNA procedure, the early adverse event rate for TUNA and TURP is similar.

From the data available, it is likely that TUNA results in fewer complications relating to sexual function (such are erectile dysfunction or retrograde ejaculation) than does TURP. The rate of these complications seen in more recent TURP series appears to be lower, however, than that reported in earlier series. As TUNA has also evolved over time, it is possible that the newer TUNA procedures may result in fewer complications than older procedures, although at this stage this remains unclear.

All the trials in this report conducted TUNA as an inpatient procedure, however, it can, in practice, be performed as an outpatient or in-clinic procedure, thus potentially avoiding risks associated with general anaesthesia. While none of the trials specifically evaluated the role of TUNA in this subset of patients, it may, theoretically, be of value in patients with a high anaesthetic risk.

Effectiveness

The body of evidence on which this review is based is relatively small. There is one randomised trial (level II evidence) and two prospective, non-randomised comparative studies (level III evidence). Remaining evidence comprises case series of patients treated with TUNA. The amount of evidence supporting the TUNA procedure is relatively small. While the Food and Drug Administration (FDA - United States) approval for TUNA is only for glands 20-50cc in size, trials generally included patients with a wider range of gland sizes up to 100cc (gms), with an average size quoted between 36.2cc and 49.6cc (gms). As TUNA does not have a significant effect on gland volume, it is most suited for smaller glands.

TUNA appears to have a therapeutic benefit, in the shorter term, with statistically significant improvements in objective and subjective measures. This appears to be initially equivalent to TURP, however, after six to 12 months, objective measures of function such as peak flow rates are statistically significantly better with TURP. A subjective difference in symptoms between patients treated with TUNA and TURP is also apparent at 12 months. Based on longer term data available only in abstracts, these differences between treatment groups appear to increase with time.

Data from one prospective trial indicated that, over two years follow-up, fewer patients treated with TURP required retreatment compared to patients treated with TUNA (4% vs 20%). Case series data indicates that retreatment (TURP or prostatectomy) rates for patients treated with TUNA ranged from 5-30 per cent over follow-up periods of up to two years. Abstract data of follow-up of three to five years post-TUNA suggests a failure rate of approximately 5 per cent to 15 per cent per annum, although it should be noted

that in many cases, retreatment rates are based on patients treated with older procedures (as would be expected, given the duration of follow-up).

Overall, TUNA appears to be a relatively effective procedure for the short-term management of symptoms associated with benign prostatic hyperplasia. However, data suggests that the duration of maximum benefit for TUNA is between approximately three and 12 months, depending upon the parameter measured. This duration of benefit is shorter than that seen for patients treated with TURP (longer than three years), with more TUNA patients than TURP patients experiencing a return of BPH symptoms and more requiring retreatment in the longer term.

Cost-effectiveness

A decision analytic model was designed, based on a set of plausible assumptions, to assess the comparative cost-effectiveness of two treatment strategies: 1) TURP; or 2) TUNA, as initial treatment for symptomatic benign prostatic hyperplasia. The base case analysis indicated that treating patients initially with TURP was both more effective and less costly than treating initially with TUNA. Over a range of sensitivity analyses conducted, this conclusion varied from TURP being a cost-effective initial treatment to TUNA being a cost-effective initial treatment for patients with BPH. The analysis was particularly sensitive to the annual failure rate of both procedures, and subsequently, the duration of follow-up. The conclusion regarding optimal initial treatment changed over the plausible ranges evaluated. Additional clinical data is required to strengthen our certainty concerning particular variables before definitive conclusions can be drawn regarding the relative cost-effectiveness of TUNA and TURP in this setting.

Recommendation

Based on the evidence available, while safe and efficacious in the short term, the long term effectiveness and cost-effectiveness of TUNA has not been proven. MSAC therefore concludes that unrestricted Medicare Benefits Scheme funding of TUNA for the surgical management of symptomatic benign prostatic hyperplasia is not warranted at this time.

TUNA may, however, have a limited role as an alternative treatment for symptomatic benign prostatic hyperplasia with the following restrictions:

- that it is restricted to men with moderate to severe lower urinary tract symptoms that require specific treatment (ie those who would normally be recommended for TURP);
- that the patients must not be medically suitable for TURP; and
- that interim funding for a period of three years is recommended, and that this funding be linked to the acquisition of data on the type of patients treated and safety data to monitor the use of TUNA under these interim arrangements.

- The Minister for Health and Ageing accepted this recommendation on 17 May 2002. -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of transurethral needle ablation (TUNA®)[1], which is a therapeutic device for the treatment of benign prostatic hyperplasia. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for TUNA in benign prostatic hyperplasia.

[1] TUNA® is a registered trademark of Medtronic, Inc.

Background

Transurethral needle ablation

The procedure

The TUNA® system consists of a radio frequency generator, an optic and a disposable monopolar catheter (Figures 1 & 2). The system is designed to deliver low levels of radiofrequency energy directly into the hyperplastic prostatic tissue in order to provide selective thermal ablation, while preserving the urethra and adjacent structures from harm. Using direct optical vision, the surgeon positions the TUNA® catheter to insert two needles (which serve as radiofrequency antennae) directly into the prostatic tissue. The radiofrequency energy passes via these needles and through the prostate in a monopolar fashion to the grounding pad. Each needle has an adjustable shield surrounding it. The shields contain thermocouples for interstitial temperature monitoring, and for monitoring the temperature of the prostatic urethral wall. The shields are used to localise the lesions within the prostate and protect the urethra from thermal damage (Beduschi & Oesterling 1998; Chapple, Issa, & Woo 1999; Heaton 1995; Issa, Myrick, & Symbas 1998).

Figure 1 TransUrethral Needle Ablation system: A) Rigid TUNA® catheter and B) TUNA® catheter tip with 2 needles deployed at acute angles

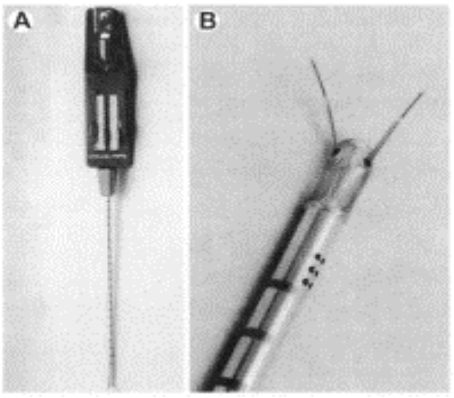
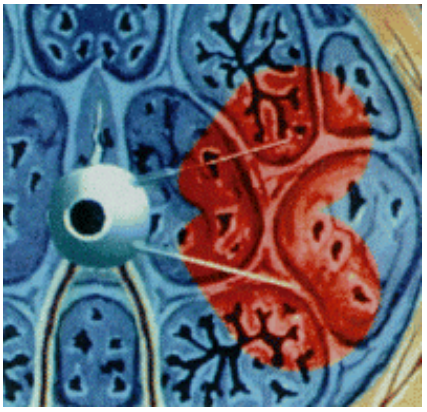


Figure 2 **Depiction of the TUNA system showing needles positioned in prostatic parenchyma producing thermolesions**



The procedure can be performed in a day-stay setting, without the need for hospitalisation. In some circumstances, it may be possible to use a lower level of anaesthesia with TUNA compared to some other surgical procedures (eg TURP). It should be noted that as TUNA has evolved over time, some procedures in early case series will be different to contemporary procedures.

Intended purpose

TUNA is intended to treat symptomatic benign prostatic hyperplasia (BPH) to relieve lower urinary tract symptoms.

Clinical need / burden of disease

BPH is the most common disease seen in the prostate. Prevalence of hyperplasia (with or without symptoms) is estimated to range from around 50 per cent of men by the end of the fifth decade, to 90 per cent in men over 80 years. Symptomatic BPH is estimated to have a prevalence of around 40 per cent for men in their seventies. Patients can present with obstructive symptoms (including diminution in the calibre and force of the urinary stream, hesitancy, inability to terminate micturition abruptly, a sensation of incomplete bladder emptying and occasional urinary retention) or irritative lower urinary tract symptoms (including dysuria, frequency, nocturia and urgency) (Australian Health Technology Advisory Committee 1994). The severity of symptoms varies widely in men with anatomical urethral obstruction, and may fluctuate or gradually progress over time. Episodes of acute urinary retention may eventuate. Left untreated, BPH may also result in upper urinary tract changes.

The number of men who undergo treatment for benign prostatic hyperplasia annually in Australia can be estimated from hospital morbidity data and ICD-9-CM codes for primary diagnosis and principal procedures (Commonwealth Department of Health and Aged Care 2000). Based on these figures, over 22,000 men were treated for prostatic hyperplasia in 1997–98 (Tables 1 & 2).

Table 1 Separations for principal diagnosis of BPH 1997–98

ICD-9-CM code	Condition	Hospital separations 1997-98[1]
600	Hyperplasia of prostate	22,020

1 (Commonwealth Department of Health and Aged Care 2000)

Table 2 Occurrences for principal procedures to treat BPH 1997–98

ICD-9-CM	Procedure	Occurrences 1997-98[1]
6021	Transurethral prostatectomy	21,190
6022	Laser assisted prostatectomy	635
6023	Transurethral needle ablation of the prostate	52
6024	Transurethral vaporisation of the prostate	295
603	Suprapubic prostatectomy	110
604	Retropubic prostatectomy	142
605	Radical prostatectomy	1485

1 (Commonwealth Department of Health and Aged Care 2000)

Existing procedures

The 'reference standard' for comparison with the TUNA procedure is transurethral resection of the prostate (TURP). Studies of TURP since 1986 have indicated satisfactory results in 90-95 per cent of patients over a 5-6 year follow-up period (Mebust 1998).

Other surgical options include open prostatectomy and transurethral incision of the prostate (TUIP). Open prostatectomy is generally recommended for patients with large prostates and the retreatment rate is reported to be around 2 per cent (Jepsen & Bruskewitz 1998; Roos et al 1989). Symptom improvement is reported in 98 per cent of patients (Jepsen & Bruskewitz 1998). The other commonly used surgical procedure is TUIP, whereby a knife, electrode or laser is used to make one or more incisions, usually from the bladder neck to the verumontanum, that are deepened until the capsule of the prostate is reached. This relieves the obstruction around the urethra. The retreatment rate is reported as similar to TURP (Baine et al 1998; Jepsen & Bruskewitz 1998).

Pharmacological interventions include type II 5-alpha-reductase inhibitors such as finasteride (Proscar) and alpha-1 adrenergic antagonists such as tamsulosin (Flomax) and terazosin (Hytrin). Type II 5-alpha reductase inhibitors prevent the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT), on which the enlargement of the prostate in BPH in dependent, thereby reducing prostate volume. Binding of alpha-1 adrenergic antagonists to the prostate results in relaxation of the prostate smooth muscle, increasing urinary flow by reducing smooth muscle tension in the prostate and urethra (Lepor et al 1996; Lieber 1998; McConnell et al 1998).

TUNA belongs to the group of less invasive procedures, which also includes transurethral vaporisation of the prostate (TVP), visually assisted laser prostatectomy (VLAP), interstitial laser coagulation of the prostate (ILCP), transurethral microwave thermotherapy (TUMT) and high-intensity focused ultrasound (HIFU) (Baine et al 1998; Blute et al 1996; Jepsen & Bruskewitz 1998).

Comparator

The review aimed to find all reports comparing TUNA to TURP, or any of the other newer, less invasive procedures detailed above.

Marketing status of the device

The equipment used for TUNA has been listed by the Therapeutic Goods Administration (TGA). The equipment and listing numbers are outlined in Table 3. It should be noted that while the TGA listing places no restrictions on the clinical use of TUNA, the Food and Drug Administration (FDA - United States) has approved TUNA use for 'treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men over the age of 50 with prostate sizes between 20 and 50 cc' (FDA 1996).

Table 3 Therapeutic listing numbers for TUNA® equipment

ARTG listing number	Product name of therapeutic good
AUST L 52689	TUNA® Catheter
AUST L 52690	TUNA® RF Generator

ARTG: Australian Register Therapeutic Goods

Current reimbursement arrangement

Currently there is no specific Medicare Benefits Schedule item number for the TUNA procedure.

Approach to assessment

Review of literature

MSAC's recommendations are primarily based on the findings of a systematic literature review conducted by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre (CTC).

The medical literature was searched to identify relevant studies and reviews. Searches were conducted up until the end of September 1999 and were repeated in August 2000, March 2001 and June 2001. The following databases were searched:

- Medline / Pre-Medline
- National Library of Medicine Health Services Research Databases
  - HealthSTAR
  - HSRProj
  - HSTAT
  - HSR Tools
  - DIRLINE
- CINAHL
- Australasian Medical Index (AMI)
- Biological Abstracts
- EBM Reviews – Best Evidence
- Current Contents
- EMBASE
- The Cochrane Library
- ISTAHC Online database (International Society for Technology Assessment in Health Care)
- National Health Service (NHS) Centre for Reviews and Dissemination databases
  - DARE (Database of Abstracts and Reviews of Effectiveness)
  - EED (Economic Evaluation Database)
  - HTA (Health Technology Assessment Database)

Search strategy

The following search strategy was used to identify papers in Medline/Pre-Medline, HealthSTAR, CINAHL, Biological Abstracts, and Best Evidence (Table 4). The same search strategy was used for EMBASE, replacing MeSH terms with EMTREE terms.

Table 4 Search strategy

Search terms
1. exp Prostatic hyperplasia/ or prostat$ hyper$.mp. or BPH.mp.
2. exp transurethral resection of prostate/ or exp Prostatectomy/ or transurethral resection.mp. or TURP.mp.
3. transurethral needle ablation.mp. or TUNA.mp.
4. 1 and (2 and 3)
5. 1 and 2
6. 4 or 5

A broad search using the terms 'TUNA or transurethral needle ablation' was used for the NHS databases.

Electronic searching also included the Internet sites of the following health technology assessment groups and information sources (Table 5).

Table 5 Health Technology Assessment Organisations

Organisation	Website
Australian Safety & Efficacy Register of New Interventional Procedures-Surgical (ASERNIP-S)	http://www.racs.edu.au/open/asernip-s/publications.htm
International Society for Technology Assessment in Health Care (ISTAHC)	www.istahc.org
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.edu.ca/bcohta
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (US)	www.ohppr.state.or.us/ohrc
Minnesota Department of Health (US)	www.health.state.mn.us
ECR I(US)	www.ecri.org
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev
National Library of Medicine Health Service/Technology Assessment text (US)	http://text.nlm.nih.gov
NHS Health Technology Assessment (UK)	www.hta.nhsweb.nhs.uk
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca
Conseil d'Evaluation des Technologies de la Sante du Quebec (Canada)	www.cets.gouv.qc.ca
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/nichsr/nichsr.html
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	http://www.stakes.fi/finohta/linkit/
Institute Medical Technology Assessment (Netherlands)	http://www.bmg.eur.nl/imta/
Agencia de Evaluación de Technologias Sanitarias (AETS) (Spain)	http://www.isciii.es/unidad/aet/cdoc.htm
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	www.anaes.fr

The evidence presented in the selected studies was assessed and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence which is shown in Table 6.

Table 6 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Source: NHMRC 2000

The above searches identified 62 papers (as of June 2001). Criteria for inclusion in the review were:

- clinical treatment of patients with BPH with TUNA;
- formal analysis of results and presentation of data; and

- English language.

In addition, other papers that provided background information on the procedure or its comparators and the condition of BPH were also collected.

Existing reviews of evidence

A systematic review of minimally invasive techniques for relief of bladder outflow obstruction (including TUNA) was conducted by Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S 1999) and updated in 2000 (ASERNIP-S 2000; Wheelahan et al 2000). This report suggested that 'TUNA may eventually prove to have a limited role in treating patients with a high symptom score and only mild obstruction, such as those in the initial stages of BPH, rather than as a replacement for TURP'. The TUNA procedure was classified as Level 2: 'The safety and/or efficacy of the procedure cannot be determined at the present time due to an incomplete and/or poor quality evidence base. An audit is recommended to assess both safety and efficacy'.

The evidence for the efficacy and safety of TUNA is based on one published, although relatively small, randomised controlled trial (level II evidence) comparing TUNA to TURP, two prospective non-randomised studies, and a number of uncontrolled case series reports. The two non-randomised studies compared TUNA to other minimally invasive procedures such as visual laser ablation and transurethral microwave thermotherapy. However, no studies reporting on pharmaceutical interventions in comparison to TUNA were identified.

Randomised evidence

Results from the single randomised trial have been published in a number of papers and abstracts, as indicated in Table 7. The first of these papers (Bruskewitz et al 1998) presents more clinical information than the second, later paper, and as such forms the basis of this review. The third paper is published in abstract form only.

Table 7 Publications of randomised controlled trials of TUNA vs TURP

Author(s)	Title	Publication	Year
Bruskewitz R, Issa M, Roehrborn C, Naslund M, Perez-Marrero R, Shumaker B and Oesterling J	A Prospective Randomised 1-Year Clinical Trial Comparing Transurethral needle ablation to Transurethral Resection of the Prostate for the Treatment of Symptomatic Benign Prostatic Hyperplasia.	The Journal of Urology, 159 (5): 1588-1594	1998
Roehrborn CG, Burkhard FC, Bruskewitz RC, Issa MM, Perez-Marrero R, Naslund MJ, Shumaker BP	The Effects of Transurethral needle ablation and Resection of the Prostate on Pressure Flow Urodynamic Parameters: Analysis of the United States Randomised Study.	The Journal of Urology 162:92-97	1999
Naslund M, Perez-Marrero R, Roehrborn C, Bruskewitz R, Issa MM	Intermediate Term Outcomes for TUNA for BPH: 36 Month Results of the TUNA Vs TURP U.S. Randomised Study.	American Urological Association Annual Meeting.	May 1999 (Abstract Only)

Controlled non-randomised evidence

Two studies were also identified that compared the efficacy of several minimally invasive procedures, including TURP and TUNA, for the treatment of benign prostatic hyperplasia. The first trial has generated two publications (Table 8). The most comprehensive efficacy data is provided in Schatzl et al (2000) and assessed TURP against four less invasive options over a two year period. An earlier publication of this trial has also been included as it provided safety and post-operative complication data not provided in the more recent publication (Schatzl et al 1997). The second trial by Arai et al (2000) also compared four treatment options (though different to the former paper), and examined the impact of these procedures on the quality of life (QOL) and sexual function of patients three months after treatment for benign prostatic hyperplasia.

Results from these trials are summarised in Appendix C, Table 30.

Table 8 Publications of prospective non-randomised trials

Author(s)	Title	Publication	Year
Schatzl G, Madersbacher S, Djavan B, Lang T, and Marberger M	Two-year results of transurethral resection of the prostate versus four 'less invasive' treatment options.	European Urology 37:695-701	2000
Schatzl G, Madersbacher S, Lang T, Marberger M	The early postoperative morbidity of transurethral resection of the prostate and of 4 minimally invasive treatment alternatives.	Journal of Urology 158(1): 105-110	1997
Arai Y, Aoki Y, Okubo K, Maeda H, Terada N, Matsuta Y, Maekawa S, Ogura K	Impact of transurethral therapy for benign prostatic hyperplasia on quality of life and sexual function: a prospective study.	J Urology 164:1206-1211	2000

A decision was made before the review commenced not to include studies reported in abstract form as they generally contain insufficient information to enable adequate assessment of methodology and results. However, as so little information was available on long term patient outcomes after TUNA, a limited number of abstracts of prospective comparisons were also reviewed. One additional prospective comparative study of TUNA versus TURP was identified with the results existing in abstract form only. Three abstracts (Virdi & Chandrasekar 2001; Virdi, Pandit & Sriram 1997; Virdi, Pandit & Sriram 1998) from this trial have been published to date. A pre-submission draft version of a publication (supplied by the author; Virdi, Chandrasekar & Kapasi 2001) indicates that the study was randomised, however, no information was reported on the method of randomisation and all other abstracts have indicated that the trial was prospective, but not randomised. It is unclear, therefore, whether the trial was randomised or simply prospective. In addition, while the pre-submission draft and the most recent abstract reports that patients have been followed for six years, this appears to be only the patients treated with TUNA, and only a small proportion of these. Follow-up of patients treated with TURP appears to have ceased at three years. At four years post-treatment 37 per cent of patients treated with TUNA had data available, at 5-6 years, the proportion of patients for whom there are follow-up data is less than 10 per cent.

The studies are listed in Table 9 and results from these abstracts are summarised in Appendix C, Table .

Table 9 Publications of Virdi's prospective trial

Author(s)	Title	Publication	Year
Virdi J, Pandit A, Sriram R	Transurethral Needle Ablation of the Prostate (TUNA): A prospective study with 2 year follow-up.	British Journal of Urology 79 (Suppl 4) Abstract 227	1997 Abstract only
Virdi J, Pandit A, Sriram R	Transurethral Needle Ablation of the Prostate (TUNA): Three Year Follow-Up. A Prospective Study.	American Urological Association Annual Meeting	1998 Abstract only
Virdi J, Chandrasekar P	Transurethral needle ablation of the prostate (TUNA) - A prospective study, six year follow-up.	American Urological Association Annual Meeting	2001 Abstract only

Uncontrolled evidence

The 14 case series papers which met the inclusion criteria are listed in Table 10 and results are summarised in Table 32 (see Appendix C). Many of these studies restricted patient inclusion to those with smaller prostates (generally <100mL). Most used similar outcome measures: both patient-oriented symptom and quality of life scores, and the objective measures of peak flow rate, post-void residual volume and residual prostate size. However, since control groups were not used in any of these papers, and the studies were generally small, the statistical significance of the results is likely to be over estimated in these reports. Adverse event reporting was generally poor in these papers, with little or no description of events. As many of these studies had several papers and abstracts published, the most recent report was used.

Table 10 List of case series papers included in review

Author(s)	Title	Publication	Year
Schulman C, Zlotta A	Transurethral needle ablation of the prostate for treatment of benign prostatic hyperplasia: early clinical experience.	Urology 45: 28-33	1995
Harewood L, Cleeve L, O'Connell H et al	Transurethral needle ablation of the prostate (TUNA): clinical results and ultrasound, endoscopic and histologic findings in pilot study of patients in urinary retention.	J Endourology 9: 407-412	1995
Millard R, Harewood L, Tamaddon K	A study of the efficacy and safety of transurethral needle ablation (TUNA) treatment for benign prostatic hyperplasia.	Neurourology and Urodynamics 15: 619-629	1996
Issa M	Transurethral needle ablation of the prostate: report of initial United States clinical trial.	J Urology 156: 413-419	1996
Zlotta A, Peny M, Matos C et al	Transurethral needle ablation of the prostate: clinical experience in patients in urinary acute retention.	Br J Urology 77: 391-397	1996
Rosario D, Woo H, Potts K et al	Safety and efficacy of transurethral needle ablation of the prostate for symptomatic outlet obstruction.	Br J Urology 80: 579-586	1997
Ramon J, Lynch T, Eardley I et al	Transurethral needle ablation of the prostate for the treatment of benign prostatic hyperplasia: a collaborative multicentre study.	Br J Urology 80: 128-135	1997
Steele G, Sleep D	Transurethral needle ablation of the prostate: a urodynamic based study with 2-year follow-up.	J Urology 158: 1834-1838	1997
Campo B, Bergamaschi F, Corrada P et al	Transurethral needle ablation (TUNA) of the prostate: a clinical and urodynamic evaluation.	Urology 49: 847-850	1997
Braun M, Zumbe J, Korte D, Solleder G, Heidenreich A, Engelmann U	Transurethral needle ablation of the prostate: an alternate minimally invasive therapeutic concept in the treatment of benign prostate hyperplasia.	Urologia Internationalis 61: 104-110	1998
Kahn S, Alphonse P, Tewari A et al	An open study on the efficacy and safety of transurethral needle ablation of the prostate in treating symptomatic benign prostatic hyperplasia: the University of Florida experience.	J Urology 160: 1695-1700	1998
Roehrborn C, Issa M, Bruskewitz R et al	Transurethral needle ablation for benign prostatic hyperplasia: 12-month results of a prospective, multicenter U.S. study.	Urology 51: 415-421	1998
Namiki K, Shiozawa H, Tsuzuki M, Mamiya Y, Matsumoto T, Miki M	Efficacy of transurethral needle ablation of the prostate for the treatment of benign prostatic hyperplasia.	International Journal of Urology 6: 341-5	1999
Holmes MA, Stewart J, Boulton JB and Chalmers RM	Transurethral needle ablation of the prostate: outcome at 1 year.	Journal of Endourology 13: 745-50	1999

Five abstracts of case series were also identified in the search process. While it has been noted that abstracts are generally lacking in clinical and methodological information, the results presented in these abstracts have been summarised in Table 33 (see Appendix E), but have not been included in the systematic review.

Expert advice

A supporting committee with the relevant expertise was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical

colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

Is it safe?

Randomised evidence

In the randomised controlled trial (RCT) (Bruskewitz et al 1998) differences between the procedures in terms of adverse effects exist in three major areas. Seven patients in the TURP group experienced erectile dysfunction, compared with none in the TUNA group. Twenty one patients (38%) in the TURP group experienced retrograde ejaculation, compared to none in the TUNA group, although it should be noted that this complication is only relevant in sexually active men. All patients in the TURP group experienced post-operative bleeding, compared with 21 (32%) of the TUNA group.

Other adverse effects, including urethral stricture, were lower in the TUNA group compared to TURP. In the TUNA group there were no cases of urinary incontinence (two cases (3.6%) in the TURP group) or dysuria (two cases (3.6%) in the TURP group).

There was no mortality associated with either procedure, and the short and long term complications of TUNA and TURP are presented in Table 11. The authors report that TUNA had significantly fewer adverse effects than TURP ($p<0.0001$). It is unclear, however, how many patients were included in the adverse event analysis for each treatment arm, and at what time point the adverse events in Table 11 were measured. The timing and resolution of adverse events is an important consideration, and the authors provide no information on these factors. For example, it is unclear from the publication whether retrograde ejaculation in the TURP group was reported in the first month, but had resolved by six or 12 months after treatment.

Table 11 Adverse events from RCT according to treatment

Adverse Event	TUNA		TURP	
	No.	%	No.	%
Retrograde ejaculation	0	0	21	38
Erectile dysfunction	0	0	7	13
Urinary incontinence	0	0	2	4
Bleeding	21	32	56	100
Dysuria	0	0	2	4
Urinary tract infection	5	8	7	13
Urethral strictures	1	2	4	7

Controlled non-randomised evidence

Little information on adverse effects is reported in the two prospective controlled studies (Table 12). Schatzl et al (2000) provide no information regarding adverse effects at two years. The earlier publication (Schatzl et al 1997) provides some information regarding early post-operative complications (at six weeks after treatment). Arai et al (2000) also

reports limited data on the adverse effects of interventions. As the primary aim of the paper was to assess the impact of non-invasive procedures on quality of life and sexual function, the authors have primarily reported on these two aspects.

Table 12 Adverse events reported in prospective non-randomised studies

Adverse Event	Schaltz et al 1997 – 6 weeks*					Arai et al 2000 – 3months*			
	TURP	TUNA	HIFU	VLAP	TUV/P	TUNA	TURP	TUMT	ILCP
Number of patients	28	15	20	15	17	42	55	34	42
Epididymitis (%)	1 (4)	0	1 (5)	0	0	-	-	-	-
Gross hematuria (%)	0	1 (7)	1 (5)	0	2 (12)	-	-	-	-
Retention (%)	3 (11)	4 (27)	0	2 (13)	1 (6)	-	-	-	-
Rehospitalisation (%)	0	1 (7)	1 (5)	1 (7)	1 (6)	-	-	-	-
Retrograde ejaculation (%)	-	-	-	-	-	(29)	(48.7)	(29)	(23.7)
Decrease in erectile function (%)	-	-	-	-	-	(20)	(26.5)	(18.2)	(18.4)
Total no patients (%)	**4 (14)**	**4 (27)**	**2 (10)**	**2 (13)**	**2 (12)**	**-**	**-**	**-**	**-**

*HIFU – high intensity focussed ultrasound; VLAP – visual laser ablation; TUV/P – Transurethral electrosurgical vaporisation; TUMT- transurethral microwave thermotherapy; ILCP – interstitial laser coagulation of the prostate

Uncontrolled evidence

Side effects were not generally well reported in the case series papers. Extreme percentages should be viewed with caution because of the small patient numbers in many series. Documented adverse effects from TUNA case series are tabulated below in Table 13.

Table 13 Adverse effects reported in TUNA case series

Study	N	Haematuria requiring hospitalisation %	Haematuria requiring treatment %	Catheterisation postoperatively	Catheterisation for acute urinary retention %	Urinary retention (treatment not stated) %	Infection %	Epididymoorchitis / epididymitis %	Retrograde ejaculation / unable to ejaculate %	Erectile dysfunction %	Urethral stricture %	Chronic prostatitis %	Deep Venous Thrombosis
(Schulman & Zlotta 1995)	20	5	-	-	25	-	-	-	-	-	-	-	-
(Harewood et al 1995)	10	-	-	-	-	-	30	10	-	-	-	-	-
(Millard, Harewood, & Tamaddon 1996)	20	-	-	-	-	-	20	20	-	-	-	-	-
(Issa 1996)	12	-	-	-	-	-	-	-	8	-	-	-	-
(Zlotta et al 1996)	38	-	-	-	5	-	-	-	-	-	-	-	-
(Rosario et al 1997)	71	-	1	-	-	-	15	1	1	3	-	1	1
(Ramon et al 1997)	76	1	-	33	-	29	11	1	-	-	1	-	-
(Steele & Sleep 1997)	47	-	-	-	17	-	-	1	-	-	-	-	-
(Campo et al 1997)	120	-	-	13	-	-	1	-	-	-	-	-	-
(Braun et al 1998)	33	-	6	48	-	-	21	-	3		3	-	-
(Kahn et al 1998)	45	4	-	-	-	-	-	-	-	-	-	-	-
(Roehrborn et al 1998)	130	-	-	41	12	-	-	5	1	2	-	-	-
(Kahn et al 1998)	30 (33)	-	7	-	66	-	-	-	-	-	7	-	-
(Holmes et al 1999)	25	-	-	-	-	-	-	-	-	-	-	-	-
Namiki et al 1999	33	-	6	-	-	61	-	-	-	-	6	-	-

Based on two studies (Schulman 1995; Kahn 1998), 4-5 per cent of patients had haematuria, which required hospitalisation. Only four of the 15 studies provided any information on the proportion of patients who required treatment for haematuria (Rosari 1997; Braun 1998; Kahn 1998; Namiki 1999). Based on these four studies, between 1 per cent and 7 per cent of patients required some form of treatment for haematuria. Recent reviews of TURP do not specifically report on the incidence of haematuria, however, they do indicate that between 0 per cent and 13 per cent of patients required transfusion for haemorrhage (a more serious complication) after surgery (Table 14).

Table 14 Adverse effects reported for TURP in recent reviews

Study	Haemorrhage requiring transfusion	Urethral Strictures	Retrograde ejaculation / unable to ejaculate	Erectile dysfunction	Chronic Urinary tract infection	Bladder neck contracture	Dribbling / urge incontinence	Perforation of prostatic capsule	Acute urinary retention
	%	%	%	%	%	%	%	%	%
(Australian Health Technology Advisory Committee 1994)	< 5*	5-15	Up to 50	5-40	< 5		20-50		
(Madersbacher & Marberger 1999)	0-13	0-12	11-100	0.2-13	NR	0-31	NR		
(Wasson et al 1995)	1	0	0	0	NR	NR	1%	2%	
WHO Consultation statement (Debruyne et al 2000)	0.4 – 6.4%	3.1-3.8%	~30%	4.2%		1.7-4.7%			10–13%

* no indication of transfusion status

Data on post treatment infection was reported in six of 14 case series with an incidence of between 1 per cent and 33 per cent. This may be related to the rate of post TUNA catheterisation in patients, and appeared more prevalent in earlier series. It was 8 per cent versus 13 per cent for TUNA and TURP, respectively, in the randomised controlled trial.

Post-operative catheterisation (generally for 24-48 hours after TUNA surgery) was necessary in up to 48 per cent of patients, and it is often unclear from the case series whether this was considered a routine procedure. Between 5 per cent and 66 per cent of TUNA patients developed acute urinary retention after the post-operative period.

Retrograde ejaculation / inability to ejaculate, erectile dysfunction, urethral strictures and chronic prostatitis were reported in a limited number of case series in approximately 1-3 per cent of patients treated with TUNA. This appeared to be a higher frequency than the RCT, where no patients with TUNA reported these adverse effects. Recent reviews of TURP (Debruyne et al 2000) indicate that approximately 3-4 per cent of TURP patients develop urethral strictures and approximately 2-5 per cent develop bladder neck contractures. The recent World Health Organization (WHO) consultation on BPH (Debruyne et al 2000) indicates that *de novo* post-operative impotence occurred in 3-4.2 per cent of patients treated with TURP, while a study comparing TURP with watchful waiting indicated no greater rate of impotence in the treated compared to observed group. The WHO report concluded that contemporary peri-operative and post-operative complications are significantly lower than historical series. The improvement over time noted for TURP may also be applicable for the TUNA procedure.

As no tissue sample is available for histological examination with the TUNA procedure, possible malignancy must be excluded prior to the surgery. This may involve prostate specific antigen (PSA) screening or biopsy.

No postoperative deaths were noted in the randomised trial or the case series.

Conclusions on safety

TUNA appears to be a relatively safe procedure. Data from the randomised trial suggest that TUNA has fewer post-operative complications, such as bleeding, than does TURP. Non-randomised evidence suggests that apart from urinary retention, which appears more common with the TUNA procedure, the early adverse event rates for TUNA and TURP are similar.

From the data available, it is likely that TUNA results in fewer complications relating to sexual function (such are erectile dysfunction or retrograde ejaculation) than does TURP. However, the rates of these complications seen in more recent TURP series appear to be lower than those reported in historical series. As TUNA has also evolved over time, it is possible that the newer TUNA procedures may result in fewer complications than older procedures, although at this stage this remains unclear.

All the trials in this report conducted TUNA as an inpatient procedure, however, it can, in practice, be performed as an outpatient or in-clinic procedure, thus potentially avoiding risks associated with general anaesthesia. While none of the trials specifically evaluated the role of TUNA in this subset of patients, it may, theoretically, be of value in patients with a high anaesthetic risk.

Is it effective?

Controlled evidence: randomised

One published multi-centre (United States) randomised controlled trial comparing the safety and efficacy of TUNA and TURP was identified, and presents results at 12 months post-treatment (Bruskewitz et al 1998). A second paper, published later, was also identified (Roehrborn et al 1999), but provided less clinical detail than the Bruskewitz et al paper, and therefore has not been included here. There was also one abstract of this trial identified, which presented results of this study at 36 months of follow-up (Naslund et al 1999).

The methods used in the one published randomised trial are well described. The method of generating the randomisation allocation sequence is a standard method, consisting of stratified blocks of six patients. It is not clear from the published paper, however, whether central randomisation was used, and therefore how well the next treatment allocation was concealed. Inclusion and exclusion criteria are well described.

While the published paper provided no discussion of sample size or power of the trial to detect a clinically important difference between the two treatments, the clinical trial protocol provided by the applicant to MSAC for evaluation does provide this information. A sample size of a minimum of 150 patients in total was required, and enrolment of 167 was required to allow for 17 dropouts.

A total of 121 men with symptomatic BPH were enrolled in this trial: 65 (54%) were treated with TUNA and 56 (46%) were treated with TURP. Baseline characteristics of both treatment groups appear comparable, with the only significant difference between the two groups occurring with the mean post-void residual volume (TUNA: 91.8 ± 10.0ml vs TURP: 82.6 ± 9.5ml, $p < 0.001$) (Table 15).

Table 15 Baseline characteristics of TUNA and TURP cohorts

Parameter	TUNA	TURP	p value
Number of men	65	56	
Age	66±1.0	66±1.0	0.75
Mean AUA symptom score	23.9±0.8	24.1±0.8	0.94
Mean AUA bother score	17.8±0.8	18.0±0.8	0.90
Mean quality of life score	11.8±0.5	12.8±0.5	0.15
Mean peak urinary floe rate (ml/sec)	8.8±0.3	8.8±0.3	0.99
Mean post-void residual volume (ml)	91.8±10.0	82.6±9.5	<0.001
Mean prostate volume (cc)	36.2±1.5	35.7±1.9	0.11

Loss of follow-up data was significant in this trial, with six of 65 (9.3%) in the TUNA group and nine of 56 (16.1%) in the TURP group having no clinical data at the one year follow-up (Table 16).

Table 16 TUNA versus TURP: loss to follow-up at 12 months

	TUNA		TURP	
Reason	**No.**	**%**	**No.**	**%**
Ineffective	2	3.1	0	0.0
Moved, lost to follow-up	2	3.1	5	8.9
Deceased, cancer	2	3.1	2	3.6
Voluntarily withdrew	-	-	2	3.6
Totals	**6**	**9.3**	**9**	**16.1**

Within the published study, the authors appear to place equal weighting on the importance of all five measures used (American Urological Association (AUA) symptom score, AUA bother score, quality of life score, peak urinary flow rate and post-void residual urine volume). The clinical trial protocol provided by the applicant to MSAC for evaluation does indicate, however, that primary efficacy determination was based upon symptom score (AUA) and peak uroflow (urinary flow rate) improvement. Secondary outcome measures include quality of life, AUA bother score, prostate volume and residual urine volume (Table 17).

Table 17 TUNA versus TURP: primary and secondary efficacy variables (Mean ± standard error during 12 month follow-up)

	Baseline		1 month		3 months		6 months		12 months	
Parameter	**TUNA**	**TURP**	**TUNA**	**TURP**	**TUNA**	**TURP**	**TUNA**	**TURP**	**TUNA**	**TURP**
Primary										
AUA Symptom Score	24.7±0.8	23.3±0.8	13.4±0.8	13.4±0.9	10.1±0.9	9.4±0.7	11.0±1.0	8.4±0.8	11.1±1.0	8.3±0.9
P value (vs baseline)			<0.0001	0.0005	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
P value (btwn groups)	0.4002		0.7669		0.7547		0.4513		**0.0402***	
Peak Urinary Flow rate (ml/sec)	8.7±0.3	8.4±0.3	15.2±1.0	19.9±1.3	15.4±0.7	21.9±1.4	14.0±0.8	21.4±1.2	15.0±1.0	20.8±1.3
P value (vs baseline)			<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
P value (btwn groups	0.6599		0.0231		0.0081		0.0005		**0.0163***	
Secondary										
AUA Bother Score	19.4±0.8	17.9±0.8	8.8±0.7	9.9±0.7	6.0±0.6	7.2±0.7	7.3±0.8	6.9±0.7	7.2±0.8	6.3±0.8
P value (vs baseline)			<0.0001	0.0001	<0.0001	0.0002	≤0.0001	0.0001	≤0.0001	0.0004
P value (btwn groups	0.2975		0.1896		0.2279		0.8697		0.2470	
Quality of life	13.5±0.5	12.7±0.5	6.7±0.5	8.4±0.7	4.2±0.5	5.6±0.7	4.8±0.6	5.1±0.6	5.0±0.5	4.7±0.9
P value (vs baseline)			<0.0001	0.0175	<0.0001	0.0015	<0.0001	0.0001	<0.0001	0.0015
P value (btwn groups	0.3494		0.2337		0.3279		0.6603		0.7230	
Post-void residual volume (ml)	101±10.0	111.9+9.5	68.7±8.8	57.0±7.5	52.4±8.2	84.8±10.7	69.0±8.2	24.9±8.1	73.2±11.4	53.7±7.1
P value (vs baseline)			0.0259	0.0149	0.0003	0.0277	0.0190	0.0011	0.0249	0.0035
P value (btwn groups	0.4479		0.4866		0.4606		0.0475		0.7840	
Prostate volume (cc)	37.4±1.5	32.3±1.9	-	-	-	-	34.4±2.4	27.9±2.3	38.3±2.9	26.8±3.5
P value (vs baseline)			-	-	-	-	0.1023	0.0386	0.7151	0.0061
P value (btwn groups	0.1179		-		-		0.7244		**0.0142***	

* indicates significant between group difference favouring TURP

It would appear from these results that the mean baseline values in Table 17 may have been calculated only for the subgroup who completed 12 months follow-up, as the corresponding baseline values for the whole patient cohort presented in Table 15 are

different. Noticeably, the baseline value for mean post-void residual volume reported in Table 15 (TUNA: 91.8 ± 10.0ml vs TURP: 82.6 ± 9.5ml), which was significantly different between the two treatment groups ($p < 0.001$), is no longer significantly different in Table 5 (TUNA: 101 ± 10.0ml vs TURP: 111.9± 9.5ml, $p=0.4479$). Indeed, the direction of the difference has changed to favour TUNA. It is also not possible to determine from the paper how many patients were available for end point follow-up at each given time point.

It can be seen that both primary efficacy variables, AUA symptom score and peak urinary flow rate, were significantly better at 12 months for those patients treated with TURP compared to those patients treated with TUNA ($p=0.0402$ and $p=0.0163$, respectively). Of the secondary outcome variables, prostate volume was the only one which demonstrated a significant difference between TUNA and TURP treated patients (favouring TURP). This reflects the different mechanisms of action between the two treatments.

The authors also presented the results for primary and secondary efficacy variables in terms of the proportion of patients who achieve a given percentage improvement from baseline (although between-group statistical comparisons were not performed for this analysis). Table 18 presents results for primary outcomes of AUA symptom score and peak urinary flow rate only.

Table 18 TUNA versus TURP primary efficacy variables – per cent improvement over 12 months

	1 month		3 months		6 months		12 months	
Parameter	**TUNA (%)**	**TURP (%)**	**TUNA (%)**	**TURP (%)**	**TUNA (%)**	**TURP (%)**	**TUNA (%)**	**TURP (%)**
AUA Symptom Score								
None	8.3	13.6	5.5	0.0	8.3	0.0	0.0	9.1
>30% improvement	72.2	68.2	80.5	81.8	86.1	95.5	77.8	90.9
>50% improvement	47.2	45.5	66.6	68.2	63.9	63.6	63.9	81.8
>80% improvement	5.5	9.1	19.4	13.6	25.0	31.8	22.2	31.8
Peak Urinary Flow rate (ml/sec)								
None	15.6	0.0	3.1	0.0	12.5	0.0	18.8	9.1
>30% improvement	65.6	90.9	71.9	95.5	68.8	95.5	68.8	86.4
>50% improvement	46.9	72.7	62.5	86.4	46.9	86.4	62.5	81.8
>80% improvement	37.5	59.1	43.8	72.7	28.1	68.2	40.6	72.7

A higher proportion of patients experienced symptom control and improvement in peak urinary flow in the TURP arm at 12 months compared to TUNA treated patients. The authors did not indicate the number of patients available for follow-up at each time point, and have not provided any discussion of the clinical significance of these results.

As discussed earlier, there is no peer-reviewed data available for longer than 12 months of follow-up for these patients. Naslund et al (1999) presented an abstract of three year follow-up data (Table 19) for the primary outcome variables of AUA symptom score and peak flow rate.

Table 19 TUNA versus TURP primary efficacy variables at 36 months (mean)

	AUA Score		Peak urinary flow rate (ml/sec)	
Timepoint	**TUNA**	**TURP**	**TUNA**	**TURP**
Baseline	23.9	24.1	8.8	8.8
36 months	14.4	10.2	13.2	18.9
p-value (from baseline)	<0.001	<0.001	<0.001	<0.001
p-value (between treatment groups)	**0.036**		**0.018**	

These results indicate that TURP appears to remain superior to TUNA in terms of symptom control and peak urinary flow rate at 36 months after treatment. It is not possible, however, to determine how many patients were still being followed at three years post-procedure for either arm. It should also be noted that the difference in baseline values between 12 months (Table 17) and 36 months (Table 19) follow-up data also tend to suggest that the authors have again calculated a baseline only for the subgroup of patients with 36 months of follow-up. The limited information concerning adverse events provided in the abstract also indicates exactly the same percentage of patients experiencing retrograde ejaculation, urinary tract infections, stricture and erectile dysfunction as those reported in the 12 month published data. This tends to suggest that adverse event and complication monitoring has not continued past the 12 months.

The long term outcomes of patients treated with TUNA remain fairly unclear, with the best available information at this stage coming from abstracts. From the data available, TURP appears to offer superior long term (three years) symptom control and urinary flow rate compared to TUNA.

Controlled evidence: non-randomised

Two prospective non-randomised papers were identified that assessed the efficacy of TURP and a number of other less invasive procedures, including TUNA.

Schatzl et al (2000) compared TURP to four less invasive options (TUNA, VLAP, HIFUTUV/P - transurethral electrosurgical vaporisation) over a 24 month period. Patients were assigned sequentially to one of the less invasive treatment procedures, with patients not willing to undergo one of these procedures being treated by TURP. It is possible this led to selection bias, however, baseline characteristics of age, peak flow rate, International Prostate Symptoms Score (IPSS), prostate size and degree of bladder outflow obstruction were comparable between the five treatment arms. The proportion of patients lost to follow-up at 24 months was as follows: TURP 4 per cent; TUNA 20 per cent; VLAP 27 per cent; HIFU 20 per cent; and TUVP 24 per cent.

Results are reported below in Table 20. IPSS was measured at six, 12 and 24 months, and appeared to improve compared to baseline for all procedures. The only significant difference between treatments was between VLAP and TURP at six months.

All treatments improved peak flow rate compared to baseline values. However, the duration of this improvement varied between treatments. For between treatment comparisons, peak flow rate was significantly higher at 12, 18 and 24 months for patients

treated with TURP compared to patients treated with TUNA. It was also significantly higher at 24 months for TURP patients compared to VLAP and HIFU treated patients.

Post-void residual volume is also reduced compared to baseline after all five procedures. Between treatment comparisons indicated that there was a statistically significant difference between TURP and HIFU at all time points.

Table 20 TURP versus TUNA, VLAP, HIFU and TUVP (Mean ± standard error during 24 month follow-up)

Parameter		TURP (n)	TUNA (n)	VLAP (n)	HIFU (n)	TUV/P (n)
IPSS	Baseline	19.5 +/- 5.7 (28)	17.75 +/- 5.7 (15)	19.7 +/- 7.3 (15)	14.7 +/- 5.9 (20)	19.1 +/- 5.8 (17)
	6mo	4.7 +/- 2.7 (27)	8.7 +/- 5.9 (14)	12.4 +/- 9.4 (15) p<0.05*	6.4 +/- 5.4 (20)	6.0 +/- 4.7 (15)
	12mo	4.7 +/- 3.4 (27)	6.5 +/- 4.0 (14)	8.9 +/- 7.3 (12)	4.3 +/- 1.6 (16)	5.8 +/- 1.7 (13)
	18mo	5.4 +/- 2.8 (27)	7.9 +/- 5.7 (12)	6.7 +/- 3.4 (11)	5.3 +/- 2.3 (16)	5.8 +/- 1.8 (13)
	24mo	5.6 +/- 2.6 (27)	7.7 +/- 5.5 (12)	6.8 +/- 6.7 (11)	7.7 +/- 5.9 (16)	6.4 +/- 1.9 (13)
Qmax	Baseline	8.2 +/- 4.8 (28)	9.3 +/- 2.2 (15)	6.1 +/- 4.1 (15)	9.2 +/- 2.5 (20)	8.9 +/- 2.9 (17)
(Peak flow	6mo	19.5 +/- 3.5 (27)	13.6 +/- 8.0 (14)	14.7 +/- 8.0 (15)	13.1 +/- 3.2 (20)	20.6 +/- 4.7 (15)
rate, ml/sec)	12mo	21.1 +/- 5.4 (27)	11.9 +/- 3.3 (14) p<0.05*	13.9 +/- 7.9 (12)	13.1 +/- 3.8 (16)	21.3 +/- 5.8 (13)
	18mo	20.1 +/- 4.9 (27)	10.7 +/- 3.3 (12) p<0.05*	12.1 +/- 7.4 (11)	12.1 +/- 2.6 (16) p<0.05*	20.9 +/- 5.5 (13)
	24mo	19.7 +/- 4.6 (27)	11.6 +/- 3.7 (12) p<0.05*	11.7 +/- 6.2 (11) p<0.05*	11.2 +/- 1.7 (16) p<0.05*	20.0 +/- 6.1 (13)
Post-void residual volume (ml)	Baseline	104 +/- 102 (28)	85 +/- 78 (15)	94 +/- 68 (15)	94+/- 33 (20)	70 +/- 27 (17)
	6mo	15 +/- 21 (27)	41 +/- 36 (14)	31 +/- 23 (15)	46 +/- 33 (20) p<0.05*	23 +/- 20 (15)
	12mo	15 +/- 10 (27)	32 +/- 35 (14)	30 +/- 27 (12)	49 +/- 32 (16) p<0.05*	19 +/- 21 (13)
	18mo	17 +/- 12 (27)	29 +/- 36 (12)	27 +/- 36 (11)	52 +/- 26 (16) p<0.05*	16 +/- 19 (13)
	24mo	19 +/- 15 (27)	30 +/- 37 (12)	26 +/- 36 (11)	58 +/- 26 (16) p<0.05*	21 +/- 22 (13)

*p<0.05 vs TURP ie TURP was statistically significantly better than the less invasive intervention

Schatzl et al (2000) also reported the proportion of patients who required retreatment with TURP. This information is discussed in the section below, 'Requirement for Retreatment'.

Arai et al (2000) compared patients treated with TURP to those treated with TUNA, TUMT and ILCP. The study initially recruited 204 men, between ages 52 and 84. For the outcomes of IPSS, peak flow rate and post-void residual volume, data on 173 participants were reported. For the outcomes of quality of life and sexual functioning, 163 and 155 participants, respectively, were included. Allocation of patients to treatment arms was not random and was based primarily on patient views of benefits compared to risks for each procedure.

There were few significant differences in baseline characteristics between the four groups: patients in the ILCP group had larger prostates (ANalysis Of VAriance (ANOVA) p=0.024, versus TURP/TUMT/TUNA); TURP patients had a higher post-

void residual volume than TUMT patients ($p<.05$); and TUMT patients had higher baseline erectile function scores than TURP patients ($p<.05$).

The authors noted that the improvement in IPSS from baseline was most marked in the TURP and ILCP groups. Compared to baseline, treatment with TURP and ILCP led to significant improvements in peak flow rate and significant reductions in post-void residual volume. All treatment groups reported significant improvements in post-treatment quality of life compared to baseline. Despite this, however, there was no significant difference between baseline and three months for any treatment group in measures of either sexual desire or erectile function. This indicates that erectile functioning was not significantly affected by treatment, even in patients treated with TURP (Table 21).

Table 21 Quality of life and sexual functioning for TURP, TUNA, TUMT and ILCP (Mean ± standard error during 3 month follow-up)

Parameter		TURP (55)	TUNA (42)	TUMT (34)	ILCP (42)	p value (ANOVA)
IPSS N=173	Baseline	19.0 +/- 7.2	19.8 +/- 5.9	18.4 +/- 6.2	19.3 +/- 8.4	0.862
	3 months	7.6 +/- 4.9 p<0.001	10.5 +/- 6.5 <0.001	13.2 +/- 6.8 p<0.001	6.9 +/- 4.9 p<0.001	<0.001[1]
Qmax (Peak flow rate, ml/sec) N=173	Baseline	7.7 +/- 4.6	8.2 +/- 4.1	7.7 +/- 4.3	7.6 +/- 3.5	0.92
	3 months	14.4 +/- 7.8 p<0.001	9.2 +/- 4.2 p=0.187	8.6 +/- 4.9 p=0.0844	12.6 +/- 4.7 p<0.001	<0.001[2]
Post-void residual vol (ml) N=173	Baseline	133.3 +/- 211.4)	81.5 +/- 90.5	58.1+/- 65.7	102.3 +/- 86.1	0.084[3]
	3 months	39.2 +/- 58.8 p=0.014	59.4 +/- 54 p=0.052	63.6 +/- 80.6 p=0.624	30.4 +/- 35.9 p<0.001	0.036[4]
QOL (0-6) N=163	Baseline	4.5 +/- 1.1	4.7 +/- 0.6	4.4 +/- 1.2	4.3 +/- 1.5	0.36
	3 months	1.9 +/- 1.3 p<0.001	2.4 +/- 1.4 p<0.001	2.7+/-1.4 p<0.001	1.8+/-1.3 p<0.001	0.005[5]
Sexual desire score (0-10) n=155	Baseline	2.7 +/- 1.8	2.9 +/- 1.9	3.2 +/- 1.7	3.3 +/- 2.0	0.465
	3 months	2.7 +/- 1.9 p=0.921	3.0 +/- 1.7 p=0.923	3.3 +/- 1.8 p=0.913	3.1 +/- 1.8 p=0.368	0.546
Erectile function score (0-10) N=155	Baseline	3.1 +/- 2.4	3.5 +/- 2.4	4.2 +/- 2.5	4.0 +/- 2.4	0.183[6]
	3 months	3.0 +/- 2.5 p=0.831	3.2 +/- 2.2 p=0.363	4.1 +/- 2.3 p=0.919	3.7 +/- 2.5 p=0.48	0.161[6]

[1] ILCP/TURP p<0.001 vs TUMT; ILCP p<0.01 vs TUNA; TURP p<0.05 vs TUNA
[2] TURP p<0.001 vs TUMT/TUNA; ILCP p<0.01 vs TUMT/TUNA
[3] TURP p<0.05 VS TUMT
[4] ILCP p<0.05 vs TUMT/TUNA
[5] TURP/ILCP p<0.05 vs TUNA
[6] TUMT p<0.05 vs TURP

Uncontrolled evidence

Clinical data extracted from uncontrolled studies is presented in Table 32, Appendix D and summarised in Table 22. In most studies, outcomes improved significantly from baseline. The evidence from the case series is generally consistent with the TUNA group results in the randomised trial, and the non-randomised prospective comparisons. Some case series indicated proportions of patients requiring retreatment following TUNA. This information is presented below in the section 'Requirement for retreatment'.

Table 22 Mean pre and post-treatment values for peak flow rate, AUA score and retreatment rates

Study	N	F/U (mos)	Mean Peak flow rate (ml/s)				Mean AUA score			
			Pre-TUNA	N	Post-TUNA	N	Pre-TUNA	N	Post-TUNA	N
(Schulman & Zlotta 1995)	20	6	9.5	20	15.0	12	-	-	-	-
(Harewood et al 1995)	10	6	0	-	11.9	3	15.3	10	11.5	4
(Millard, Harewood, & Tamaddon 1996)	20	12	3.02	13	11.4	?	19.0	-	8.25	-
(Issa 1996)	12	6	7.8	12	13.5	10	25.6	-	9.8	10
(Rosario et al 1997)	71	12	9.0	71	11.3	58	21.9	70	10.6	57
(Ramon et al 1997)	76	12	8.7		11.6	55	-	-	-	-
(Steele & Sleep 1997)	47	24	6.6	47	11.2	31	22.4	47	9.5	38
(Campo et al 1997)	120	18	8.2	120	14.1	42	-	-	-	-
(Braun et al 1998)	33	6	9.4	33	15.4	33	-	-	-	-
(Kahn et al 1998)	45	12	8.3	45	14.9	16	-	-	-	-
(Roehrborn et al 1998)	130	12	8.7	130	14.6	88	23.7	129	11.9	93
(Namiki et al 1999)	33	18	8.0	30	11.8	11	-	-	-	-
(Holmes et al 1999)	25	12	8.3	14	10.4	7	-	-	-	-

? - unclear

Requirement for retreatment

Retreatment with additional procedures or medical management following TURP or TUNA is a good measure of the post-trial efficacy of the procedure. Unfortunately, much of the published information available is only for patients with approximately two years post-procedure follow-up. A number of abstracts (Bergamaschi et al 2000; Namasivayam et al 1999; Zlotta, Giannakopoulos, & Schulman 2001), while providing limited information on the methodology of the series, provided some additional information on retreatment rates out to 3-5 years.

Unfortunately, the one randomised controlled trial provided no information about the long term retreatment rates (repeat TUNA, TURP or open prostatectomy) in patients treated with TUNA or TURP, so it is not possible to assess this measure of effectiveness with respect to this study.

One of the prospective non-randomised studies reported the proportions of patients treated with a TURP or a minimally invasive procedure who required retreatment with TURP (Schatzl et al 2000). As can be seen in Table 23, the proportion of patients who required retreatment after initial treatment with TURP was lower than for other, less invasive initial procedures.

Table 23 Retreatment rates over time

	TURP	TUNA	VLAP	HIFU	TUV/P
No:	**28**	**15**	**15**	**20**	**17**
Retreatment with TURP required cumulative n & (%) *					
6 months	1 (4)	1 (7)	-	-	2 (12)
12 months	1 (4)	1 (7)	3 (20)	4 (15)	4 (24)
18 months	1 (4)	3 (20)	4 (27)	4 (15)	4 (24)
24 months	1 (4)	3 (20)	4 (27)	4 (15)	4 (24)
Total	**1 (4)**	**3 (20)**	**4 (27)**	**4 (15)**	**4 (24)**

* % based on baseline patient numbers

A number of the uncontrolled case series also indicated the proportion of patients who required retreatment with prostatectomy or TURP following treatment with TUNA (Table 24).

Table 24 Proportion of patients requiring retreatment following TUNA (case series)

Study	N	Follow-up (months)	Prostatectomy required (%)
(Schulman & Zlotta 1995)	20	6	5
(Harewood et al 1995)	10	6	30
(Millard, Harewood, & Tamaddon 1996)	20	12	25
(Issa 1996)	12	6	-
(Rosario et al 1997)	71	12	-
(Ramon et al 1997)	76	12	-
(Steele & Sleep 1997)	47	24	13
(Campo et al 1997)	120	18	-
(Braun et al 1998)	33	6	-
(Kahn et al 1998)	45	12	4
(Roehrborn et al 1998)	130	12	-
(Namiki et al 1999)	33	18	10
(Holmes et al 1999)	25	12	24

As can be seen in Table 24, up to 30 per cent of patients required treatment with prostatectomy following TUNA. This is consistent with information reported in the prospective controlled studies, however, no information on retreatment rates was reported in the randomised trial. It is possible that inappropriate selection of patients for TUNA by Harewood et al (1995) may have contributed to the high rate of retreatment in this study (30% at six months).

Namasivayam (1999) reported that of 91 patients treated with TUNA, 39 required further prostate surgery within three years (43%), while another three (3%) were on a waiting list to have TURP performed over the same time period.

Zlotta et al (2001) provides some additional longer term (five year) information on retreatment rates of patients treated initially with TUNA. It is difficult to assess the methodological quality of this series, as data are only available in abstract form. In a group of 162 consecutive patients treated with TUNA, five year follow-up data is available for 150 patients. The authors indicate that 37 of 150 (24.6%) patients required additional treatment at five years. Medical treatment was provided to 12 patients, a

second TUNA performed in seven patients and surgery (although it is not indicated which procedure) was performed in 18 patients.

Bergamaschi et al (2000) also provide some additional information on retreatment rates at five years. They reported on 206 patients (31 available for follow-up at five years). Over the five year follow-up 55/206 patients (27%) were considered to have failed TUNA: 43 underwent TURP and 12 received medical management with alpha blockers.

These papers provide a crude estimate of an annual retreatment rate of between approximately 5 per cent and 15 per cent per annum. It should be noted that in many cases, retreatment rates are based on patients treated with older procedures (as would be expected, given the duration of follow-up).

TUNA as a treatment for acute urinary retention

There is some suggestion that TUNA may be useful in patients with urinary retention due to BPH, who are considered to be of poor surgical risk. The series by Millard et al reported that voiding was re-established in 17 of 20 patients, although two of these subsequently required TURP (Millard, Harewood, & Tamaddon 1996). Similarly in the series reported by Zlotta, 30 of 38 patients (79%) resumed normal voiding within a mean of 8.7 days. Six of the eight patients who did not resume voiding underwent retropubic prostatectomy or TURP (Zlotta et al 1996). Follow-up information beyond six months is not available for this series.

Conclusions on effectiveness

While the FDA approval for TUNA is only for glands 20-50cc in size, trials generally included patients with a wider range of gland sizes up to 100cc (gms), with an average size quoted between 36.2cc and 49.6cc (gms). As TUNA does not have a significant effect on gland volume, it is most suited for smaller glands.

TUNA appears to have a therapeutic benefit, in the shorter term, with statistically significant improvements in objective and subjective measures. This appears to be initially equivalent to TURP, however, after six to 12 months, objective measures of function, such as peak flow rates, are statistically significantly better with TURP. A subjective difference in symptoms between patients treated with TUNA and TURP is also apparent at 12 months. Based on longer term data available only in abstracts, these differences between treatment groups appear to increase with time.

Early (<6 months) post-treatment peak flow rates (ml/sec) reported in one prospective non-randomised study for TUNA treated patients appeared to be similar to those achieved in TURP treated patients. By twelve months after treatment, peak flow rate in patients treated with TURP was significantly higher than those treated with TUNA. The randomised study and the other prospective comparison indicate that between one and three months after treatment, patients treated with TURP have a significantly higher peak flow rate than at baseline and than patients treated with TUNA. This difference continues for at least three years (the longest follow-up time for comparative studies).

Measures of post-void residual volume out to two years post-treatment, suggest that there were no significant differences between patients treated with TURP and those treated with TUNA.

Symptom scores such as the AUA symptom score or the IPSS suggest, at least in some studies, that in the short term TUNA may offer an approximately comparable improvement in symptoms to treatment with TURP. Data from the randomised trial suggest that for up to 12 months, the two treatments offer similar improvements, however, after this time, TURP offered better control of BPH symptoms than did TUNA. This difference continues for at least three years, where the difference between the treatments was more marked. One prospective trial supported these results, with a difference in symptom score seen between TURP and TUNA at three months post-treatment. The other prospective study suggested, however, that there were no significant difference in symptom scores between TURP and TUNA for at least two years after treatment.

The one prospective study which specifically examined self reported measures of sexual desire and erectile functioning found that there was no significant difference between patients treated with TUNA and those treated with TURP at three months post-treatment. It also found that for both treatments there was no difference between pre- and post-treatment parameters.

Data from one prospective trial indicated that, over two years follow-up, fewer patients treated with TURP required retreatment compared to patients treated with TUNA (4% vs 20%). Case series data indicates that retreatment (TURP or prostatectomy) rates for patients treated with TUNA ranged from 5 per cent to 30 per cent over follow-up periods of up to two years. Abstract data of follow-up of three to five years post TUNA suggests a failure rate of approximately 5 per cent to 15 per cent per annum, although it should be noted that in many cases, retreatment rates are based on patients treated with older procedures (as would be expected, given the duration of follow-up).

Overall, TUNA appears to be a relatively effective procedure for the short-term management of symptoms associated with benign prostatic hyperplasia. However, data suggest that the duration of maximum benefit for TUNA is between approximately three and 12 months, depending upon the parameter measured. This duration of benefit is shorter than that seen for patients treated with TURP (longer than three years), with more TUNA patients than TURP patients experiencing a return of BPH symptoms and more requiring retreatment in the longer term.

What are the economic considerations?

As there is insufficient long term data on the safety, efficacy and costs of treating patients with TURP and TUNA, it is not possible to estimate likely long term effects and costs based purely on the data contained within this report.

Based on plausible assumptions of adverse events, efficacy and costs associated with the two procedures, a model, following a hypothetical cohort of patients through twenty years of follow-up, has been constructed. The full model report is in Appendix F.

Background

A decision analytic model incorporating a Markov process was used to model the passage of two hypothetical cohorts of patients with symptomatic benign prostatic hyperplasia. One cohort of patients is initially treated with TURP and the second cohort is initially treated with TUNA. Patients pass through a number of discrete health states in six month cycles over a period of 20 years (ie 40 cycles). It has been assumed that cycles terminate when a patient reaches 20 years of follow-up. As the cycle length is six months, all annual probabilities have been halved, to approximate six month (cycle length) probabilities. Benefits have been measured by quality adjusted life years (QALYs), a measure of survival, with an adjustment for quality of life (a utility weight). Costs are based on the MSAC application and estimates.

Costs and benefits have been discounted by a standard 5 per cent per annum, and the model incorporates a half-cycle correction factor to prevent consistent under or overestimating of outcomes and costs. In reality, patients move between states continuously, not at discrete points in time. Costs and outcomes, therefore, could occur at any point throughout the six month cycle period. For the sake of simplicity in modelling, it is assumed that they occur at a set point in time, the beginning, middle or end of a time period. Rather than assume that patients move between health states at the beginning or end of a cycle, a half cycle correction can be employed, which is equivalent to an assumption that, on average, patients will move between states halfway through the cycle. For outcomes such as life expectancy, a Markov model will either consistently under or overestimate life expectancy without a half cycle correction.

The tables below (25-27) indicate base case values used in the model and upper and lower limits of sensitivity ranges and the sources of these values. These data are presented for utility weights, model probabilities and costs. Components of costs are discussed in full in the report in Appendix F.

Utility weights are designed to reflect the likely decrement to a patient's quality of life due to either failing treatment (ie where either procedure was not successful) or experiencing long term side effects of either procedure (ie where the procedure was effective in relieving the symptoms of BPH, but resulted in adverse effects). A full description of the states of 'failed treatment' and 'side effects' are provided in Appendix F.

Table 25 Utility weights and sensitivity analysis range for model

Name of model variable	Description	Base Value	Sensitivity range		Source
			Low	High	
u_failed_treatment	Utility of failed treatment	0.9	0.8	0.95	Estimate
u_side_effects	Utility of side effects	0.95	0.85	0.95	Estimate
u_well	Utility of well state	1	-	-	Estimate (convention)
u_dead	Utility of dead state	0	-	-	Estimate (convention)

Table 26 Costs included in model

Name of model variable	Description	Base Value	Sensitivity range		Source
			Low	High	
c_side_effects	cost of treating side effects from either procedure for 1 year	500	0	2000	Estimate
c_treatment_failure	cost of treating patients who have failed either procedure for 1 year	1000	0	3000	Estimate
c_TURP	Cost of TURP	4700	3700	5700	MSAC Application (1999)
c_TUNA	Cost of TUNA	3700	3700	5000	MSAC Application (1999)

Table 27 Transition probabilities of model

Name of model variable	Description	Formula	Value	Sensitivity range		Source
				Low	High	
Duration of follow-up						
follow_up	cycles of follow-up (1 cycle=6mo)		40	1	40	20 years follow-up
Procedural mortality						
p_death_TURP	Probability of death from TURP		0.002	0.001	0.003	(Mebust et al 1989)
p_death_TUNA	Probability of death from TUNA		0.001	0.0005	0.002	Estimate
Side effects						
p_side_effects_TURP	Probability of side effects from TURP		0.06	0.06	0.2	(Mebust et al 1989) (Bruskewitz et al 1998)(RCT TUNA vs TURP) (Debruyne et al 2000) WHO consensus document
p_side_effects_TUNA	Probability of side effects from TUNA	p_side_effects_TURP*risk_ratio_for_side_effects	0.0198	0.015	0.2	See below
risk_ratio_for_side_effects	Ratio of probability of side effects from TUNA versus TURP		0.33	0.25	1	(Bruskewitz et al 1998)(RCT TUNA vs TURP) (Ramon et al 1997) (Case series) (Rosario et al 1997) (case series 12 mo f/up)
Early Procedural failure (failure within 6 months)						
p_TURP_NOT_ successful	Probability that TURP was NOT successful (failure within 6 months)		0.1	0.05	0.2	(Bruskewitz et al 1998) (RCT TUNA vs TURP)
p_TUNA_NOT_ successful	Probability that TUNA is NOT successful (failure within 6 months)		0.2	0.1	0.3	(Bruskewitz et al 1998) (RCT TUNA vs TURP) (Millard, Harewood, & Tamaddon 1996) (case series - Australian data) (Zlotta et al 1996) (case series) (Rosario et al 1997) (case series 12 mo f/up) (Ramon et al 1997) (Case series)
Long term failure rate						
r_fail_TURP	Annual failure rate of TURP		0.01	0.005	0.02	(Roos et al 1989) (TURP re-treated within 10 years) (Wasson et al 1995) (RCT TURP vs waiting)
r_fail_TUNA	Annual failure rate for TUNA		0.05	0.01	0.15	(Zlotta, Giannakopoulos, & Schulman 2001) Five year follow-up of TUNA patients (abstract)

Table continues next page

Table 27 continued

Name of model variable	Description	Formula	Value	Sensitivity range		Source
				Low	High	
Retreatment						
p_2nd_TURP	Probability of having a second TURP after first TURP fails		0.35	0.10	0.7	(Wasson et al 1995) (RCT TURP vs waiting)
p_TURP_after_TUNA	Probability of having TURP after TUNA fails		0.75	0.38	1	(Harewood et al 1995) (case series Australian data) (TUNA followed by TURP within 6mo) (Millard, Harewood, & Tamaddon 1996) (case series - Australian data) (TUNA followed by TURP within 6mo) (Rosario et al 1997) (case series 12 mo f/up) (Steele & Sleep 1997) (case series 2 yr f/up)
p_Nothing after TUNA failure	Probability of having no further treatment after TUNA failure	(100%-x%) x 75%, where x% is the probability of TURP after TUNA failure	Calculated			Estimate Of the patients who do not have TURP after TUNA failure, 75% will have no further treatment and the other 25% will have a repeat TUNA
p_repeat TUNA	Probability of TUNA after TUNA failure	1-(probability of TURP after TUNA failure + probability of nothing after TUNA failure	Calculated			Estimate Of the patients who do not have TURP after TUNA failure, 75% will have no further treatment and the other 25% will have a repeat TUNA

Effectiveness

In the base-case model the QALYs gained for patients treated initially with TURP were 12.3082 and for patients treated initially with TUNA were 12.2869. This indicates that treating patients with TURP initially is a more favourable treatment option under the set of baseline conditions described in Table 25 to 27.

Costs

In the base-case model the average costs accrued over the follow-up period for patients treated initially with TURP were $6,910 and for patients treated initially with TUNA were $8,296. This indicates that treating patients with TURP initially is a less expensive treatment option under the set of baseline conditions described in Table 25 to 27.

Incremental cost-effectiveness ratio

An incremental cost-effectiveness ratio provides an estimate of the additional cost per unit of benefit of one treatment over another (eg $/QALY gained).

The base case analysis indicates that when patients are treated with TURP initially, they gain an average 12.3082 QALYs over the follow-up period at an average cost of $6,910. If patients are treated with TUNA first they gain fewer QALYs (12.2869) at a higher average cost ($8,296) (Table 28).

Initial treatment with TURP is both a more effective and less costly strategy than treating with TUNA initially.

For this reason it is not necessary to calculate an incremental cost-effectiveness ratio, as treatment with TURP initially is the better option.

Table 28 Base case analysis results

Initial Treatment	Cost ($)	QALYs	ICER compared with TURP first strategy ($/QALY)
TURP	6910	12.3082	N/A
TUNA	8296	12.2869	Dominated

Cost – mean cumulative costs over the follow-up period of 20 years
ICER – Incremental cost-effectiveness ratio. To calculate ICER the following formula is used (Cost Treatment A – Cost Treatment B)/(Benefits Treatment A – Benefits Treatment B).
'Dominated' indicates that this treatment strategy (TUNA) cost more and yielded fewer QALYs.
Costs and QALYs are discounted at 5% annually

The sensitivity analyses conducted in the model indicate that for both outcomes, ie benefits and costs, the optimal treatment strategy can change from TURP initially to TUNA initially. Table 29 summarises the implications of changes in values (as determined in sensitivity analyses), on the calculation of an incremental cost-effectiveness ratio. The first value used for variables was a value determined to be close to the point where one-way sensitivity analyses indicated that the optimal treatment strategy changed from TURP first to TUNA first. The second value (in italics) is the upper or lower limit of the sensitivity range for the variables. By changing these values one at a time, estimates of cost and benefits altered. Standard treatment is TURP.

Table 29 Effect on ICER by changing variables based on sensitivity analyses and upper/lower sensitivity range

Base case analysis				
	Cost	**QALY**		**ICER**
TURP first (Standard)	$6910	12.3082		n/a
TUNA	$8296	12.2869		dominated
Sensitivity analyses				
Variable	**Strategy**	**Base case value**	**Change in variable**	**Strategy ICER ($/QALY)**
Probability that TURP fails within 6 mos	TUNA first	0.10	increase to 0.14	$6,179,304
			Increase to 0.2 (upper sensitivity limit)	$20,752
Probability of a 2nd TURP after first TURP fails	TUNA first	0.35	decrease to 0.21	$1,652,500
			Decrease to 0.1 (lower sensitivity limit)	$69,569
Annual failure rate of TURP	TUNA first	0.01	increase to 0.015875	$897,815
			Increase to 0.02 (upper sensitivity limit)	*$51,621*
Duration of follow-up	TUNA first	40 cycles (20 years)	Decrease to 5 years of follow-up only (ie 10 cycles)	$20,645
			Decrease to 10 years of follow-up (ie 20 cycles)	TURP dominates TUNA
Utility of side effects state	TUNA first	0.95	decrease to 0.875	$2,529,741
			Decrease to 0.85 (lower sensitivity limit)	*$176,924*
Annual failure rate of TUNA	TUNA first	0.05	decrease to 0.038	$504,874
			decrease to 0.024	$4,965
			Decrease to 0.01 (lower sensitivity limit)	*Dominant*
Probability of side effects from TURP	TUNA first	0.06	increase to 0.15	$1,224,836
			Increase to 0.20 (upper sensitivity limit)	*$71,851*
Probability of having TURP after TUNA fails	TUNA first	0.75	increase to 0.82	$1,070,505
			Increase to 1.0 (upper sensitivity limit)	*$19,727*
Probability that TUNA fails within 6 mos	TUNA first	0.20	decrease to 0.13	$805,660
			Decrease to 0.10 (lower sensitivity limit)	*$84,265*
Probability of death from TURP	TUNA first	0.002	All values in sensitivity range	dominated
Utility of failed treatment state	TUNA first	0.90	All values in sensitivity range	dominated
Ratio of probability of side effects from TUNA versus TURP	TUNA first	0.33	All values in sensitivity range	dominated
Probability of side effects from TUNA	TUNA first	0.0198	All values in sensitivity range	dominated
Probability of death from TUNA	TUNA first	0.001	All values in sensitivity range	dominated

Dominated indicates that strategy is more costly and less effective than the standard strategy (initial treatment with TURP)
Dominant indicates that the strategy is less costly and more effective than the standard strategy (initial treatment with TURP)
Values in italics are the upper or lower limits of the sensitivity range.

Limitations of the model are discussed in Appendix F.

Conclusions on economic considerations

The base case analysis indicates that treating patients with benign prostatic hyperplasia initially with TURP is a more effective and less costly strategy than treating patients initially with TUNA. This conclusion can change, however, depending on our certainty with some variables in the model. Depending upon values of these variables, an incremental cost-effectiveness ratio of between approximately $20,000 per QALY to over $11 million per QALY can be generated when TUNA is used as an initial treatment rather than TURP. The model appears to be quite sensitive to the annual failure rate of both the procedures. When the annual failure rate of TUNA decreases from the base case value of 5 per cent per annum to less than 2 per cent per annum, the dominant treatment strategy changes from TURP initially to TUNA initially. This dependence on the annual failure rate of procedures means that the model was also sensitive to changes in the length of follow-up of patients. This suggests that it is important to collect good quality long term data on the annual failure rate of the procedures.

Conclusions

Safety

TUNA appears to be a relatively safe procedure. Data from the randomised trial suggest that TUNA has fewer post-operative complications, such as bleeding, than does TURP. Non-randomised evidence suggests that apart from urinary retention, which appears more common with the TUNA procedure, the early adverse event rate for TUNA and TURP is similar.

From the data available, it is likely that TUNA results in fewer complications relating to sexual function (such are erectile dysfunction or retrograde ejaculation) than does TURP. The rate of these complications seen in more recent TURP series appears to be lower, however, than that reported in earlier series. As TUNA has also evolved over time, it is possible that the newer TUNA procedures may result in fewer complications than older procedures, although at this stage this remains unclear.

All the trials in this report conducted TUNA as an inpatient procedure, however, it can, in practice, be performed as an outpatient or in-clinic procedure, thus potentially avoiding risks associated with general anaesthesia. While none of the trials specifically evaluated the role of TUNA in this subset of patients, it may, theoretically, be of value in patients with a high anaesthetic risk.

Effectiveness

The body of evidence on which this review is based is relatively small. There is one randomised trial (level II evidence) and two prospective, non-randomised comparative studies (level III evidence). Remaining evidence comprises case series of patients treated with TUNA. The amount of evidence supporting the TUNA procedure is relatively small. While the FDA approval for TUNA is only for glands 20-50cc in size, trials generally included patients with a wider range of gland sizes up to 100cc (gms), with an average size quoted between 36.2cc and 49.6cc (gms). As TUNA does not have a significant effect on gland volume, it is most suited for smaller glands.

TUNA appears to have a therapeutic benefit, in the shorter term, with statistically significant improvements in objective and subjective measures. This appears to be initially equivalent to TURP, however, after six to 12 months; objective measures of function such as peak flow rates are statistically significantly better with TURP. A subjective difference in symptoms between patients treated with TUNA and TURP is also apparent at 12 months. Based on longer term data available only in abstracts, these differences between treatment groups appear to increase with time.

Data from one prospective trial indicated that, over two years follow-up, fewer patients treated with TURP required retreatment compared to patients treated with TUNA (4% vs 20%). Case series data indicates that retreatment (TURP or prostatectomy) rates for patients treated with TUNA ranged from 5 to 30 per cent over follow-up periods of up to two years. Abstract data of follow-up of three to five years post TUNA suggests a

failure rate of approximately 5-15 per cent per annum, although it should be noted that in many cases, retreatment rates are based on patients treated with older procedures (as would be expected, given the duration of follow-up).

Overall, TUNA appears to be a relatively effective procedure for the short-term management of symptoms associated with benign prostatic hyperplasia. However, data suggest that the duration of maximum benefit for TUNA is between approximately three and 12 months, depending upon the parameter measured. This duration of benefit is shorter than that seen for patients treated with TURP (longer than three years), with more TUNA patients than TURP patients experiencing a return of BPH symptoms and more requiring retreatment in the longer term.

Cost-effectiveness

A decision analytic model was designed, based on a set of plausible assumptions, to assess the comparative cost-effectiveness of two treatment strategies: 1) TURP; or 2) TUNA, as initial treatment for symptomatic benign prostatic hyperplasia. The base case analysis indicated that treating patients initially with TURP was both more effective and less costly than treating initially with TUNA. Over a range of sensitivity analyses conducted, this conclusion varied from TURP being a cost-effective initial treatment to TUNA being a cost-effective initial treatment for patients with BPH. The analysis was particularly sensitive to the annual failure rate of both procedures, and subsequently, to the duration of follow-up. The conclusion regarding optimal initial treatment changed over the plausible ranges evaluated. Additional clinical data is required to strengthen our certainty concerning particular variables before definitive conclusions can be drawn regarding the relative cost-effectiveness of TUNA and TURP in this setting.

Recommendation

Based on the evidence available, while safe and efficacious in the short term, the long term effectiveness and cost-effectiveness of TUNA has not been proven. MSAC therefore concludes that unrestricted Medicare Benefits Scheme funding of TUNA for the surgical management of symptomatic benign prostatic hyperplasia is not warranted at this time.

TUNA may, however, have a limited role as an alternative treatment for symptomatic benign prostatic hyperplasia with the following restrictions:

- that it is restricted to men with moderate to severe lower urinary tract symptoms that require specific treatment (ie those who would normally be recommended for TURP);
- that the patients must not be medically suitable for TURP; and
- that interim funding for a period of three years is recommended, and that this funding be linked to the acquisition of data on the type of patients treated and safety data to monitor the use of TUNA under these interim arrangements.

- The Minister for Health and Ageing accepted this recommendation on 17 May 2002. -

Appendix A MSAC terms of reference and membership

The terms of reference of MSAC are to:

- advise the Commonwealth Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Commonwealth Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Commonwealth Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC), and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Dr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Professor Ian Fraser	reproductive medicine
Associate Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Emeritus Professor Peter Phelan	paediatrics

Dr Ewa Piejko	general practice
Dr David Robinson	plastic surgery
Professor John Simes	clinical epidemiology and clinical trials
Professor Richard Smallwood	Chief Medical Officer, Commonwealth Department of Health and Ageing
Professor Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council
Associate Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Supporting committee

Supporting committee for MSAC application 1014 TransUrethral Needle Ablation (TUNA)

Dr Michael Kitchener (Chair) MBBS, FRACP Senior Visiting Medical Specialist, Queen Elizabeth Hospital, Adelaide	member of MSAC
Dr Ross Cartmill MB, BS(QLD), FRCS, FRACS Chairman, Therapeutic Devices and Instrument Sub-Committee, Urological Society of Australia	nominated by the Urological Society of Australasia
Mr Alan Crosthwaite MB, BS, FRACS Past Chairman, Therapeutic Devices and Instrument Sub-Committee, Urological Society of Australia	nominee of the Royal Australasian College of Surgeons and the Urological Society of Australasia
Dr Brian Kable Cert. T, BA, MBBS, FRACGP Chairman, Royal Australian College of General Practitioners National Preventive & Community Medicine Committee	nominee of the Royal Australian College of General Practitioners
Professor Villis Marshall MBBS, MD, FRACS Clinical Director, Surgical Specialties Service Royal Adelaide Hospital	co-opted member
Mr Don Thomson Consumer Representative	nominee of the Continence Foundation

Table 30 Results from controlled non-randomised studies

Paper	No of patients	Eligibility criteria	Parameter	Results (mean ± SD)					Adverse effects
			Outcome	**Timepoint**	**TUNA (42)**	**TURP (55)**	**TUMT (34)**	**Laser (42)**	
(Arai et al 2000)	173	Symptomatic BPH	IPSS	Baseline	19.8 +/- 5.9	19.0 +/- 7.2	18.4 +/- 6.2	19.3 +/- 8.4	
				3 mo	10.5 +/- 6.5 <0.001	7.6 +/- 4.9 p<0.001	13.2 +/- 6.8 p<0.001	6.9 +/- 4.9 p<0.001	
			Peak flow rate	Baseline	8.2 +/- 4.1	7.7 +/- 4.6	7.7 +/- 4.3	7.6 +/- 3.5	
				3 mo	9.2 +/- 4.2 p=0.187	14.4 +/- 7.8 p<0.001	8.6 +/- 4.9 p<0.0844	12.6 +/- 4.7 p<0.001	
			Post-void residual volume ml	Baseline	81.5 +/- 90.5	133.3 +/- 211.4)	58.1+/- 65.7	102.3 +/- 86.1	
				3 mo	59.4 +/- 54 p=0.052	39.2 +/- 58.8 p=0.014	63.6 +/- 80.6 p=0.624	30.4 +/- 35.9 p<0.001	
			QOL (163)	Baseline	4.7 +/- 0.6	4.5 +/- 1.1	4.4 +/- 1.2	4.3 +/- 1.5	
				3 mo	2.4 +/- 1.4 p<0.001	1.9 +/- 1.3 p<0.001	2.7+/-1.4 p<0.001	1.8+/-1.3 p<0.001	
			Sexual desire score (155)	Baseline	2.9 +/- 1.9	2.7 +/- 1.8	3.2 +/- 1.7	3.3 +/- 2.0	
				3 mo	3.0 +/- 1.7 p=0.923	2.7 +/- 1.9 p=0.921	3.3 +/- 1.8 p=0.913	3.1 +/- 1.8 p=0.368	
			Erectile function score	Baseline	3.5 +/- 2.4	3.1 +/- 2.4	4.2 +/- 2.5	4.0 +/- 2.4	
				3 mo	3.2 +/- 2.2 p=0.363	3.0 +/- 2.5 p=0.831	4.1 +/- 2.3 p=0.919	3.7 +/- 2.5 p=0.48	

Paper	No of patients	Eligibility criteria	Parameter	Results (mean ± SD)					Adverse effects	
(Schatzl et al 2000)	95	Lower urinary tract symptoms Urodynamically proven BOO	**Outcome**	**Time period**	**TUNA (42)** TUNA (15)	**TURP (55)** TURP (28)	**TUMT (34)** VLAP (15)	**Laser (42)** HIFU (20)	TUVP (17)	Re-treatment rate within 24mo was 15 HIFU; 20 TUNA; 23 TUVP and 27 VLAP
			IPSS	Baseline	17.75 +/- 5.7 (15)	19.5 +/- 5.7 (28)	19.5 +/- 5.7 (15)	14.7 +/- 5.9 (20)	19.1 +/- 5.8 (17)	
				6 mo	8.7 +/- 5.9 (14)	4.7 +/- 2.7 (27)	12.4 +/- 9.4 (15) p<0.05*	6.4 +/- 5.4 (20)	6.0 +/- 4.7 (15)	
				12 mo	6.5 +/- 4.0 (14)	4.7 +/- 3.4 (27)	8.9 +/- 7.3 (12)	4.3 +/- 1.6 (16)	5.8 +/- 1.7 (13)	
				18 mo	7.9 +/- 5.7 (12)	5.4 +/- 2.8 (27)	6.7 +/- 3.4 (11)	5.3 +/- 2.3 (16)	5.8 +/- 1.8 (13)	
				24 mo	7.7 +/- 5.5 (12)	5.6 +/- 2.6 (27)	6.8 +/- 6.7 (11)	7.7 +/- 5.9 (16)	6.4 +/- 1.9 (13)	
			Peak flow rate	Baseline	9.3 +/- 2.2 (15)	8.2 +/- 4.8 (28)	6.1 +/- 4.1 (15)	9.2 +/- 2.5 (20)	8.9 +/- 2.9 (17)	
				6 mo	13.6 +/- 8.0 (14)	19.5 +/- 3.5 (27)	14.7 +/- 8.0 (15)	13.1 +/- 3.2 (20)	20.6 +/- 4.7 (15)	
				12 mo	11.9 +/- 3.3 (14) p<0.05*	21.1 +/- 5.4 (27)	13.9 +/- 7.9 (12)	13.1 +/- 3.8 (16)	21.3 +/- 5.8 (13)	
				1 mo	10.7 +/- 3.3 (12) p<0.05*	20.1 +/- 4.9 (27)	12.1 +/- 7.4 (11)	12.1 +/- 2.6 (16) p<0.05*	20.9 +/- 5.5 (13)	
				24 mo	11.6 +/- 3.7 (12) p<0.05*	19.7 +/- 4.6 (27)	11.7 +/- 6.2 (11) p<0.05*	11.2 +/- 1.7 (16) p<0.05*	20.0 +/- 6.1 (13)	
			Post-void residual volume ml	Baseline	85 +/- 78 (15)	104 +/- 102 (28)	94 +/- 68 (15)	94+/- 33 (20)	70 +/- 27 (17)	
				6 mo	41 +/- 36 (14)	15 +/- 21 (27)	31 +/- 23 (15)	46 +/- 33 (20) p<0.05*	23 +/- 20 (15)	
				12 mo	32 +/- 35 (14)	15 +/- 10 (27)	30 +/- 27 (12)	49 +/- 32 (16) p<0.05*	19 +/- 21 (13)	
				18 mo	29 +/- 36 (12)	17 +/- 12 (27)	27 +/- 36 (11)	52 +/- 26 (16) p<0.05*	16 +/- 19 (13)	
				24 mo	30 +/- 37 (12)	19 +/- 15 (27)	26 +/- 36 (11)	58 +/- 26 (16) p<0.05*	21 +/- 22 (13)	

Table 31 Results from Virdi abstracts

Paper	No pts	Patient characteristics	Follow-up time	Results (mean ± SD)									Adverse effects
					TUNA (51)				TURP (51)				
				Time	IPSS	QOL	Peak flow rate (mL/s)	Post-void residual volume (ml)	IPSS	QOL	Peak flow rate (mL/s)	Post-void residual volume (ml)	
(Virdi, Pandit, & Sriram 1997)	102	TUNA: Mean age 66.2 (58-71) Mean prostatic weight 53.3.g (25-85) Treated between April 1994 – May 1996 TURP not reported	2 years	Baseline (n=51)	20.3±7	4.6±1	7.8±3	166±105	32.0±4	5.1±1	7.0±3	130±90	No ejaculatory dysfunction was reported after TUNA compared with 68% after TURP, with no blood transfusion was required after TUNA, compared with 24% after TURP. The mean hospital stay was 1.2 days after TUNA and 3.5 days after TURP. Short term failure occurred in 2% after TUNA **NB no information is presented on how many patients were available for assessment at each time point.**
				6 mo (n=?)	11.7±8	2.6±1	13.6±5	92±149	5.2±4	2.3±1	23.6±5	30±45	
				12 mo (n=?)	12.0±8	2.8±1	13.8±4	80±99	7.3±3	1.6±1	28.1±4	35±40	
				24 mo (n=?)	5.4±4	1.8±1	14.4±4	32±15	3.8±1	1.5±1	27.1±4	40±10	
					TUNA (71)				TURP (69)				
(Virdi, Pandit, & Sriram 1998)	140	All patients Mean age 60.2 (50-84) Mean prostatic weight 49.6g (25-80) Treated between April 1994 – December 1996	3yrs	Time	IPSS	QOL	Peak flow rate (mL/s)	Post-void residual volume (ml)	IPSS	QOL	Peak flow rate (mL/s)	Post-void residual volume (ml)	No ejaculatory dysfunction was reported with TUNA as compared to 66% in TURP. No blood transfusion was required followed TUNA as compared to 14% in TURP. 5.8% patients failed TUNA therapy during first two yrs. Mean hospital stay was 1.2 days c.f 3.5 with TURP **NB no information is presented on how many patients were available for assessment at each time point.** * p<0.001 vs baseline **NB no comparison between groups at any time point.** NR – Not Reported
				Baseline	22.3±6	4.6±1	7.0±3	NR	29.0±4	5.1±1	7.0±3	NR	
				6 mo (n=?)	12.7±8	2.6±1	13.6±5	NR	5.2±4	2.3±1	28.6±5	NR	
				12 mo (n=?)	10.0±8	2.8±1	13.8±4	NR	7.3±3	1.6±1	28.1±4	NR	
				24 mo (n=?)	9.4±4	2.1±1	14.8±3	NR	3.8±1	1.5±1	27.1±4	NR	
				36 mo (n=?)	7.4±4*	2.0±1*	14.2±4*	NR	3.5±1*	1.5±1*	28.2±4*	NR	

Paper	No pts	Patient characteristics	Follow-up time	Results (mean ± SD)									Adverse effects
					TUNA (76)				TURP (76)				
				Time	IPSS	QOL	Peak flow rate (mL/s)	Post-void residual volume (ml)	IPSS	QOL	Peak flow rate (mL/s)	Post-void residual volume (ml)	
(Virdi & Chandrasekar 2001)	152 / 142? Two values report-ed in abstra-ct	All patients Mean age 67.5 (47-87) Mean prostatic weight 43.3g (20-88) Treated between April 1994 – October 1998	6 yrs (TUNA only) 3 yr TURP	Baseline	19.1± 5	4.1±1	7.5±2	NR	20.5±5	3.8±1	8.3±2	NR	No ejaculatory dysfunction was reported with TUNA as compared to 76% in TURP. No blood transfusion was required followed TUNA as compared to 10.5% in TURP. 13.2% patients failed TUNA therapy during six years. Mean hospital stay was 1.2 days c.f 3.5 with TURP Acute urinary retention 13.2% TUNA vs 2.9% TURP **NB no information is presented on how many patients were available for assessment at each time point.** **It is unclear how average Peak flow rates could be so much worse for TURP patients compared to the above publication to this one, particularly as no data is recorded for these patients past 3 year follow-up**
				6 mo (n=?)	7.8±5	1.7±1	15.7±5	NR	6.0±8	1.2±1	19.3±8	NR	
				12 mo (n=?)	7.8±5	1.6±1	15.0±5	NR	5.1±4	1.2±1	19.6±7	NR	
				24 mo (n=?)	8.1±5	1.8±1	14.2±6	NR	5.1±4	1.2±1	19.3±7	NR	
				36 mo (n=?)	7.9±5	1.5±1	14.1±5	NR	5.7±5	1.0±1	19.2±7	NR	
				48 mo (n=?)	8.9±6	1.6±1	12.5±5	NR	No data	No data	No data	NR	
				60 mo (n=?)	8.6±5	1.6±1	13.1±6	NR	No data	No data	No data	NR	
				72 mo (n=?)	5.3±4	2.1±1	11.1±2	NR	No data	No data	No data	NR	NR – Not Reported

Table 32 Results from case series papers

Paper	No pts	Entry criteria	Outcome	Results (significance level)					Adverse effects
(Schulman & Zlotta 1995)	20	Symptomatic BPH IPSS >15 Umax <15mL/s Voided vol>=125mL Residual volume <=200ml Various safety exclusions		**Baseline**	**3mo**	**6mo**	**12mo**	**24mo**	Prostatectomy required (1) Haematuria requiring hospitalisation (1) Urinary retention requiring catheter (5)
			Peak flow rate	9.5	_	15.0mL/s			
			Resid. urine vol	71	_	36mL (p<0.05)			
			IPP symptom score	21.9	_	6.7 (p<0.05)			
			Quality of life	4.4	_	1.6 (p<0.05)			
			Prostatic vol.	39.6	_	33.0g N.S.			
(Harewood et al 1995)	10	refractory urinary retention various safety exclusions		**Baseline**	**3mo**	**6mo**	**12mo**	**24mo**	Prostatectomy required (3) Infection (3) Epidid4ymo-orchitis (1)
			AUA symptom score	15.3	_	11.5			
			Quality of life	5.5	_	1.8			
			Peak flow rate	0.0	_	11.9mL/s			
			Pdet at Peak flow rate	73.3	_	39.0cmH20			
(Millard, Harewood, & Tamaddon 1996)	20	acute urinary retention prostate size 15 to 100 mL various safety exclusions		**Baseline**	**3mo**	**6mo**	**12mo**	**24mo**	Epididymoorchitis (4) Infection (4) Prostatectomy required (5)
			Quality of life	5.4	1.5	1.5	1.4 p=0.001		
			Mean symptom score	19.0	6.4	7.8	8.25 p=0.06		
			Sexual function	No changes in potency or ejaculation status					
			Pdet at Peak flow rate	70.7 cm	_	59.5 cm (N.S)	_		
			Void volume	82ml	220.00ml	271.00ml	206.00ml p=0.051		
			Prostate vol.	65.8 CC	48.6 CC	55.7 CC	56.0 CC		
			Measures of obstruction	Non-significant improvement in all measures					
			Mean PSA	10.3ng/ml	6.2ng/ml	7.2ng/ml	3.96ng/ml		
			Peak flow rate	3.02ml/s	10.7ml/s	10.7ml/s	11.4ml/s p=0.005		

Paper	No pts	Entry criteria	Outcome	Results (significance level)					Adverse effects
(Issa 1996)	12	symptomatic BPH AUA symptom score > 13 Peak flow < 12 mL/s Voided volume > 125mL Residual volume < 350mL Prostate size 20 to 75mL Various safety exclusions		**Baseline**	**3 mo**	**6 mo**	**12 mo**	**24 mo**	Retrograde ejaculation (1)
			Bother score	18.8	7.3 p<0.0001	7.3 p<0.0002			
			QOL score	13.7	4.7 p<0.0001	4.1 p<0.0001			
			Peak flow rate	7.8	13.8 p<0.0002	13.5 p<0.0001			
			Post-void residual	111	79 p=0.3475	50 p=0.0457			
			AUA symptom score	25.6	10.7 p<0.0001	9.8 p<0.0001			
			Pdet at Peak flow rate	91.8	_	70.9 (9) p=0.0094			
			Opening pressure	74.5	_	56.3 (9) p=0.0468			
			Prostate size	39.7	_	33.6 (11) p=0.0057			
(Zlotta et al 1996)	38	symptomatic BPH acute urinary retention > 2 weeks cancer of prostate ruled out prostate volume <= 90 mL various safety exclusions		**Baseline**	**3 mo**	**6 mo**	**12 mo**	**24 mo**	Prostatectomy required (6) Long term urinary catheter (2)
			Number with resumption of spontaneous voiding	_	_	30 success, 8 failure			
(Rosario et al 1997)	71	symptomatic BPH obstruction on pressure-flow urodynamics		**Baseline**	**3 mo**	**6 mo**	**12 mo**	**24 mo**	Routine catheterisation for 6 days given to all but 1st 9pts entered Acute urinary retention in those not routinely catheterised (8) Haematuria requiring bladder irrigation (1) Urinary tract infection (10) Epididymitis (1) Prostatitis (1) Deep Venous Thrombosis following spinal anaesthesia (1) Erectile dysfunction (2) Unable to ejaculate (1) TURP required (22)
			AUA score	21.9	10.0	10.0	10.6 p<0.001		
			Quality of life	4.8	2.5	2.5	2.2 p<0.001		
			Q max	9	11.8	11.8	11.3 p<0.001		
			PVR	70ml	60	60	35.0ml p<0.001		
			Pdet	112	110.0	93.0	p<0.001		
			Prostate size	49ml			41ml (N.S.)		
			Frequency volume chart	Daytime frequency 8.7 to 5.6 (p<0.001), nocturia 2.7 to 1.7 (p<0.001), voided volume 162ml to 182ml (N.S.).					

Paper	No pts	Entry criteria	Outcome	Results (significance level)					Adverse effects
(Ramon et al 1997)	76	>= 45 years lateral lobe BPH IPSS >= 13 Peak flow rate <= 12 mL/s Prostate size 15-75g Various safety exclusions		**Baseline**	**3 mo**	**6 mo**	**12 mo**	**24 mo**	Irritative symptoms requiring oxybutynin (1) Catheterisation for 24-48 hours (25) Acute urinary retention in those not initially catheterised (22) Infection (8) Haematuria (1) Epididymitis (1) Urethral stricture (1)
			IPSS	22.0	7.0 (65) p<0.001	7.0 (61) p<0.001	7.5 (60) p<0.001		
			QOL	4.3	2.0 (65) p<0.001	2.0 (61) p<0.001	2.0 (60) p<0.001		
			Peak flow rate	8.7	12.8 (64)p<0.001	12.4 (57) p<0.001	11.6 (55) p<0.001		
			Prostate size		41.4 (58) p<0.05	41.6 (39) NS	36.0 (31) NS		
			PVR	93	67.0 (60) p<0.05	52.9 (52) p<0.001	53.6 (47 p<0.001		
(Steele & Sleep 1997)	47	symptomatic BPH 50-75 years prostate size <65g residual volume <250mL bladder outlet obstruction on flow study various safety exclusions		**Baseline**	**3 mo**	**6 mo**	**12 mo**	**24 mo**	Prostatectomy required (6) Acute urinary infection (8) Epididymitis (1)
			AUA symptom score	22.4 (47)	8 (42) p<0.05	6.6 (42) p<0.05	7.0 (41) p<0.05	9.5 (38) p<0.05	
			Quality of life	4.6 (47)	1.7 (42) p<0.05	1.6 (42) p<0.05	2.1 (41) p<0.05	1.9 (38) p<0.05	
			Peak flow rate (ml/sec)	6.6 (47)	11.1 (39) p<0.05	10.0 (34) p<0.05	10.2 (29) p<0.05	11.2 (31) p<0.05	
			PVR	76.1 (47)	37.2 (39) p<0.05	40.2 (34) p<0.05	51.9 (29) p<0.05	36.9 (31) p<0.05	
			Pdet	92.4 (47)	68.5(39) p<0.05	54.8 (34) p<0.05	66.5 (29) p<0.05	58.9 (31) p<0.05	
(Campo et al 1997)	120	symptomatic BPH > 3mo IPSS >13 Prostate size 15-75g Age 50-75 Peak flow rate < 13 mL/s Obstruction on flow study Lateral lobe hyperplasia only various safety exclusions		**Baseline (120)**	**3 mo (108)**	**6 mo (86)**	**12 mo (72)**	**18 mo (42)**	Catheterisation for up to 48 hours (16) Infection (1)
			IPSS	20.8	9.7 p<0.001	6.8 p<0.001	6.2	6.7	
			Quality of life	4.1	1.9	2.1	2.2	2.0	
			Peak flow rate	8.2	4.6 p<0.01	15.1 p<0.01	15.9 p<0.01	14.1 p<0.01	
			Pdet at Peak flow rate	85.3	53.2 p<0.01	61.3 p<0.01	63.7 p<0.01	67.8 p<0.01	
(Braun et al 1998)	33	1. symptomatic BPH		**Baseline**	**3 mo**	**6 mo**			Catheterisation for up to 48 hours (16) Haematuria requiring bladder irrigation (2) Infection (7) Retrograde ejaculation (1) Urethral stricture (1)
			IPSS score	50% improvement recorded					
			Peak flow rate	9.4	_	15.4			
			Residual vol	67ml	_	17ml			
			Pdet at Peak flow rate	81cm H20	-	44cm H20			

Paper	No pts	Entry criteria	Outcome	Results (significance level)					Adverse effects
(Kahn et al 1998)	45	symptomatic BPH IPSS > 12 QoL score > 3 Various safety exclusions		**Baseline**	**3 mo**	**6 mo**	**12 mo**	**24 mo**	Haematuria requiring hospitalisation (2) Prostatectomy required (2)
			IPSS score	20.9	_	_	9.9		
			Peak flow rate	8.3 mL/s	_	_	14.9 mL/s		
			Quality of life	4.75	_	_	1.03		
			Residual vol	97 mL	_	_	35 mL		
(Roehrborn et al 1998)	130	symptomatic BPH AUA >= 13 Peak flow rate <= 12mL/s Various safety exclusions		**Baseline**	**3 mo**	**6 mo**	**12 mo**	**24 mo**	Catheterisation postoperatively (53) Secondary catheterisation (15) Retrograde ejaculation (1) Infection (6) Impotence (2)
			AUA score	23.7 (129)	_	10.5 (112) p<0.0001	11.9 (93) p<0.0001		
			BPH II score	7.5 (124)	_	2.3 (113) p<0.0001	2.5 (91) p<0.0001		
			Quality of lie	4.7 (124)	_	1.8 (113) p<0.0001	2 (91) p<0.0001		
			Peak flow rate	8.7 (130)	_	13.8 (112) p<0.0001	14.6 (88) p<0.0001		
			Residual volume	93 (128)	_	62 (108) p=0.0005	72 (86) p=0.0290		
(Namiki et al 1999)	33	>50 yrs age symptoms of bladder outlet obstruction Duration of obstructive symptoms >3 mo IPSS score > 13 Peak flow rate <12mL/S >150cc Various exclusion criteria		**Baseline**	**3 mo**	**6 mo**	**12 mo**	**18 mo**	Balloon tracted needed after operation to stop bleeding (2) 61% had urinary retention after removal of a catheter placed immediately after TUNA TURP given (3) Mean duration of pyuria was 18.7 days after treatment Urethral stricture at 3 and 5 months (2)
			IPSS	20.7±5.4 (30)	8.9±7.3 (30)	10.4±6.9 (28)	11.2±7.2 (21)	12.2±7.5 (10) p<0.01	
			QOL	4.9±0.8 (30)	1.8±1.6 (30)	2.3±1.4 (28)	2.1±1.4 (19)	2.9±1.8 (10) p<0.01	
			Residual urine volume	466±456 (30)	321±35 (30) p<0.01	278±198 (28) p<0.05	226±277 (22) p<0.01	243±185 (11) p<0.01	
			Prostate Volume	37.8±15.0 (30)	28.9±12.5 (27)	29.2±14.0 (29)	29.8±13.1 (22) p<0.01	30.5±8.6 (8) p<0.05	
			Peak flow rate	8.0±2.1 (30)	10.6±5.2 (30) p<0.01	11.8±5.0 (29)	11.0±4.2 (23) p<o.01	11.8±4.5 (11) p<0.01	
(Holmes et al 1999)	25	Symptomatic BPH Spontaneously voiding Public waiting list for TURP		**Baseline**	**6 wks**	**7 mo**	**12 mo**	**24 mo**	TURP request at 12 mo (6)
			Mean Peak flow rate	8.3 ± 2.6 (14)	12.8±4.9 (14)	13±4.6 (11)	10.4±4.5 (7)		
			Mean IPSS	20.5 ±5.4 (17)	8.8±3.9 (15)	11.5 ±9.3 (14)	11.8±9 (12)		
			AUA Quality of life	5 (2-6) 17	2 (0-6) 15	2.5 (2-5) 15	2 (1-6) 12		

Table 33 Results from case series abstracts

Paper	No. pts	Entry criteria	Follow-up time	Outcomes Used	Results (significance-level)						Adverse effects (no. pts)
(Namasivay-am et al 1999)	91	symptomatic BPH bladder outflow obstruction	3 yrs; N=52 (not req further surgery)		**Baseline**	**3 mo**	**6 mo**	**36 mo**	**48 mo**	**60 mo**	Further prostate surgery (39) Waiting list for TURP (3) Unfit to have surgery (2);Died (2) Pts still obstructed 3yrs after surgery
				IPSS	21.9	_	_	10.5 p<0.001			
				Peak flow rate	8.8 mL/S	_	_	11.9 p<0.001			
[(Bergamaschi et al 2000)	206 n=31 at 60 mo	Urinary outlet obstruction Exclusions: neurogenic bladder, PSA>4ng/ml	6,12,18 mo up to 60 mo (mean follow-up 33.2 mo)		**Baseline (206)**	**12 mo (204)**	**24 mo (194)**	**36 mo (147)**	**48 mo (94)**	**60 mo (31)**	Failure of TUNA considered (55) TURP undergone (43) Treatment with alpha blockers (12) Obstruction 2yrs post (142) Acute urinary retention (43)
				IPSS	20.4	6.2	7.7	9.7	10.2	10.9	
				QL	4.1	2.1	1.8	2.0	2.2	2.5	
				Peak flow rate (mL/S)	8.2 (+/- 3.3)	14.8 (+/- 2.9)	13.1 (+/- 3.1)	12.7 (+/- 2.4)	12.3 (+/- 2.7)	11.8 (+/- 2.2)	
(Naslund et al 2000)	48	Symptomatic BPH Median lobe enlargement TRUS vol.23-92	12 months		**Baseline**	**3 mo**	**6 mo**	**12 mo**	**48 mo**	**60 mo**	Catheter for > 5 days (5) Retrograde ejaculation (1) Transient irritative symptoms (4) Transient haematuria (4) Acute urinary retention (5)
				IPSS	21.6	9.4	8.2	6.0			
				Peak flow rate	8.0 mL/S	13.5	11.5	10.4			
				PVR	73	51	63	33			
				QOL	4.5	2.0	1.8	1.0			
(Schulman & Zlotta 2000)	49	Symptomatic BPH	3 years		**Baseline**	**12 mo**	**24 mo**	**36 mo**	**48 mo**	**60 mo**	Transient retention (2-5days) was observed in 39% of cases. No retrograde ejaculation or impotence noted. An improv't of 50% or more in flow rate observed in 53% pts at 3yrs 10pts operated on, 5pts also died
				Peak flow rate (mL/S)	9.9	16.8 (36) p<0.01	15.5 (25)	16.2 (17) p<0.01			
				IPSS	21.6	7.8 p<0.001	8.5	7.6 p<0.001			
				Resid. vol (mL)	85	42	47	40 (p<0.01)			
(Zlotta, Giannakopoulos, & Schulman 2001)	162	Symptomatic BPH	5 years (median) 63 mo (mean)		**Baseline**	**60 mo**					Mean prostate vol. and PSA didn't change sig. (55.9cc preop vs 55.3 cc and 3.1 ng/ml vs 3.6 ng/ml resp.); 2 pts died of unrelated comorbidities; 10 lost to f/up; 37 of 150 patients (25%) required additional treatment at 5 yrs (12 had medical treatment; 7 had 2nd TUNA; 18 had surgery) at 5 years
				Peak flow rate	8.6	12.1 (p<0.01)					
				IPSS	20.8	8.6 p<0.01					
				Resid. vol (mL)	197	155p<0.01					

Appendix F Decision analysis report

Transurethral needle ablation for the treatment of benign prostatic hyperplasia

A decision analytic model for MSAC application 1014

F1 Introduction

TransUrethral Needle Ablation (TUNA) is one of several new minimally invasive thermal technologies for transurethral treatment of the prostate in symptomatic benign prostatic hyperplasia. It is designed to provide selective thermal ablation of the interstitial prostate tissue.

The TUNA system consists of a radio frequency generator, an optic and a disposable monopolar catheter. The system is designed to deliver low levels of radiofrequency energy directly into the hyperplastic prostatic tissue in order to provide selective thermal ablation, while preserving the urethra and adjacent structures from harm. Using direct optical vision, the surgeon positions the TUNA® catheter to insert two needles (which serve as radiofrequency antennae), directly into the prostatic tissue. The radiofrequency energy passes via these needles and through the prostate in a monopolar fashion to the grounding pad. Each needle has an adjustable shield surrounding it. The shields contain thermocouples for interstitial temperature monitoring, and for monitoring the temperature of the prostatic urethral wall. The shields are used to localise the lesions within the prostate and protect the urethra from thermal damage (Beduschi & Oesterling 1998; Chapple, Issa, & Woo 1999; Heaton 1995; Issa, Myrick, & Symbas 1998).

The 'gold standard' for comparison with the TUNA procedure is transurethral resection of the prostate (TURP). Studies of TURP since 1986 have indicated satisfactory results in 90–95 per cent of patients over a 5-6 year follow-up period (Mebust 1998).

Information reported on the long term follow-up of patients was generally poor. Few papers reported follow-up of patients treated with TUNA of longer than 2-3 years. As a result, it is difficult to assess the likely benefits and costs of the procedures over a clinically relevant time frame (such as 10 to 20 years).

In the absence of long term follow-up data on the comparative effectiveness of TUNA and TURP, a decision analytic model has been constructed. This model is intended to investigate whether TUNA or TURP was likely to be more effective and cost-effective under a broad range of plausible assumptions, and to identify the critical determinants of the effectiveness and cost-effectiveness of these two surgical procedures for treatment of benign prostatic hyperplasia.

F2 Methods

A decision analytic model incorporating a Markov process was used to model the passage of two hypothetical cohorts of patients with symptomatic benign prostatic hyperplasia. One cohort of patients is initially treated with TURP and the second cohort is initially treated with TUNA. Patients pass through a number of discrete health states in six month cycles over a period of 20 years (ie 40 cycles). It has been assumed that cycles terminate when a patient reaches 20 years of follow-up. As the cycle length is six months, all annual probabilities have been halved, to approximate six month (cycle length) probabilities.

Costs and benefits have been discounted by a standard 5 per cent per annum, and the model incorporates a half-cycle correction factor to prevent consistent under- or overestimating of outcomes and costs. In reality, patients move between states continuously, not at discrete points in time. Costs and outcomes, therefore, could occur at any point throughout the six month cycle period. For the sake of simplicity in modelling, it is assumed that they occur at a set point in time, the beginning, middle or end of a time period. Rather than assume that patients move between health states at the beginning or end of a cycle, a half cycle correction can be employed, which is equivalent to an assumption that, on average, patients will move between states halfway through the cycle. For outcomes such as life expectancy, a Markov model will either consistently under- or overestimate life expectancy without a half cycle correction. The analysis is done from the healthcare provider perspective, as it has not tried to capture the true cost to society of treating patients with benign prostatic hyperplasia.

F2.1 Overview of Model

Figure 3 below indicates the structure of the model used for calculations. Markov nodes are incorporated after the initial decision to treat with either TURP or TUNA. Appendix F1 shows a tree with probabilities assigned.

Figure 3 Decision analysis incorporating Markov processes

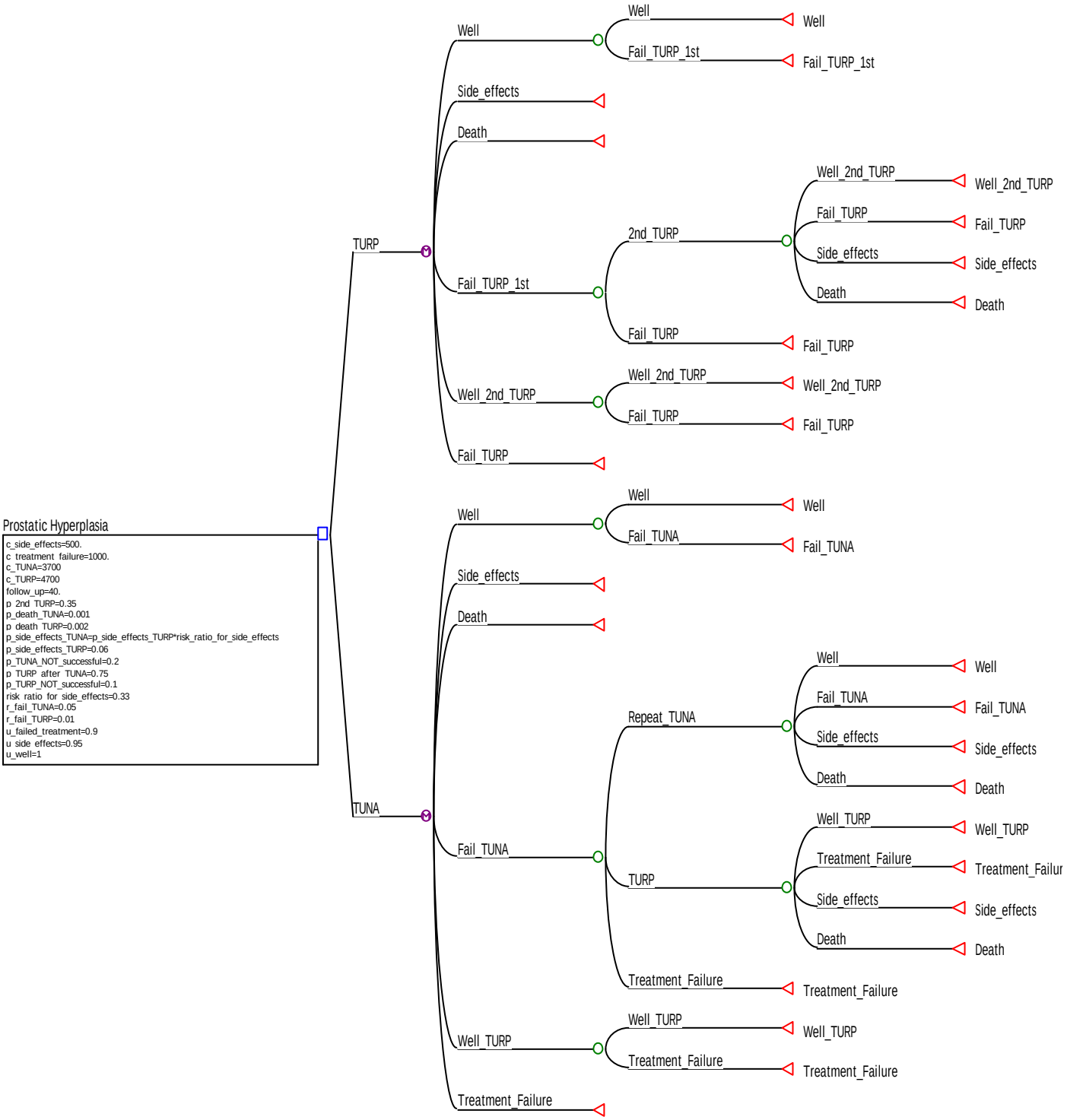
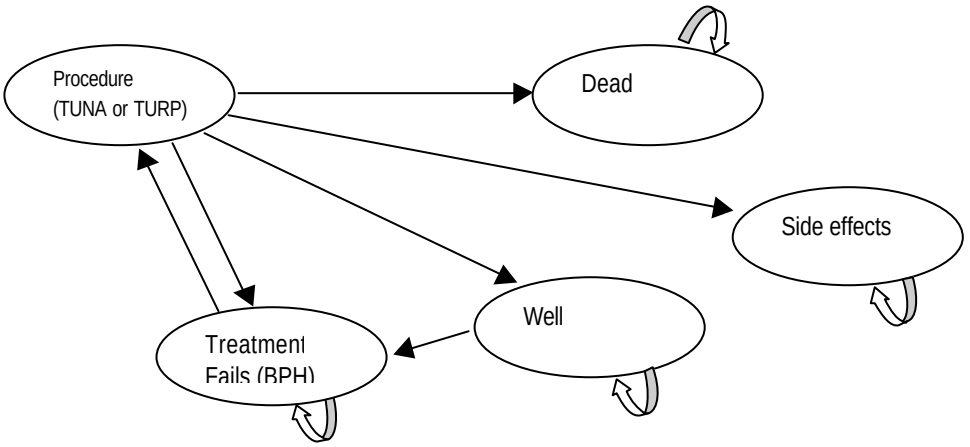


Figure 4 provides a schema of the Markov nodes showing the discrete health states and relationships among them.

Figure 4 Schema of Model



The Markov model includes four health states: **Well** (treatment successful), **Side Effects** (treatment largely successful but resulting in significant and persistent side effects), **Treatment Failure** (treatment was not successful but did not cause new significant or persistent side effects), and **Dead** (death from the procedure). The states of Side Effects and Dead are absorbing states (ie once a patient enters them they do not leave). 'Procedure' indicates either TUNA or TURP.

Patients begin each cycle in one of the four states described above. Patients who begin a cycle in the Well state, ie those who had undergone a successful procedure, face a recurring risk that the procedure would fail in subsequent cycles of the model. This means that a patient may remain well or may experience treatment failure at some point in time over the duration of follow-up.

A patient that begins a cycle in the Treatment Failure state faces the possibility of undergoing another procedure or of remaining indefinitely in this state (ie having no further procedures performed). The procedures that could be performed depended upon the initial procedure. Patients in whom the initial TURP failed could undergo a second TURP or remain in the Failed Treatment state indefinitely. Patients in whom TUNA failed could receive an additional TUNA, a TURP, or remain in the Treatment Failure state indefinitely. The model did not allow patients to undergo more than two TURP procedures. Patients could undergo multiple TUNA procedures, but the likelihood of undergoing multiple TUNA procedures was small because TURP was more likely to be chosen after TUNA failure.

Patients who begin a cycle in the Side Effects state, ie those who had undergone a largely successful procedure but sustained significant and persistent side effects in the process, remained indefinitely in the Side Effects state.

F2.2 Health states and utilities

As discussed above, the Markov model included four health states: Well (treatment successful), Side Effects (treatment largely successful but resulted in significant and

persistent side effects), Treatment Failure (treatment was not successful but did not cause new significant or persistent side effects), and Dead (death from the procedure). Mortality from other causes over the 20 year period was not factored into the model. Mortality rates for other causes should be equivalent in the two hypothetical cohorts and thus should not have a significant impact on the treatment that the model identifies as superior. However, this simplification is important to bear in mind when interpreting the absolute estimates of efficacy produced by the model, as opposed to the order in which the model ranks the treatments.

Time spent in a health state may be adjusted by a weight that reflects the desirability of the state. These weights are conventionally referred to as utilities and are expressed on a scale from 0 to 1 (where 1=most preferable and 0=least preferable). When utilities are applied, the model may be used to estimate the expected quality-adjusted survival time associated with the treatment policies being compared. The Well state and Dead state were assigned utilities of 1 and 0 respectively as these represented the best and worst states in the model.

The Side Effects state was intended to capture the scenario where the patient had a successful procedure, but experienced significant or persistent problems caused by the procedure. These include deterioration of sexual function, erectile failure, urethral strictures and urinary incontinence. The Side Effects state was assigned a utility of 0.95 in the base-case analysis but varied in a sensitivity analysis between 0.85 and 0.95.

The Treatment Failure state was intended to capture the various symptoms that indicate the treatment has failed, ie the symptoms of benign prostatic hyperplasia. These include restricted urinary flow rate, post-void residual volume and incontinence. The Treatment Failure state was assigned a utility of 0.9 in the base-case analysis but varied in a sensitivity analysis between 0.80 and 0.95.

Table 34 Utility weights and sensitivity analysis range for model

Name of model variable	Description	Base Value	Sensitivity range		Source
			Low	High	
u_failed_treatment	Utility of failed treatment	0.9	0.8	0.95	Estimate
u_side_effects	Utility of side effects	0.95	0.85	0.95	Estimate
u_well	Utility of well state	1	-	-	Estimate (convention)
u_dead	Utility of dead state	0	-	-	Estimate (convention)

F2.3 Probabilities

A series of transition probabilities regulate the likelihood of entering or leaving the various health states in the Markov process. Probabilities used in the model are listed in Table 27, along with sensitivity ranges and sources of estimates.

F2.3.1 Procedural mortality

Procedural mortality of TURP has been estimated from Mebust et al (1989) at 0.2 per cent. A sensitivity range of 0.1 to 0.3 per cent has been used. As no estimates of procedural mortality associated with TUNA could be found, it has been estimated to be half that of TURP for the base value, ie 0.1 per cent. In a sensitivity analysis it has been varied down to half the lower range of TURP (0.05%) up to the same as the base value for TURP (0.2%).

F2.3.2 Side effects

The probability of side effects associated with TURP has been estimated from a number of publications, including the recent WHO Consultation on Benign Prostatic Hyperplasia (Debruyne et al 2000) and the only randomised controlled trial comparing TURP to TUNA (Bruskewitz et al 1998). In the initial analysis the likelihood of side effects resulting from the TURP procedure was estimated to be six per cent. This was varied in a sensitivity analysis up to an incidence of 20 per cent. The likely differences between TURP and TUNA in terms of sexual side effects have been accounted for in the relative proportions of patients who develop side effects on each treatment.

Based on data from the randomised controlled trial of TUNA vs TURP (Bruskewitz et al 1998), and a number of case series reports of TUNA (Ramon et al 1997; Rosario et al 1997), it was assumed that patients treated with TUNA had approximately one third the incidence of side effects as those treated with TURP. This is represented by the risk ratio (RR) of side effects for TUNA being set at 0.33 in the base analysis. A sensitivity analysis on the probability of side effects from TUNA was conducted by varying the risk ratio of side effects for TUNA from one quarter that of TURP (RR 0.25) to the same as TURP (RR 1).

F2.3.3 Procedural failure

The probability of treatment failure after TUNA or TURP was modelled in terms of an initial probability relating to whether or not the procedure was successful, and, assuming that the procedure was initially successful, in terms of a recurring longer term failure rate. The short term failure rate attempts to capture the situation where the procedure was simply never successful, or where it failed within six months. The longer term risk attempts to reflect the rate of the progressive failure of the procedure over the duration of clinical follow-up, ie 20 years.

F2.3.3.1 Early treatment failure

The base case probability that TURP fails within six months is estimated to be 10%, based on data from the Bruskewitz et al (1998) randomised trial of TUNA versus TURP. This value is varied from 5 to 20 per cent in a sensitivity analysis. The base case probability that TUNA fails within six months is estimated to be double that of TURP ie 20 per cent. This is based on the randomised trial of Bruskewitz et al (1998) and a number of TUNA case series (Millard, Harewood, & Tamaddon 1996; Ramon et al 1997; Rosario et al 1997; Zlotta et al 1996). A sensitivity analysis varies this value down to the same as the TURP base case (10%) and increases it to 30 per cent.

F2.3.3.2 Long term treatment failure

The longer term failure rate of TURP was estimated to be one per cent per annum, and was varied in a sensitivity analysis from 0.5 to 2 per cent. These figures are estimates based on a randomised controlled trial of TURP versus watchful waiting (Wasson et al 1995) and on retrospective data of a cohort of patients which reports TURP retreatment rates over a follow-up period of 10 years (Roos et al 1989). It is likely that this will be a closer estimate to retreatment rates seen in clinical practice, rather than retreatment rates of patients selected to participate in clinical trials. Very few published case series of TUNA treatment report long term patient data. The series by Zlotta et al (2001), published in abstract form provides data on the proportion of TUNA patients requiring

additional treatment after five years, giving an annual TUNA failure rate of 5 per cent. This value is varied in a sensitivity analysis from 1 per cent to 15 per cent.

F2.3.4 Retreatment after treatment failure

For patients treated with TURP, the probability of receiving another TURP after failing the initial procedure was set to 35 per cent and varied between 10 per cent and 70 per cent in a sensitivity analysis (Table 35). This base value is estimated from retreatment rates in a randomised controlled trial of TURP versus watchful waiting (Wasson et al 1995).

The probability of receiving a TURP after failing TUNA was set to 75 per cent and varied between 38 per cent and 100 per cent in a sensitivity analysis (Table 35). The base value is estimated from a number of TUNA case series (including two reporting on Australian patients), which report on the proportion of patients who are retreated with TURP after failing TUNA (Harewood et al 1995; Millard, Harewood, & Tamaddon 1996; Rosario et al 1997; Steele & Sleep 1997).

The probability of no further treatment after failing TUNA is defined based upon the assumption that of the patients who do not have TURP after TUNA failure, 75 per cent will have no further treatment and the other 25 per cent will have a repeat TUNA. It is calculated in the model by the expression [(100%-x%)*75%], where x is the probability of having a TURP after TUNA failure.

Based on this same assumption, the probability of receiving another TUNA after failing TUNA is therefore defined in the model by the expression [1-(probability of TURP after TUNA failure + probability of nothing after TUNA failure)].

Table 35 Transition probabilities of model

Name of model variable	Description	Formula	Value	Sensitivity range Low	Sensitivity range High	Source
Duration of follow-up						
follow_up	cycles of follow-up (1 cycle=6mo)		40	1	40	20 years follow-up
Procedural mortality						
p_death_TURP	Probability of death from TURP		0.002	0.001	0.003	(Mebust et al 1989)
p_death_TUNA	Probability of death from TUNA		0.001	0.0005	0.002	Estimate
Side effects						
p_side_effects_TURP	Probability of side effects from TURP		0.06	0.06	0.2	(Mebust et al 1989) (Bruskewitz et al 1998)(RCT TUNA vs TURP) (Debruyne et al 2000) WHO consensus document
p_side_effects_TUNA	Probability of side effects from TUNA	p_side_effects_TURP* risk_ratio_for_side_ effects	0.0198	0.015	0.2	See below
risk_ratio_for_side_effects	Ratio of probability of side effects for TURP versus TUNA		0.33	0.25	1	(Bruskewitz et al 1998)(RCT TUNA vs TURP) (Ramon et al 1997) (Case series) (Rosario et al 1997) (case series 12mo f/up)
Early Procedural failure (failure within 6 months)						
p_TURP_NOT_successful	Probability that TURP was NOT successful (failure within 6 months)		0.1	0.05	0.2	(Bruskewitz et al 1998) (RCT TUNA vs TURP)
p_TUNA_NOT_successful	Probability that TUNA is NOT successful (failure within 6 months)		0.2	0.1	0.3	(Bruskewitz et al 1998) (RCT TUNA vs TURP) (Millard, Harewood, & Tamaddon 1996) (case series - Australian data) (Zlotta et al 1996) (case series) (Rosario et al 1997) (case series 12mo f/up) (Ramon et al 1997) (Case series)
Long term failure rate						
r_fail_TURP	Annual failure rate of TURP		0.01	0.005	0.02	(Roos et al 1989) (TURP re-treated within 10years) (Wasson et al 1995) (RCT TURP vs waiting)
r_fail_TUNA	Annual failure rate for TUNA		0.05	0.01	0.15	(Zlotta, Giannakopoulos, & Schulman 2001) Five year follow-up of TUNA patients (abstract)

Name of model variable	Description	Formula	Value	Sensitivity range Low	Sensitivity range High	Source
Retreatment						
p_2nd_TURP	Probability of having a second TURP after first TURP fails		0.35	0.10	0.7	(Wasson et al 1995) (RCT TURP vs waiting)
p_TURP_after_TUNA	Probability of having TURP after TUNA fails		0.75	0.38	1	(Harewood et al 1995) (case series Australian data) (TUNA followed by TURP within 6mo) (Millard, Harewood, & Tamaddon 1996) (case series - Australian data) (TUNA followed by TURP within 6mo) (Rosario et al 1997) (case series 12mo f/up) (Steele & Sleep 1997) (case series 2 yr f/up)
p_Nothing after TUNA failure	Probability of having no further treatment after TUNA failure	(100%-x%) x 75%, where x% is the probability of TURP after TUNA failure	Calculated			Estimate Of the patients who do not have TURP after TUNA failure, 75% will have no further treatment and the other 25% will have a repeat TUNA
p_repeat TUNA	Probability of TUNA after TUNA failure	1-(probability of TURP after TUNA failure + probability of nothing after TUNA failure	Calculated			Estimate Of the patients who do not have TURP after TUNA failure, 75% will have no further treatment and the other 25% will have a repeat TUNA

F2.4 Costs

F2.4.1 Procedural costs

The cost of TUNA was estimated at $3,700 in the base-case analysis, and increased to $5,000 in a sensitivity analysis. The cost of TURP was estimated at $4,700, and decreased to the same price as TUNA ($3,700) and increased to $5,700 in a sensitivity analysis. These estimates are based on the costs provided by the applicant within the submission to MSAC.

F2.4.2 Costs of Side Effects

The cost associated with the Side Effects state is intended to represent the average annual cost of treating a patient who has developed side effects from either procedure. It may include costs such as:

- any general practitioner or specialist consultations;
- any surgical management required as a result of procedural side effects;

- any hospitalisations required; and
- any pharmacological or medical management of side effects including the management of erectile dysfunction, eg Sildenafil.

It has been assumed that the average cost of treating side effects from TURP is the same as that for TUNA, only the proportions of patients experiencing side effects varies between the two procedures.

F2.4.3 Costs of Treatment Failure

The cost associated with the Treatment Failure state is intended to represent the average annual cost of treating a patient who has failed treatment with either TUNA or TURP, ie a patient with symptomatic benign prostatic hyperplasia. It may include costs such as:

- any general practitioner or specialist consultations;
- any other surgical management attempted as a treatment for BPH;
- any hospitalisations required for BPH; and
- any pharmacological or medical management of symptoms of BPH including, for example, treatment with 5-alpha-reductase inhibitors such as finasteride (Proscar) or alpha-1 adrenoceptor antagonists such as terazosin, Tamsulosin etc.

It has been assumed that the average cost of treating treatment failures from TURP is the same as that for TUNA, only the proportion of patients failing treatment varies between the two procedures (Table 36).

Table 36 Costs included in model

Name of model variable	Description	Base Value	Sensitivity range		Source
			Low	High	
c_side_effects	cost of treating side effects from either procedure for 1 year	500	0	2000	Estimate
c_treatment_failure	cost of treating patients who have failed either procedure for 1 year	1000	0	3000	Estimate
c_TURP	Cost of TURP	4700	3700	5700	MSAC Application (1999)
c_TUNA	Cost of TUNA	3700	3700	5000	MSAC Application (1999)

F3 Results

Costs and benefits have been discounted using a standard 5 per cent per annum discount rate, and a half cycle correction has been incorporated into the model.

F3.1 Effectiveness

In the model, effectiveness of the interventions has been measured by QALYs. This measure incorporates an adjustment for the estimated quality of life of patients in various health states in the model.

F3.1.1 Baseline scenario

In the base-case model the QALYs gained for patients treated initially with TURP was 12.3082 and for patients treated initially with TUNA was 12.2869. This indicates that treating patients with TURP initially is a more favourable treatment option under the set of baseline conditions described in the previous section. The rolled back decision tree for the effectiveness analysis is shown in Appendix F2.

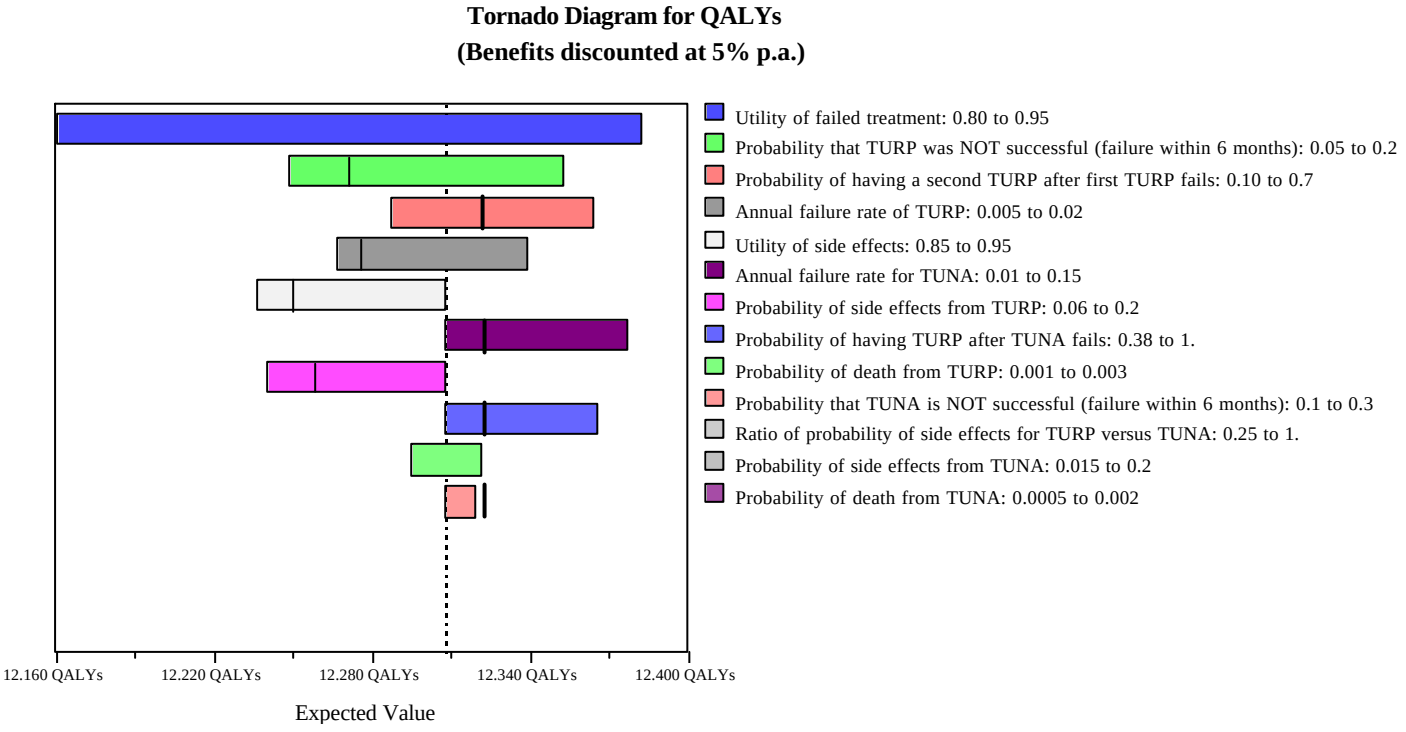
F3.1.2 One way sensitivity analyses

F3.1.2.1 Tornado Diagram

A tornado diagram is a set of one way sensitivity analyses on any variables in the tree brought together in a single graph. A horizontal bar is generated for each variable analysed. The Expected Value is displayed on the horizontal axis, and each bar represents the node's range of expected values generated by varying the related variable over the pre-defined sensitivity range. The bars are arranged from top to bottom with the widest bars at the top. A wide bar indicates that the associated variable has a large potential effect on the expected value of the model.

The tornado diagram in Figure 5 summarises the results from the one-way sensitivity analyses for variables on the effectiveness outcome of QALYs. The graph highlights those factors that affected estimates of quality-adjusted survival time for both groups, and does not necessarily identify those factors most critical to how the treatments were ranked by the model. The dotted vertical line indicates the optimal expected value of the outcome ie the 12.3082 QALYs achieved by treating initially with TURP, as discussed above. The heavy vertical lines on the variable bars indicate the expected value at which the optimal treatment strategy changes from one initial treatment to another.

Figure 5 Tornado Diagram for the outcome of QALYs

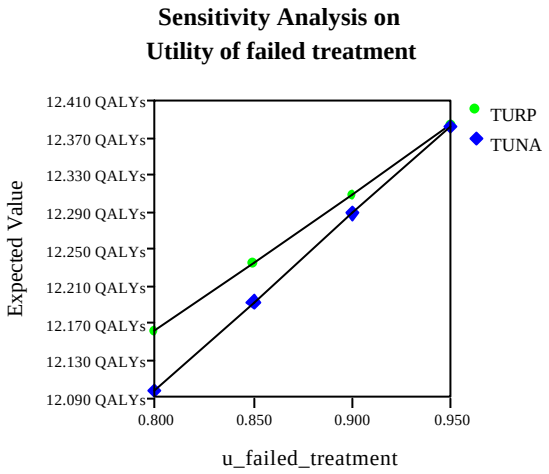


One way and two way sensitivity analyses were performed on the variables in the above tornado diagram which were most likely to affect quality adjusted survival.

F3.1.2.2 Utility weight of the state of Treatment Failure

In the baseline analysis using a utility weight for Treatment Failure of 0.9, treatment with TURP initially is the optimal strategy. The sensitivity analysis indicates that over all values in the pre-specified sensitivity range of the utility weight for the state Treatment Failure (0.80 to 0.95), TURP remains the optimal initial treatment strategy (ie expected QALYs are higher for TURP than for TUNA).

Figure 6 One way sensitivity analysis on the utility weight of the state Treatment Failure

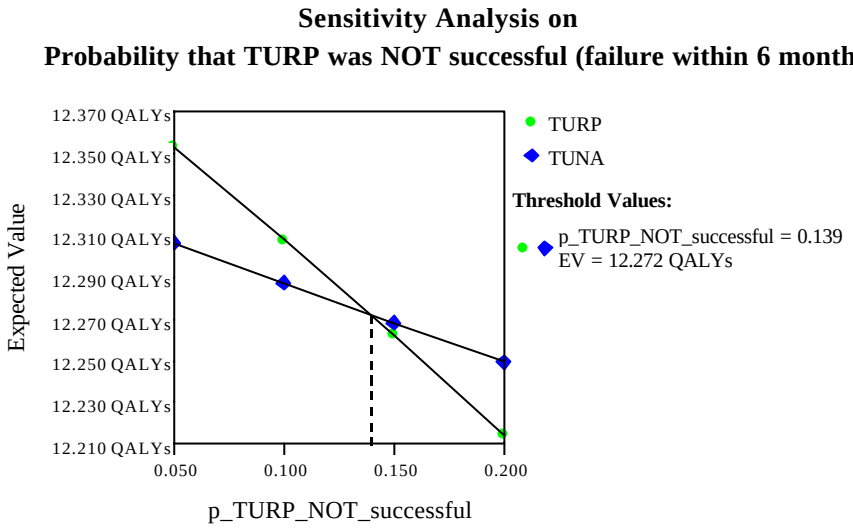


A threshold analysis indicates that the utility for Treatment Failure needs to be higher than 0.953 before initial treatment with TUNA is the optimal choice.

F3.1.2.3 Probability that TURP fails within six months

In the baseline analysis using a probability of TURP failing within six months of 10 per cent, treatment with TURP initially is the optimal strategy. The sensitivity analysis indicates that this remains true until the probability of TURP failing within six months reaches 13.9 per cent. If the likelihood of TURP failing within six months is greater than this threshold value, and all other model variables remain unchanged, then the optimal strategy is to treat with TUNA. At the point where the best initial treatment changes from TURP to TUNA, the expected value is 12.272 QALYs.

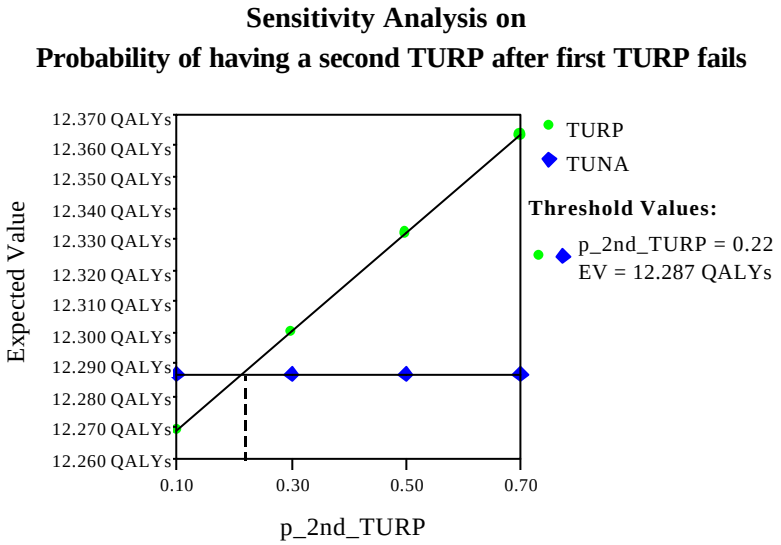
Figure 7 **One way sensitivity analysis on the probability that TURP fails within six months**



F3.1.2.4 Probability of retreatment with TURP after first TURP fails

In the baseline analysis using a probability of having a second TURP after the first TURP has failed of 35 per cent, treatment with TURP initially is the optimal strategy. The sensitivity analysis indicates that this remains true until the probability of receiving a second TURP falls below 22 per cent. If the likelihood of receiving a second TURP is less than this threshold value and all other model variables remain unchanged, then the optimal strategy is to treat with TUNA. At the point where the best initial treatment changes from TURP to TUNA, the Expected Value is 12.287 QALYs.

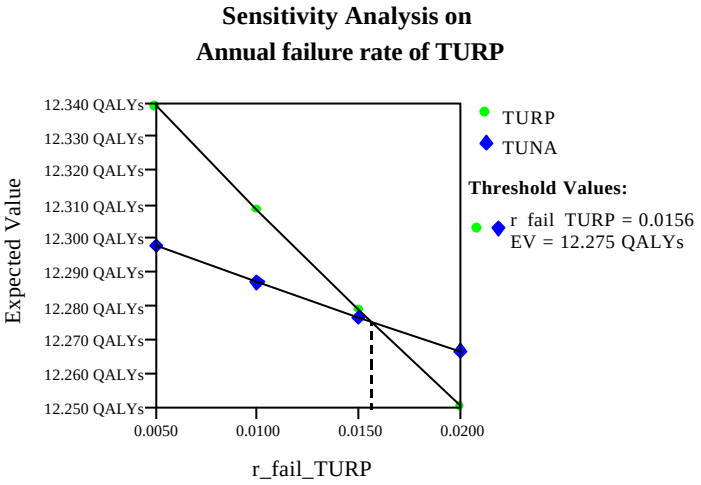
Figure 8 **One way sensitivity analysis on the probability of retreatment with TURP after first TURP fails**



F3.1.2.5 Annual failure rate of TURP

In the baseline analysis using an annual failure rate for TURP of 1 per cent per annum treatment with TURP initially is the optimal strategy. The sensitivity analysis indicates that this remains true until the annual failure rate of TURP is greater than 1.56 per cent. If the annual failure rate of TURP is greater than this threshold value, and all other model variables remain unchanged, then the optimal strategy is to treat with TUNA. At the point where the best initial treatment changes from TURP to TUNA, the Expected Value is 12.275 QALYs.

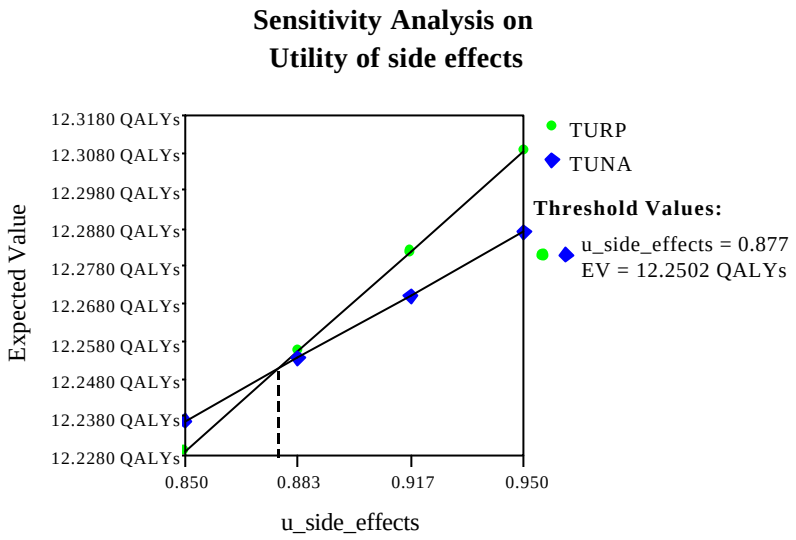
Figure 9 One way sensitivity analysis on the Annual failure rate of TURP



F3.1.2.6 Utility weight of the state of Side Effects

In the baseline analysis using a utility weight of 0.95 for the state of Side Effects, treatment with TURP initially is the optimal strategy. The sensitivity analysis indicates that this remains true until the utility weight of the state Side Effects falls below 0.877. If the utility weight is less than this threshold value and all other model variables remain unchanged, then the optimal strategy is to treat with TUNA. At the point where the best initial treatment changes from TURP to TUNA, the Expected Value is 12.2502 QALYs.

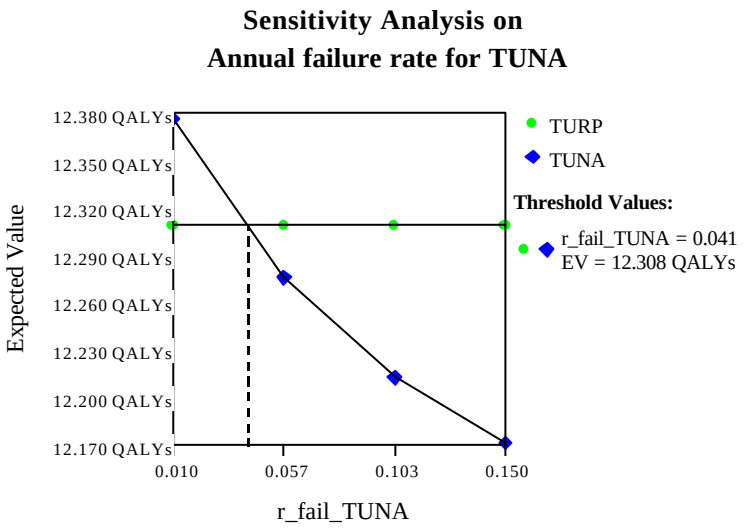
Figure 10 One way sensitivity analysis on the Utility weight of the state of Side Effects



F3.1.2.7 Annual failure rate of TUNA

In the baseline analysis using an annual failure rate for TUNA of 5 per cent per annum, treatment with TURP initially is the optimal strategy. The sensitivity analysis indicates that this remains true until the annual failure rate of TUNA is less than 4.1 per cent. If the annual failure rate of TUNA is less than this threshold value and all other model variables remain unchanged, then the optimal strategy is to treat with TUNA. At the point where the best initial treatment changes from TURP to TUNA, the Expected Value is 12.308 QALYs.

Figure 11 One way sensitivity analysis on the Annual failure rate of TUNA

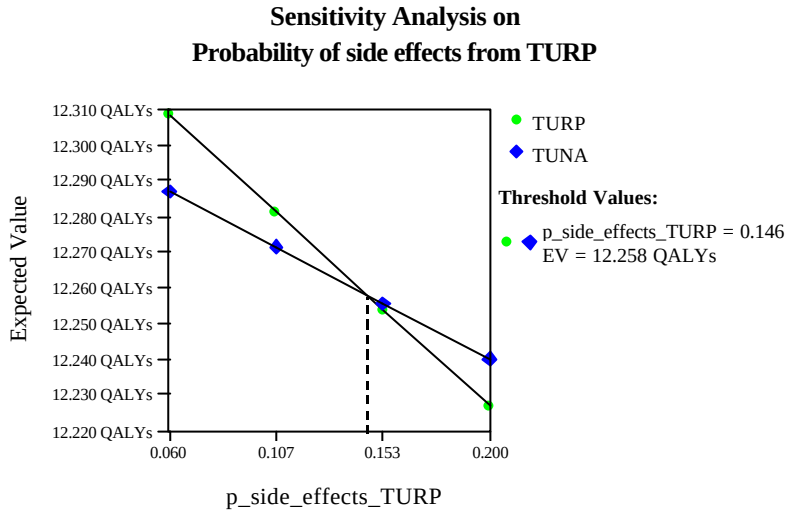


F3.1.2.8 Probability of side effects from TURP

In the baseline analysis using a probability of side effects from TURP of 6 per cent, TURP initially is the optimal strategy. The sensitivity analysis indicates that this remains

true until the probability of side effects from TURP is greater than 14.6 per cent. If the likelihood of side effects from TURP is greater than this threshold value, and all other model variables remain unchanged, then the optimal strategy is to treat with TUNA. At the point where the best initial treatment changes from TURP to TUNA, the Expected Value is 12.258 QALYs.

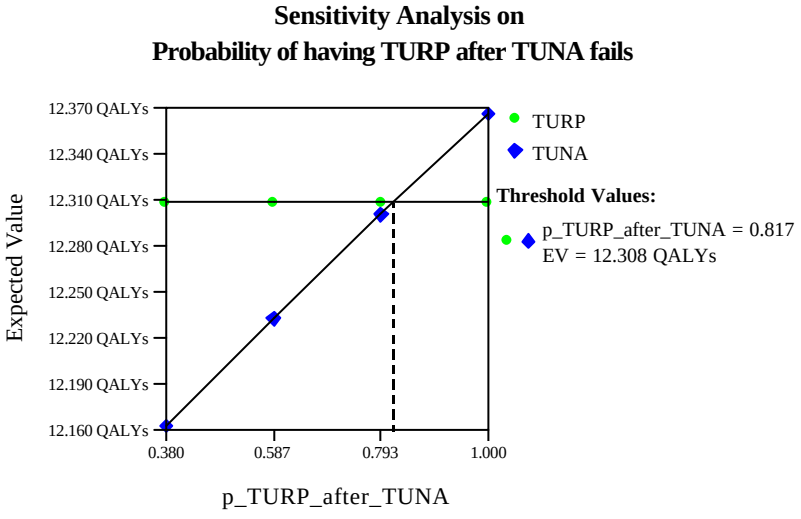
Figure 12 One way sensitivity analysis on Probability of side effects from TURP



F3.1.2.9 Probability of retreatment with TURP after TUNA fails

In the baseline analysis using a probability of receiving treatment with TURP after TUNA fails of 75 per cent, TURP initially is the optimal strategy. The sensitivity analysis indicates that this remains true until the probability of receiving a TURP after TUNA failure is greater than 81.7 per cent. If the likelihood of having a TURP after TUNA failure is greater than this threshold value, and all other model variables remain unchanged, then the optimal strategy is to treat with TUNA. At the point where the best initial treatment changes from TURP to TUNA, the Expected Value is 12.308 QALYs.

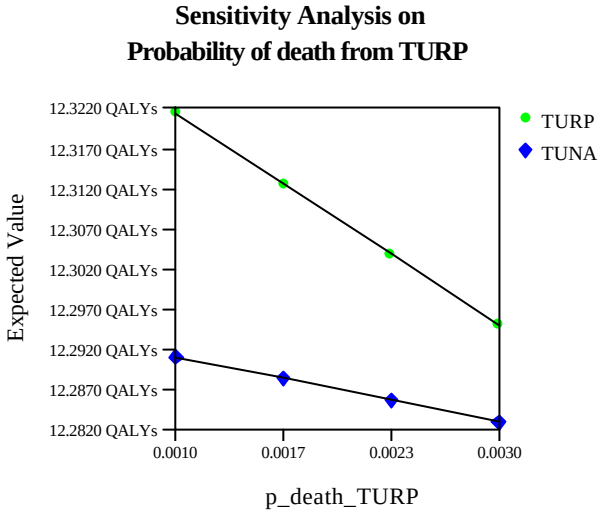
Figure 13 One way sensitivity analysis on the Probability of retreatment with TURP after TUNA fails



F3.1.2.10 Probability of death from TURP

In the baseline analysis using a procedural mortality for TURP of 0.2 per cent, treatment with TURP initially is the optimal strategy. The sensitivity analysis indicates that over all values in the pre-specified sensitivity range of the procedural mortality of TURP (0.1% to 0.3%), TURP remains the optimal initial treatment strategy (ie expected QALYs are always higher for TURP than for TUNA).

Figure 14 One way sensitivity analysis on the Probability of death from TURP

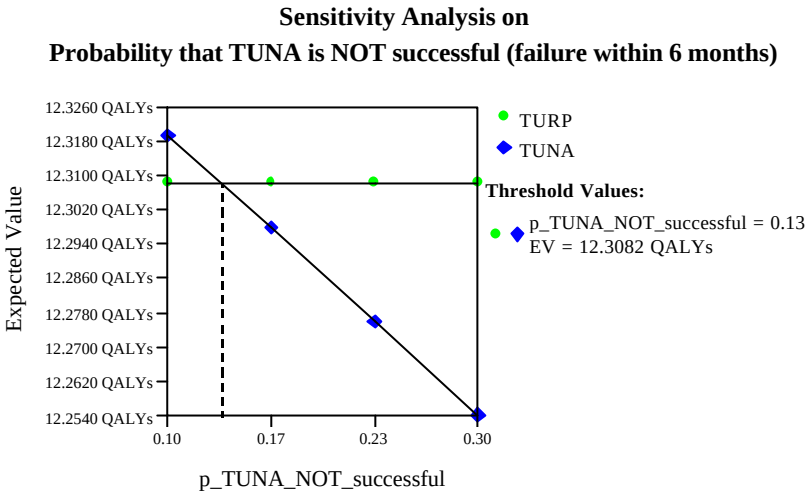


A threshold analysis indicates that the procedural mortality rate for TURP needs to be higher than 0.45 per cent before initial treatment with TUNA is the optimal choice.

F3.1.2.11 Probability that TUNA fails within six months

In the baseline analysis using a probability of TUNA failing within six months of 20 per cent, treatment with TURP initially is the optimal strategy. The sensitivity analysis indicates that this remains true until the probability of TUNA failing within six months falls to 13 per cent. If the likelihood of TUNA failing within six months is less than this threshold value and all other model variables remain unchanged, then the optimal strategy is to treat with TUNA. At the point where the best initial treatment changes from TURP to TUNA, the expected value is 12.3082 QALYs.

Figure 15 One way sensitivity analysis on the probability that TUNA fails within six months



F3.1.2.12 Other variables in tornado diagram

The following variables were also examined in one way sensitivity analyses:

- Ratio of probability side effects of TUNA relative to side effects of TURP;
- Probability of side effects from TUNA; and
- Probability of death from TUNA.

Over all the values in the sensitivity range for each of these variables, initial treatment with TURP remained the optimal treatment strategy.

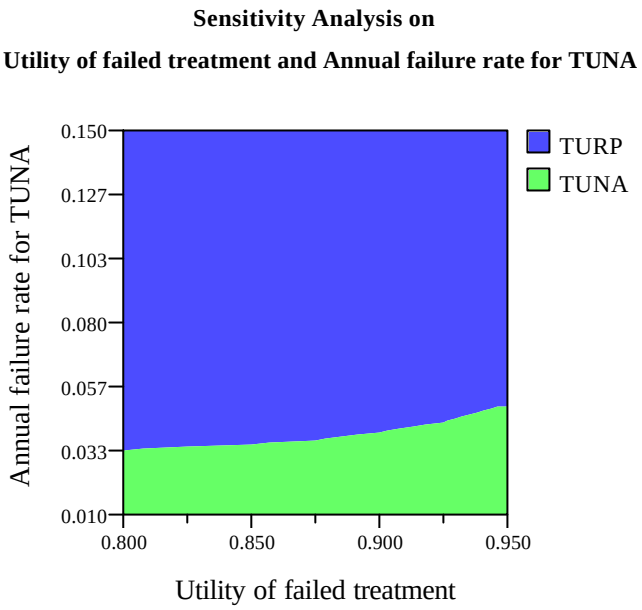
F3.1.3 Two way sensitivity analyses

Two way sensitivity analyses indicate, by varying two variables simultaneously, the conditions under which each treatment is superior to the other. Figures 16 to 19 indicate two way sensitivity analyses for combinations of two variables.

F3.1.3.1 Utility weight of the failed treatment state

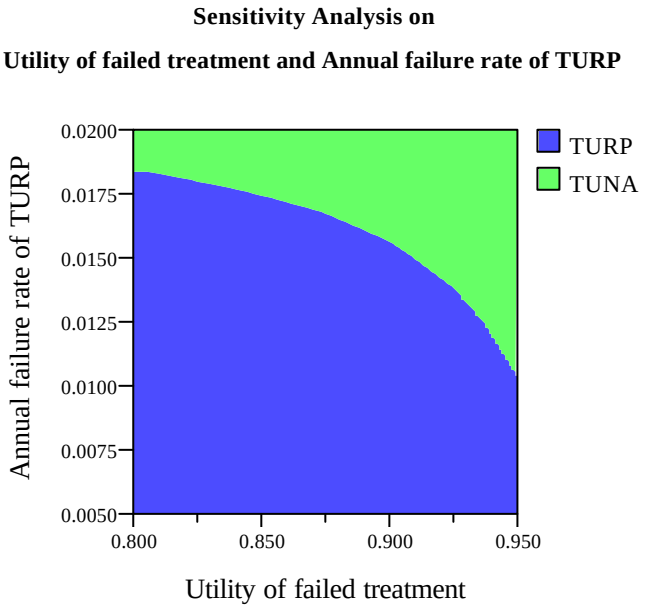
By varying both the utility weight of the state of Treatment Failure and the annual failure rate of TUNA at the same time, the conditions under which TURP was found to be superior to TUNA can be demonstrated. TURP was found to be superior over all values in the sensitivity range for the utility of failed treatment, providing the annual failure rate for TUNA was greater than approximately 3.3 per cent.

Figure 16 **Two way sensitivity analysis of the Utility of failed treatment and the annual failure rate of TUNA**



By varying both the utility weight of the state of Treatment failure and the annual failure rate of TURP at the same time, the conditions under which TURP was found to be superior to TUNA can be demonstrated in Figure 17.

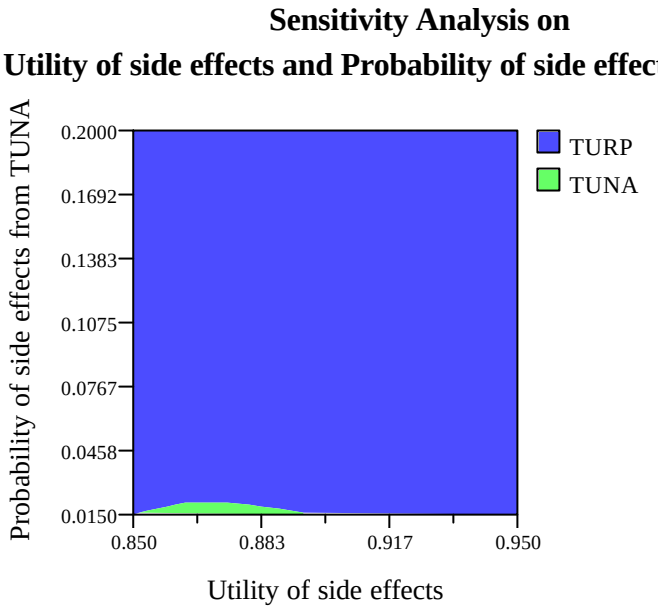
Figure 17 **Two way sensitivity analysis of the Utility of failed treatment and the annual failure rate of TURP**



F3.1.3.2 Utility weight of the side effects state

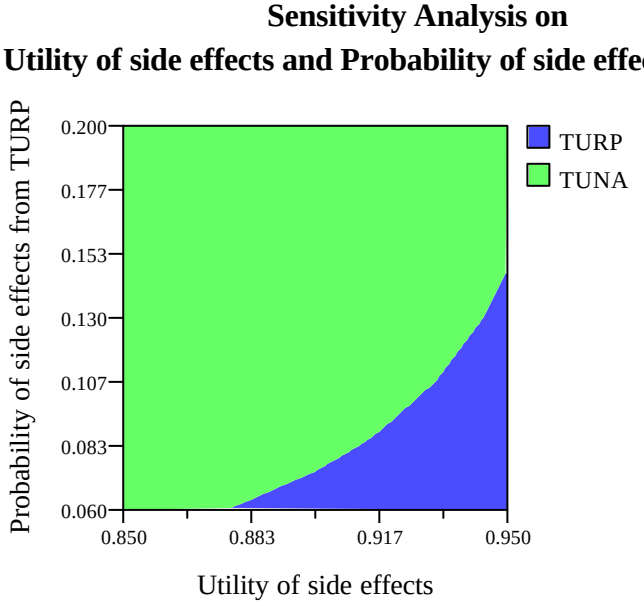
By varying both the utility of side effects state and the probability of side effects from TUNA, the conditions under which TURP was found to be superior to TUNA can be demonstrated in Figure 18.

Figure 18 Two way sensitivity analysis of the utility of side effects and the probability of side effects from TUNA



By varying both the utility of side effects state and the probability of side effects from TURP fails, the conditions under which TURP was found to be superior to TUNA can be demonstrated in Figure 19.

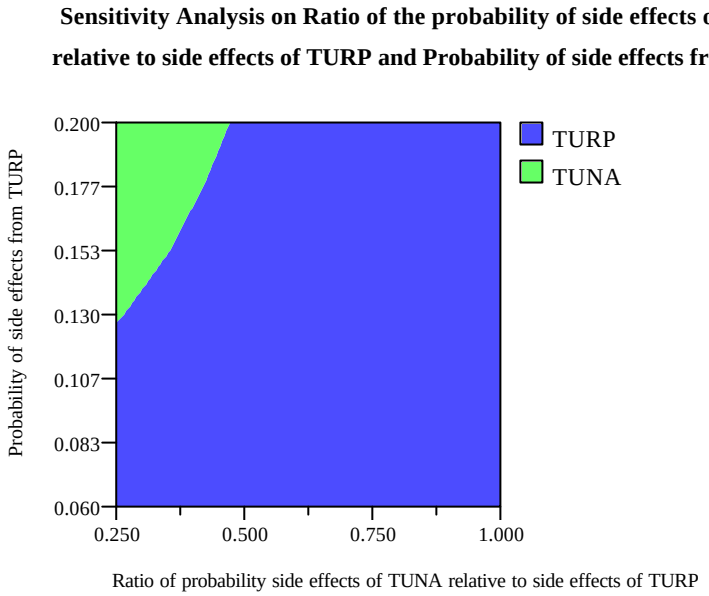
Figure 19 Two way sensitivity analysis of the utility of side effects and the probability of side effects from TUNA



F3.1.3.3 Ratio of side effects from TUNA compared to TURP

By varying both the ratio of TUNA side effects to TURP side effects and the probability of side effects from TURP, the conditions under which TURP was found to be superior to TUNA can be demonstrated in Figure 20.

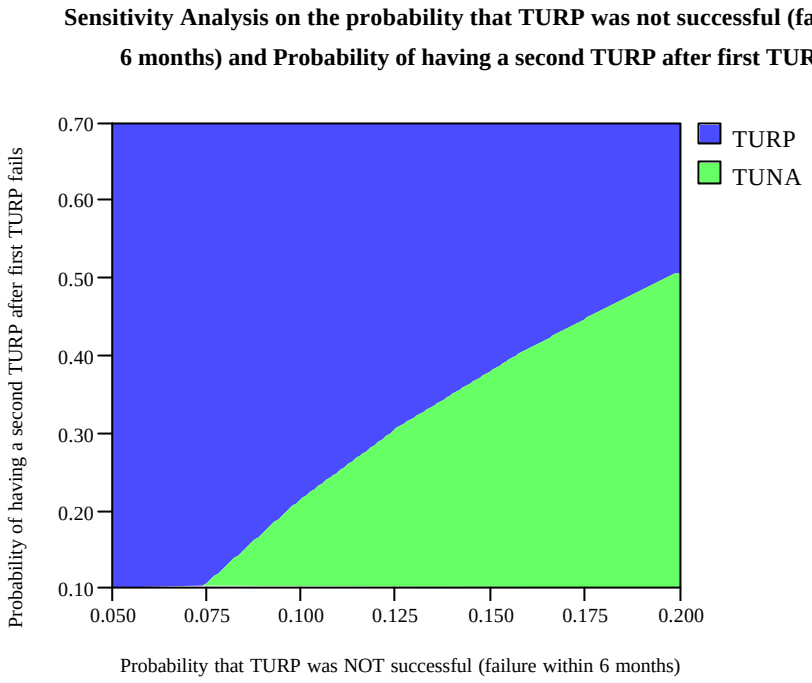
Figure 20 Two way sensitivity analysis of the ratio of side effects from TUNA relative to side effects from TURP and the probability of side effects from TURP



F3.1.3.4 Early treatment failure rates

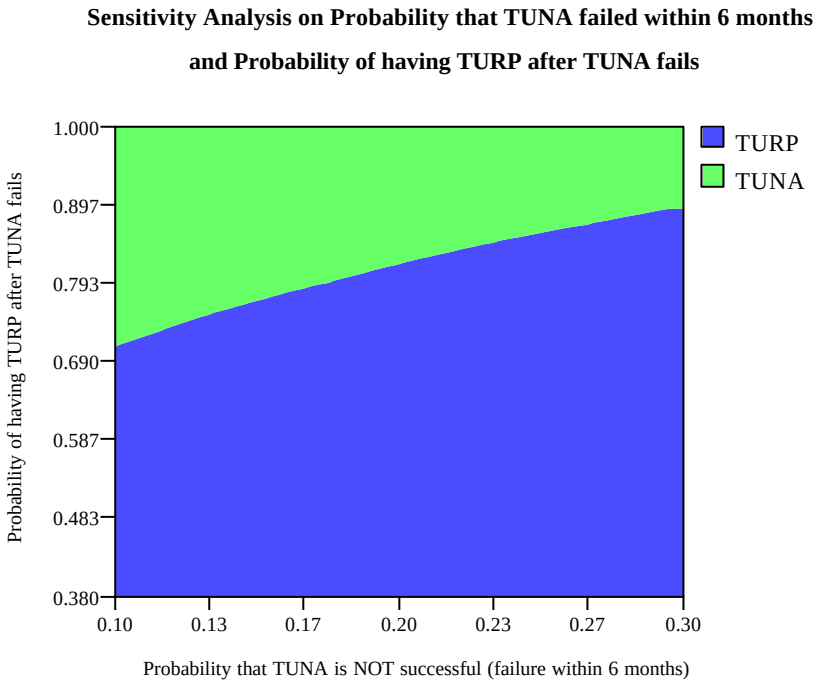
By varying both the probability that TURP fails within six months and the probability of having a second TURP after the first one fails, the conditions under which TURP was found to be superior to TUNA can be demonstrated in Figure 21.

Figure 21 **Two way sensitivity analysis of the probability that TURP fails within 6 months and the probability of having a second TURP after the first TURP fails**



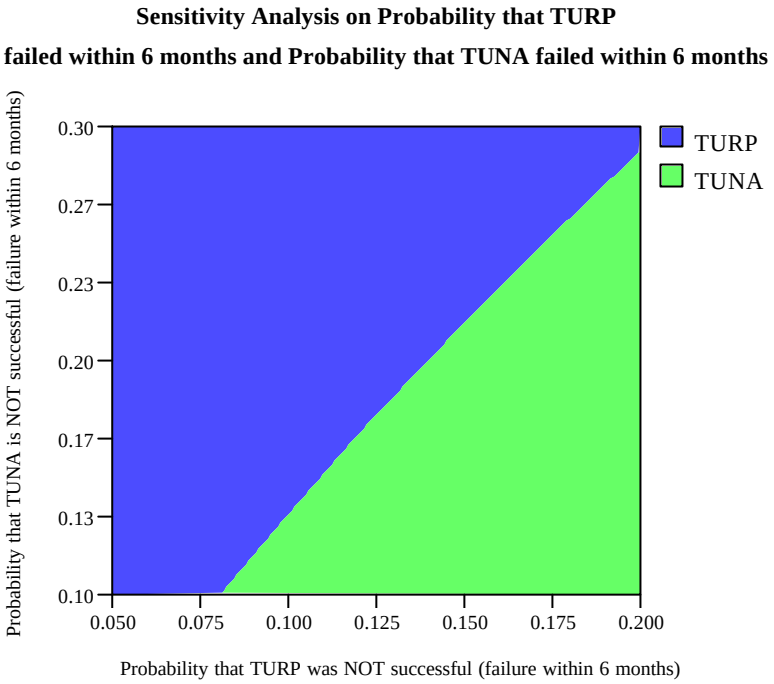
By varying both the probability that TUNA fails within six months and the probability of having a TURP after the TUNA fails, the conditions under which TURP was found to be superior to TUNA can be demonstrated in Figure 22.

Figure 22 **Two way sensitivity analysis of the probability that TUNA fails within 6 months and the probability of having a TURP after TUNA fails**



By varying both the probability that TURP fails within six months and the probability that TUNA fails within six months, the conditions under which TURP was found to be superior to TUNA can be demonstrated in Figure 23.

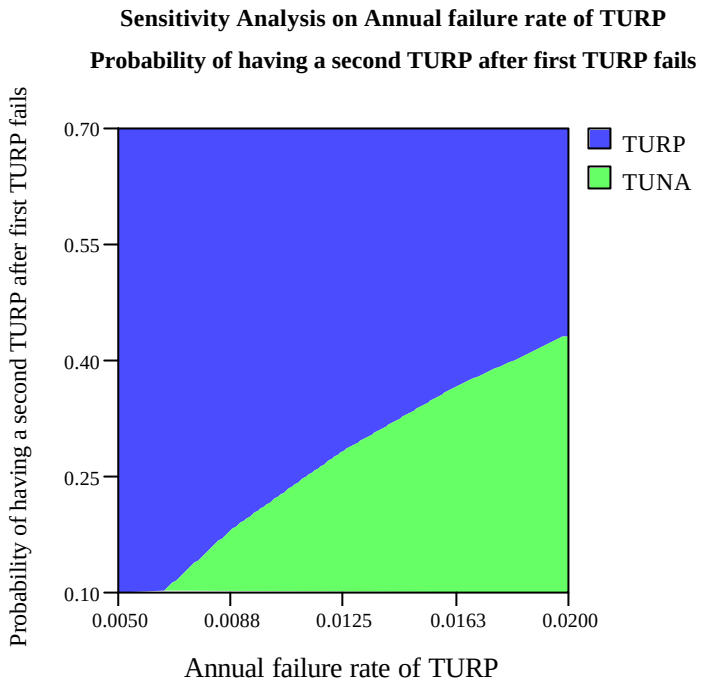
Figure 23 Two way sensitivity analysis of the probability that TURP fails within 6 months and the probability that TUNA fails within 6 months



F3.1.3.5 Long term treatment failure rates

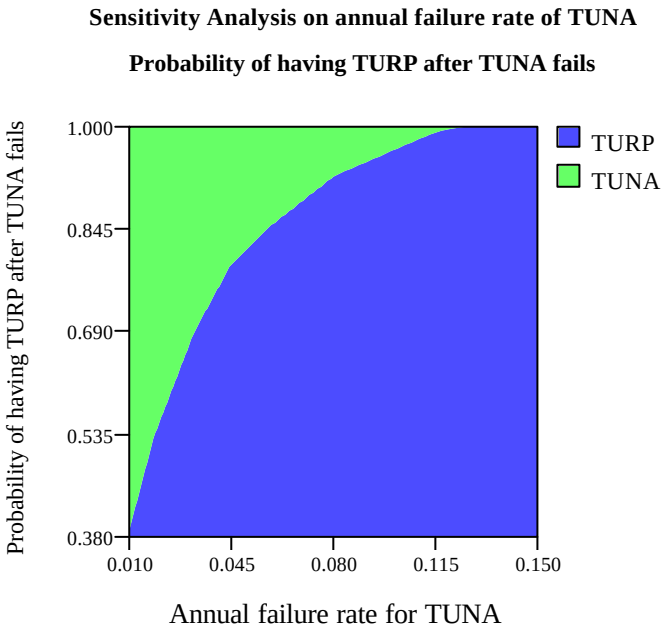
By varying both the annual failure rate of TURP and the probability of having a second TURP after the first one fails, the conditions under which TURP was found to be superior to TUNA can be demonstrated in Figure 24.

Figure 24 **Two way sensitivity analysis on the annual failure rate of TURP and probability of having a 2nd TURP after the first fails**



By varying both the annual failure rate of TUNA and the probability of having a TURP after the TUNA fails, the conditions under which TURP was found to be superior to TUNA can be demonstrated in Figure 25.

Figure 25 **Two way sensitivity analysis on the annual failure rate of TUNA and probability of having a TURP after TUNA fails**



F3.2 Costs

Costs which are accrued over the duration of follow-up (ie 20 years) such as costs of treating side effects and patients who have failed treatment have been discounted at a standard annual rate of 5 per cent.

F3.2.1 Baseline scenario

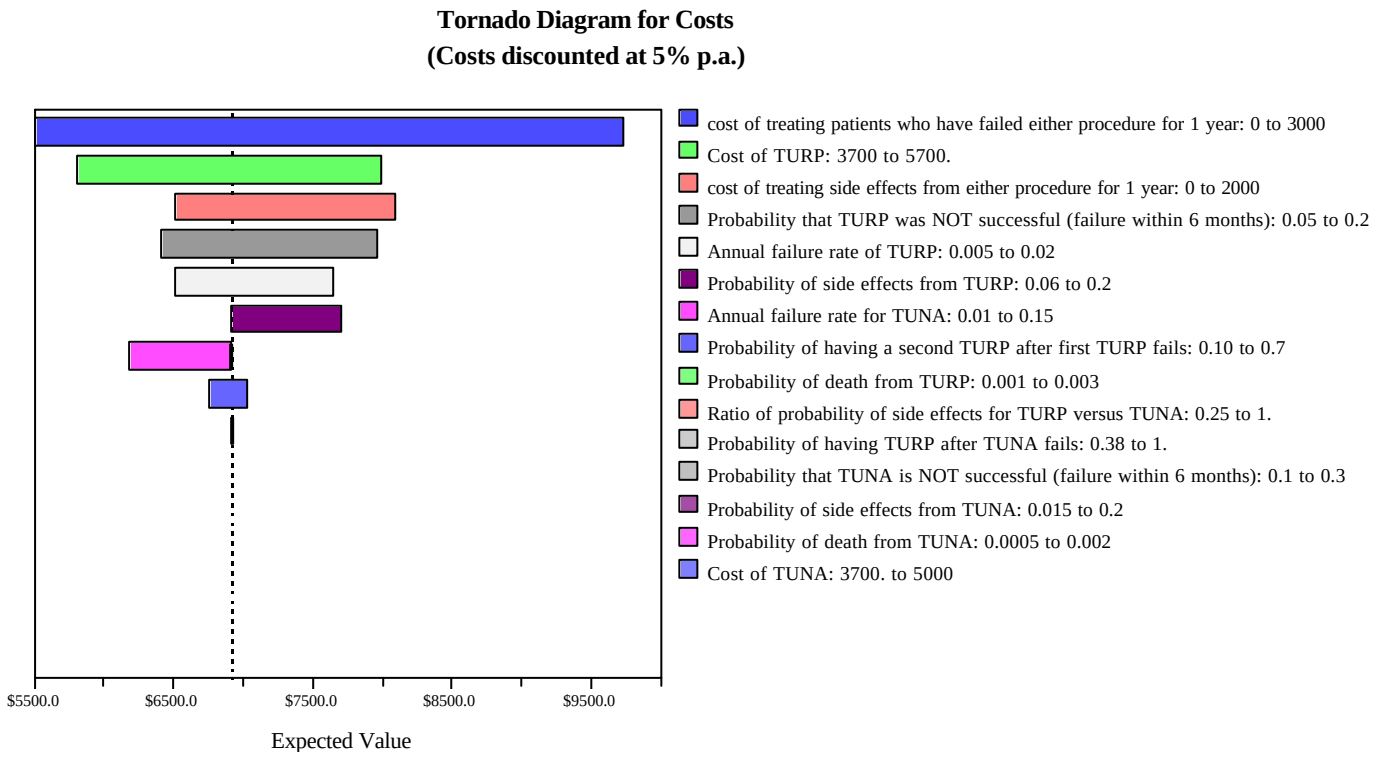
In the base-case model the costs accrued over the follow-up period for patients treated initially with TURP were $6,910 and were $8,296 for patients treated initially with TUNA. This indicates that treating patients with TURP initially is a less expensive treatment option under the set of baseline conditions described in the previous section. The rolled back decision tree for the cost analysis is shown in Appendix F3.

F3.2.2 One way sensitivity analyses

F3.2.2.1 Tornado Diagram

The tornado diagram in Figure 26 summarises the results from the one-way sensitivity analyses for variables on the effectiveness outcome of cost. The graph highlights those factors that affected estimates of cost for both groups, and does not necessarily identify those factors most critical to how the treatments were ranked by the model. The dotted vertical line indicates the optimal expected value of the outcome, ie the $6,910 achieved by treating initially with TURP, as discussed above. The heavy vertical lines on the variable bars indicate the expected value at which the optimal treatment strategy changes from one initial treatment to another.

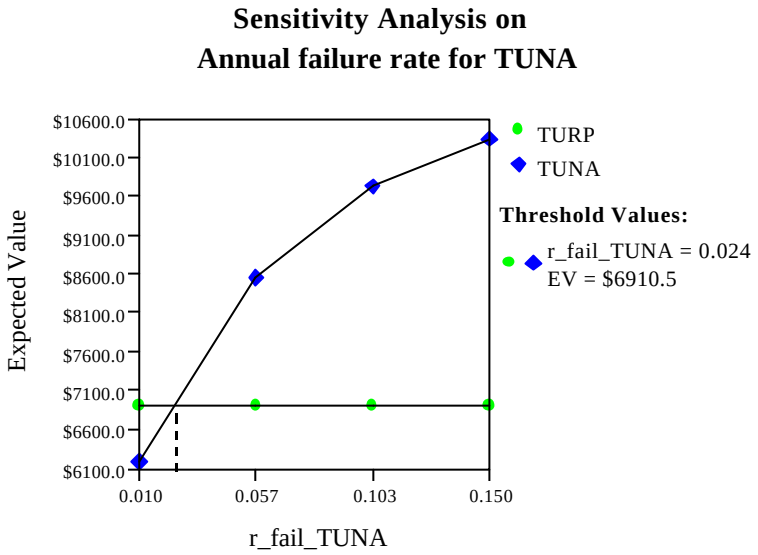
Figure 26 Tornado Diagram for the outcome of Costs



F3.2.2.2 Annual failure rate of TUNA

In the baseline analysis using an annual failure rate for TUNA of 5 per cent per annum, treatment with TURP initially is the least expensive strategy. The sensitivity analysis indicates that this remains true unless the annual failure rate of TUNA is less than 2.4 per cent. If the annual failure rate of TUNA is less than this threshold value, and all other model variables remain unchanged, then the least expensive strategy is to treat with TUNA initially. At the point where the best initial treatment changes from TURP to TUNA, the expected value is $6,910.

Figure 27 One way sensitivity analysis on annual failure rate of TUNA



F3.2.2.3 Other variables

One way sensitivity analyses were also conducted for the variables listed below. Over the sensitivity range for each variable, the cost of treating a patient with TUNA initially is always more expensive than using TURP as the initial treatment.

- Cost of treating patients who have failed either procedure for one year
- Cost of TURP
- Cost of treating side effects from either procedure for one year
- Probability that TURP was not successful (failure within six months)
- Annual failure rate of TURP
- Probability of side effects from TURP
- Probability of having a second TURP after first TURP fails
- Probability of death from TURP
- Ratio of probability of side effects for TURP versus TUNA

- Probability of having TURP after TUNA fails
- Probability that TUNA is not successful (failure within 6 months)
- Probability of side effects from TUNA
- Probability of death from TUNA
- Cost of TUNA

F3.2.3 Two way sensitivity analyses

Figure 28 below indicates the conditions with respect to the annual failure rate of TUNA and the annual cost of treating patients who have failed either treatment, under which TURP is less costly than TUNA. Over the range of no cost to $3,000 per annum for treating patients who have failed either procedure, if the annual rate of failure of TUNA is greater than or equal to approximately 2 per cent, TURP is the least costly treatment option. TUNA becomes less costly only when it has a very low annual failure rate (less than 2% per year).

Figure 28 Two way sensitivity analysis of Annual failure rate of TUNA and the annual cost of treating patients who have failed either procedure

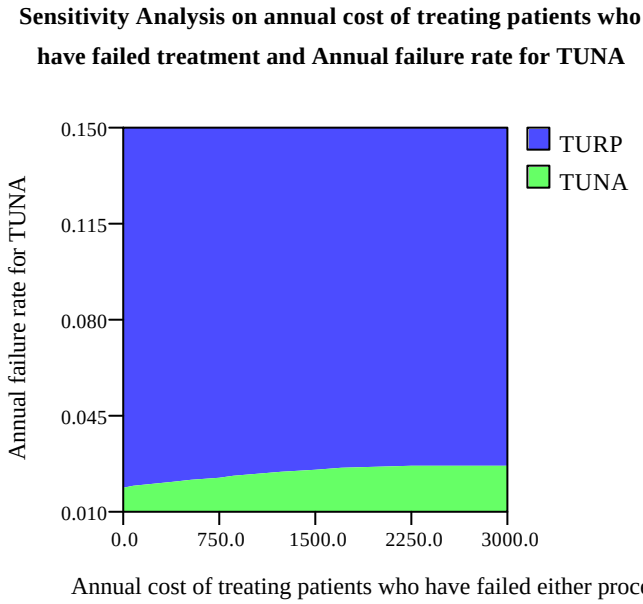
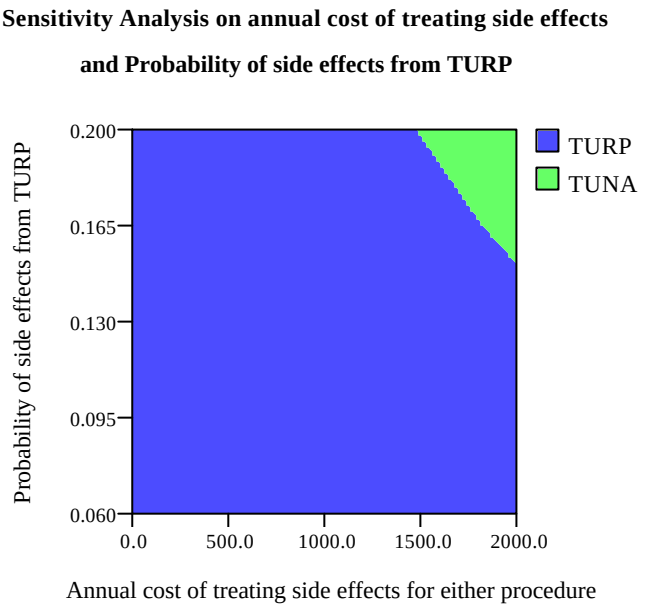


Figure 29 below indicates the conditions with respect to the probability of developing side effects from TURP and the annual cost of treating side effects from either procedure, under which TURP is less costly than TUNA. TUNA is less costly than TURP only when the annual cost of treating side effects ranges between $1,500 and $2,000, and when the probability of developing significant side effects from TURP ranges between approximately 15 per cent and 20 per cent. If the cost is $1,500 per annum, then the likelihood of developing side effects needs to be 20 per cent, and if the cost is $2,000 per annum, then the likelihood of developing side effects from TURP needs to be at least 15 per cent for TUNA to become less costly than TURP.

Figure 29 Two way sensitivity analysis for probability of side effects from TURP and annual cost of treating side effects from either procedure



Two way sensitivity analyses were also conducted for the following combinations of variables. Treating with TURP initially was the least costly treatment option over all values in the respective sensitivity ranges of these combinations.

- Annual failure rate of TURP and annual cost of treatment failure
- Probability of side effects from TUNA and annual cost of treating side effects
- Risk ratio of TUNA side effects to TURP side effects and cost of treating side effects
- Probability that TURP fails within six months and cost of TURP
- Probability that TUNA fails within six months and cost of TURP
- Probability that TUNA fails within six months and cost of TUNA
- Probability of having a 2nd TURP after first TURP fails and cost of TURP
- Probability of having TURP after TUNA fails and cost of TURP

- Probability of having TURP after TUNA fails and cost of TUNA
- Probability that TURP fails within six months and probability of having a 2nd TURP after first TURP fails
- Probability that TUNA fails within six months and probability of TURP after TUNA fails

F3.3 Incremental cost-effectiveness analyses

The base case analysis indicates that when patients are treated with TURP initially, they gain an average 12.3082 QALYs over the follow-up period at an average cost of $6,910. If patients are treated with TUNA first they gain fewer QALYs (12.2869) at a higher average cost ($8,296) (see Table 28).

For this reason it is not necessary to calculate an incremental cost-effectiveness ratio, as treatment with TURP initially is the better option.

Table 37 Base case analysis results

Initial Treatment	Cost ($)	QALY	ICER compared with TURP first strategy ($/QALY)
TURP	6,910	12.3082	N/A
TUNA	8,296	12.2869	Dominated

Cost – mean cumulative costs over the follow-up period of 20 years
ICER – Incremental cost-effectiveness ratio. To calculate ICER the following formula is used (Cost Treatment A – Cost Treatment B)/(Benefits Treatment A – Benefits Treatment B).
'Dominated' indicates that this treatment strategy (TUNA) cost more and yielded fewer QALYs.
Costs and QALYs are discounted at 5% annually

The sensitivity analyses conducted above indicate that for both outcomes, ie benefits and costs, the optimal treatment strategy can change from TURP initially to TUNA initially. Table 37 summarises the implications of changes in values (as determined in sensitivity analyses) on the calculation of an incremental cost-effectiveness ratio. The first value used for variables was a value determined to be close to the point where one-way sensitivity analyses indicated that the optimal treatment strategy changed from TURP first to TUNA first. The second value (in italics) is the upper or lower limit of the sensitivity range for the variables. By changing these values one at a time, estimates of cost and benefits altered. Standard treatment is TURP.

Table 38 Effect on ICER by changing variables based on sensitivity analyses and upper/lower sensitivity range

Base case analysis				
	Cost	**QALY**		**ICER**
TURP first (Standard)	$6910	12.3082		n/a
TUNA	$8296	12.2869		dominated
Sensitivity analyses				
Variable	**Strategy**	**Base case value**	**Change in variable**	**Strategy ICER ($/QALY)**
Probability that TURP fails within 6 months	TUNA first	0.10	increase to 0.14	$6,179,304
			Increase to 0.2 (upper sensitivity limit)	*$20,752*
Probability of a 2nd TURP after first TURP fails	TUNA first	0.35	decrease to 0.21	$1,652,500
			Decrease to 0.1 (lower sensitivity limit)	*$69,569*
Annual failure rate of TURP	TUNA first	0.01	increase to 0.015875	$897,815
			Increase to 0.02 (upper sensitivity limit)	*$51,621*
Duration of follow-up	TUNA first	40 cycles (20 years)	Decrease to 5 years of follow-up only (ie 10 cycles)	$20,645
			Decrease to 10 years of follow-up (ie 20 cycles)	TURP dominates TUNA
Utility of side effects state	TUNA first	0.95	decrease to 0.875	$2,529,741
			Decrease to 0.85 (lower sensitivity limit)	*$176,924*
Annual failure rate of TUNA	TUNA first	0.05	decrease to 0.038	$504,874
			decrease to 0.024	$4,965
			Decrease to 0.01 (lower sensitivity limit)	*Dominant*
Probability of side effects from TURP	TUNA first	0.06	increase to 0.15	$1,224,836
			Increase to 0.20 (upper sensitivity limit)	*$71,851*
Probability of having TURP after TUNA fails	TUNA first	0.75	increase to 0.82	$1,070,505
			Increase to 1.0 (upper sensitivity limit)	*$19,727*
Probability that TUNA fails within 6 months	TUNA first	0.20	decrease to 0.13	$805,660
			Decrease to 0.10 (lower sensitivity limit)	*$84,265*
Probability of death from TURP	TUNA first	0.002	All values in sensitivity range	dominated
Utility of failed treatment state	TUNA first	0.90	All values in sensitivity range	dominated
Ratio of probability of side effects from TUNA versus TURP	TUNA first	0.33	All values in sensitivity range	dominated
Probability of side effects from TUNA	TUNA first	0.0198	All values in sensitivity range	dominated
Probability of death from TUNA	TUNA first	0.001	All values in sensitivity range	dominated

Dominated indicates that strategy is more costly and less effective than the standard strategy (initial treatment with TURP)
Dominant indicates that the strategy is less costly and more effective than the standard strategy (initial treatment with TURP)
Values in italics are the upper or lower limits of the sensitivity range.

F4 Discussion

F4.1 Principal findings

The results of the base case analysis suggest that it is not cost-effective to treat patients with benign prostatic hyperplasia initially with TUNA. Under the base case assumptions it was less costly and more effective to treat patients initially with TURP. For this reason it was not necessary to calculate an incremental cost-effectiveness ratio.

Incremental cost-effectiveness ratios can be calculated based on changes in variables identified from sensitivity analyses. The figures provide the basis for the change in variables and Table 38 summarises how altering variables affects the ICER. For example, if the probability that the initial TURP fails within six months is increased from the base case of 10 to 14 per cent, then treatment with TUNA first becomes the most effective strategy. This generates an incremental cost-effectives ratio of approximately $11 million dollars per QALY gained. If, however, the probability of the initial TURP failing within six months is increased to the upper limit of the pre-specified sensitivity range, 20 per cent, the ICER becomes approximately $21,000 per QALY gained. Similar situations have been evaluated for other variables. Table 38, therefore, provides an idea of the likely ICER if we are uncertain about the value a particular variable should hold in the model.

F4.2 Limitations

As discussed previously, this model was designed because of a paucity of long term data regarding the costs and benefits of treating patients with TUNA for benign prostatic hyperplasia. A number of assumptions have therefore been made. Where possible, these assumptions have been based on published literature, however, this was not always possible, and even when possible, quality of the evidence was sometimes less than ideal. This analysis has also not taken into consideration the effect of mortality from other causes over the follow-up period. While we feel that 20 years follow-up is a reasonable time frame, patients could have been followed to time of death, or indeed over a shorter period of time. Patient follow-up of five or 10 years has been tested in sensitivity analyses. As indicated in Table 38, the length of follow-up will affect the ICER generated, primarily because of the uncertainty associated with longer term failure rates of the procedures, and therefore subsequent downstream costs and effects. Limitations of the current analyses therefore include these points.

Utility weights have been estimated, and the analysis assumes that the utility weights for the states of treatment failure and side effects are the same for patients treated with TUNA as for TURP. It has also been assumed that utility weights for each state remain constant over the follow-up period of the model. In order to address these issues, an empirical study of quality of life, using a utility based measure in patients treated by each procedure and then prospectively followed over time, would be required.

Costs have primarily been based on the MSAC application, which included an overall cost estimate for each procedure, done in 1999. These costs may now be out of date, although the relative cost of TUNA to TURP would still be expected to be approximately similar. These average treatment costs included direct costs, and have not taken into account any indirect or non-healthcare based costs. Annual cost of treating patients with side effects and those who have failed treatment have been based on estimates, and although a wide sensitivity range has been used, this is a limitation of using these figures. Again these estimates were really only designed to capture direct costs, and

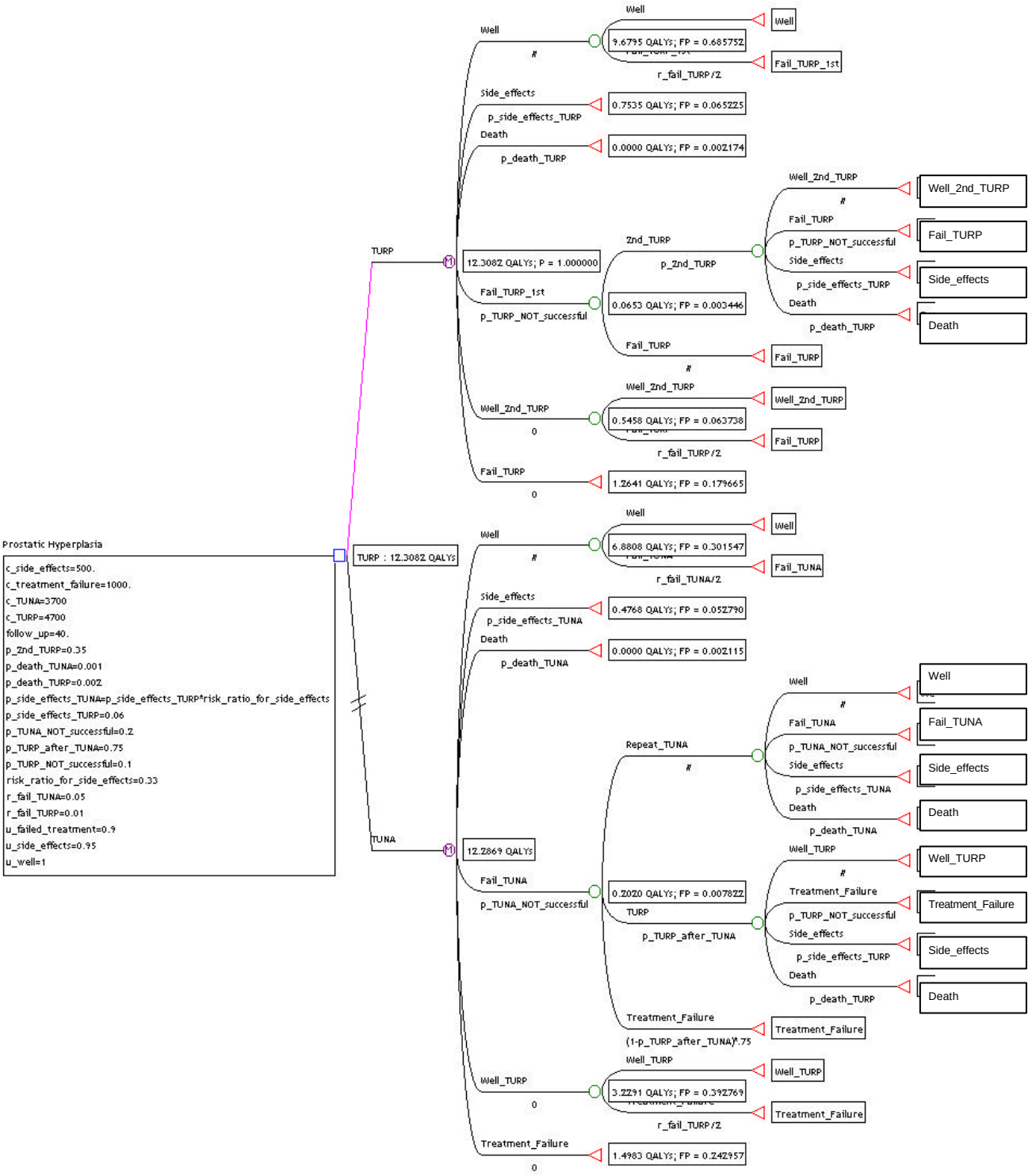
have not taken into account any indirect costs to the patient or society. The analysis has therefore not been done from a societal perspective. As with utility weights, it has also been assumed that these annual costs remain constant over the follow-up period of the model. An empirical costing study of patients treated with each procedure which collected costing information over an extended period of time after initial treatment would need to be done to elucidate this information.

F5 Conclusions

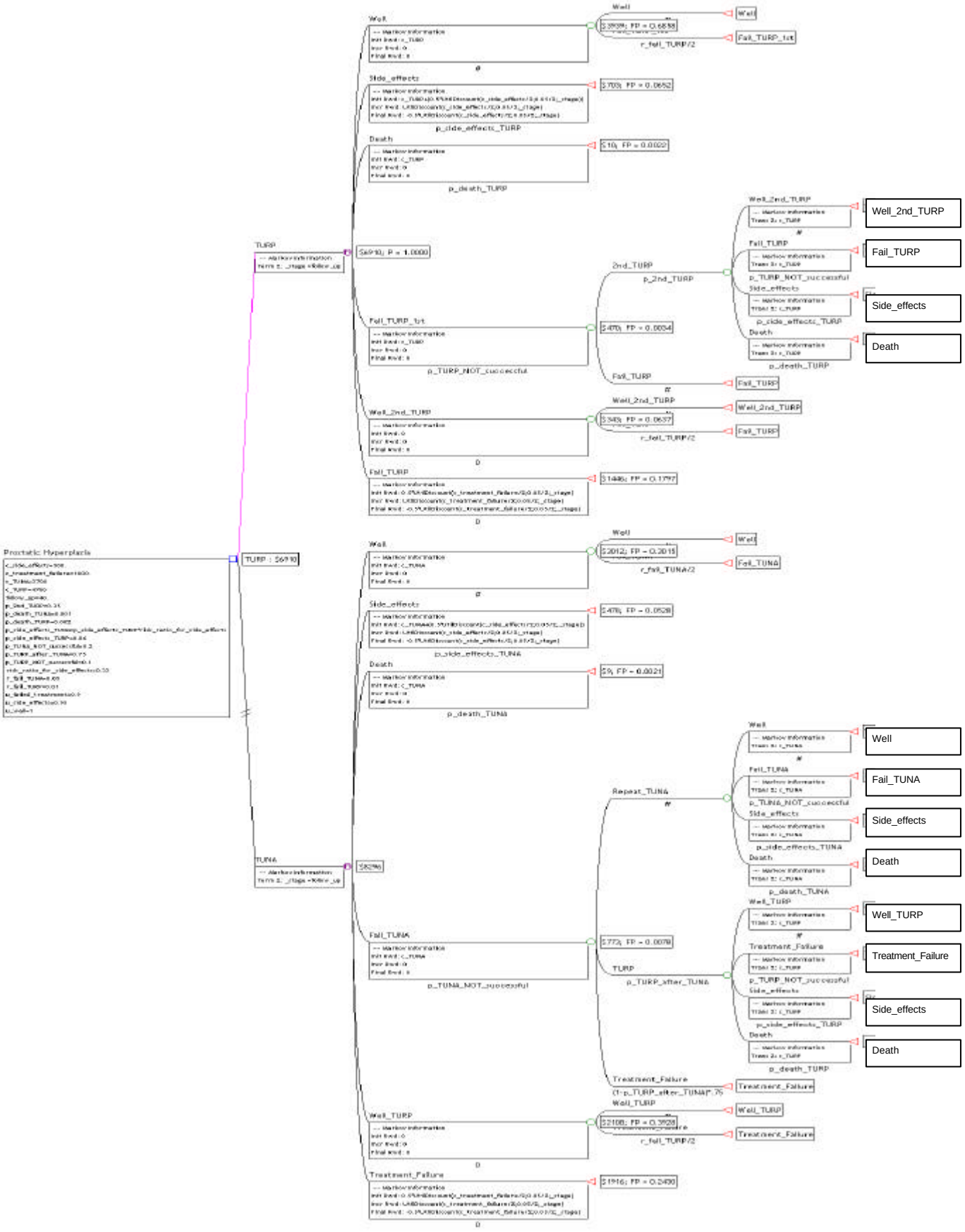
The base case analysis indicates that treating patients with benign prostatic hyperplasia initially with TURP is a more effective and less costly strategy than treating patients initially with TUNA. This conclusion can change, however, depending on our certainty with some variables in the model. Depending upon values of these variables, an incremental cost-effectiveness ratio of between approximately $20,000 per QALY to over $11 million per QALY can be generated when TUNA is used as an initial treatment rather than TURP. The model appears to be quite sensitive to the annual failure rate of the procedures. When the annual failure rate of TUNA decreases from the base case value of 5 per cent per annum to less than 2 per cent per annum, the dominant treatment strategy changes from TURP initially to TUNA initially. The model was also quite sensitive to the annual failure rate of TURP. This dependence on the annual failure rate of procedures means that the model was also sensitive to changes in the length of follow-up of patients. This suggests that it is important to collect good quality long term data on the annual failure rate of the procedures.

Appendix F1 Tree Format

Appendix F2 Effectiveness Analysis Quality Adjusted Life Years (QALYs)



Appendix F3 Cost analysis



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Abbreviations

ARTG	Australian Registered Therapeutic Goods
AUA	American Urological Association
BPH	benign prostatic hyperplasia
DHT	dihydrotestosterone
DVT	deep venous thrombosis
FDA	Food & Drug Administration (USA)
HIFU	High-Intensity Focused Ultrasound
ICER	incremental cost-effectiveness ratio
ILCP	Interstitial Laser Coagulation of the prostate
IPSS	International Prostate Symptoms Score
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
PSA	Prostate Specific Antigen
QALY	quality adjusted life year
QOL	quality of life
RCT	randomised controlled trial
RR	risk ratio
TGA	Therapeutic Goods Administration
TUIP	TransUrethral Incision of the Prostate
TUMT	TransUrethral Microwave Thermotherapy
TUNA	TransUrethral Needle Ablation
TURP	TransUrethral Resection of the Prostate
TVP	TransUrethral Vaporisation of the Prostate
VLAP	Visually Assisted Laser Prostatectomy
WHO	World Health Organization

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