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Title

Comparative cost-effectiveness of robotic prostatectomy and laparoscopic prostatectomy as alternatives to open radical prostatectomy for the treatment of men with localized prostate cancer: A Health Technology Assessment from the Perspective of the United Kingdom National Health Service.

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Glossary: A glossary explaining further the heath-economic terms used in this paper is available at URL: http://www.nlm.nih.gov/nichsr/edu/healthecon/glossary.html

Abstract

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Background: Robot-assisted laparoscopic prostatectomy is increasingly used compared to a standard laparoscopic technique but it remains uncertain whether potential benefits offset higher costs.

Objective: To determine cost-effectiveness of robotic prostatectomy.

Design, Setting, Participants: Care pathway description and model-based cost-utility analysis. We studied men with localised prostate cancer able to undergo either robotic or laparoscopic prostatectomy for cure.

Data Sources: We used data from a meta-analysis, other published literature, and costs from United Kingdom (UK) National Health Service (NHS) and commercial sources.

Outcome Measurements and Statistical Analysis: Care received by men for ten years following radical prostatectomy was modelled. Clinical events, their effect on quality of life, and associated costs were synthesised assuming 200 procedures were performed annually.

Results and Limitations: Over ten years robotic prostatectomy was on average [95% confidence interval] £1412 (€1595) [£1304 (€1473) to £1516 (€1713)] more costly than laparoscopic prostatectomy but more effective with mean (95% confidence interval) gain in quality adjusted life years (QALY) of 0.08 (0.01 to 0.15). The incremental cost-effectiveness ratio (ICER) was £18,329 (€20,708) with an 80% probability that robotic prostatectomy was cost-effective at a threshold of £30,000 (€33,894)/QALY. The ICER was sensitive to the throughput of cases and the relative positive margin rate favouring robotic prostatectomy.

Conclusions: Higher costs of robotic prostatectomy may be offset by modest health gain resulting from lower risk of early harms and positive margin provided more than 150 cases are performed each year. Considerable uncertainty persists in the absence of directly comparative randomised data.

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Introduction

Men in Europe and the United States diagnosed with localised prostate cancer mostly choose radical prostatectomy as their preferred treatment option [1,2]. Standard laparoscopic prostatectomy [3] and robot-assisted laparoscopic prostatectomy [4] are used as alternatives to the open technique as they cause less bleeding and allow quicker return to activity [5]. Robot-assisted surgery is preferred by many surgeons as it has better ergonomics but the technology remains expensive [6]. The high cost has led a number of authorities to question the value of robotic technology to patients and health care systems [7]. Consequently the standard laparoscopic technique continues to be practised in a number of centres [6,8]; for example in the United Kingdom (UK) in 2012, of 5464 radical prostatectomies performed 2467 (45%) were open, 1393 (26%) standard laparoscopic and 1604 (29%) robot-assisted [9], whereas in the United States the proportions were open 44%, laparoscopic 3% and robotic 53% [10]. None of the many simple cost comparisons of different radical prostatectomy techniques have included cost-effectiveness analysis taking into account the value of relative health gains that men may achieve if a particular technique has better outcomes [7]. To determine whether the extra financial cost of robotic prostatectomy can be offset in this way we set out to estimate relative health gain, costs and cost-effectiveness of robotic prostatectomy compared to laparoscopic prostatectomy for men with localised prostate cancer in a discrete event simulation health-economic model. The work was part of a health technology assessment (HTA) commissioned by the United Kingdom (UK) Government and designed to inform decision makers whether robotic or standard laparoscopic prostatectomy was the more worthwhile alternative to open prostatectomy [11].

Materials and Methods

Mapping a Care Pathway

We specified cohorts of men with clinically localised prostate cancer [clinical (c) stage T1 or T2] suited to undergo radical prostatectomy using either a robotic or standard laparoscopic technique. We defined a care-pathway according to current guidance [12,13] and consensus opinion from an expert panel including patients and specialist clinicians, describing possible sequences of clinical and care events known to occur following radical prostatectomy.

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Discrete Event Simulation Model

We chose discrete event simulation to model the clinical events and health care consequences for individual men within cohorts throughout a ten year model period [14]. This was designed using R, a freely available statistical software program [15]. The model included interconnecting health states describing cancer status and persistent harms such as urinary incontinence. The perspective was that of the UK National Health Service (NHS). Change in health status of men in the model was governed by outcomes of surgery, pathological categorisation of removed prostate cancer, epidemiology of disease progression, and effectiveness of further treatment for persistent or recurrent cancer and for urinary incontinence and sexual dysfunction.

Central estimates (mean or median), and sampling distributions (used to reflect statistical imprecision) for variables required to populate the model were from a systematic literature review and meta-analysis, conducted as part of the HTA [11], from other literature, an individual patient dataset, and consensus opinion of the expert panel (Table 1). We used known sampling distributions or assigned triangular distributions where these were missing. Lower and upper limits for triangular distributions were either known minimum and maximum values, or taken to be +/-25% of the central estimate. Following radical prostatectomy men either entered surveillance or received adjuvant treatment. Adjuvant treatment was given to men at high risk of cancer recurrence determined by firstly considering lymph node status (positive *versus* negative), and then a matrix of possible combinations of surgical margin status (positive *versus* negative); pathological (p) tumour stage (pT1/pT2 *versus* pT3/pT4), and Gleason score (<8 *versus* ≥8). Our expert panel defined decisions rules using this matrix between immediate further treatment and surveillance with the probability that men would follow a particular path derived from a patient data set. Surveillance was by repeated prostate specific antigen (PSA) measurement [12] with biochemical recurrence (BCR) defined as two consecutive PSA readings > 0.2 ng/mL. If BCR occurred then the man would progress to further treatment using either external beam radiotherapy for presumed locally recurrent disease; or medical castration therapy for metastatic disease; or a combination of both; or continued surveillance; the probability of each option was derived from the literature. Recovery from prostatectomy could be complicated by bladder neck contracture, urinary incontinence and sexual dysfunction requiring specific management with probabilities of each derived from the systematic review. To estimate quality of life-adjusted years (QALYs) we assigned a the value for the quality of life (a utility value) placed by men on a particular health state between 0 (death)

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and 1 (complete health) from published sources (Table 2). We used the product of utility values applying to each state when men occupied more than one state and assumed that lowered utility values associated with recurrent cancer, incontinence or sexual dysfunction resolved following successful treatment.

Costs were estimated from relevant UK NHS and commercial sources (Table 3) and were calculated in 2009 Sterling (£). Costs for the da Vinci® Surgical System at NHS procurement prices were provided by the manufacturer (Intuitive Surgical, CA. USA). We assumed that the highest specification robotic system would be purchased and that 200 robotic or laparoscopic procedures would be performed each year. We did not include out-patient, primary care, patient or societal costs.

Cost-effectiveness predicted by the model was reported as the difference in cost between the two options over ten years divided by the additional QALYs gained by men who underwent robotic prostatectomy; the incremental cost effectiveness ratio (ICER). Monte Carlo simulation estimated average costs, QALYs and incremental cost per QALY, using two independent cohorts of 5000 men undergoing either robotic or laparoscopic prostatectomy over a 10-year time-horizon with both costs and QALYs discounted by 3.5% [16] (discounting reflects that people have a preference over when costs are incurred and benefits received and that people prefer to delay paying costs until the future but would like benefits now). We calculated the probability of each intervention being cost-effective within the maximum willingness-to-pay threshold of £30,000 (€33,894) suggested by the UK National Institute for Health and Clinical Excellence (NICE) [16]. As cohorts modelled for robotic or laparoscopic prostatectomy were independent imprecision surrounding estimates of costs, QALYs, cost-effectiveness and cancer-specific survival rates were based on 1000 bootstrapped estimates. We also modelled survival at ten years following surgery.

Sensitivity Analyses

Impacts of uncertainty surrounding our estimates of key variables such as positive margin rate were investigated using sensitivity analyses. This was achieved by varying point estimates used in the standard model within the confidence interval estimated in the meta-analysis conducted as part of the HTA. We also considered lower throughput of cases, the use of a lower specification robot, and

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extending the model duration to the patient lifetime to account for long life-expectancy allowing men more time to benefit from any health gain.

Results

Effectiveness and cost-effectiveness

Use of robotic prostatectomy was on average [95% confidence interval (CI)] £1412 (€1595) [£1304 (€1473) to £1516 (€1713)] more costly than laparoscopic prostatectomy and was more effective with mean (95% confidence interval) gain in quality adjusted life years (QALY) of 0.08 (0.01 to 0.15) over ten years for a case load of 200 procedures per year. The ICER was £18,329 (€20,708) with an 80% probability that robotic prostatectomy was cost-effective at the UK NICE threshold of £30,000 (€33,894)/QALY (Table 4a; Figure 1). There was considerable uncertainty in these findings as reflected by width of confidence intervals and results of sensitivity analyses. There was no difference in the relative probability of dying from prostate cancer at ten years for robotic prostatectomy compared to laparoscopic prostatectomy [mean (95% confidence interval) = 0.93 (0.79 to 1.09)].

Sensitivity analyses

Results of the sensitivity analyses are given in Table 4b, Table 5 and Supplementary Figures 2a-f (Appendix 2 online only). Using the upper 95% confidence limit for positive margin rate after robotic prostatectomy from our meta-analysis increased the ICER and robotic prostatectomy was unlikely to be cost-effective. Progressive reduction in throughput of cases also increased the ICER beyond £30,000 (€33,894) and decreased the probability that robotic prostatectomy would be cost-effective to less than 1% with 50 cases per year. Purchase of the most basic robotic system made it more likely that robotic prostatectomy would be cost-effective over ten years. Using a model time-horizon of patient's lifetime reduced the ICER resulting in a very high chance of robotic prostatectomy being cost-effective.

Discussion

We developed a discrete event simulation health economic model with input variables derived from what we considered to be the best available information on the relative benefits, harms, and costs of robotic and laparoscopic prostatectomy. The model predicted that robotic prostatectomy would always

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be more costly than standard laparoscopy but was also more effective and might be considered a cost-effective alternative to open prostatectomy over ten years depending on willingness-to-pay thresholds used by decision makers and funders of health care. However potential cost-effectiveness of robotic prostatectomy was dependent on a sufficient throughput of cases and a favourable positive margin rate.

Because of the complexity of health-related events experienced following radical prostatectomy we considered that a Markov model most commonly used to estimate cost-effectiveness was unsuitable as we needed to model the many pathways that men might follow after surgery. Instead we used discrete event simulation to encompass interconnecting events such as cancer recurrence and urinary incontinence together with their subsequent successful or unsuccessful treatment, allowing men to re-enter health states that they had previously occupied. This was important since the main difference in outcome was in positive margin status which influenced rates of later cancer recurrence [17]. Uncertainty in the parameters used for key variables which might considerably impact on prediction of long-term outcome was a limitation. However our model explicitly included these uncertainties in its calculations in contrast to a Markov approach which would have had to make potentially inappropriate assumptions from imperfect data [14].

We used the meta-analysis conducted as part of our HTA to define pre-specified key variables for the model; particularly rates of early complications and cancer outcome [11]. As with previous reviews the only cancer outcome with sufficient data for meta-analysis was positive margin rate [5] which is an established indicator of surgical quality and is considered by some to be a proxy measure of longer term cancer outcomes such as biochemical recurrence [17]. The difficulty in meta-analysing data from non-randomised studies is illustrated by alternative estimates of positive margin rates for robotic and laparoscopic prostatectomy given by four further meta-analyses contemporary to our own which used either random effects models including only direct comparisons [18,19,20] or a propensity matching approach including both comparative studies and non-comparative cohorts [21]. Our meta-analysis used robust mixed treatment comparison methodology currently recommended by a number of authorities for evidence synthesis when direct comparative data is limited [22]. Sensitivity analysis using the upper confidence limit for positive margin rate least favourable to robotic prostatectomy (0.23) showed that robotic prostatectomy would be unlikely to be cost-effective. This value almost identical to that used for laparoscopic prostatectomy (0.24) and the difference (0.01) was lower than the central estimates from other comparative meta-analyses. We await larger, preferably randomised, high quality comparative studies to give more precise estimates of differential positive margin rate or more direct

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measures of cancer outcome to better populate our model but in the meantime careful judgement concerning which meta-analytical technique is most likely to provide accurate outcome estimates is needed. Despite a rigorous and systematic approach to data collection, the lack of accurate and precise comparative estimates for some cancer related outcomes and longer term post-operative harms with which to populate the model increased the uncertainty of predicted cost-effectiveness and our results should therefore be interpreted cautiously.

The aim of our work was to find out which laparoscopic technique was the most worthwhile alternative to open prostatectomy and therefore open prostatectomy was not a treatment option in the model. Cost comparisons, particularly from the United States where standard laparoscopic prostatectomy is little used, suggested that open prostatectomy was less costly than robotic prostatectomy and had higher rates of harms [10]. - A retrospective cohort study from Denmark compared costs and outcomes between robotic and open prostatectomy and found the robotic technique to be more costly but more effective with an ICER of €64,343 at one year. This was improved with a higher throughput of cases but cost-utility analysis reporting outcomes as QALYs was not performed [23]. A large cohort study from Sweden also indicated that for robotic prostatectomy case volume is linked to lower risks of positive margin and later biochemical recurrence [24]. A further limitation for us was the lack of data concerning differences in surgeon skill which is thought to be an important factor in outcomes such as positive margin and harms [25].

Two HTAs contemporary to our own have been published from the perspectives of the Canadian [19] and Irish [20] health care systems. The Canadian HTA included a systematic review of studies directly comparing outcomes of robotic and laparoscopic prostatectomy. Their meta-analysis, using only direct comparative data, showed no significant differences between the two techniques so they used a cost-minimisation model assuming no possibility of any difference in QALYs. This assumption has been widely criticised as being inappropriate given the availability of mixed treatment comparison models [26]. As part of their work a sensitivity analysis using our assumptions of 200 procedures per year over ten years showed robotic prostatectomy to be CAN$2200 (£1389; €1600) more costly at 2011 prices.

The Irish HTA [20] updated the Canadian systematic review and used the point estimates of differential positive margin rate, recovery of continence and recovery of sexual function, which all favoured robotic prostatectomy although the associated confidence intervals all included no difference. They used a Markov model to compare robotic prostatectomy with standard care defined as mixed provision of laparoscopic and open prostatectomy. Their prediction using 2011 prices was that robotic

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prostatectomy was €2487 (£2159) more costly but resulted in a gain of 0.09 QALYs over ten years. As it is not possible re-calculate the model outputs using only laparoscopic prostatectomy as the comparator this analysis cannot be directly compared to our own. Nevertheless, these three independent HTAs have predicted similar longer term extra costs associated with robotic prostatectomy despite use of different model designs and therefore provide some degree of mutual external validity.

Implications for practice

Health care decision makers have to judge whether benefits of a technology justify reallocation of funding from elsewhere to pay for it. We have shown that robotic prostatectomy will almost always be more costly than a standard laparoscopic technique as an alternative to open prostatectomy across a number of possible scenarios. We have also demonstrated that possible lower immediate complication rate and reduced need for adjuvant treatment arising from lower positive margin rate may be sufficient to justify allocation of resources for its implementation provided a throughput of more than 150 cases per year is maintained. There is considerable uncertainty around our cost-effectiveness estimates and our derivation of costs from the perspective of the UK NHS may need adjustment for other health care systems. Decision-makers will therefore have to look carefully at the evidence we present to decide whether robotic prostatectomy should be adopted and how the service should be configured to ensure maximum health gain at the lowest additional cost.

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Ethic approval was not required.

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Appendix 1

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Table 1a: Effectiveness variable values and associated distributions that were modelled as differing between robotic and laparoscopic prostatectomy*

Parameter (probability unless stated)	**Central value**	**Sampled distribution**	**Central value**	**Sampled distribution**
	Robotic		**Laparoscopic**	
Procedural				
Operative time (minutes)	225	N/A	238	N/A
Conversion to other technique	0.003	0 to 0.006	0.009	0 to 0.018
Hospital stay (days)	3.5	N/A	3.5	N/A
Early harms				
Clavien I	0.021	0.006 to 0.064	0.041	0 to 0.167
Clavien II	0.039	0.016 to 0.064	0.072	0.019 to 0.143
Clavien IIIa	0.005	0 to 0.033	0.013	0 to 0.077
Clavien IIIb	0.009	0.002 to 0.033	0.036	0.01 to 0.16
Clavien IVa	0.006	0.001 to 0.027	0.008	0 to 0.039
Longer term harms				
Positive surgical margin	0.18	0.12 to 0.23	0.24	0.08 to 0.39
Immediate further cancer treatment	0.10	N/A	0.11	N/A
Bladder neck contracture	0.008	0.002 to 0.052	0.021	0.008 to 0.15
Urinary incontinence at 12 months	0.043	0.007 to 0.224	0.079	0 to 0.357

***All values and distributions were defined from the systematic review and meta-analysis that accompanied this study [9]. Document complications from studies included in the review were classified according to the Clavien system independently by two surgeon reviewers with a third acting as arbiter with Clavien I = deviation from standard care not needing intervention, Clavien II = deviation from standard care needing non-surgical intervention, Clavien IIIa = deviation from standard care needing surgical intervention without general anaesthetic, Clavien IIIb = deviation from standard care needing surgical intervention under general anaesthetic, Claivien IV = deviation from standard care with organ failure needing intensive care. Organ injury was classified as Clavien IIIb since reporting of timing of repair was uncertain.

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Table 1b: Effectiveness variable values and associated distributions that were model as being the same for robotic and laparoscopic prostatectomy

Parameter (probabilities unless stated)	Central value	Sampled distribution	Source
Demographic			
Age (years)	61.5	39-74	Ramsay 2012 [9]
Immediate outcomes			
Rate of pelvic lymphadenectomy	0.58	0.44 to 0.73	Sharma 2011 [s1]
Need for treatment of erectile dysfunction	0.57	0.43 to 0.71	Glazener 2011 [s2]
Cancer outcomes			
Rate of lymph-node metastasis	0.026	0.02 to 0.033	Kawakami 2006 [s3]
Biochemical recurrence at up to one year	0.013	0..009 to 0.016	Menon 2010 [s4]
Biochemical recurrence between one and three years	0.011	0.008 to 0.014	Menon 2010 [s4]
Biochemical recurrence between three and five years	0.01	0.007 to 0.012	Menon 2010 [s4]
Biochemical recurrence between five and ten years	0.01	0.007 to 0.012	Menon 2010 [s4]
Use of further treatment options at biochemical recurrence and outcomes			
Radiotherapy	0.2	0.15 to 0.25	Moreira 2010 [s5]
Androgen deprivation therapy	0.21	0.16 to 0.26	Moreira 2010 [s5]
Combined radiotherapy and androgen deprivation therapy	0.1	0.08 to 0.13	Moreira 2010 [s5]
Continued surveillance	0.49	0.37 to 0.61	Moreira 2010 [s5]
Cancer – free survival at ten years	0.76	0.69 to 0.83	Bria 2009 [s6]
Overall survival at ten years	0.86	0.8 to 0.93	UK mortality statistics 2011 [s7]
Use of treatments and outcome for urinary incontinence			
Urinary Sphincter Implantation	0.05	0.04 to 0.07	Expert panel
Cure rate following artificial sphincter implantation	0.9	0.68 to 1	Expert panel
Use of treatments and outcome for erectile dysfunction			
Trial of sildenafil	0.82	0.62 to 1	Schover 2002 [s8]
Success rate of sildenafil therapy	0.69	0.23 to 0.86	Blander 2000 [s9]
Trial of alprostadil	0.15	0.12 to 0.19	Schover 2002 [s8]
Success rate of alprostadil therapy	0.43	0.43 to 0.54	Costabile 1998 [s10]
Penile Prosthesis Implantation	0.002	0.002 to 0.003	Schover 2002 [s8]
Success rate of penile prosthesis implantation	0.92	0.69 to 1	Meuleman 2003 [s11]
Discontinuation of erectile dysfunction treatment	0.16	0.12 to 0.2	Matthew 2005 [s12]

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Table 2: Utility values* associated with health states in the care pathway that men might experience after radical prostatectomy

Health state	Central value	Sampling distribution	Source
Cancer states			
Surveillance after treated localised prostate cancer	0.90	0.75 to 1	Korfage 2005 [s13]
Biochemical recurrence with continued surveillance	0.73	0.55 to 0.91	Volk 2004 [s14]
Localised cancer recurrence treated with radiotherapy	0.82	0.66 to 0.98	Korfage 2005 [s13]
Metastatic cancer recurrence treated by androgen deprivation therapy	0.42	0.31 to 0.53	Cowen 1998 [s15]
Persistent harm states			
Unresolved bladder neck contracture	0.72	0.56 to 0.93	Volk 2004 [s14]
Unresolved sexual dysfunction	0.84	0.77 to 1	Volk 2004 [s14]
Unresolved urinary Incontinence	0.83	0.75 to 1	Volk 2004 [s14]

*Utility values are average values that men put on their being in a particular health state on a linear scale where 0 represents death and 1 represents complete well-being (full health). This gives a relative measure of the desirability or preference of being in each health so for example men value being free of prostate cancer higher than having a localised recurrence. The time spent in each health state is then multiplied by the utility value to give the number of quality-adjusted life years (QALYs) accrued by men over the ten year time span of our model.

Table 3a: Average procedure costs values for robotic and laparoscopic prostatectomy in 2009 Sterling (£). For cohort analysis values for each individual were taken across the sampling distribution assigned to each variable.

Item	Robotic prostatectomy		Laparoscopic prostatectomy	
	Total	***Procedure****	***Total***	***Procedure****
Equipment**				
Robot system	£3,090,000	£2207	N/A	N/A
Equipment	£88,038	£174	£101,549	£94
Consumables	£1086	£1086	£1371	£1371
Sub-total		***£3467 (€3917)***		***£1465 (€1655)***
Hospital care				
Operating room [s16]	£1156 per hour	£4334	£1156 per hour	£4575
Bed stay LB22Z [s17]	£255 per day	£887	£255 per day	£887
Pathology***	£330	£330	£330	£330
Sub-total		***£5551 (€6272)***		***£5792 (€6544)***
Total				
Total		**£9018 (€10.189)**		**£7257 (€8199)**

Cost in Euro (€) is based on average exchange rate for year ending 31st March 2010 at £1 = €1.1298 (http://www.hmrc.gov.uk/exrate/exchangerates-0910.pdf). *****For base case analysis we assumed 200 procedures per year over ten years. ****Equipment life span was either according to years of estimated potential use or to the number of procedures for reusable instruments resulting in higher total equipment costs for laparoscopic

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prostatectomy but a lower cost per case compared to robotic. *****Cost from Business Services, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK.

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Table 3b: Costs variable values for events experienced by men following robotic or laparoscopic prostatectomy in 2009 Sterling (£).

Item	Price	Source
Items associated with harms		
Clavien I (+1 bed-day)*	£255	NHS reference costs 2008-2009 [s17]
Clavien II (+2 bed-days)*	£510	NHS reference costs 2008-2009 [s17]
Clavien IIIa (+3 bed-days)*	£765	NHS reference costs 2008-2009 [s17]
Clavien IIIb (+3 bed-days)*	£765	NHS reference costs 2008-2009 [s17]
Clavien IV (+4 bed-days)*	£1020	NHS reference costs 2008-2009 [s17]
Conversion to open prostatectomy (+3 bed-days)*	£765	NHS reference costs 2008-2009 [s17]
Treatment of bladder neck contracture (LB27Z)	£1269	NHS reference costs 2008-2009 [s17]
Self-management of urinary Incontinence (yearly)	£264	Glazener 2011 [14]
Implantation artificial urinary sphincter (LB50Z)	£3928	NHS reference costs 2008-2009 [s17]
Artificial urinary sphincter device (LB50Z)	£4918	NHS reference costs 2008-2009 [s17]
Sildenafil 100 mg (one weekly)	£6	British National Formulary 2010 [s18]
Alprostadil 20 μg (one weekly)	£12	British National Formulary 2010 [s18]
Implantation penile prosthesis (LB47Z)	£2262	NHS reference costs 2008-2009 [s18]
Penile prosthesis device	£5023	NHS Service cost**
Items associated with further cancer treatment		
PSA testing year 1	£24	NHS Service cost**
PSA testing years 2 to 10 (per year)	£6	NHS Service cost**
Radiotherapy (33 sessions; SC24Z)	£4455	NHS reference costs 2008-2009 [s17]
Goserelin acetate (6 months)	£404	British National Formulary 2010 [s18]
Cyproterone acetate (2 weeks)	£63	British National Formulary 2010 [s18]

Clavien I = deviation from standard care not needing intervention, Clavien II = deviation from standard care needing non-surgical intervention, Clavien IIIa = deviation from standard care needing surgical intervention without general anaesthetic, Clavien IIIb = deviation from standard care needing surgical intervention under general anaesthetic, Claivien IV = deviation from standard care with organ failure needing intensive care. PSA = prostate specific antigen. *****Consensus estimate of duration of additional hospital stay by expert panel. ******Cost from Business Services, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK.

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Table 4a: Model-predicted cost-effectiveness of robotic compared to laparoscopic prostatectomy over ten years assuming 200 procedures per year and costs in 2009 Sterling (£) and from the perspective of the United Kingdom National Health service.

Procedure	Average Cost in £ (€*)	Average QALYs**	Mean (95% confidence interval) difference in cost	Mean (95% confidence interval) difference in QALYs	Incremental cost-effectiveness ratio (ICER)***
Robotic prostatectomy	£9040 (€10,213)	6.52	£1,412 (£1304 to £1516) [€1595 (€1473 to €1713)]	0.08 (0.01 to 0.15)	£18,329 (€20,708)
Laparoscopic prostatectomy	£7628 (€8618)	6.44	N/A	N/A	N/A

*Cost in Euro (€) is based on average exchange rate for year ending 31st March 2010 at £1 = €1.1298 (http://www.hmrc.gov.uk/exrate/exchangerates-0910.pdf). **QALY = quality-adjusted life year; the average time spent in each health state over ten years multiplied by the utility value for the respective health state summated over ten years for the cohort of men undergoing each procedure. For illustration, If all men had experienced complete perfect health over the ten years (utility value = 1) then the average QALYs would = 10. *** Incremental cost-effectiveness ratio (ICER): A ration calculated by dividing the difference in costs over 10 years between the two procedures by the difference in effectiveness. In our model effectiveness was measured by the average number of QALYs accrued by men undergoing each procedure which is termed a cost-utility analysis. Here ICER = Δcost ÷ ΔQALYs. Both costs and QALYs were discounted at a rate of 3.5% per year to allow for the preference of individuals and society to experience health benefits immediately but defer the extra cost of those benefits into the future (analogous to the interest rate charged for a financial loan).

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Table 4b: Model-predicted cost-effectiveness of robotic compared to laparoscopic prostatectomy using alternative plausible values for key variables as sensitivity analyses for base-case result

Alternative value	Procedure	Cost	QALY	Mean (95% CI) Difference in cost	Mean (95% CI) difference in QALYs	Incremental cost-effectiveness ratio
Reduced throughput of cases per year						
Value = 150	Robotic	£9,799	6.52	£2170 (£2064 to £2282)	0.08 (0.01 to 0.15)	£28,172
Value = 150	Laparoscopic	£7,628	6.44			
Value = 100	Robotic	£11,312	6.52	£3684 (£3579 to £3759)	0.08 (0.01 to-0.15)	£47,822
Value = 100	Laparoscopic	£7,628	6.44			
Value = 50	Robotic	£15,859	6.52	£8231 (£8126 to £8337)	0.08 (0.01 - 0.15)	£106,839
Value = 50	Laparoscopic	£7,628	6.44			
Use of lowest priced robotic system						
Value = £1,870,000	Robotic	£8,168	6.52	£540 (£435 to £642)	0.08 (0.01 to 0.15)	£7,009
N/A	Laparoscopic	£7,628	6.44			
Use of least favourable positive margin rate for robotic prostatectomy [13]						
Value = 0.23	Robotic	£9,099	6.47	£1,471 (£1,369 to £1,585)	0.03 (0 to 0.1)	£50,503
Value = 0.24	Laparoscopic	£7,628	6.44			
Use of patient life-time for model duration						
Value = 40 years	Robotic	£9,179	12.12	£1,104 (£986 - £1,220)	0.77 (0.57 to 0.99)	£1,436
Value = 40 years	Laparoscopic	£8,075	11.36			

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Table 5: Data table for the sensitivity analysis comparative cost-effectiveness acceptability curves in Figures 3a-f

		Probability of cost-effectiveness at willingness to pay thresholds*				
		£0 (€0)	***£10,000 (€11,298)***	***£20,000 (€22,596***	***£30,000 (€33,894)***	***£50,000 (€56,490***
Reduced throughput of cases per year						
Value = 150	Robotic prostatectomy	0.00	0.00	0.20	0.53	0.82
Value = 150	Laparoscopic prostatectomy	1.00	1.00	0.80	0.47	0.18
Value = 100	Robotic prostatectomy	0.00	0.00	0.00	0.11	0.52
Value = 100	Laparoscopic prostatectomy	1.00	1.00	1.00	0.89	0.49
Value = 50	Robotic prostatectomy	0.00	0.00	0.00	0.00	0.00
Value = 50	Laparoscopic prostatectomy	1.00	1.00	1.00	1.00	1.00
Use of lowest priced robotic system						
Value = £1,870,000	Robotic prostatectomy	0.00	0.72	0.93	0.96	0.97
N/A	Laparoscopic prostatectomy	1.00	0.28	0.07	0.04	0.03
Use of least favourable positive margin rate for robotic prostatectomy [13]						
Value = 0.23	Robotic prostatectomy	0.00	0.00	0.13	0.30	0.49
Value = 0.24	Laparoscopic prostatectomy	1.00	1.00	0.87	0.70	0.51
Use of patient life-time for model duration						
Value = 40 years	Robotic prostatectomy	0.00	1.00	1.00	1.00	1.00
Value = 40 years	Laparoscopic prostatectomy	1.00	0.00	0.00	0.00	0.00

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*Willingness-to-pay threshold represents the maximum amount on money a person or organisation is willing to pay for a particular health benefit. In our cost-utility analysis we used quality adjusted life year (QALY) as our measure of benefit and have given willingness-to-pay thresholds from the perspective of the United Kingdom (UK) National Health Service (NHS). Typically the UK NHS through its National Institute for Health and Clinical Excellence (NICE) specify that new treatments are only suitable for introduction if the incremental cost per gain in QALY over standard therapy is less than £30,000 [16]. Other health care systems have different payers; the patient or a commercial health insurer for example who may set differing thresholds of willingness-to-pay depending on their perspective and resources. Values in Euro (€) are based on average exchange rate for year ending 31st March 2010 at £1 = €1.1298 (http://www.hmrc.gov.uk/exrate/exchangerates-0910.pdf).

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Figure Legends and footnotes

Figure 1: Main analysis comparative cost-effectiveness acceptability curve for robotic prostatectomy against laparoscopic prostatectomy according to increasing thresholds for funders' willingness to pay. Model predictions are over ten years assuming 200 procedures per year, and costs in 2009 Sterling (£) from the perspective of the United Kingdom National Health Service. Source data are detailed in accompanying table.

Appendix 2

Supplementary Figures only available online

Supplementary Figure 3a: Sensitivity analyses comparative cost-effectiveness acceptability curves for robotic prostatectomy against laparoscopic prostatectomy according to increasing thresholds for funders' willingness to pay. Model predictions are according to definition of throughput of 50 cases per year over ten years. Source data are detailed in Table 5.

Supplementary Figure 3b: Sensitivity analysis comparative cost-effectiveness acceptability curves for robotic prostatectomy against laparoscopic prostatectomy according to increasing thresholds for funders' willingness to pay. Model predictions are according to definition of throughput of 100 cases per year over ten years. Source data are detailed in Table 5.

Supplementary Figure 3c: Sensitivity analysis comparative cost-effectiveness acceptability curves for robotic prostatectomy against laparoscopic prostatectomy according to increasing thresholds for funders' willingness to pay. Model predictions are according to definition of throughput as 150 cases per year over ten years. Source data are detailed in Table 5.

Supplementary Figure 3d: Sensitivity analysis comparative cost-effectiveness acceptability curves for robotic prostatectomy against laparoscopic prostatectomy according to increasing thresholds for funders' willingness to pay. Model predictions are according to use of the lowest priced variant of the robotic system. Source data are detailed in Table 5.

Supplementary Figure 3e: Sensitivity analysis comparative cost-effectiveness acceptability curves for robotic prostatectomy against laparoscopic prostatectomy according to increasing thresholds for funders' willingness to pay. Model predictions are according to definition of the positive margin rate for robotic prostatectomy as 0.23; the upper bound of the 95% confidence interval from the meta-analysis [9]. Source data are detailed in Table 5.

Supplementary Figure 3f: Sensitivity analysis comparative cost-effectiveness acceptability curves for robotic prostatectomy against laparoscopic prostatectomy according to increasing thresholds for funders' willingness to pay. Model predictions are according to definition of model time-horizon as patient lifetime. Source data are detailed in Table 5.