

Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer

C Ramsay,^{1*} R Pickard,² C Robertson,¹ A Close,³ L Vale,^{1,4}
N Armstrong,⁵ DA Barocas,⁶ CG Eden,⁷ C Fraser,¹
T Gurung,¹ D Jenkinson,¹ X Jia,¹ TB Lam,⁹ G Mowatt,¹
DE Neal,¹⁰ MC Robinson,¹¹ J Royle,⁸ SP Rushton,³
P Sharma,¹ MDF Shirley³ and N Soomro¹²

¹Health Services Research Unit, University of Aberdeen, Aberdeen, UK

²Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

³School of Biology, Newcastle University, Newcastle upon Tyne, UK

⁴Health Economics Group, Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK

⁵Kleijnen Systematic Reviews Ltd, York, UK

⁶Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA

⁷Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK

⁸Department of Urology, Aberdeen Royal Infirmary, Grampian NHS Trust, Aberdeen, UK

⁹Academic Urology Unit, University of Aberdeen, Aberdeen, UK

¹⁰Department of Oncology, University of Cambridge, Cambridge, UK

¹¹Department of Cellular Pathology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

¹²Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

*Corresponding author

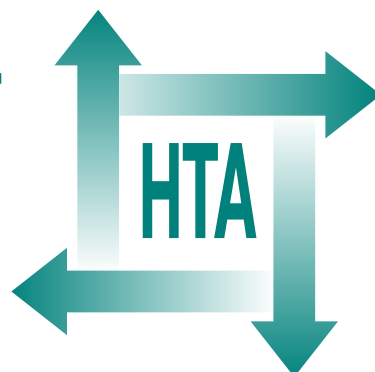


Executive summary

Health Technology Assessment 2012; Vol. 16: No. 41

DOI: 10.3310/hta16410

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk



Executive summary

Background

Men diagnosed with cancer of the prostate, a sex gland located at the base of the bladder in the pelvis, have different treatment options depending on the severity of disease. One option is complete removal of the prostate, radical prostatectomy, which approximately 5000 men in the UK undergo each year. A keyhole surgical technique of radical prostatectomy either by standard laparoscopy or with the aid of robotic technology does appear to offer advantages in terms of reduced blood loss and quicker return to activity over the traditional open surgical approach. Advocates of the robotic system claim greater precision in dissection and more rapid gaining of surgeon competence than with the laparoscopic approach but the robotic system is costly. This review was designed to help inform decisions regarding the commissioning and use of robotic and laparoscopic surgery for men with localised prostate cancer in the NHS. The study aimed to:

- describe clinical care pathways in a UK NHS context
- determine the relative clinical effectiveness and safety of each procedure
- perform a systematic review of existing economic evaluations of each procedure
- determine which procedure is most likely to be cost-effective for implementation in the NHS
- determine the influence of the learning curve on estimates of effectiveness, safety and cost-effectiveness
- identify future research needs.

Methods

Clinical effectiveness review

MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS, Science Citation Index and Cochrane Central Register of Controlled Trials were searched from 1995 onwards for primary studies. Conference abstracts from meetings of the European, American and British Urological Associations were also searched, websites consulted and reference lists scanned. Evidence was considered from randomised controlled trials (RCTs) and non-randomised comparative studies and, for estimates of learning curve effects only, case series. Participants were men with clinically localised prostate cancer (preoperative clinical classification of tumour stage: cT1 or cT2) undergoing radical prostatectomy. Robotic radical prostatectomy was considered as the intervention and laparoscopic radical prostatectomy as the comparator. Outcome measures were adverse events, cancer-related outcomes, functional outcomes, patient-driven outcomes and descriptors of care. Two reviewers abstracted data and assessed the risk of bias of the included studies. For meta-analyses, a Bayesian indirect mixed-treatment comparison was used.

Cost-effectiveness

A systematic review of economic evaluations comparing the two forms of surgery was attempted. It was anticipated that this would be insufficient for decision-making and consequently a modelling exercise was planned. A discrete-event simulation model was produced reflecting the likely care pathways. Parameter estimates were derived from the systematic review of clinical effectiveness, a review of previous economic evaluations, other literature, the expert advisory group and other UK sources. The outputs of the model were costs and quality-adjusted life-years (QALYs) for each procedure, incremental costs and QALYs, and incremental cost per QALY for a 10-year time horizon. Both costs and QALYs were discounted at the rate recommended

by the UK Treasury of 3.5%. Probabilistic sensitivity analysis was performed to explore the uncertainty surrounding parameter estimates. This was combined with deterministic sensitivity analysis around variables believed to be key determinants of cost-effectiveness, including cost of the robotic system, number of procedures performed, positive margin rates and risk of biochemical recurrence.

Results

Clinical effectiveness

The searches identified 2722 potentially relevant titles and abstracts, from which 914 reports were selected for full-text eligibility screening. From these, data were included from 19,064 patients across one RCT and 57 non-randomised comparative reports. Few of these were considered to have a low risk of bias. The results, although associated with some uncertainty, demonstrated that robotic surgery was associated with a lower risk of major adverse events such as organ injury, and lower rates of surgical margins positive for cancer [odds ratio (OR) 0.69; 95% credible interval 0.51 to 0.96; probability outcome favours robotic prostatectomy = 0.987]. The predicted probability of a positive margin was 17.6% following robotic prostatectomy compared with 23.6% for laparoscopic prostatectomy. Restriction of the meta-analysis to studies at low risk of bias did not change the direction of effect, but did decrease the precision of the effect size (odds ratio 0.73; 95% credible interval 0.29 to 1.75). The available data suggested no evidence of a difference in the proportion of men suffering urinary incontinence at 12 months (OR 0.55; 95% credible interval 0.09 to 2.84; probability outcome favours robotic prostatectomy = 0.783). There were insufficient data to draw any conclusions on the likely size of a differential effect on rates of cancer-related, patient-driven or erectile dysfunction outcomes. The data provided no evidence that learning contributed differently to positive margin rates between the two procedures ($p = 0.755$).

Cost-effectiveness

In the base-case analysis (10-year time horizon) the incremental cost per QALY for robotic prostatectomy was <£30,000 provided that the number of procedures performed per year with each robotic system was > 150 [when the number of procedures per year was 100, the incremental cost-effectiveness ratio (ICER) was £47,822]. The probabilistic sensitivity analysis showed that the two procedures had a roughly equal likelihood of being considered cost-effective when the number of procedures per year was 150. When a lifetime time horizon was adopted the costs and QALYs for both procedures increased but the increase in QALYs more than compensated for the increase in cost of the robotic system and hence the incremental cost per QALY was <£30,000 for all of the scenarios considered. This includes a scenario in which the number of procedures performed per year was 50 and for which the most costly robotic equipment was used.

The results of the economic evaluation suggested that when the difference in positive margin rate estimated by meta-analysis of all included studies was used (base case), robotic radical prostatectomy was on average associated with an incremental cost per QALY that was less than the threshold value typically adopted by the NHS (£30,000) when the number of cases performed per year was ≥ 150 . Only when optimistic assumptions were made for the positive margin rate (OR = 0.506) did the incremental cost per QALY for robotic prostatectomy fall below £30,000 for a throughput of 100 cases per year (when only 50 cases per year are performed the incremental cost per QALY was >£66,000).

In the base-case analysis, biochemical recurrence rates were assumed to be the same between treatments. A sensitivity analysis using the point estimate for the OR of differential rates between the treatments (0.89) resulted in a slight reduction in the incremental cost per QALY for all surgical capacity scenarios. In contrast to using the point estimate, doubling the chance

of biochemical recurrence in line with the absolute rates documented in the meta-analysis further reduced the incremental cost per QALY such that it was <£30,000 when the number of procedures performed using the robotic system was ≥ 100 cases per year.

Strengths and limitations

The main limitations were the low quantity and poor quality of the data available on cancer-related outcomes and long-term adverse events of urinary and sexual dysfunction. Many published studies were poorly reported or lacked sufficient detail and much of the information available was unsuitable for meta-analysis. The paucity of data had implications for the economic evaluation. In particular, the limited data meant that there was insufficient evidence to assume that there was any difference between interventions for a number of parameters, a particular issue for biochemical recurrence. The impact of these assumptions was explored in sensitivity analyses.

Conclusions

The results of this study should be interpreted with caution because of uncertainty but they do demonstrate that robotic prostatectomy has advantages in terms of reducing both perioperative morbidity and the risk of a positive surgical margin. Although direct cancer outcome data were lacking, use of the differential margin rate in our model suggests that use of robotic prostatectomy may be associated with improved overall survival. There were no data to infer whether use of robotic surgery resulted in a lower risk of incontinence or sexual dysfunction, although this was modelled.

Robotic prostatectomy will always be more costly to the NHS because of the fixed capital and maintenance charges for the robotic system. Our modelling shows that this excess cost per case might be reduced by commercial negotiation and by maintaining a high throughput of cases in each centre of at least 100–150 procedures per year. The cost-effectiveness of robotic prostatectomy was predominantly driven by the difference in positive margin rate. Uncertainties remain concerning the potential for bias in the estimates and how positive margin rates impact on long-term outcomes; therefore, a degree of caution is warranted in the interpretation of the results.

Recommendations for further research

- Well-designed prospective cohort studies directly comparing robotic and laparoscopic prostatectomy are required. Ideally such studies would be multicentre with long-term follow-up and would include independent assessment of prespecified measures of prostate cancer-specific survival, as well as independent recording of learning curve, urinary and sexual function and health-related quality of life.
- Further evidence on the relationship between positive margin rates and long-term outcomes.
- Research to elicit the short- and long-term postoperative health-state valuations (e.g. utility values) associated with prostatectomy and the contribution of different adverse consequences of surgery as perceived by men.
- Agreed definitions of outcomes in urology and measures for recording them. This would require consensus work in partnership with governing bodies.
- Research into strategies to improve the evaluation and potential dissemination of costly new technologies in the UK NHS.

Funding

- Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Publication

Ramsay C, Pickard R, Robertson C, Close A, Vale L, Armstrong N, *et al*. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. *Health Technol Assess* 2012;**16**(41).

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needed in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 09/14/02. The contractual start date was in March 2011. The draft report began editorial review in July 2011 and was accepted for publication in February 2012. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley CBE
Series Editors: Dr Martin Ashton-Key, Professor Aileen Clarke, Dr Peter Davidson, Dr Tom Marshall, Professor William McGuire, Professor John Powell, Professor James Raftery, Dr Rob Riemsma, Professor Helen Snooks and Professor Ken Stein
edit@southampton.ac.uk

Editorial Contact:

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

© Queen's Printer and Controller of HMSO 2012. This work was produced by Ramsay *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to NETSCC.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (<http://www.publicationethics.org/>).

This journal may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Charlesworth Press.