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Relative effectiveness of robot-assisted and standard laparoscopic prostatectomy as alternatives to open radical prostatectomy for treatment of localised prostate cancer: a systematic review and mixed treatment comparison meta-analysis

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Objective

- To compare the effectiveness of robot-assisted and standard laparoscopic prostatectomy.

Methods

- A care pathway was described.
- We performed a systematic literature review based on a search of Medline, Medline in Process, Embase, Biosis, Science Citation Index, Cochrane Controlled Trials Register, Current Controlled Trials, Clinical Trials, WHO International Clinical Trials Registry and NIH Reporter, the Health Technology Assessment databases, the Database of Abstracts of Reviews of Effects, and relevant conference abstracts up to 31st October 2010). Additionally, reference lists were scanned, an expert panel consulted, and websites of manufacturers, professional organisations, and regulatory bodies were checked.
- We selected randomised controlled trials (RCTs) and non-randomised comparative studies, published after 1st January 1995, including men with localised prostate cancer undergoing robot-assisted or laparoscopic prostatectomy compared with the other procedure or with open prostatectomy. Studies where at least 90% of included men had clinical tumour stages T1 to T2 and which reported at least one of our specified outcomes were eligible for inclusion.
- A mixed-treatment comparison meta-analysis was performed to generate comparative statistics on specified outcomes.

Results

- We included data from 19 064 men across one RCT and 57 non-randomised comparative reports.
- Robotic prostatectomy had a lower risk of major intra-operative harms such as organ injury [0.4% robotic vs 2.9% laparoscopic], odds ratio ([OR] {95% credible interval [CrI]} 0.16 [0.03 to 0.76]), and a lower rate of surgical margins positive for cancer [17.6% robotic vs 23.6% laparoscopic], OR [95% CrI] 0.69 [0.51 to 0.96]). There was no evidence of a difference in the proportion of men with urinary incontinence at 12 months (OR [95% CrI] 0.55 [0.09 to 2.84]). There were insufficient data on sexual dysfunction.
- Surgeon learning rates for the procedures did not differ, although data were limited.

Conclusions

- Men undergoing robotic prostatectomy appear to have reduced surgical morbidity, and a lower risk of a positive surgical margin, which may reduce rates of cancer recurrence and the need for further treatment, but considerable uncertainty surrounds these results.
- We found no evidence that men undergoing robotic prostatectomy are disadvantaged in terms of early outcomes.
- We were unable to determine longer-term relative effectiveness.

Keywords

prostate cancer, robotic surgery, laparoscopic surgery, systematic review, meta-analysis

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Introduction

Radical prostatectomy performed using open or minimally invasive techniques is the preferred treatment option for men diagnosed with localised prostate cancer with ~88 000 procedures carried out in the USA in 2008 [1] and 5500 in the UK in 2012 [2]. Surgical innovation to reduce blood loss and hasten recovery led to the introduction of firstly standard laparoscopic prostatectomy [3] and then remote laparoscopic surgery using a master-slave manipulator, known as robot-assisted or robotic prostatectomy [4], as alternatives to open surgery. In the USA there has been a predominantly direct transition from open to robotic prostatectomy, with 44% of procedures performed using the open technique and 53% using the robotic technique in 2008 [5]. By contrast, the European experience has been a transition from open to the standard laparoscopic technique followed, mainly in richer nations, by a second transition to the robot-assisted procedure; for example in the UK in 2012, 45% of procedures used the open, 26% the standard laparoscopic and 29% the robot-assisted techniques [2].

Expert appraisal of the robotic technique suggests quicker surgeon learning and better ergonomics, although high cost of the robotic system remains a concern [6,7]. When we started this work there were no high-quality direct comparative data from individual studies or meta-analyses available to decide between robot-assisted or standard laparoscopic prostatectomy as the better alternative to open surgery [8]. These data are needed as the robotic system may only be affordable if its use benefits individual patients and society in terms of better cancer control and quicker return to health. We aimed to address this by estimating differences in clinical outcomes between robotic and laparoscopic prostatectomy for men with localised prostate cancer using a mixed-treatment comparison meta-analysis. The work formed part of a Health Technology Assessment (HTA) commissioned by the UK Government which has been published as a monograph [9].

Methods

Mapping a Care Pathway

A care pathway was defined for men undergoing robotic or laparoscopic prostatectomy as curative treatment for localised prostate cancer using published guidance [10,11] and validated by consensus amongst an expert panel including patients and clinicians (Fig. 1).

Systematic Literature Review

Eligibility criteria

We specified robotic prostatectomy as the intervention and laparoscopic prostatectomy as the comparator. We looked for reports of randomised control trials (RCTs) and non-randomised studies comparing outcomes specified in the

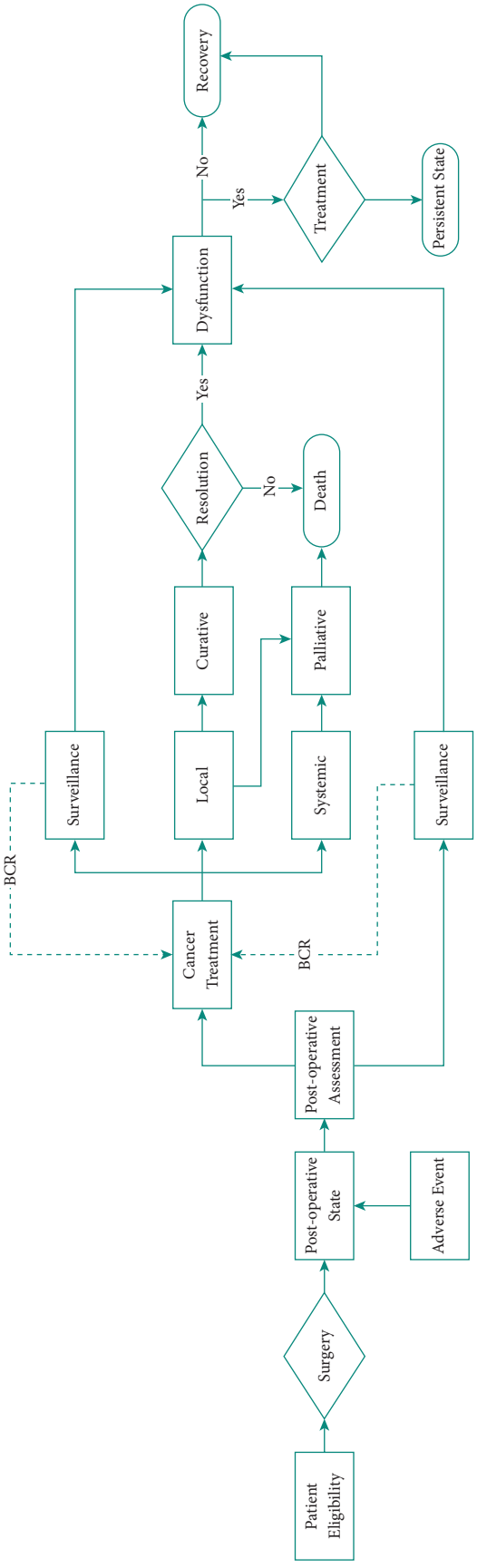


Fig. 1 Care pathway.

care pathway. As well as studies directly comparing robotic and laparoscopic prostatectomy, we included comparisons of either of the two procedures with open prostatectomy. Our population was men with localised prostate cancer [clinical stage (c) T1 or T2] undergoing radical prostatectomy for cancer cure who were suited to either the robotic or laparoscopic approach. We excluded studies where >10% of included men had locally advanced (cT3–cT4) disease. We also identified case series involving at least 200 men undergoing robotic or laparoscopic prostatectomy but only for analysis of learning-curve effects. There was no language restriction but we limited our search to between 1st January 1995 and 31st October 2010. We specified the following outcome measures for review:

- *Cancer-related:* rate of surgical margin positive for cancer; biochemical (PSA) recurrence; need for further cancer treatment; and disease-free survival.
- *Harms during or shortly after surgery:* blood transfusion; organ injury; anastomotic leak; wound infection; ileus; venous thrombo-embolic events; bladder neck contracture; and death.
- *Functional:* urinary continence and recovery of sexual function.
- *Patient-driven:* pain after surgery; time to return to full activity; and health-related quality of life.
- *Descriptors of care:* equipment failure; conversion to open procedure; operating time; duration of catheterisation; hospital stay; and learning curve.

Information sources

Medline, Medline in Process, Embase, Biosis, the Science Citation Index and the Cochrane Controlled Trials Register (CENTRAL) were searched for primary studies, while the Database of Abstracts of Reviews of Effects (DARE) and the HTA databases were searched for reports of evidence syntheses. Reference lists were scanned, an expert panel consulted, and websites of manufacturers, professional organisations, and regulatory bodies were checked to identify additional reports. Abstracts from the European Association of Urology, AUA and BAUS meetings were searched. Search strategies are detailed in Table S1.

Study selection and data extraction

Titles and abstracts were screened and the full texts of potentially relevant reports were assessed for inclusion against pre-stated criteria by two reviewers, with a third acting as an arbiter. Data were extracted by three reviewers using a specifically designed form [9]. The reviewers checked each other's work for errors or inconsistencies. Diverse early harms of surgery were categorised using the Clavien–Dindo system by two surgeon reviewers independently, with a third acting as an arbiter [12]. Organ injury was categorised as Clavien IIIb as reporting of timing of repair was unclear. The method of pathological examination of the removed prostate in the included studies was assessed against the international consensus standard by a pathologist reviewer [13]. The quality of included full text English-language studies was assessed by three pairs of reviewers independently using the Cochrane risk of bias tool [14] modified for use with non-randomised studies and with inclusion of specific confounders. Risk of bias for each study was classified using judgements incorporating risk of bias domains and individual outcomes into high risk of bias, low risk of bias or unclear risk of bias categories with any disagreement between reviewers resolved by consensus.

Data synthesis and analysis

Extracted data were tabulated and summarised. Meta-analysis was by a mixed-treatment comparison statistical model incorporating direct comparative studies, and indirect comparisons against the index procedure of open prostatectomy. This made maximum use of the available predominantly non-randomised comparative data in line with recommended practice [15]. Summary statistics for dichotomous variables describing the outcomes of robotic or laparoscopic prostatectomy compared with open prostatectomy were calculated using the logarithm of the odds ratios (ORs). Model parameters were estimated within Bayesian methodology with WinBUGS software, version 1.4.3 [16,17]. A random effects model was used for studies that compared all three techniques of prostatectomy to adjust for any correlations between study arms. Variables expressed as continuous data from direct comparative studies of robotic and laparoscopic prostatectomy were analysed using mean and SD values with medians substituted for means if necessary, and missing SD values separately imputed for each type of surgery [18]. ORs and their 95% credible intervals (CrIs) were estimated between robotic and laparoscopic prostatectomy for each outcome. An OR >1 shows that the event is more likely to occur after robotic prostatectomy whilst an OR <1 means that the event is more likely to occur after laparoscopic prostatectomy. The probability of each OR being different from 1 was calculated, values of $P \geq 0.95$ being considered to indicate statistical significance. Finally, an individual estimate of the probability of the event occurring for each surgical technique was calculated using a prior distribution for the probability of occurrence with open radical prostatectomy and combining that with the OR between robotic and laparoscopic prostatectomy. The prior distribution was estimated by applying a normal distribution to the log odds of the probability of each outcome and using the standard Bayesian random effects model to calculate its mean and variance. As a sensitivity analysis the statistical models were run using data only from studies categorised as having a low risk of bias. In addition, for surgical margins, we intended to explore heterogeneity of effects by analysing only data from studies that reported all key pathological data. Vague prior distributions were used on the logarithm of the ORs of robotic

and laparoscopic techniques vs open surgery, the individual study event rates, and the random effects SD. To assess publication bias, a funnel plot was constructed for included direct comparisons reporting the positive margin outcome. For most outcomes a burn-in period of 20 000 iterations was adequate to achieve convergence, although a further 100 000 samples were taken for each outcome.

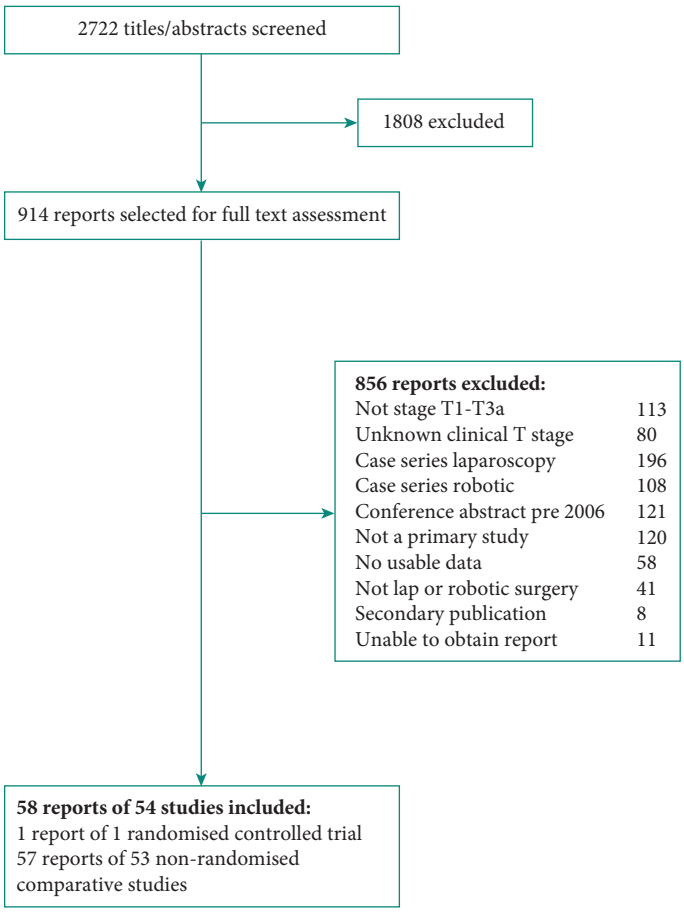
The effect of surgeon learning on outcome was assessed by categorizing previous experience of participating surgeons and plotting this against the positive margin rate. In addition, data on starting level of expertise, rate of learning and defined expert level were extracted and meta-analysed using a random effects model to estimate pooled effect and associated uncertainty expressed as 95% CI.

Results

Details of Included Studies

We identified one RCT comparing laparoscopic with open prostatectomy and 57 reports from 53 non-randomised comparative studies (eight robotic vs laparoscopic, three robotic vs laparoscopic vs open, 16 robotic vs open and 26 laparoscopic vs open) that fulfilled our inclusion criteria (Fig. 2; Supporting Information References S1–S69; Table S2). Of the 80 reports excluded because categorisation of patients by clinical tumour stage was unclear, 69 (86%) had details enabling contact and 19 replied. This information added one additional report comparing laparoscopic with open prostatectomy for inclusion but was received too late for our planned meta-analysis [19]. The characteristics of included reports are summarised in Table 1 [S1, S2, S13–68]. A list of excluded studies with reasons for exclusion is available from the authors. Data from 19 064 men were used in the meta-analysis; 6768 underwent robotic radical prostatectomy, 4952 underwent laparoscopic radical prostatectomy, and 7344 underwent open radical prostatectomy. Personal and disease characteristics of included men were well matched between robotic and laparoscopic groups (Table 2). The yearly number of published laparoscopic vs open comparisons peaked in 2007 whilst those for robotic vs open surgery peaked in 2010 (Fig. 3), in line with the sequence of introduction of the technologies.

Fig. 2 Flow chart for the systematic literature review.



Quality Assessment

Overall assessment of risk of bias

The risk of bias was assessed for 48 studies and summary results for each outcome across the assessed domains are shown in Fig. 4, with study level assessment in Fig. S4. A total of 24 reports (50%) were categorised as having a high overall risk of bias, 13 (27%) as having a low risk and for 11 (23%) the risk of bias was rated unclear. The single identified RCT was judged to be at low risk of bias for sequence generation [S1] and one further study was judged to be at low risk of bias for allocation concealment [S2]; all other studies were at high risk of bias or unclear for these two key domains. Funnel plot analysis including the six studies directly comparing robotic with laparoscopic prostatectomy and reporting positive margin outcome did not suggest publication bias (Fig. 5).

Outcome level assessment for risk of bias

Of the 37 studies reporting positive margin rates or cancer recurrence, 30 (81%) were considered to be at low risk of bias for confounding. Of the studies reporting urinary and sexual function outcomes, 12/23 (52%) and 10/20 (50%), respectively, were at low risk of bias for blinding and 9/23 (39.1%) and 9/20 (45%), respectively, were at low risk for incomplete outcome data.

Meta-analysis

The results of the meta-analysis are summarised in Table 3 and Fig. 6. The positive surgical margin rate was significantly lower for robotic (18%) than for laparoscopic prostatectomy (24%) with an OR (95% CrI) of 0.69 (0.51 to 0.96), $P = 0.99$.

Table 1 Summary characteristics of included reports.

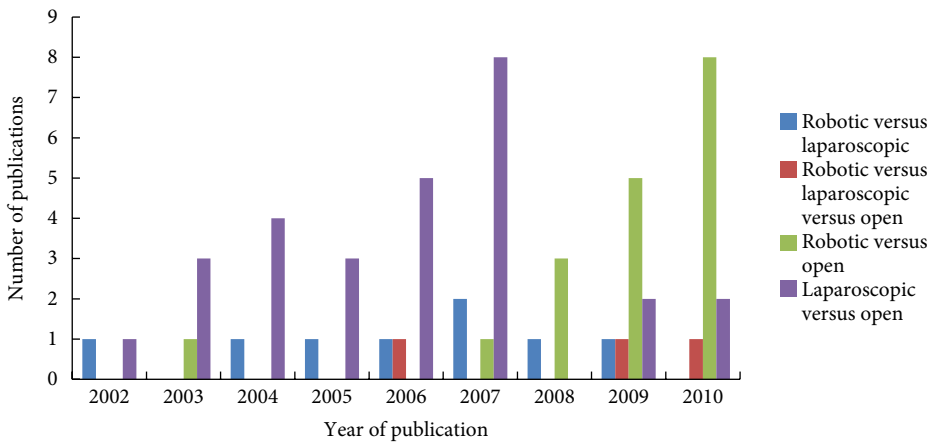
Comparison	Country of Origin	Number of centres	Number of participants recruited		
			Robotic	Laparoscopic	Open
Robotic vs laparoscopic					
Gosseine 2009 [S17]	France	1	122	125	
Hu 2006 [S18]	USA	1	322	358	
Joseph 2007 [S19]	France and USA	2	754	800	
Joseph 2005 [S20]	USA	1	50	50	
Menon 2002 [S13]	France	1	50	48	
Rozet 2007 [S21]	France	1	133	758	
Sundaram 2004 [S22]	USA	1	10	10	
Trabulsi 2008 [S23]	USA	1	50	190	
Robotic vs laparoscopic vs open					
Ball 2006 [S14]	USA	1	82	124	135
Bolenz 2010 [S15]	USA	1	262	211	156
Bolenz 2009 [S24] (secondary to Bolenz 2010)	USA	1	264	220	162
Drouin 2009 [S16]	France	Not reported	71	85	83
Robotic vs open					
Barocas 2010 [S25]	USA	1	1413		491
Kordan 2010 [S26] (secondary to Barocas 2010)	USA	1	830		414
Chan 2008 [S27] (secondary to Barocas 2010)	USA	1	660		340
Carlsson 2010 [S28]	Sweden	1	1253		485
Doumerc 2010 [S29]	Australia	Not reported	212		502
Ficarra 2009 [S30]	Italy	1	103		105
Fracalanza 2008 [S31]	Italy	1	35		26
Krambeck 2009 [S32]	USA	1	294		588
Loeb 2010 [S33]	USA	Not reported	152		137
Malcolm 2010 [S34]	USA	1	447		135
Miller 2007 [S35]	USA	1	42		120
Nadler 2010 [S36]	USA	1	50		50
Ou 2009 [S37]	Taiwan	1	30		30
Rocco 2009 [S38]	Italy	1	120		240
Schroeck 2008 [S39]	USA	1	362		435
Tewari 2003 [S40]	USA	1	200		100
Truesdale 2010[S41]	USA	1	99		217
White 2009 [S42]	USA	1	50		50
Laparoscopic vs open					
Al-Shaiji 2010 [s43]	Canada	1		70	70
Anastasiadis 2003 [S44]	France	1		230	70
Artibani 2003 [S45]	Italy	2		71	50
Bhayani 2003 [S46]	USA	1		33	24
Brown 2004 [S47]	USA	1		60	60
Dahl 2009 [S48]	USA	1		104	102
Dahl 2006 S49 (secondary to Dahl 2009)	USA	1		286	714
Fornara 2004 [S50]	Germany	1		32	32
Ghavamian 2006 [S51]	USA	1		70	70
Greco 2010 [S52]	Italy	1		150	150
Guazzoni 2006 [S1]	Italy	1		60	60
Jacobsen 2007 [S53]	Canada	1		57	148
Jurczok 2007 [S54]	Germany	1		163	240
Kim 2007 [S55]	Korea	1		30	45
Lama 2009 [S56]	Chile	1		56	59
Martorana 2004 [S57]	Italy	1		50	50
Namiki 2005 [S58]	Japan	4		45	121
Namiki 2006 [S59]	Japan	4		64	283
Poulakis 2007 [S60]	Germany	1		204	70
Raventos 2007 [S61]	Spain	Not reported		105	75
Remzi 2005 [S62]	Austria	1		80	41
Salomon 2002 [S63]	France	4		155	151
Silva 2007 [S64]	Brazil	2		90	89
Soderdahl 2005 [S65]	USA	1		116	186
Soric 2004 [S66]	Croatia	1		26	26
Terakawa 2008 [S67]	Japan	1		137	220
Touijer 2007 [S2]	USA	1		485	692
Wagner 2007 [S68]	USA	1		75	75

Table 2 Summary description of patient cohort characteristics extracted from the included studies.

	Robotic	Laparoscopic	Open
N	6768	4952	7344
Median (IQR) age, years	61 (59–62)	62 (60–64)	63.0 (60–65)
Clinical (c) stage, *n* (%)			
cT1	4380 (64.7)	3257 (65.7)	3956 (53.9)
cT2	1743 (25.7)	1312 (26.5)	2194 (29.9)
cT3	58 (0.9)	26 (0.5)	148 (2.0)
cT4	1 (0.01)	8 (0.2)	0 (0)
Missing/Unknown*	586 (8.7)	349 (7.1)	1046 (14.2)
Preoperative core biopsy pathological Gleason score, *n* (%)			
≤6	2179 (32.2)	989 (20.0)	2389 (32.5)
7	949 (14.0)	429 (8.7)	1574 (21.4)
8–10	198 (2.9)	54 (1.1)	333 (4.5)
Missing/Unknown*	3442 (50.9)	3480 (70.3)	3048 (41.5)
Median (IQR) preoperative PSA, ng/mL	6.3 (5.4–7.1)	7.2 (6.3–8.6)	7.9 (6.0–9.3)
Pathological tumour stage, *n* (%)			
pT0	7 (0.1)	6 (0.1)	22 (0.3)
pT1	0 (0)	29 (0.6)	25 (0.3)
pT2	2060 (30.4)	2373 (47.9)	4246 (57.8)
pT3	571 (8.4)	669 (13.5)	1368 (18.6)
pT3/4*	23 (0.3)	45 (0.9)	76 (1.0)
pT4	7 (0.1)	17 (0.3)	33 (0.4)
Missing/Unknown*	4203 (62.1)	1710 (34.5)	1574 (21.4)
Postoperative whole prostate pathological Gleason score, *n* (%)			
≤6	1200 (17.7)	485 (9.8)	1666 (22.7)
7	1110 (16.4)	415 (8.4)	1634 (22.3)
8–10	161 (2.4)	49 (1.0)	379 (5.2)
Missing/Unknown†	4297 (63.5)	4003 (80.8)	3665 (49.9)

**pT3 and pT4 not differentiated in two study reports. †Either owing to missing, unsuitable or non-reported data. IQR, interquartile range.*

Fig. 3 Year of publication of included studies according to comparison.



Uncertainty surrounding this estimate was increased when only studies with a low risk of bias were analysed with the CrI, including the finding of no difference; OR (95% CrI) of 0.73 (0.29 to 1.75), $P = 0.78$ (Table 4 [S1, S13, S16, S19, S21–S23, S25, S29–S33, S36–S40, S42, S44, S45, S47, S49, S50, S52–S57, S60, S62–S64, S66–S68]). Methods of pathological analysis reported by included studies showed high variability and non-compliance with recommended protocols, with no two studies reporting the same method for ascertainment of positive margin status. It was therefore not possible to undertake the planned sensitivity analysis restricted to studies using a standard method. Duration of surgery was, on average, 12 min shorter for the robotic procedure ($P = 0.99$) but differing definitions made accuracy of this result highly uncertain. Men had a lower risk of major harms occurring during or immediately after robotic prostatectomy, such as injury to adjacent organs and leakage from the vesico-urethral anastomosis, but these events were uncommon. Other outcomes, including risk of biochemical recurrence at 12 months and rates of urinary incontinence, showed no

Fig. 4 Summary chart of the proportion of the 47 studies assessed for risk of bias showing low, high or unclear risk of bias for methodological constructs and meta-analysed outcomes.

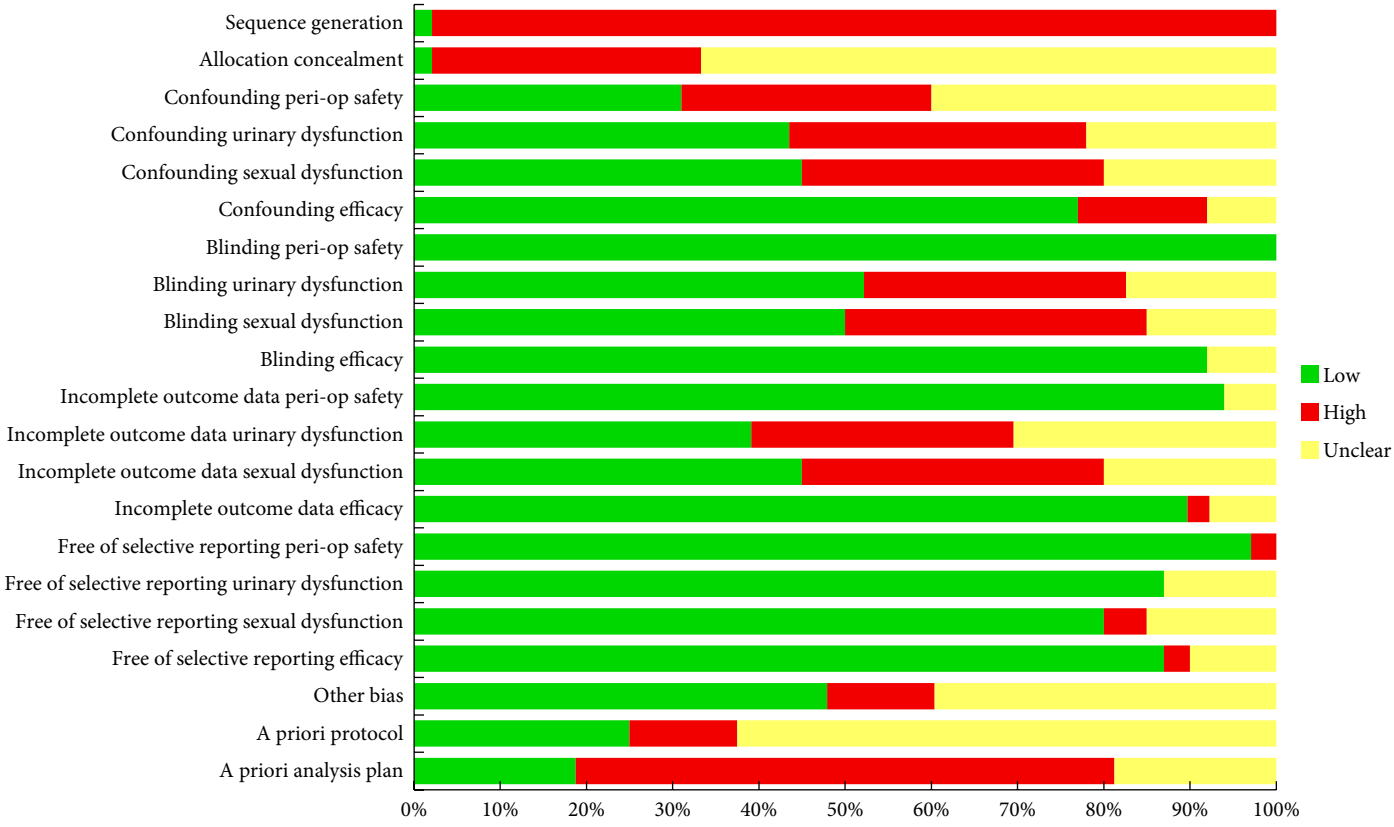
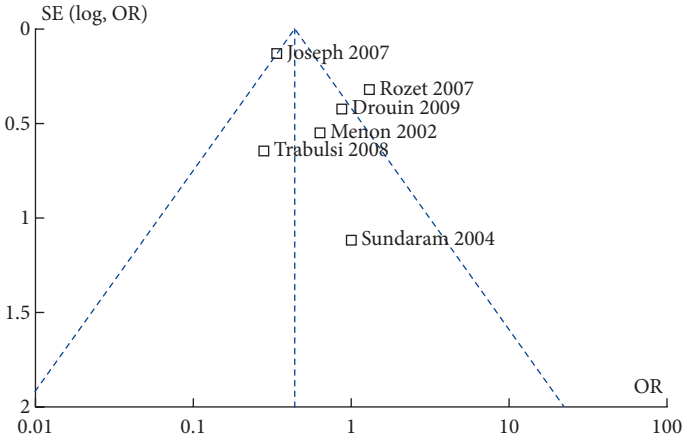


Fig. 5 Funnel plot of studies directly comparing robotic with laparoscopic prostatectomy and reporting positive surgical margin outcome. Vertical axis shows variance measured by SE of the logarithm of the OR and the horizontal axis shows the OR with values <1 favouring robotic prostatectomy. Vertical blue line represents central estimate, with sloped lines representing 95% CrI.



difference. Rates of these outcomes reported by individual studies are given in Table S1. We were unable to perform a meta-analysis for a number of pre-specified outcomes, such as sexual function and those describing patient experience, mainly owing to a lack of data and the use of widely varying outcome measurement tools (Table 5).

Learning Curve

We used positive surgical margin rate as the key outcome to assess the effect of increasing surgeon experience in line with the main meta-analysis. In general, available data assessing surgeon learning was limited and often not in a form suited to meta-analysis with variable descriptive categorisation of surgeon prior experience. Regression modelling using data from studies included in the main meta-analysis showed no evidence of outcome trends with increasing experience (R^2 < 0.02%; Fig. 7). Extending study eligibility criteria to include case series identified four reports of robotic prostatectomy [S3–S6] and six reports of laparoscopic prostatectomy (Table 6) [S7–S12]. Two studies [S7,S9] only reported a mathematical shape to the learning curve, preventing extraction of relevant variables. All studies reported a decrease in positive surgical margin rates with increasing surgeon experience except one [S7], which reported a constant low rate

Table 3 Results of the mixed-treatment comparison meta-analysis illustrating the probability of clinical outcomes for robotic prostatectomy and laparoscopic prostatectomy.

Outcome	Predicted probability of event		OR	95% CrI	Probability of outcome
	RP	LP			*P*
Cancer					
Positive surgical margin	0.176	0.236	0.69	0.51 to 0.96	0.99
Biochemical recurrence	0.087	0.097	0.89	0.24 to 3.34	0.59
Procedural					
Change to another intervention	0.003	0.009	0.28	0.03 to 2.00	0.89
Mean operating time (minutes)	225	238	−12.4	−16.5 to −8.1	0.99
Peri-operative harms					
Clavien I	0.021	0.041	0.48	0.15 to 1.55	0.90
Infection	0.008	0.011	0.75	0.18 to 3.35	0.66
Anastomotic leak	0.010	0.044	0.21	0.05 to 0.76	0.99
Clavien II	0.039	0.072	0.52	0.22 to 1.18	0.94
Blood transfusion	0.035	0.050	0.71	0.31 to 1.62	0.78
Ileus	0.011	0.024	0.46	0.12 to 1.51	0.92
Deep venous thrombosis	0.006	0.002	2.67	0.26 to 50.3	0.19
Clavien IIIa	0.005	0.013	0.36	0.03 to 2.57	0.85
Clavien IIIb*	0.009	0.036	0.25	0.06 to 0.92	0.98
Organ injury	0.004	0.029	0.16	0.03 to 0.76	0.99
Clavien IV	0.006	0.008	0.76	0.14 to 3.44	0.64
Clavien V	0.000	0.002	0.00	0.00 to 0.12	0.99
Postoperative harms					
Bladder neck contracture	0.010	0.021	0.48	0.09 to 2.93	0.81
Urinary incontinence	0.045	0.079	0.55	0.09 to 2.84	0.60

*RP, robotic prostatectomy; LP, laparoscopic prostatectomy. 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; Clavien V = death of patient. *Includes organ injury.*

for laparoscopic prostatectomy. The mean positive margin rates for both procedures fell from 26% at case one to 15% by case 250, and to 12% by case 1000. There was no evidence that this observed rate of learning differed between robotic and laparoscopic procedures with a mean (95% CI) difference of −0.02 [(−0.16 to 0.12), $P = 0.76$].

Discussion

Our mixed-treatment comparison meta-analysis made best use of the available, predominantly non-randomised comparative data to estimate the relative benefits and harms of robotic and laparoscopic prostatectomy as alternatives to open surgery. Imprecision and uncertainty surrounding these estimates mean that our findings should be interpreted cautiously. The significant reduction in the rate of a surgical margin positive for cancer after robotic prostatectomy is important since it is likely to be linked to a lower risk of disease recurrence and the need for further cancer treatment in the longer term [19]; however, the limited data from included studies did not suggest lower rates of biochemical (PSA) cancer recurrence after robotic prostatectomy. The lower risk of major harms during and immediately after robotic prostatectomy suggests a superior safety profile, although these events were infrequent. There was no evidence of lower rates of urinary incontinence but we could not draw any conclusions about sexual dysfunction because of a lack of usable data. There was no evidence to suggest that surgeon learning rates were faster using the robotic system, although data were limited. The relative effects on patient experience and cancer-free survival remain unknown. Overall, we found no evidence that robotic prostatectomy was inferior to standard laparoscopic prostatectomy for treatment of men with localised prostate cancer.

We pre-defined the search strategy and outcomes of interest and used systematic, exhaustive search and data extraction techniques to ensure that all available data were identified and included in our meta-analysis. We may have missed usable data, although communication with authors of studies where fulfilment of our inclusion criteria was uncertain showed that only one of these studies was suitable. We specified a cut-off date for our search of 31st October 2010 to allow time and resources for data extraction, risk of bias assessment and meta-analysis which underpinned the completion of a careful and high-quality evidence review. We performed an updated search of literature published between November 2010 and December 2011 identifying a further 15 comparative studies meeting our inclusion criteria, including one RCT which found as a secondary outcome a positive margin rate of 6/60 (10%) after laparoscopic prostatectomy and 8/52 (15%) after robotic prostatectomy [20].

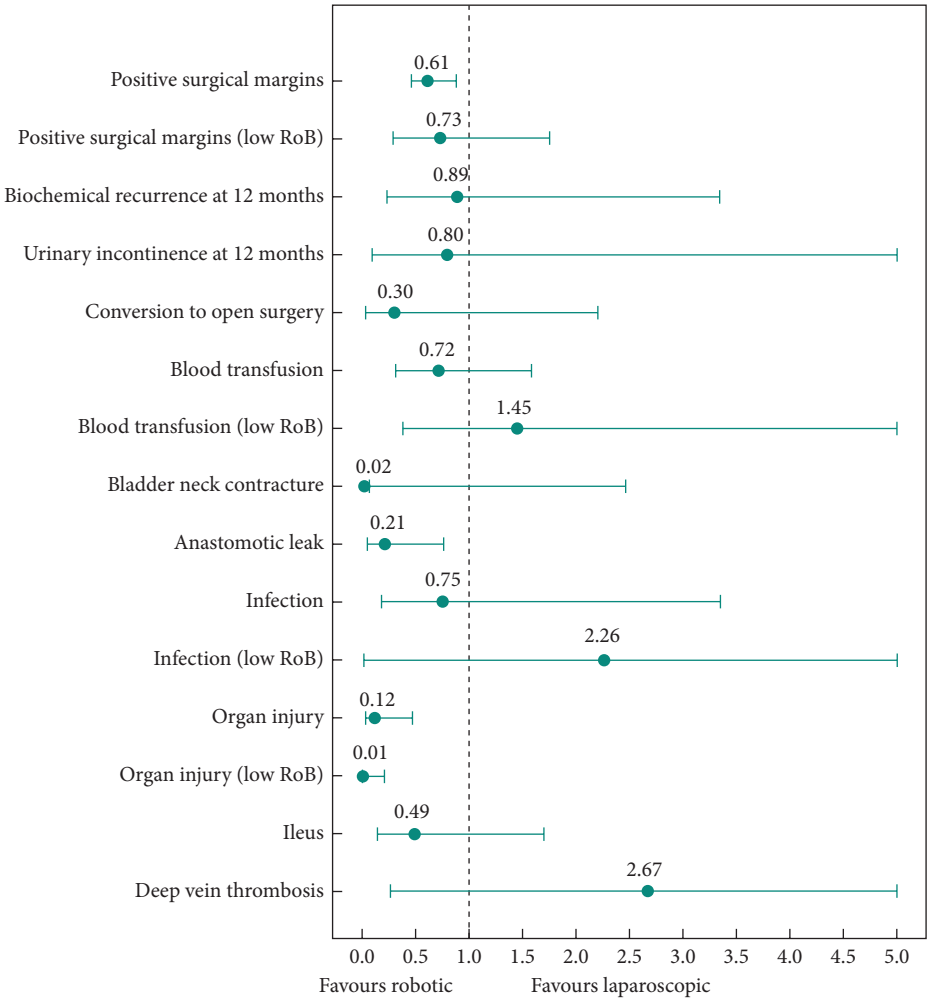


Fig. 6 Summary of the clinical effect sizes (OR and 95% CrI) from meta-analyses. To improve visual display, the upper CrI has been truncated to 5.0. Estimates from only low risk of bias (RoB) studies are shown.

We chose to exclude case series since meta-analysis of such studies are more likely to introduce selection bias stemming from lack of control of patient profiles across different societies and institutions. They are also less likely to address key outcomes, and are wasteful of research resources [21]. Personal and disease characteristics for included men were equivalent between the two procedures and reflected those of men undergoing radical prostatectomy in the UK [22], suggesting that our findings were reliable and generalisable, and that potential confounders such as preoperative PSA value and Gleason score were balanced. To address confounding by disease stage, we excluded studies involving >10% of men with locally advanced (cT3) disease, as their greater risk of positive margin and disease persistence would have a disproportionate effect on outcomes if there was imbalance between study groups. This appeared effective since >80% of included studies contributing to positive margin outcome were categorised as at low risk of confounder bias. We made concerted efforts to prevent the inclusion of duplicate data resulting from multiple reports of the same cohort but it is possible that some instances were missed. Included studies were generally of low quality and data too few for meta-analysis of some important

Fig. 7 Proportion of positive surgical margins with increasing experience of operating surgeon in included studies (learning curve). Dashed line is the predicted linear relationship for laparoscopic studies and the solid line is the predicted linear relationship for robotic studies.

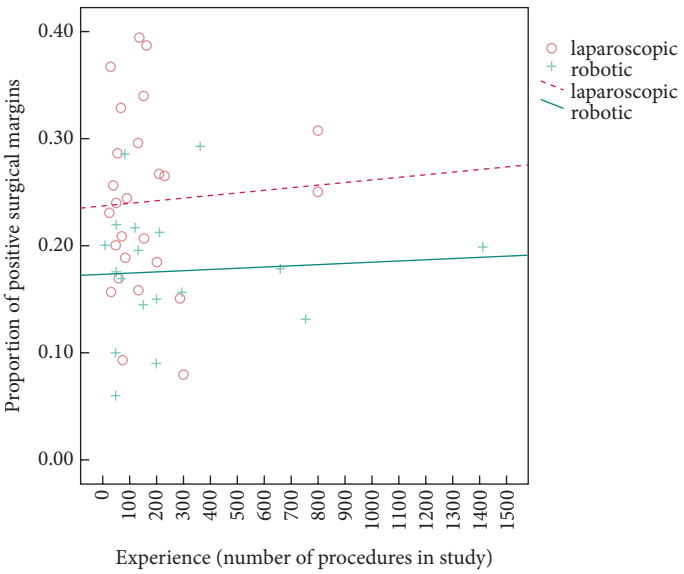


Table 4 Patient cohort characteristics of included studies providing data for positive surgical margin outcome meta-analysis with summary results.

Study	Positive surgical margins, *n*/*N* (%)		
	Robotic	Laparoscopic	Open
Anastasiadis 2003 [S44]*		61/230 (26.5)	20/70 (28.6)
Artibani 2003 [S45]		21/71 (30)	12/50 (24)
Barocas 2010 [S25]	281/1413 (19.9)		148/491 (30.1)
Brown 2004 [S47]		10/59 (16.9)	12/60 (20)
Dahl 2006 [S49]		43/286 (15)	124/714 (17.4)
Doumerc 2010 [S29]	45/212 (21.2)		84/502 (16.7)
Drouin 2009 [S16]*	12/71 (16.9)	16/85 (18.8)	15/83 (18.1)
Ficarra 2009 [S30]	35/103 (34)		21/105 (21)
Fornara 2004 [S50]		5/32 (16)	7/32 (22)
Fracalanza 2008 [S31]	10/35 (28.6)		6/26 (23)
Greco 2010 [S52]*		12/150 (8)	17/150 (11.3)
Guazzoni 2006 [S1]*		16/60 (26.7)	13/60 (21.7)
Jacobsen 2007 [S53]		22/67 (38)	60/148 (40)
Joseph 2007 [S19]	99/754 (13.1)	246/800 (30.75)	
Jurczok 2007 [S54]		63/163 (38.8)	104/240 (43.6)
Kim 2007 [S55]		11/30 (36.7)	11/45 (24.4)
Krambeck 2009 [S32]	46/294 (15.6)		100/588 (17.2)
Lama 2009 [S56]		16/56 (28.6)	21/59 (35.6)
Loeb 2010 [S33]	22/152 (14.5)		25/137 (18.2)
Martorana 2004 [S57]		12/50 (24)	13/50 (26)
Menon 2002 [S13]	7/40 (17.5)	10/40 (25)	
Nadler 2010 [S36]	5/50 (10)		12/50 (24)
Ou 2009 [S37]	15/30 (50)		6/30 (20)
Poulakis 2007 [S60]		15/72 (20.8)	16/70 (22.8)
Remzi 2005 [S62]		10/39 (25.6)	8/41 (19.5)
Rocco 2009 [S38]	26/120 (22)		60/240 (25)
Rozet 2007 [S21]	26/133 (19.5)	21/133 (15.8)	
Salomon 2002 [S63]		32/155 (20.6)	30/151 (19.9)
Schroeck 2008 [S39]	106/362 (29)		122/435 (28)
Silva 2007 [S64]		22/90 (24.44)	37/89 (41.57)
Soric 2004 [S66]		6/26 (23)	3/26 (11.5)
Sundaram 2004 [S22]	2/10 (20)	2/10 (20)	
Terakawa 2008 [S67]		54/137 (39.4)	52/220 (23.6)
Tewari 2003 [S40]	18/200 (9)		23/100 (23)
Trabulsi 2008 [S23]	3/50 (6)	35/190 (18)	
Wagner 2007 [S68]		7/75 (9)	14/75 (19)
White 2009 [S42]*	11/50 (22)		18/50 (36)
Predicted probability of event	**0.18**	**0.24**	**0.24**
OR (95% CrI); probability outcome favours robotic prostatectomy	**All studies**	**0.69 (0.51 to 0.96);0.99**	
	Low risk of bias studies only	**0.73 (0.29 to 1.75);0.78**	

**Study included in the low risk of bias meta-analysis. OR, odds ratio.*

outcomes including sexual function, postoperative pain, and quality of life.

We included studies that used either contemporaneous or sequential comparative cohorts since we considered that such differences in design would not result in a particular direction of bias but rather that the overall quality of each included study was of greater importance [23]. An additional factor for this review was the likelihood that surgeons had less experience with the newer technique than the previous technique with which it was compared. Four of the eight robotic vs laparoscopic comparisons gave descriptive information on this issue with all stating that the surgeons were experienced in laparoscopic prostatectomy and had completed a structured training in robotic prostatectomy [S13–S16]. Publication bias for direct comparisons of the newer technique (robotic) against the alternative (laparoscopic) might be expected in the early phase of technology assessment which may be driven by individual surgeon enthusiasm or commercial pressures, but a restricted funnel plot analysis did not suggest such bias for reporting of positive surgical margins in line with previous reviews [24–26].

Included studies were of short duration and data regarding disease-free survival were not available. A pathological finding of a surgical margin positive for cancer was therefore used as the measure by which to judge relative effectiveness. Achievement of a negative margin is considered to be an immediate marker of successful surgery, both in terms of

Table 5 Pre-planned outcome variables not included in meta-analysis with reasons.

Outcome variable	Number of studies reporting	Reason for no meta-analysis	Comment
Harms during and soon after surgery			
Death	10	Too few events reported	
Hernia	3	No comparative data	
Pulmonary embolism	5	Event rate too low	
Blood loss volume	29	Diverse methods of measurement and wide variation	Quantified as transfusion rate
Diverse postoperative complications	31	Varying terminology wide diversity	Categorised *post hoc* according to Clavien–Dindo [11]
Cancer-related			
Disease-free survival	0	No data in included studies	
Need for further cancer treatment	1	No comparative data	
Local recurrence	1	No comparative data	
Metastatic recurrence	1	No comparative data	
Functional			
Sexual dysfunction	19	Diversity of outcomes and types of data	One comparative study favoured robotic and one favoured laparoscopic
Faecal incontinence	3	Diverse definitions and timing of outcome measurement	
Treatment of functional harms	1	No comparative data	
Patient-driven			
Postoperative pain		Not reported by included studies	
Changes to quality of life	5	Diversity of outcomes and types of data	Insufficient data for comparison
Return to productivity	3	Data not evaluable	
Descriptors of care			
Duration of catheterisation	23	Diverse policies and outcome measures	Of four direct comparative studies, two favoured robotic and two laparoscopic
Hospital stay	28	Diverse methods of measurement	Of four direct comparative studies, two favoured robotic and two laparoscopic
Early mobilisation	3	No comparative data	
Oral intake	4	No comparative data	

cancer control and surgical quality, as a positive margin increases the risk of disease recurrence and the need for further cancer treatment [27,28]. It is possible that variability and lack of consistency in the reporting of pathological examination techniques led to a systematic bias in the detection of positive margins, in particular for studies using a non-contemporary control group, but we found insufficient data to assess this. We chose not to re-analyse positive margin rate according to pathological stage given our limited inclusion of men with cT3 disease and concerns regarding analysis of sub-groups defined by non-baseline characteristics.

In line with best practice and to encompass all the factors described above, we individually assessed each included study for risk of bias using an established tool and multiple independent raters [14]. The positive margin re-analysis using low risk of bias study data showed a similar point estimate of effect but increased the degree of uncertainty to include the finding of no difference. For organ injury, the result showed an increased likelihood that robotic prostatectomy was safer with less uncertainty. For other outcomes, low risk of bias studies were too few for meaningful meta-analysis. Although the main limiting factor for these sensitivity analyses was low study quality there may also be inadequacies of the tool used [23] and the findings reinforce the need for methodological research [29].

We identified four further systematic reviews and one published as three papers, contemporary to our own which used different meta-analytic techniques [24,26,30–33]. All five reviews found that positive margin rate was the only cancer outcome with sufficient data for meta-analysis and, although central estimates of risk all favoured robotic prostatectomy, effect size and degree of uncertainty varied, with only our results and those of Tewari et al. [26] showing statistical significance (Table 7 [24,26,30–33]). The aim of any meta-analysis is to calculate the most accurate and precise estimate of the true absolute or relative value for any outcome from the data deemed eligible for inclusion. It continues to be a challenge to achieve this without high-quality randomised controlled data and a number of statistical models have evolved to make use of non-randomised data with reduced uncertainty. We considered that a mixed-treatment comparison including indirect comparisons was the most appropriate model, in line with guidance from evidence-synthesis organisations [14,34–37]. This achieved a large sample size whilst maintaining the advantage of estimation of outcomes as relative differences rather than crude absolute rates to minimise effects of selection and reporting bias. The method also captured different transitions of surgeon experience, such as that from open to robotic prostatectomy and open to laparoscopic to robotic, and avoided procedural bias that could arise from only including

Table 6 Summary of learning curve measures in cases series.

Study	Reported outcomes	*N*	Robotic measured outcome	Laparoscopic measured outcome	Other information reported in study
Secin 2010 [S11]	Positive margin rate	6274		Case 1: 24% Case 250: 19%	
Hong 2010 [S3]	Positive margin rate	469	Case 1: 27% Case 200: 25% Case 400: 21%:		Linear trend
Tewari 2010 [S6]	Positive margin rate	1340	Case 1: 9% Case 100: 7%:		
McNeill 2010 [S9]	Positive margin rate Operation time Complications	300		Case 1–50: 27% Case 251–300: 14.7% Case 1: 200 min Case 200: 140 min Case 1: 29% Case 250: <1%	Log linear trend
Samadi 2010 [S5]	Positive margin rate	1181	Case 1: 8.5% Case 590: 4.3%		
Rodriguez 2010 [S10]	Positive margin rate	400		Case 1: 32% Case 400: 13.3%	
Jaffe 2009 [S4]	Positive margin rate Operation Time	278	Case 1–12: 58% Case 12–189: 23% Case 278: 9% Case 1–12: 250 min Case 12–189: 165 min Case 278: 134 min		
Eden 2009 [S7]	Positive margin rate Complications Blood loss Normal sexual function Operation time	1000		Series mean: 13.3% Series mean: 200 mL Case 1: 23% Case 1000: 86% Series mean: 177 min	No trend noted No trend noted Stabilised after 200 cases Stabilised after 700 cases Stabilised after 200 cases
Vickers 2009 [S12]	Biochemical (PSA) recurrence	4702		Case 10: 16% Case 250: 15.5% Case 750: 8.2%	
Martinez-Pineiro 2006 [S8]	Positive margin rate Blood transfusion rate Operation time	604		Case 1: 25% Case 600: 7% Series mean: 201 min	Decreased significantly by 101 cases Stabilised by 200 cases

Table 7 Estimates of relative outcomes for robotic vs laparoscopic prostatectomy from contemporary meta-analyses.

Study	Type of meta-analysis	Expression of difference	Positive margin*	Early complications*	Urinary incontinence at 12 months*
			Median (CI) number of patients	Median (CI) number of patients	Median (CI) number of patients
Present paper	Mixed-treatment comparison	OR	0.69 (0.51 to 0.96) $N = 7186$	0.16 (0.06 to 0.76) $N = 5383$[†]	0.55 (0.09 to 2.84) $N = 2322$
Ho et al. (2011) [31]	Random-effects	RR	0.89 (0.66 to 1.19) $N = 1061$	0.85 (0.5 to 1.44) $N = 1845$	1.08 (0.99 to 1.18) $N = 400$
Flattery et al. (2011) [24]	Random-effects	RR	0.93 (0.70 to 1.22) $N = 1114$	0.96 (0.53 to 1.73) $n = 1911$	1.09 (1.02 to 1.14) $N = 512$
Tewari et al. (2012) [26]	Pairwise with propensity adjustment	OR	0.80 (0.76 to 0.85[‡]) $N = 62\,130$	0.68 (0.62 to 0.74[‡]) $N = 30\,698$	N/A
Novara et al. (2012) [30,32,33]	Fixed or random-effects	OR	0.89 (0.64 to 1.23) $N = 2514$	0.71 (0.37 to 1.37) $N = 1720$	0.42 (0.23 to 0.78) $N = 738$

*RR, relative risk. *Values <1 favour robotic prostatectomy. †Organ injury only. ‡Additional data obtained from the authors.*

publications from centres able to perform both robotic and laparoscopic techniques. For positive margin outcome, random effects meta-analyses using only direct comparative studies all gave broadly similar results but had small total sample size which varied according to different judgements on study eligibility [24,30–33] (Fig. 7). Tewari et al. [26] expanded total sample size further by including case series of both techniques and used propensity-matching to control for differences in baseline characteristics. Whilst this gave a more precise estimate of difference in positive margin rate it may

not have adequately controlled for risk of selection bias and confounding [21,29,38]. In terms of other outcomes we reported comparative data for individual complications specifically recorded in the source material, whilst in the other studies they were grouped together using varying criteria preventing any comment of the relative accuracy of estimates. One review found a significantly higher rate of continence for robot-assisted than for standard laparoscopic prostatectomy at 1 year [30], whilst the other three studies reporting this outcome, including our own, found no evidence of a differential risk between the two procedures [24,26]; this may have resulted from varying study inclusion criteria. For the seeker of evidence, these five meta-analyses can be thought of as sensitivity analyses exploring the impact of different methodological judgments. The consistency in the direction of relative difference in positive margin rate and the lack of any outcomes assessed as inferior after robotic prostatectomy across the studies are reassuring, but interpretation of any meta-analysis based on non-randomised data should always be cautious [29].

Our finding of no evidence for differential surgeon learning between the two techniques differs from other publications [39]. This may be attributable to the use of positive margin rates rather than operating time or blood transfusion rates as a competency marker or possibly to the limited nature of the data available. Our results suggest that the individual surgeon's rate of learning is the dominant factor rather than the technology used [40].

The need for radical prostatectomy is likely to be maintained or to increase over the next 5 years with PSA-driven higher detection rates for localised prostate cancer, although new less invasive treatments may expand the choice of management [41]. Our results will help guide patients, clinicians and healthcare managers in the choices they make regarding the implementation and use of robotic prostatectomy but, given uncertainty around the meaning of the data, cautious interpretation is emphasised and other sources of evidence, particularly contemporary meta-analyses should be considered. It seems unlikely that a large robustly designed RCT comparing robotic with laparoscopic prostatectomy will be carried out (a feasibility study was recently unsuccessful in the UK) but well-designed prospective multicentre cohort studies with longer-term outcome assessment as well as independent verification of baseline data and outcome should be possible. Without such studies assessment of the value of costly new technology to patients and healthcare systems such as the UK NHS will continue to be imperfect.

Ethics approval was not required.

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Conflict of Interest

None declared.

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Abbreviations: RCT, randomised controlled trial; HTA, Health Technology Assessment; OR, odds ratio; CrI, credible interval.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Search Strategies for databases used to identify source data for meta-analysis.
Table S2 Reference List of included studies.