Open, laparoscopic and robot-assisted laparoscopic radical prostatectomy for localised prostate cancer

What is an evidence note

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions and are produced in an approximately 3 month period. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review. Evidence notes do not make recommendations for NHSScotland.

Key points

- The quality of the clinical-effectiveness evidence base in general is low, and its limitations need to be considered when interpreting the findings and the results from economic evaluations based on them.
- Laparoscopic radical prostatectomy (LRP) versus open radical prostatectomy (ORP): There is evidence that LRP is superior to ORP in reducing length of stay, intraoperative blood loss and transfusion, but inconclusive evidence of a difference in functional or cancer outcomes.
- Robot-assisted LRP (RALRP) versus ORP: There is evidence that RALRP is superior to ORP in reducing length of stay, intraoperative blood loss and transfusion, and may have better functional outcomes, but inconclusive evidence of a difference in cancer outcomes.
- RALRP versus LRP: There is no consistent evidence that RALRP is superior to LRP in reducing operative time, intraoperative blood loss, transfusion or improving functional or cancer outcomes.
- The UK health technology assessment found no evidence of a differential learning effect between LRP and RALRP, which the authors concluded is consistent with the suggestion that it is the individual surgeon’s rate of learning that is the dominant factor rather than the technology used.

Literature search

A systematic literature search from 2009 to September 2012 was undertaken to update the previous version of this evidence note. A search of the secondary literature was conducted to identify published systematic reviews, health technology assessments (HTAs), evidence-based guidelines, policy documents and economic evaluations. The search terms used were ‘prostate cancer’ or ‘prostatectomy’ or ‘radical prostatectomy’ combined with ‘laparoscopy’ or ‘laparoscopic surgery’ as well as ‘robotics’ or ‘robotic surgery’.

- There is insufficient evidence to conclude that any procedure is superior with respect to quality of life.
- Available evidence does not identify a difference in overall intraoperative or perioperative complications between ORP and LRP, or between LRP and RALRP. There is inconsistent evidence of a difference between ORP and RALRP.
- RALRP versus ORP: A cost-utility analysis stated that, based on 200 procedures per year, RALRP is cost-effective with an incremental cost per quality-adjusted life year (QALY) of €26,647 (£21,504) (95% confidence interval (CI); €14,241 (£11,492) to €61,220 (£49,405)). However, the results must be treated with caution given the considerable uncertainty surrounding the model inputs and parameter values.
- RALRP versus LRP: A cost-utility analysis stated that RALRP is cost effective compared with LRP, with an incremental cost per QALY of £18,329. However, this presumed that there is a difference in positive surgical margin (PSM) rates between the two interventions and the number of RALRP procedures is greater than 150 per year. If either of these assumptions are not met – and evidence from the meta-analysis of there being a difference in PSM rate was inconclusive – RALRP would not be considered cost effective. As such, the results of the economic evaluation must be treated with caution.
The following databases were also searched using the same terms with the results limited to review articles published in English:

- Medline
- Medline in process
- Embase
- Cinahl
- Web of Science

A supplementary search of the primary literature was undertaken using the same terms with the addition of a ‘volume and outcome’ filter. Full details are available on request.

**Introduction**

This evidence note updates evidence note 31 published in September 2010. It summarises the clinical and cost-effectiveness evidence from published HTAs and systematic reviews comparing open radical prostatectomy (ORP), laparoscopic radical prostatectomy (LRP) and robot-assisted LRP (RALRP).

The Scottish Government and Healthcare Improvement Scotland published clinical Quality Performance Indicators (QPIs) for prostate cancer in May 2012 that include targets for radical prostatectomy. A national minimum core dataset to support monitoring and reporting of the QPIs has been implemented for all patients diagnosed with prostate cancer on or after 1 July 2012.

The clinical QPIs for NHSScotland set a minimum target of 12 RP procedures per surgeon per year and propose the following outcomes targets following RP:

- <25% of patients with stage pT2 (see health technology description below) prostate cancer with positive surgical margins (PSM).
- <20% of patients using >0 urinary incontinence pads per day, and <10% using >1 pad per day, approximately 1 year (10–14 months) after surgery.
- <20% of patients with intermediate-risk prostate cancer who undergo radical treatment with curative intent (including RP) with prostate-specific antigen (PSA) relapse (>0.2 µg/l) at 1 year (10–14 months) after surgery.

**Health technology description**

RP is a treatment option for men with localised prostate cancer which is cancer that is only in the prostate gland and has not spread to another part of the body. Tumour staging differentiates localised prostate cancer into T1 and T2 stage tumours which are completely inside the prostate gland and T3 tumours which have broken through the capsule covering the gland but have not spread into other organs. Tumour stage is determined definitively by pathology after surgery (pathological stage denoted pT). RP involves surgical removal of the entire prostate gland and seminal vesicles. It is traditionally performed by open surgery via an incision in the lower abdomen (retropubic) or, less commonly, in the perineum. A nerve-sparing technique may be used to minimise nerve damage. LRP is a minimally invasive technique to perform the same retropubic surgical procedure by inserting a telescope (endoscope) and surgical instruments through small incisions in the abdomen. RALRP is a further development of minimally invasive laparoscopic surgery. The technology comprises a console, computerised control system, and robotic arms that hold the endoscope and surgical instruments. The surgeon operates the robotic arms by remote control from the console while viewing the magnified surgical field on the monitor. The da Vinci® System (Intuitive Surgical Inc., California) with three or four robotic arms is the only commercially available technology. The da Vinci® S HD System integrates three-dimensional high-definition endoscopy, and the da Vinci® Si HD System has dual-console capability to support surgical training and collaboration. The first generation da Vinci® Surgical System is no longer commercially available.

Information Services Division (ISD) recorded 399 radical prostatectomies for prostate cancer performed in Scotland in the financial year 2011–2012, 215 (54%) by open surgery and 184 (46%) by laparoscopic surgery (ISD IR2012-02037). The ISD data show that most of the laparoscopic procedures were performed in NHS Lothian with the others in Tayside, Grampian and Highland (ibid.). In 2012, 112/136 (82%) prostatectomies were performed by laparoscopic surgery in the South East Scotland Cancer Network (SCAN) area, 75/114 (66%) in the North...
of Scotland Cancer Network area, and 4/122 (3%) in the West of Scotland Cancer Network (WoSCAN) area (ISD IR2013-00865). RALRP is currently not available in Scotland. LRP and RALRP each accounted for around 23% of radical prostatectomies performed in England where, in 2010, 16 cancer centres had access to a da Vinci® System6. There are currently 25 robots installed in England, with most located in London and the South East7.

Epidemiology

Prostate cancer is the most common cancer in men in Scotland, and in the United Kingdom (UK) as a whole6. There were 900 deaths from prostate cancer in Scotland in 2011, corresponding to a European age-standardised rate (EASR) of 24.5 (95% confidence interval (CI) 22.9 to 26.1) deaths per 100,000 person years at risk, making it the third most common cause of cancer death in men after lung and colorectal cancers7.

The incidence of prostate cancer in Scotland was 82.1 (95% CI 79.0 to 85.3) cases per 100,000 person years at risk (EASR) in 2010, estimated from 2,679 diagnoses registered in that year7. Incidence increases with age, with 70% of cases occurring in men over the age of 65 years and very few (1.3%) in men younger than 507. The latest available data show a peak in incidence at 65–69 years in the SCAN area (2010)5 and 70–74 years in the WoSCAN area (2009)8. Incidence is expected to rise, mainly due to the aging population, with a predicted increase of approximately 22% in new cases every 5 years to 20209. The prevalence of prostate cancer in Scotland was estimated at 751.9 per 100,000 population (0.752%) in 2009 based on 18,970 men living with prostate cancer, of whom 84.4% were over the age of 657.

The reported incidence of prostate cancer is significantly lower in Scotland compared with the rest of the UK, which may in part be explained by differences in the availability and uptake of PSA-testing6. There are no data on the current extent of PSA testing across Scotland. The incidence of prostate cancer in Scotland is negatively correlated with deprivation, with a higher incidence in less deprived areas, which may also reflect higher rates of PSA testing in more affluent populations7. Unlike prostate cancer incidence, prostate cancer mortality in Scotland is not correlated with deprivation7.

Data for tumour stage at diagnosis across Scotland are not available to date but are now being collected by ISD from incidence date 1 January 2012 onwards (ISD, Personal Communication, 28 Nov 2012).

In the SCAN area in 2010, 428 men were diagnosed with localised prostate cancer, of whom 109 (25.5%) underwent surgery from diagnosis, 30.1% chose radical radiotherapy and 36.0% embarked upon an initial period of watchful waiting or active monitoring3. In the WoSCAN area, 1,201 men were diagnosed with prostate cancer in 2009 of whom 10.6% were offered radical prostatectomy and 2% radical radiotherapy8.

Clinical effectiveness

A systematic review that informed the previous version of this evidence note has been updated in several publications, comparing RALRP with retropubic ORP and LRP10-13. Two recent HTAs conducted in the UK14 and Ireland15 also report systematic reviews of studies comparing RALRP with ORP and LRP, but did not restrict ORP to retropubic surgery. One systematic review that compared all three surgical approaches provided the only new secondary evidence for the comparison of retropubic ORP with LRP16. The UK National Institute for Health and Care Excellence (NICE) guidance on LRP and RALRP has not been updated since its publication in 20061.

Two of the four included systematic reviews pooled results from primary studies that directly compared RALRP with ORP or LRP (direct evidence) using standard pair-wise meta-analysis10-13,15. The UK HTA conducted a mixed treatment comparison (MTC) to compare RALRP with LRP by combining direct evidence (from studies comparing RALRP with LRP) and indirect evidence (from studies comparing RALRP or LRP with ORP) in a network meta-analysis14. Tewari et al. took a different approach to meta-analysis of direct and indirect evidence including comparative and single-arm studies of retropubic ORP, LRP and RALRP. They used propensity scoring to adjust single-treatment cohort outcomes for differences in patient characteristics outcomes to compare the three surgical approaches16.
The published evidence base comprises a large number of observational studies and only three randomised controlled trials (RCTs). The published meta-analyses are therefore based mainly on observational studies. One RCT comparing ORP with LRP was included in two of the meta-analyses, and one of two RCTs comparing LRP with RALRP was included in two of the meta-analyses. All the RCTs were single-surgeon studies, two conducted in Italy and one in France, and each enrolled 120 patients.

**LRP versus ORP**

**Operative time**

In the only published RCT, the mean operative time for retropubic ORP was statistically significantly shorter than for LRP as reported previously. This was also shown in a meta-analysis of the RCT together with observational studies.

**Length of stay**

Meta-analysis combining observational data from comparative and single-arm studies showed a statistically significant reduction in length of hospital stay following LRP compared with retropubic ORP, both in studies conducted in the United States of America (USA) (propensity-adjusted difference=0.97 days; 95% CI 0.8 to 1.2; p<0.0001) and in non-USA studies (propensity-adjusted difference=1.83 days; 95% CI 0.5 to 3.2; p=0.008).

**Catheterisation**

In the RCT, a significantly higher proportion of patients had their catheter removed on post-surgery day 5 following LRP (86.7%) compared with ORP (66.7%) (p<0.001).

**Positive surgical margins**

The RCT showed no statistically significant difference in positive margin rates (PSM). Meta-analysis combining data from comparative and single-arm studies also showed no statistically significant difference after propensity score adjustment between retropubic ORP and LRP overall (24.2% versus 20.4%; propensity-adjusted difference=2.24%; 95% CI -0.7 to 5.2; p=0.13) or in pT2 cancer (16.6% versus 13.0%; propensity-adjusted difference=0.15%; 95% CI -1.7 to 2.0; p=0.57) or pT3 cancer (42.6% versus 39.7%; propensity-adjusted difference=2.9%; 95% CI -6.2 to 0.2; p=0.07). The pooled analyses showed highly heterogenous results among studies (p<0.0001).

**Other outcomes**

As described in the previous evidence note, observational studies reported similar rates of recurrence-free survival and PSA relapse for both procedures, and showed no statistically significant difference in urinary continence at 12 months or postoperative erectile function. The RCT found a significant difference in pain scores in favour of LRP only on the day after surgery, and meta-analysis of observational studies showed no significant difference in postoperative analgesia. No new secondary evidence pertaining to these outcomes was identified.

**Quality of life**

The UK HTA identified two reports by the same investigators in Japan who used the Short Form questionnaire-36 items (SF-36) to assess health-related quality of life (HRQoL) up to 12 months after ORP and LRP. The investigators concluded that open (retropubic and perineal) and laparoscopic approaches performed by an experienced surgeon appeared to be equivalent in terms of HRQoL at 12 months.

**RALRP versus ORP**

RALRP has not been compared with ORP in an RCT.

**Operative time**

Meta-analysis of observational studies comparing RALRP with ORP by any surgical approach showed a statistically significantly longer operative time for RALRP (weighted mean difference (WMD)=36 minutes; 95% CI 18 to 54; p=0.0001). The analysis revealed substantial heterogeneity (I²=97%, indicating that 97% of the variation among studies was not due to chance). A meta-analysis restricted to studies of retropubic ORP showed no significant difference in operative time between open surgery and RALRP (WMD=-15.8 minutes; 95% CI -68.6 to 37.0; p=0.56; I²=97.8%).

**Length of stay**

Meta-analysis of observational studies comparing RALRP with ORP showed a statistically significant reduction in the length of hospital stay following RALRP (WMD=-1.5 days; 95% CI -2.1 to -0.9).
p<0.0001), again with substantial heterogeneity (I²=99.3%)\textsuperscript{15}. Studies conducted in Europe showed a mean reduction of 2 days (95% CI 1.2 to 2.8)\textsuperscript{15}. Meta-analysis combining data from comparative and single-arm studies also showed a statistically significant reduction in length of hospital stay following RALRP compared with retropubic ORP both in studies conducted in the USA (propensity-adjusted difference=1.69 days; 95% CI 1.5 to 1.9; p<0.0001) and in non-USA studies (propensity-adjusted difference=3.65 days; 95% CI 2.8 to 4.5; p<0.0001)\textsuperscript{16}.

**Catheterisation**

Observational studies comparing RALRP with retropubic ORP reported insufficient data on postoperative catheterisation times to enable meta-analysis\textsuperscript{10}. The studies identified reported mixed results\textsuperscript{10}.

**Positive surgical margins**

Meta-analysis of observational studies comparing RALRP with ORP by any surgical approach showed a statistically significant reduction in the rate of positive margins in favour of RALRP in patients with stage pT2 cancer (ORP 18%; RALRP 11%; relative risk (RR)=0.67; 95% CI 0.51 to 0.88; p=0.004; I²=25.6%), but not in patients with stage pT3 cancer (ORP 45%; RALRP 50%; RR=1.11; 95% CI 0.86 to 1.42; p=0.42; I²=53.3%)\textsuperscript{15}. When all studies were combined regardless of cancer stage, there was no statistically significant difference between the two procedures in the rate of positive margins (ORP 23%; RALRP 20%; RR=0.89; 95% CI 0.74 to 1.07; p=0.22; I²=74.6%)\textsuperscript{15}. A meta-analysis restricted to retropubic ORP similarly showed no difference in positive margin rates overall (ORP 45%, RALRP 50%; odds ratio (OR)=1.21; 95% CI 0.91 to 1.63; p=0.19; I²=80.7%), but also showed no difference in pT2 cancer (12% versus 11%; OR=1.25; 95% CI 0.81 to 1.93; p=0.19; I²=58.5%)\textsuperscript{15}. The latter findings are consistent with meta-analysis of data from comparative and single-arm studies that reported overall PSM rates of 16.2% for RALRP and 24.2% for ORP, but no statistically significant difference after propensity score adjustment overall (adjusted difference=0.29%; 95% CI -1.9 to 2.4; p=0.79) or in pT2 cancer (16.6% versus 10.7%; adjusted difference=0.17%; 95% CI -1.7 to 2.0; p=0.86) or pT3 cancer (42.6% versus 37.2%; adjusted difference=-3.91%; 95% CI 7.3 to -0.5; p=0.03 (not significant on adjustment for multiple comparisons)). The pooled analyses showed highly heterogenous results among studies (p<0.0001)\textsuperscript{16}.

**Biochemical recurrence**

Meta-analysis of observational studies comparing retropubic ORP with RALRP showed no statistically significant difference in biochemical recurrence-free (PSA ≥0.2 ng/ml) survival (hazard ratio (HR)=0.9; 95% CI 0.7 to 1.2; p=0.53)\textsuperscript{12}.

**Functional outcomes**

Meta-analysis of observational studies comparing RALRP with ORP by any surgical approach showed a statistically significant difference in urinary continence in favour of RALRP at 12 months (RR=1.06; 95% CI 1.01 to 1.12; p=0.027; I²=58.8%), and also at 3 and 6 months\textsuperscript{15}. Continence was defined as the use of 0–1 incontinence pads per day\textsuperscript{15}. A meta-analysis restricted to retropubic ORP similarly showed a significant difference in continence recovery at 12 months in favour of RALRP (OR=1.53; 95% CI 1.04 to 2.25; p=0.03; I²=62.4%)\textsuperscript{11}.

Meta-analysis of observational studies comparing RALRP with ORP showed a significantly higher proportion of patients with adequate sexual function at 12 months following RALRP (RR=1.56; 95% CI 1.27 to 1.92; p<0.0001)\textsuperscript{15}. A meta-analysis restricted to retropubic ORP showed similar results (expressed as sexual dysfunction) in favour of RALRP (OR=2.84; 95% CI 1.48 to 5.43; p=0.002)\textsuperscript{13}. Sexual function was defined as the ability to maintain an erection sufficient for intercourse with or without the use of oral phosphodiesterase type 5 (PDE5) inhibitors, determined by interview or validated questionnaire. Both meta-analyses demonstrated considerable heterogeneity (I²=70.7% and 82.1%, respectively).

**Quality of life**

The UK HTA failed to identify comparative studies of RALRP and ORP reporting on general HRQoL\textsuperscript{14}.

### RALRP versus LRP

**Operative time**

Both RCTs found no statistically significant difference in operating time between LRP and RALRP\textsuperscript{18,19}. Meta-analysis combining one of the RCTs together with observational studies that compared RALRP with LRP showed no statistically
significant difference in operative time (WMD=-24 minutes; 95% CI -51 to 3; p=0.079) with substantial heterogeneity (I²=97.0%)\textsuperscript{15}.

Another meta-analysis also showed no significant difference between LRP and RALRP (WMD=34.8 minutes; 95% CI -1.36 to 70.93; p=0.06; I²=86.1%)\textsuperscript{10}. MTC meta-analysis in the UK HTA, when restricted to observational studies that directly compared RALRP with LRP (in order to minimise the effect of substantive variation in how this outcome was defined and measured) did show a statistically significant reduction in operative time in favour of RALRP (WMD=-12.4 minutes; 95% central credible interval (CrI) -16.5 to –8.1)\textsuperscript{14}. The authors advised caution in interpreting this finding because of uncertainty as to whether all studies included robot docking time (generally 15–20 minutes) in the operative time\textsuperscript{14}.

**Length of stay**

One RCT reported mean length of stay, showing no difference between RALRP (4.6 days, standard deviation (SD) -2.1) and LRP (4.8 days, SD 1.9)\textsuperscript{19}. The UK HTA authors decided against meta-analysis of length of hospital stay given the diversity in how this was measured\textsuperscript{14}. In the other HTA, meta-analysis of observational studies showed a statistically significant reduction in length of hospital stay for RALRP compared with LRP (WMD=-0.64 days; 95% CI -1.19 to -0.09; p=0.022) with substantial heterogeneity among studies (I²=91.2%)\textsuperscript{15}. When studies conducted in the USA were omitted, the difference was no longer statistically significant\textsuperscript{15}. Conversely, meta-analysis combining data from comparative and single-arm studies showed a statistically significant reduction in length of stay following RALRP compared with LRP both in studies conducted in the USA (propensity-adjusted difference=0.78 days; 95% CI 0.7 to 0.9; p<0.0001) and in non-USA studies (propensity-adjusted difference=1.04 days; 95% CI 0.3 to 1.8; p=0.005)\textsuperscript{16}.

**Catheterisation**

Both RCTs reported mean catheterisation durations of 7–7.5 days for both procedures\textsuperscript{18,19}. Considerable variation in postoperative catheterisation policies and outcome measures in observational studies precluded meta-analysis in the UK HTA\textsuperscript{14}. Two of the four observational studies that directly compared RALRP with LRP reported a shorter duration of catheterisation for LRP and two reported a shorter duration for RALRP\textsuperscript{14}.

**Positive surgical margins**

Both RCTs found no statistically significant difference in positive margin rates overall (LRP 10.0%, RALRP 15.4%; p=0.39\textsuperscript{18} and LRP 20.0%, RALRP 26.6%; p=0.39\textsuperscript{19}) or in pT2 or pT3 cancers, although patient numbers were low and PSM rate was not the primary outcome. Meta-analysis of one of the RCTs together with observational studies in the Irish HTA and another systematic review also showed no statistically significant difference in positive margin rates between RALRP and LRP, overall\textsuperscript{12,15} or in pT2\textsuperscript{12,15} or pT3\textsuperscript{15} subgroups. The positive margin rates in the HTA meta-analysis were 16% for RALRP and 18% for LRP overall (RR=0.93; 95% CI 0.70 to 1.22; p=0.58); 14% and 15%, respectively in pT2 cancers (RR=0.92; 95% CI 0.63 to 1.34; p=0.68); and 46% and 41% in pT3 cancers (RR=1.09; 95% CI 0.69 to 1.72; p=0.71)\textsuperscript{15}. The other review reported similar positive margin rates of 18% for both LRP and RALRP overall, and 12% and 11% in the pT2 cancer subgroup\textsuperscript{12}.

Conversely, meta-analysis combining data from comparative and single-arm studies did show a statistically significant difference in positive margin rates in favour of RALRP over LRP after propensity score adjustment, overall (16.2% versus 20.4%; adjusted difference=3.02%; 95% CI 1.1 to 5.0; p=0.002) and for pT2 cancer (10.7% versus 13.0%; adjusted difference=2.54%; 95% CI 0.5 to 4.6; p=0.01), but not for pT3 cancer (37.2% versus 39.7%; adjusted difference=3.34%; 95% CI 0.05 to 6.6; p=0.05 (not significant on adjustment for multiple comparisons))\textsuperscript{16}. The pooled analyses showed highly heterogenous results among studies (p<0.0001)\textsuperscript{16}. MTC meta-analysis in the UK HTA also showed a statistically significant improvement in positive margin rates for RALRP compared with LRP (OR=0.69; 95% CI 0.51 to 0.96) (separate analyses by T-stage were not reported)\textsuperscript{14}. The model predicted the probability of a positive margin following RALRP as 17.0% compared with 23.6% for LRP. However when the MTC meta-analysis was restricted to studies at low risk of bias, the probability that the positive margin rate was lower for RALRP was no longer statistically significant (OR=0.73; 95% CI 0.29 to 1.75)\textsuperscript{14}.
Biochemical recurrence

Although not primary outcomes, one RCT found no statistically significant difference in rates of biochemical recurrence between LRP and RALRP (3% versus 8%; p=0.3)\(^1\)\(^8\) and the other RCT reported no difference in biochemical recurrence-free survival at 1 year (LRP 92.5%, RALRP 98.0%; p=0.190)\(^1\)^9\(^9\). MTC meta-analysis of biochemical recurrence rates up to 1 year after surgery showed no statistically significant difference between RALRP and LRP (OR=0.89; 95% CrI 0.24 to 3.34)\(^1\)^4. Pair-wise meta-analysis based on two observational studies reporting 3-year or 5-year follow up also showed no statistically significant difference in biochemical recurrence-free (PSA ≥ 0.2 ng/ml) survival between LRP and RALRP (HR=0.5; 95% CI 0.2 to 1.3; p=0.14)\(^1\)^1\(^2\).

Functional outcomes

Urinary continence (0–1 pads per day) 3 months after catheter removal was the primary outcome in one RCT, which found a statistically significant higher rate following RALRP compared with LRP (80.0% versus 61.6%; p=0.044)\(^1\)^9. The difference was also statistically significant at 12 months\(^1\)^9. The other RCT found no statistically significant difference in urinary continence (no leakage or need of pads) between LRP and RALRP at 12 months, or in time to continence\(^1\)^8. Meta-analysis of observational studies comparing RALRP with LRP showed a statistically significant difference in favour of RALRP at 12 months (RR=1.09; 95% CI 1.02 to 1.17; p=0.013; I²=0%), and at 6 months, but not at 3 months\(^1\)^1\(^5\). Continence was defined as the use of 0–1 pads per day\(^1\)^1\(^5\). A similar meta-analysis showed a statistically significant difference in urinary continence in favour of RALRP at 12 months (RR=1.09; 95% CI 1.02 to 1.17; p=0.013; I²=0%), and at 6 months, but not at 3 months\(^1\)^1\(^5\). Quality of life

The UK HTA identified insufficient data to assess any difference in quality of life following RALRP or LRP, and identified no comparative studies of RALRP and LRP reporting on postoperative or long-term pain\(^1\)^1\(^4\).

Safety

- **LRP versus ORP**

  **Blood loss and transfusion**

  In the only RCT, retropubic ORP was associated with significantly higher blood loss and need for transfusion than LRP\(^1\). Meta-analysis using data from comparative and single-arm studies also showed statistically significant differences favouring LRP over retropubic ORP for blood loss (propensity-adjusted difference=363.1 ml; 95% CI 272.4 to 453.8; p<0.0001) and transfusion rates (propensity-adjusted difference=8.89%; 95% CI 4.8 to 13.0; p<0.0001)\(^1\)^1\(^6\). Complications

  Meta-analysis of comparative and single-arm studies showed no significant difference in total intraoperative complication rates (proportion of patients experiencing the event) between retropubic ORP and LRP (1.5% versus 1.6%; propensity-adjusted difference=-0.32%; 95% CI -1.0 to 0.4; p=0.93) or perioperative complication...
evidence note

rates (within 30 days of surgery) (17.9% versus 11.1%; propensity-adjusted difference=5.24%; 95% CI -0.7 to 11.1; p=0.08)\textsuperscript{16}. The pooled analyses showed highly heterogenous results among studies (p<0.0001)\textsuperscript{16}. The authors also reported meta-analyses for 21 specific complications, showing statistically significant propensity-adjusted differences in readmission, rectal injury and fistula in favour of ORP, and in ureteral injury, deep vein thrombosis (DVT), pneumonia, anastomotic leakage and wound infection in favour of RALRP\textsuperscript{16}. Mortality rates were low for both procedures (ORP 0.1%, RALRP 0.04%) and not statistically significantly different after propensity score adjustment\textsuperscript{16}.

\textbf{RALRP versus ORP}

\textbf{Blood loss and transfusion}

Meta-analysis of observational studies comparing RALRP with ORP showed a statistically significant reduction in blood loss for RALRP (WMD=-516 ml; 95% CI -596 to -437; p<0.0001) but substantial heterogeneity ($I^2=99.0\%$)\textsuperscript{15}. Meta-analysis also showed a statistically significant reduction in the need for transfusion with RALRP (RR=0.21; 95% CI 0.15 to 0.30; p<0.0001; $I^2=23.7\%$)\textsuperscript{15}. A meta-analysis restricted to studies of retropubic ORP\textsuperscript{10} and meta-analysis of comparative and single-arm studies of retropubic ORP and RALRP\textsuperscript{16} reached the same conclusion.

\textbf{Complications}

A meta-analysis of complications reported in observational studies comparing RALRP with ORP showed a lower complication rate for RALRP with borderline statistical significance (RR=0.72; 95% CI 0.52 to 1.00; p=0.049; $I^2=73.0\%$)\textsuperscript{15}. A meta-analysis restricted to retropubic ORP reported no statistically significant difference in overall complications (OR=1.25; 95% CI 0.53 to 2.93; p=0.61; $I^2=94.7\%$)\textsuperscript{10}. Conversely, meta-analysis combining data from comparative and single-arm studies reported statistically significant reductions in total intraoperative complications (0.4% versus 1.5%; propensity-adjusted difference=1.15%; 95% CI 0.7 to 1.6; p<0.0001) and perioperative (within 30 days) complications (7.8% versus 17.9%; propensity-adjusted difference=13.76%; 95% CI 9.5 to 18.0; p<0.0001) in favour of RALRP over retropubic ORP. The pooled analyses showed highly heterogenous results among studies (p<0.0001)\textsuperscript{16}. Meta-analyses of specific complications showed statistically significant differences in favour of RALRP for readmission, ureteral injury, DVT, haematoma, lymphocele, anastomotic leakage, and wound infection\textsuperscript{16}.

\textbf{RALRP versus LRP}

\textbf{Blood loss and transfusion}

Both RCTs comparing RALRP with LRP found that blood loss was similar for the two procedures\textsuperscript{18,19}. Meta-analyses of one of the RCTs together with observational studies comparing RALRP with LRP also found no statistically significant reduction in blood loss, with substantial heterogeneity (WMD=-72 ml; 95% CI -148 to 5; p=0.066; $I^2=98.2\%$)\textsuperscript{15}. Two meta-analyses of transfusion rates combining the RCT with observational studies comparing RALRP with LRP reported conflicting results, one showed no statistically significant difference (RR=0.66, 95% CI 0.32 to 1.36; p=0.26; $I^2=38.7\%$)\textsuperscript{15} whereas the other showed a statistically significant difference in favour of RALRP (OR=2.56; 95% CI 1.32, 4.96; p=0.005; $I^2=31.0\%$)\textsuperscript{10}. Meta-analysis combining data from comparative and single-arm studies showed a statistically significant reduction in blood loss for RALRP compared with LRP (propensity-adjusted difference=127.8 ml; 95% CI 95.4 to 160.2; p<0.0001), but no statistically significant difference in transfusion rates (1.8% versus 4.7%; propensity-adjusted difference=1.02%; 95% CI -0.1 to 2.1; p=0.07)\textsuperscript{16}. Similarly, MTC meta-analysis found no statistically significant difference in the need for blood transfusion between RALRP and LRP (OR=0.71; 95% CrI 0.31 to 1.62)\textsuperscript{14}. However, when the analysis was restricted to studies at lowest risk of bias, the direction of effect changed to favour LRP over RALRP (OR=1.45; 95% CrI 0.38 to 6.21)\textsuperscript{14}.

\textbf{Complications}

Both RCTs reported finding no significant difference in complication rates between LRP and RALRP although neither RCT had complications as a primary outcome\textsuperscript{18,19}. Two meta-analyses including one of the RCTs together with observational studies comparing RALRP with LRP also showed no statistically significant difference in complication rates (RR=0.96; 95% CI 0.53 to 1.73; p=0.90; $I^2=63.4\%$\textsuperscript{15}; and OR=1.40, 95% CI 0.73 to 2.69; p=0.31; $I^2=79.2\%$\textsuperscript{10}).
Both of the meta-analytic studies that included indirect evidence reported on specific complications. MTC meta-analysis in the UK HTA found no statistically significant differences between RALRP and LRP for bladder neck contracture, wound or urinary infection, ileus, or DVT. There were statistically significant reductions in anastomotic leaks (OR=0.21; 95% CI 0.05 to 0.76) and organ (rectum, ureter, bowel) injury (OR=0.16; 95% CI 0.03 to 0.76) in favour of RALRP. Meta-analysis combining data from comparative and single-arm studies showed statistically significant reductions in total intraoperative complications (0.4% versus 1.6%; propensity-adjusted difference=1.10%; 95% CI 0.7 to 1.5; p<0.0001) and perioperative (within 30 days) complications (7.8% versus 11.1%; propensity-adjusted difference=6.74%; 95% CI 2.6 to 10.9; p=0.002) in favour of RALRP over LRP. The pooled analyses showed highly heterogenous results among studies (p<0.0001). It reported statistically significant results in favour of RALRP for readmission, reoperation, nerve injury, rectal injury and DVT; but no statistically significant differences between LRP and RALRP for ileus, wound infection or anastomotic leaks. Meta-analysis of pulmonary embolism was not possible in the MTC due to insufficient data whereas meta-analysis incorporating uncontrolled studies showed no statistically significant difference between RALRP and LRP after propensity score adjustment. Mortality rates were low for both procedures (both 0.04%).

Three meta-analyses reported no significant difference in rates of conversion from LRP or RALRP to open surgery. The UK HTA model predicted conversion rates of 0.3% for RALRP and 0.9% for LRP, similar to rates reported in the other meta-analyses.

Learning curve

A recent literature review (2002–2010) did not identify any studies comparing the learning curve for RALRP with ORP or LRP. The review found substantial variation in reported numbers of RALRP cases that a surgeon needs to perform in order to achieve and sustain acceptable operative times and/or outcomes. A systematic review of oncologic outcomes highlighted that published data on the impact of RALRP surgical experience on PSM rates were inconclusive, and noted recent unpublished data from a large multicentre cohort suggesting that it may take around 1,600 procedures to consistently achieve PSM rates <10%.

On combining large case series (>200 men) with data from comparative observational studies, the UK HTA found some evidence of improved positive margin rates with increasing surgical experience (number of procedures performed) for LRP and RALRP; but no evidence of a differential learning effect between the two techniques. This suggested to the authors that the individual surgeon’s rate of learning is the dominant factor rather than the technology used.

Hospital and surgeon volume

A systematic review of published studies (1997–2007) suggested that for RP, high-volume hospitals may have some benefits over low-volume hospitals in terms of lower rates of postoperative complications, readmissions and mortality, but there was insufficient evidence to support conclusions regarding surgeon volume or to determine hospital or surgeon volume thresholds. All of the studies were in patients who had undergone RP in the USA between 1989 and 2003, and variation in definitions of high and low volume precluded meta-analysis. The review did not differentiate between different surgical approaches.

A recent regression analysis using 8,032 RP cases recorded in the British Association of Urological Surgeons (BAUS) Complex Operations Database (2004–2009; open retropubic n=5,429, LRP n=2,219, open perineal n=125, other/not recorded n=259) found a statistically significant association between surgeon case volume and PSM rates (p<0.01). Although follow-up data were limited (4,206 cases; median 9 months, range 1–34), plotting outcomes against surgeon volume showed a trend towards improvements in PSM rates, biochemical relapse, anastomotic stricture, intraoperative complications and blood loss as surgeons’ annual case volume increased (procedure types were not differentiated). The investigators recommended that to improve outcomes, the current recommended threshold in England of 5 cases per surgeon per annum be increased to no fewer than 20, and ideally ≥35.
RALRP in England suggests that each surgeon should ideally undertake ≥50–100 cases per year\(^\text{24}\).

The UK HTA’s economic modelling showed that maintaining a throughput of at least 100–150 procedures per year could reduce the excess cost associated with RALRP compared with LRP\(^\text{14}\).

**Cost effectiveness**

- **RALRP versus ORP**

  An Irish HTA carried out a cost-utility analysis to assess the cost effectiveness of RALRP compared with routine care\(^\text{15}\). Routine care comprised a mix of ORP (93%) and LRP (7%). The analysis therefore essentially assessed the cost effectiveness of RALRP compared with ORP. The model used a lifetime time horizon and was developed from a health system perspective.

  The clinical-effectiveness evidence used in the economic model was drawn from the results of the HTA’s systematic review and meta-analyses described in the clinical effectiveness section of this evidence note\(^\text{15}\).

  Outcomes were measured in quality-adjusted life years (QALYs). Utility values were based solely on differences in urinary function and sexual function between RALRP and the comparator.

  Costs in the model included all robot costs, theatre costs, hospital stay costs, and the costs associated with adverse events. The cost of adjuvant radiotherapy was included within the cost calculations to take into account any difference in PSM rates between the treatment arms.

  The incremental cost per QALY was €26,647 (£21,504) for RALRP compared with routine care (95% CI €14,241 (£11,492) to €61,220 (£49,405)/QALY) (note: all reported costs converted to Great British pounds (GBP) using the exchange rate as 12 December 2012). Based on willingness to pay thresholds, the probability of RALRP being cost effective is 0.20 at a threshold of €20,000 per QALY, 0.63 at €30,000 per QALY, and 0.85 at €40,000 per QALY (for the GBP thresholds, the respective probabilities would be increased).

  The key uncertainties surrounding the economic model are as follows:

  - The model is based on the results from a meta-analysis of mainly observational studies whose results were highly variable. The uncertainty surrounding the inputs to the economic model is inevitably translated to uncertainty surrounding the model outputs.

  - The economic model assumes that QALY gain is achieved only as a result of improved urinary and sexual function post surgery. The meta-analysis showed only a slightly improved outcome for RALRP compared with ORP which diminished between months 3 and 12 of follow up. The HTA authors acknowledge a lack of longer term follow-up data on urinary function post-prostatectomy yet the model assumes that improved urinary function, along with the associated utility gain, is maintained for over 12 years, which is an optimistic assumption.

  - The economic evaluation stated that length of stay was the most influential parameter relating to the incremental cost of RALRP. The base-case analysis assumed that between 99 and 199 prostatectomy procedures are carried out per year for the first 5 years of the model. It was then stated that over the first 5 years, RALRP reduces bed days by 2,415. Based on the number of procedures per year, and the evidence from the meta-analysis (ie that RALRP reduces length of stay by 1.5 days (95% CI 0.9 to 2.0) and 2.0 days (95% CI 1.2 to 2.8) per procedure for all studies and European studies respectively), the bed-day reduction estimates appear anomalous and optimistic.

  In summary, although the results of the economic evaluation suggest that RALRP is cost effective compared with ORP, the results must be treated with caution given the considerable uncertainty surrounding the model inputs and parameter values.

- **RALRP versus LRP**

  A UK HTA conducted a cost-utility analysis to evaluate the cost effectiveness of RALRP compared with LRP\(^\text{14}\).

  A discrete-event simulation model was developed in which the surgical procedure, steps in the care pathway, occurrence of adverse events and ultimately death were modelled for each individual within the model. The model used a 10-year time horizon and was developed from a UK NHS perspective.
The clinical effectiveness evidence used to populate the model was taken principally from the associated systematic review and MTC meta-analysis described in the clinical effectiveness section of this evidence note. Outcomes were measured in QALYs. Utility values for the various health states within the model were obtained from the literature, and covered all cancer management states and adverse event states.

Costs included in the model included robot costs (dual console da Vinci Si HD System®), hospital stay costs, equipment costs, and the costs associated with postoperative care including further cancer treatment.

In the base-case analysis, where it was assumed that a single robot would be used to perform 200 procedures per year, the incremental cost per QALY associated with RALRP compared with LRP was £18,329.

Within the model cost calculations, it is worth noting that the additional procedure cost of RALRP over LRP is approximately £2,000, based on 200 procedures per year per robot.

One-way sensitivity analyses indicated that the main drivers of the results were the number of procedures carried out each year, the respective positive margin rates for RALRP and LRP, and the model time horizon.

- If the number of procedures falls to 150, 100 and 50 per year, the respective costs per QALY are £28,172, £47,822, and £106,839.
- The base case assumes a significant difference in PSM rates between RALRP and LRP (OR 0.69; 95% CrI 0.51 to 0.96). If the difference in positive margin rates used in the model was assumed to be the lower (0.51) and upper (0.96) CrI limits, the cost per QALY would be £11,731 and £50,502, respectively.
- If the base-case analysis is altered to incorporate a lifetime time horizon, the incremental cost per QALY falls to £1,436.

The key uncertainties surrounding the economic model are as follows:

- The model is based on the results from MTC meta-analysis of mainly observational studies and the limitations of the clinical-effectiveness data therefore also apply to the economic data. When only studies at low risk of bias were included, the meta-analysis of PSM rates showed no significant difference between RALRP and LRP. The assumption of an OR of 0.96 in the model (as shown earlier) resulted in an incremental cost per QALY of £50,502. If no difference in positive margin rates was assumed (ie, OR=1), the cost per QALY would be even higher and the conclusions of the evaluation would change.

- Within the model, it is estimated that RALRP results in fewer postoperative cancer-related treatments and deaths than LRP based largely on the assumption that positive margins are predictive of cancer control. As this assumption has an impact upon both the cost and QALY aspects of the model, it is likely to have an important impact upon the overall conclusions of the evaluation. The HTA authors admit that it is unclear in the literature how the observed differences in positive margins impact on cancer recurrence and long-term efficacy outcomes.

In summary, although the results of the economic evaluation suggest that RALRP is cost effective compared with LRP, the results must be treated with caution. There is uncertainty regarding the model inputs, particularly surrounding the differences in, and long-term impact of, PSM's.

**Conclusion**

Based on evidence from one RCT and observational studies, LRP takes longer to perform than open surgery but is associated with less intraoperative blood loss, lower transfusion rates and a shorter length of hospital stay. The evidence reviewed did not show a difference in PSM rates, PSA relapse, recurrence-free survival, urinary continence, erectile function, or intraoperative or perioperative complications.

Based on evidence from observational studies, RALRP takes longer to perform than open surgery but is associated with less intraoperative blood loss, lower transfusion rates and a shorter length of hospital stay. The evidence reviewed did not show a difference in PSM rates overall or in T3 cancer, and is inconsistent on whether or not RALRP reduces PSM rates in T2 cancer. The evidence shows better urinary continence and erectile function at 1 year following RALRP, but did not show a difference in biochemical
reurrence-free survival. The evidence is inconsistent on whether or not RALRP is associated with fewer intraoperative or perioperative complications than open surgery.

Based on two RCTs and observational studies, there is no consistent evidence of a difference in operative time or length of hospital stay between LRP and RALRP. The evidence is also inconsistent on whether or not RALRP reduces blood loss, transfusion rates or PSM rates, or improves urinary continence or erectile function outcomes compared with LRP. There is no evidence of a difference in biochemical recurrence or in overall intraoperative or perioperative complications.

There is insufficient evidence to conclude that any procedure is superior with respect to postoperative pain or HRQoL and, to date, there is a lack of evidence on long-term clinical effectiveness following RALRP. There was some evidence of improvement in prostatectomy outcomes with increasing surgeon volume, but no evidence of a difference in the learning curve based on PSM rates comparing LRP with RALRP.

The authors of the secondary sources used to inform this evidence note concur that the quality of the clinical effectiveness evidence is poor, and that its interpretation needs to take account of its limitations. The RCT reports do not provide reassurance that steps were taken to avoid selection bias, and over half of the comparative observational studies were retrospective or used historical controls.

The published meta-analyses are based primarily on observational studies and show substantial statistical heterogeneity for most outcomes including key outcomes (PSM rates, urinary continence, and erectile function) used in the economic evaluations. The secondary evidence also illustrates that meta-analysis results are variable, even contradictory, depending on the meta-analytical method used. Standard pairwise meta-analyses of observational studies did not take account of the potential for bias and confounding in the primary studies, or differences among studies that might have influenced their results. The validity of MTC meta-analysis depends on the assumption that the included studies are similar in terms of potential moderators of relative treatment effects. The UK HTA report does not provide reassurance that the studies were sufficiently homogeneous to combine, and exploration of statistical heterogeneity consisted of repeating the analyses including only data from studies considered to be at low risk of bias. When this was done for PSM rates, a key parameter used in the economic evaluation, the initial result in favour of RALRP was no longer statistically significant. Further exploration of the heterogeneity was not possible because of variation in pathology protocols, which, the HTA authors cautioned, may have affected the determination of PSM status and thereby increased the risk of bias in the results. Tewari et al. caution that statistical methods (such as propensity scoring) cannot fully correct for differences in outcomes between treatment groups as combined in their meta-analysis, and that the larger quantity of data analysed by including single-arm studies may have produced results that are statistically significant but not clinically important.

The Irish HTA’s economic evaluation found RALRP to be cost effective compared with ORP. The results were driven by improvements in urinary and sexual function, alongside reductions in length of stay. Although the evidence from meta-analysis of observational studies (whose limitations are described) showed some improvement in these outcomes in favour of RALRP, considerable concern that these benefits may have been overestimated in the economic model means that the results must be treated with caution.

The UK HTA’s economic evaluation found RALRP to be cost effective compared with LRP, provided that the number of prostatectomy procedures was greater than 150 per robot per year. One of the key assumptions is that RALRP reduces the PSM rate and that this leads to improvements in long-term cancer control relative to LRP. The evidence supporting these assumptions is inconclusive. Given the uncertainty surrounding the assumptions in the model, caution is warranted when interpreting the results.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.
The evidence note process has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

**About evidence notes**

This evidence note will be considered for review 2 years post-publication, and at 2-yearly intervals thereafter. For further information about the evidence note process see http://www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

**Acknowledgements**

Healthcare Improvement Scotland and the Scottish Health Technologies Group (SHTG) invited the following individuals and organisations to peer review the draft evidence note:

- Mr Adam Gaines, Director, Prostate Scotland, patient/public representative
- Professor Sam McClinton, Chairman of the Urological Cancer Charity (UCAN)/Consultant Urologist, NHS Grampian, independent clinical expert
- Mr Alex McMahon, Director of Strategic Planning, Performance Reporting & Information, NHS Lothian, independent clinical expert
- Mr Alan McNeill on behalf of the South East Scotland Cancer Network (SCAN)/Consultant Urological Surgeon, NHS Lothian, independent clinical expert
- Dr Alex Stirling, Specialty Registrar in Public Health, Scottish Government Health and Social Care Directorates, independent clinical expert
- Mr K Satchi Swami, Consultant Urologist, NHS Grampian, independent clinical expert
- Mr Seamus Teahan, Consultant Urological Surgeon, NHS Forth Valley, independent clinical expert
- Intuitive Surgical Inc., manufacturer of technology

Declarations of interest were sought from all peer reviewers. All contributions from peer reviewers were considered by the group. However the peer reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

Healthcare Improvement Scotland development team

- Heather McIntosh, Lead Author/Health Services Researcher
- Edward Clifton, Author/Senior Health Economist
- Paul Herbert, Information Scientist
- Emma Riches, Medical Writer
- Doreen Pedlar, Project Co-ordinator
- Marina Tudor, Team Support Administrator
- Members of the SHTG evidence review committee

© Healthcare Improvement Scotland 2013
ISBN 1-84404-948-5
References


References continued


