da Vinci Surgery in Urology

Clinical Literature, Health Economics and HTA update 2011 to 2013

Robotic surgery's primary contribution has centered on its ability to enable complex surgeries to be performed in a minimally invasive fashion while providing excellent clinical outcomes. Prior to the introduction of robotic surgery, the percentage of prostate cancer treated with minimally invasive surgery (MIS) was a small minority. Save for a handful of highly trained surgeons, the precision, articulation, and vision necessary to safely and efficaciously complete these procedures did not allow meaningful adoption of MIS. Some of the advantages of *da Vinci* compared to open or conventional laparoscopic approaches include:

- Superior visualization of tissue planes, target anatomy, and the neurovascular bundles
- Meticulous dissection of the prostate and surrounding structures
- Precise suturing of the dorsal vein complex, posterior reconstruction, and urethrovesical anastomosis
- Traction and counter-traction of the prostate, bladder, and adjacent anatomy through the use of the third instrument arm
- Better ergonomic positioning for the surgeon seated at the operating console

In the following we will summarize key results of recently published data (2011 – 2013) clinical and economic data comparing either RARP versus ORP or minimal invasive RP (RALP however strongly dominated the MIRP arm) versus ORP.

Clinical evidence studies

High level 2011 to 2013 clinical evidence consistently and repeatedly demonstrates improved patient relevant outcomes for RALP when compared to ORP.

Meta-analysis comparing RALRP with ORP and LRP

- Novara et al., 2012A
- Novara et al., 2012B
- Ficarra et al., 2012A
- Ficarra et al, 2012B
- Tewari et al., 2012

Large national real world database analysis

- Trinh et al., 2012
- Kowalczyk et al., 2012
- Liu et al., 2013

Please note: The database analysis by Kowalczyk et al. 2012 and Liu et al. 2013 compared open radical prostatectomies with minimal invasive radical prostatectomies (combined traditional lap and robotic).

However, as the robotic assisted prostatectomy dominates the US radical prostatectomy market the findings of these studies are strongly representative for RARP outcomes.

Health Technology Assessments (HTA)

The clinical and economic value of da Vinci surgery when compared to traditional open or laparoscopic surgery has been assessed and endorsed by various independent and internationally well recognized HTA organizations.

Recent HTAs have endorsed clinically superior results of da Vinci surgery for various patient relevant outcomes. In addition the cost-effectiveness of da Vinci surgery has also been repeatedly demonstrated.

<u>Governmental literature reviews / HTAs and Clinical Guidelines</u>

- HTA Ireland HIQA 2012 **HIQA 2012**
- HTA UK NIHR 2012 **Ramsay 2012**
- Evidence Note Scotland: **Healthcare Improvement Scotland 2013**, NICE accredited
- Clinical Guideline UK: NICE 2013 Prostate Cancer **NICE Guideline DRAFT 2013**

High Quality Health Economic Analysis

Three most recent high quality health economic analysis have consistently established the cost-effectiveness of da Vinci prostatectomy versus various alternative treatment modalities.

• Ireland Cost per QALY	HIQA 2012	**HIQA 2012**
• UK Cost per QALY	NIHR 2012	**Ramsay 2012**
• US Cost per QALY		**Cooperberg 2012**

Result summary of high quality Health Economic studies

A) Ireland: Health Economic Analysis as part of the independent HIQA HTA

Methodology: Probabilistic model to simulate the impact on costs and outcomes of introducing robot-assisted prostatectomy compared to open prostatectomy.

Key findings: The base case analysis of the prostatectomy model (based on 200 procedures annually) predicted an incremental cost effectiveness ratio (ICER) of €26,647 per quality adjusted life year (QALY). According to Internationally widely accepted criteria, cost-effectiveness is demonstrated if the cost per QALY is < 35.000 EUR. Therefore, the base case in this model demonstrates that daVinci prostatectomy when compared to open surgery is a cost-effective intervention and provides thus significant value for money to the payer.

Additional comments: The model has been informed by clinical literature until 2011. As demonstrated in this paper since 2011 a number of strongly payer relevant clinical data on reduced length of stay and reduced intra- and perioperative complications have been published. If these additional findings were incorporated into the model, the ICER would even further decrease. A scenario where da Vinci surgery compared to open prostatectomy is cheaper and better is realistic depending on the cost savings of avoided complications as well as the total number of avoided hospital days.

B) UK: Health Economic study as part of the UK NHS NIHR HTA

Methodology: State of the art discrete-event simulation model reflecting the likely care pathways of da Vinci prostatectomy compared to traditional laparoscopic prostatectomy. Parameter estimates were derived from the systematic review of clinical effectiveness, a review of previous economic evaluations, other literature, the expert advisory group and other UK sources. The outputs of the model were costs and quality-adjusted life-years (QALYs) for each procedure, incremental costs and QALYs, and incremental cost per QALY

for a 10-year time horizon. Probabilistic sensitivity analysis was performed to explore the uncertainty surrounding parameter estimates. This was combined with deterministic sensitivity analysis around variables believed to be key determinants of cost-effectiveness, including cost of the robotic system, number of procedures performed, positive margin rates and risk of biochemical recurrence.

Results: In the base-case analysis the incremental cost per QALY for robotic prostatectomy was < £30,000 provided that the number of procedures performed per year with each robotic system was > 150. The probabilistic sensitivity analysis showed that the two procedures had a roughly equal likelihood of being considered cost-effective. The results of the economic evaluation suggested that when the difference in positive margin rate estimated by meta-analysis of all included studies was used (base case), robotic radical prostatectomy was on average associated with an incremental cost per QALY that was less than the threshold value typically adopted by the UK NHS (£30,000) when the number of cases performed per year was ≥ 150.

C) US: Cooperberg et al. 2012

Methodology: A Markov model was constructed to follow men with low-, intermediate-, and high-risk prostate cancer over their lifetimes after primary treatment; probabilities of outcomes were based on an exhaustive literature search yielding 232 unique publications. In each Markov cycle, patients could have remission, recurrence, salvage treatment, metastasis, death from prostate cancer, and death from other causes. Utilities for each health state were determined, and disutilities were applied for complications and toxicities of treatment.
Perspective: Costs were determined from the USA payer perspective.
Key findings: From a US payer perspective cost of da Vinci radical prostatectomy were the lowest compared to any other treatment alternative for low risk, medium risk and high risk patients. da Vinci Surgery resulted in most cases in higher and in some case at least equivalent quality adjusted life year improvements (QALYs). Therefore robotic assisted surgery is a dominant (better and cheaper) or cost minimizing (cheaper and at least as good) treatment alternative for radical prostatectomy from a US payer perspective.

Mean discounted costs, QALYs and undiscounted survival. Copied from Cooperberg et al. table 5.

Treatment method	Mean (SD)			
	Costs, $	QALYs	Life years	% prostate cancer death
Low risk				
EBRT+BT	40 588 (3573)	10.7§ (0.5)	16.2 (0.7)	7.4 (3.9)
BT	25 067‡ (2213)	10.8§ (0.5)	16.2 (0.7)	6.9 (2.8)
3DCRT	27 626 (1830)	10.3 (0.4)	15.5 (0.6)	12.1 (2.4)
IMRT	37 718 (3033)	10.8§ (0.4)	16.2 (0.7)	6.9 (2.7)
ORP	20 245* (2701)	11.3† (0.4)	16.7 (0.6)	2.6 (2.1)
RARP	19 901* (2684)	11.3† (0.4)	16.7 (0.6)	2.7 (1.9)
LRP	20 497* (2877)	11.3† (0.4)	16.7 (0.6)	2.7 (2.1)
Intermediate risk				
EBRT+BT	43 566 (4218)	10.1§ (0.5)	15.3 (0.7)	13.3 (5.0)
BT	32 553‡ (3311)	9.6 (0.5)	14.6 (0.7)	21.2 (5.1)
3DCRT	30 838 (2699)	9.7 (0.5)	14.8 (0.7)	18.5 (4.4)
IMRT	44 639 (3096)	9.6 (0.4)	14.7 (0.6)	19.0 (3.7)
ORP	28 589* (5457)	10.4† (0.6)	15.6 (0.9)	13.0 (6.0)
RARP	28 017* (5453)	10.5† (0.6)	15.6 (0.8)	12.8 (5.9)
LRP	29 041* (5581)	10.4† (0.6)	15.6 (0.8)	13.4 (6.3)
High risk				
EBRT+BT	50 276 (4667)	9.1§ (0.6)	14.1 (0.9)	23.6 (7.1)
BT	43 952** (3477)	7.8 (0.5)	12.1 (0.8)	43.0 (5.9)
3DCRT	42 397** (2348)	7.9 (0.4)	12.5 (0.6)	38.2 (3.6)
IMRT	53 539 (4013)	8.2 (0.6)	12.9 (0.8)	34.2 (6.0)
ORP	36 279* (5902)	9.2 (0.8)	13.9 (1.1)	27.9 (8.1)
RARP	35 014* (5895)	9.3† (0.8)	14.1 (1.1)	26.8 (8.2)
LRP	35 118* (6085)	9.3† (0.7)	14.2 (1.0)	26.4 (8.2)

Summary of new clinical evidence from meta-analysis and large real world database analysis per outcome parameter

Length of stay

- Meta-analysis of observational studies comparing RALRP with ORP showed a statistically significant reduction in the length of hospital stay following RARP (WMD=-1.5 days; 95% CI -2.1 to -0.9; p<0.0001). Studies conducted in Europe showed a mean reduction of 2 days (95% CI 1.2 to 2.8), Reference HIQA 2012.
- Meta-analysis combining data from comparative and single-arm studies also showed a statistically significant reduction in length of hospital stay following RARP compared with 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), Reference Tewari 2012.
- NSQIP database analysis demonstrated that US length of stay was significantly shorter after minimal invasive prostatectomy (MRIP) when compared to ORP (1.8 vs 3.2 days), Reference Liu 2013.
- Analysis of the US Nationwide Inpatient Sample demonstrates prolonged length of stay (pLOS) rates of 14.5% for RARP and 39.6% for ORP (p < 0.001), Reference Trinh 2012.
    - Length of stay is calculated by subtracting the admission date from the date of discharge. Prolonged length of stay (pLOS) is defined as a hospitalization beyond the75th percentile cut-off point of 2 days.

- Database analysis from a 100% Medicare Sample demonstrated that patients undergoing MIRP instead of ORP experienced shorter lengths of stay (2.0 vs 4.2 d; $p < 0.001$). Reference Kowalczyk 2012.

Oncological outcomes

- Meta-analysis of observational studies comparing RARP with ORP by any surgical approach showed a statistically significant reduction in the rate of positive margins in favor of RARP in patients with stage pT2 cancer (ORP 18%, RARP 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%), Reference HIQA 2012.
- A meta-analysis showed no difference in positive margin rates overall (ORP 21%, RALRP 20%; 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%), Reference Novara 2012A.
- Another large meta-analysis of data from comparative and single-arm studies reported overall PSM rates of 16.2% for RARP and 24.2% for ORP. Unadjusted p-values were statistical significant but no statistically significant difference after propensity score adjustments were demonstrated (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, Reference Tewari 2012.

Functional outcomes

- Meta-analysis of observational studies comparing RARP with ORP by any surgical approach showed a statistically significant difference in urinary continence in favor of RARP 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 as well as 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), Reference HIQA 2012.
- A meta-analysis showed a significant difference in continence recovery at 12 months in favor of RALRP (OR=1.53; 95% CI 1.04 to 2.25; p=0.03; I2=62.4%) as well as sexual dysfunction) in favor of RALRP (OR=2.84; 95% CI 1.48to 5.43; p=0.002), Reference Ficarra 2012B and Ficarra 2012A.

Transfusion

- Meta-analysis of observational studies comparing RARP with ORP showed a statistically significant reduction in the need for transfusion with RALP (RR=0.21; 95% CI 0.15 to 0.30; p<0.0001; I2=23.7%), Reference HIQA 2012
- A meta-analysis demonstrates that transfusion rates are statistically significant in favor of RARP versus ORP (odds ratio [OR]: 7.55; $p < 0.00001$), Reference Novarra 2012B
- A meta-analysis of comparative and single-arm studies of retropubic ORP and RARP showed a statistically significant reduction in transfusion rates in favor of RARP when compared to ORP (1.8% vs. 16.5%, $p < 0.0001$), Reference Tewari 2012.
- In a large data base analysis rates of blood transfusion were significantly higher in the open group (21% vs. 1.3%, P <.0001). When transfusions were required, the median number of units transfused was 1.0 in MIRP compared with 1.5 units in open prostatectomy, Reference Liu 2013.
- In multivariable analyses of propensity score–matched populations, patients undergoing RARP were less likely to receive a blood transfusion (odds ratio [OR]: 0.34; 95% confidence interval [CI], 0.28–0.40), blood transfusion rates were 2.4% and 7.7% ($p < 0.001$), Reference Trinh 2011.

- In large database analysis of a 100% Medicare sample patients treated with a minimal invasive approached received significant less blood transfusions than patients with ORP (3.5–2.2%; p = 0.005), Reference Kowalczyk 2012.

Complications / Safety

- A meta-analysis of complications reported in observational studies comparing RALRP with ORP showed a statistical significant lower complication rate for RALRP: (RR=0.72; 95% CI 0.52 to 1.00; p=0.049; I2=73.0%), Reference HIQA 2012
- A meta-analysis reported no statistically significant difference in overall complications (OR=1.25; 95% CI 0.53 to 2.93; p=0.61; I2=94.7%), Reference Novara 2012B
- A 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 favor of RARP over ORP. Analyses of specific complications showed statistically significant differences in favour of RALRP for readmission, ureteral injury, DVT, haematoma, lymphocele, anastomotic leakage, and wound infection, Reference Tewari 2012.
- An analysis of the US Nation Wide Inpatient Sample demonstrated a rate of intraoperative complications to be 0.4% and 1.0% (p < 0.001) for RARP and ORP, respectively; postoperative complications were 9.3% and 11.1% (p < 0.001), Reference Trinh 2012.
- A NSQIP data base analysis demonstrated that major complication rates for cardiovascular, deep venous thrombosis or pulmonary embolism, deep organ space infection, and surgical site infection were all significantly lower in the MIRP group when compared to ORP. There was a trend toward fewer respiratory complications. Overall complication rate after MIRP was 5% compared with 9% in open prostatectomy (P < 0.0001), Reference Liu 2013.
- The analysis of a 100% Medicare Sample demonstrated less overall perioperative complications for the MIRP group compared to ORP (19.6 vs 29.8%; p < 0.001). MIRP was associated with fewer cardiac (2.2% vs 4.7%), GU (4.8% vs 6.9%), miscellaneous medical (8.8% vs 12.6%), miscellaneous surgical (4.2% vs 6.0%), respiratory (4.1% vs 9.4%), vascular (2.7% vs 4.3%), and wound complications (1.8% vs 3.9%; all p < 0.001), Reference Kowalczyk 2012

Comparison of Prostatectomy	Kowalczyk[i]		Liu[ii]	
	MIRP (dV dominant)	Open Surgery	MIRP (dV dominant)	Open Surgery
Number of Patients	19,594	58,638	4,036	1,283
Total OR Time	Not reported	Not reported	211 min	190 min
Mean Length of Stay	2.0 days	4.2 days	1.81 days	3.16 days
Any Perioperative Complication	19.60%	29.80%	4.98%	9.04%
Death	0.20%	0.60%	0.05%	0.39%
Blood Transfusion	2.60%	17.30%	1.34%	21.36%

Mortality

- An analysis of the NSQIP database demonstrates that mortality was low for ORP and MIRP patients, although it was significantly lower in the MIRP group (0.05%) compared with the open prostatectomy group (0.4%, p =0.1), Reference Liu 2013.
- A meta-analysis demonstrates that mortality rates were in favor of RARP but low for both procedures (ORP 0.1%, RALRP 0.04%). Results were not statistically significantly different after propensity score adjustment, Reference Tewari 2012.
- RRP was associated with an almost threefold greater odds of perioperative death (OR: 2.67; $p < 0.001$) versus MIRP (0.2 vs 0.6%; $p < 0.001$). Reference Kowalczyk 2012.

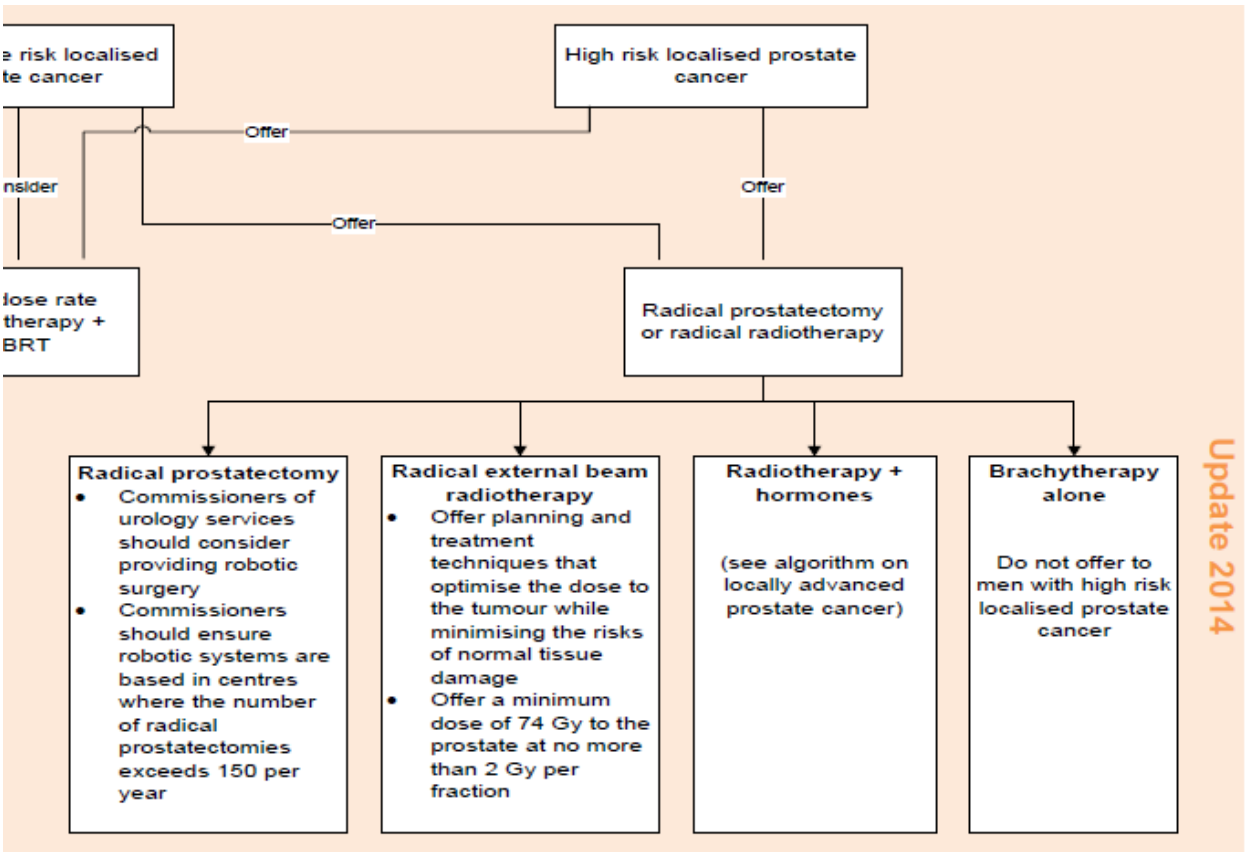
Brief summary of the HTA and clinical Guidelines conclusions and appraisals

HIQA 2012

Martin Flattery, Head of HTA Research and Planning at HIQA, said "The Authority's advice to the HSE is that robot-assisted surgery is superior to conventional open surgery for prostate surgery procedures across a range of outcomes, and is associated with better operative outcomes in conventional open hysterectomy procedures […].

NICE Guideline DRAFT 2013

Commissioners of urology services should consider providing robotic surgery to treat localised prostate cancer. Commissioners should ensure that robotic systems for the surgical treatment of localised prostate cancer are based in centres that perform at least 150 radical prostatectomies per year.



Health Care Improvement Scotland 2013

Robot-assisted laparoscopic surgery takes longer to perform than open surgery but is associated with less intraoperative blood loss, lower transfusion rates, shorter length of stay and better functional outcomes. The evidence on oncological outcomes and complications is inconsistent.

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