Robotic Assisted Prostate Surgery

General Background information and key take-away messages

- The *da Vinci* System is commonly used in Europe, Japan, and the United States. The system was used in over 570,000 procedures globally in 2014 alone. Since regulatory approval well over 2.500.000 patients have received minimally invasive robotic assisted surgery worldwide. In Austria there were in 2014 878 robotic assisted da Vinci surgeries performed on 5 da Vinci systems. AU has among the lowest dV System and dV surgery penetration per capita in Western Europe.
- The *da Vinci* System was designed to address the technical limitations of conventional laparoscopy using computation, mechatronics, 3D imaging technology, and control algorithms to allow surgeons to apply minimally invasive surgery techniques to a broader population of patients, and to improve the experience of minimally invasive surgery for patients and surgeons.
- Due to the above mentioned technical difficulties, conventional minimally invasive surgery is often plateaued at relatively low penetration rates. This is especially true for procedures involving a complex anatomy and cancer procedures. Conventional minimal invasive procedures such as laparoscopic or vaginal procedures may have strong limitations for certain patient groups including in Gynecology procedures women with a large uterus or obesity. Robotic assisted surgery does enable minimal invasive surgery for a larger group of patients than conventional minimal invasive approaches and is typically also faster to learn.
- When assessing the comparative effectiveness of da Vinci surgery, the most relevant comparator is open surgery as open surgery is still the most prevalent type of surgery in the da Vinci target markets. In addition as mentioned above potentially large patients groups may not be suitable for conventional minimal invasive approaches such as vaginal gynecological surgery.
- Analysis of market data after regulatory clearance of the da Vinci System has demonstrated that da Vinci surgery strongly improves the rate of minimal invasive surgery on the cost of invasive open surgeries.
- As demonstrated by Davis 2013 the learning curve of da Vinci is safe at non-inferior or even better safety and effectiveness results. Various studies show that beyond the initial learning curve increased experience is often related with shortened operative time, optimized instrument use and optimized functional outcomes.

- HTAs around the world as well as the 2014 NICE medical guidelines have already endorsed superior outcomes for robotic assisted prostatectomy (RARP, RALP) versus both open (ORP, RRP) and conventional laparoscopic (LRP) surgery for a variety of different outcomes
- There is overall a relative scarcity of large randomized controlled trials especially comparing dV surgery versus the most relevant comparator, open surgery. However, various RCTs pilots were unable to recruit patients (ie LOPERA) and in study advisory boards surgeons have clearly voiced their unwillingness to randomize patients for open versus robotic assisted surgical interventions. Few smaller RCTs comparing conventional laparoscopic and robotic assisted surgery were typically not adequately powered to demonstrate superiority for a variety outcomes but only for the primary outcomes.
- Today few RCTs, prospective comparative studies, systematic reviews and meta-analysis as well large real world retrospective data analysis form the basis for technology assessments of most surgical interventions as well as for robotic assisted surgery. The high relevance of these study types has been increasingly acknowledged by HTA organizations and evidence based medicine thought leaders.
- The best available evidence including RCTs, Meta-Analysis, prospective comparative trials and large real world data studies support superior RARP outcomes when compared to ORP:
    - The best available evidence consistently supports a superior RARP safety profile over ORP for a large variety of safety outcomes.
    - All analyzed studies consistently demonstrate a reduced length of stay in favor or RARP when compared to ORP.
    - A review of the included studies demonstrates a consistently strong oncological safety profile. All studies demonstrated that RARP had either a superior safety profile or a similar safety profile when compared to ORP.
    - The vast majority of analyzed studies demonstrate a superior functional outcomes profile in favor of robotic assisted surgery. The remainer of the studies demonstrates at least similar functional outcomes when compared to ORP with no studies favoring ORP.
    - With the exception of one small outlier study from India, all analyzed studies demonstrated a consistently strong reduction in transfusion rates in favor of RARP versus ORP
    - Overall mortality rates were very low in both groups. RARP seems to trend towards lower mortality rates when compared to ORP
- With the recent launch of the da Vinci Xi System a significant technology advancement has been introduced to the market which will facilitate new market opportunities especially in general surgery. Colorectal and Hernia surgery are currently especially in the US strong growth markets with increasingly developing supportive evidence. In 2014 alone more than 120.000 general surgery procedures have been performed worldwide. Head and Neck and TORS procedures are increasingly experiencing strong interest by surgeons.
- Multispecialty da Vinci programs have the potential to strongly reduce the cost per robotic assisted surgery and can increase the operational efficiency of a da Vinci program. Hospitals

thus are increasingly developing into robotic assisted centers of excellence across a various disciplines.

- Typically costs studies have a very narrow hospital view and these studies are strongly influenced by the individual efficiency of the program and many cost studies are being strongly biased by including learning curve results or sometimes specific hospital inefficiencies which might not be generalizable. US cost studies are often charge based and due to the intransparency of the US charge system the data cannot be transferred across geographies. Two more recent European studies have demonstrated that robotic assisted surgery, when compared to open or laparoscopic surgery results into lower health insurance / national health system payments up to at least 3 years after surgery (Niklas et al. 2015 and Hughes et al, manuscript in development).

Background

I. Overview of Intuitive Surgical's *da Vinci* System

ISI developed the *da Vinci* System to satisfy a need in surgery to broaden use of minimally invasive approaches and to improve the experience of minimally invasive surgery for a broader group of patients and surgeons. Conventional minimally invasive surgery (laparoscopy) advanced relatively quickly in minimizing morbidity and complications in several surgical procedures, particularly those that required relatively little surgical reconstruction (for example, cholecystectomy to treat gallbladder disease, endometriosis resection, and so on). Application of minimally invasive techniques for more complex pathology (e.g. surgery to treat cancer) and those procedures that require significant reconstruction (e.g. pelvic floor reconstruction) had proceeded not only significantly more slowly but also had often plateaued after several years at relatively low penetration rates.

The primary technical limitations of conventional laparoscopy when compared to open surgery are four-fold:

- Most laparoscopic surgery is performed using a two-dimensional image, which inhibits depth perception.
- Movement of long, rigid tubular instruments in laparoscopy is subject to direction reversal due to the pivot of the instrument at the patient's body wall and surgeon tremor, which makes fine instrument movement challenging.
- Most laparoscopic instruments do not have the same freedom of motion as a human wrist inside the body, which constrains the angles at which these instruments can approach tissue.
- The challenging ergonomics associated with conventional laparoscopy can be physically detrimental to the surgeon.

The *da Vinci* System was designed to address the above limitations using computation, mechatronics, and control algorithms. The system incorporates three-dimensional digital cameras and displays to provide an immersive 3D view of the surgical field for the surgeon, enhancing depth perception. The

system uses mechatronic arms to hold and control the instruments, and uses computational algorithms to provide the surgeon intuitive control of these instruments. It uses tubular surgical instruments that incorporate distal wrists that retain the patient benefits of port access while returning to the surgeon the two degrees of freedom of their wrist that were lost in the transition from open surgery to manual laparoscopy. Finally, surgeons are able to operate seated in a comfortable, ergonomic position. The combination of these improvements in visualization, wristed instruments, mechanisms, computer control, and ergonomics increases the precision and control of the instruments compared with manual laparoscopy. **Table 1** below summarizes these key differences.

Laparoscopy Technical Limitation	***da Vinci* System Solution**	**Benefit conferred**
Two-dimensional image	Three-dimensional image	Strengthens depth perception due to additional visual information
Counter intuitive movement	Intuitive movement afforded by mechatronic arms and computational algorithms	Greater precision and control at tool tips for fine tasks like suturing and reconstruction
Long, rigid tubular instruments	Wristed tubular instruments	Returns to surgeon the ability to reach around structures that was lost in transition from open surgery to laparoscopy
Poor ergonomics	Improved ergonomics	Less neuropathies and musculoskeletal problems from high force laparoscopic manipulation, less mental stress and workload

Table 1. How the *da Vinci* System Addresses Key Technical Limitations in Laparoscopy

Figure 1 below shows the key system elements. The *da Vinci* is comprised of a Surgeon's Console and optional dual Surgeon's Console (for training), a Patient Side Cart, and an Imaging System (Vision) Tower.

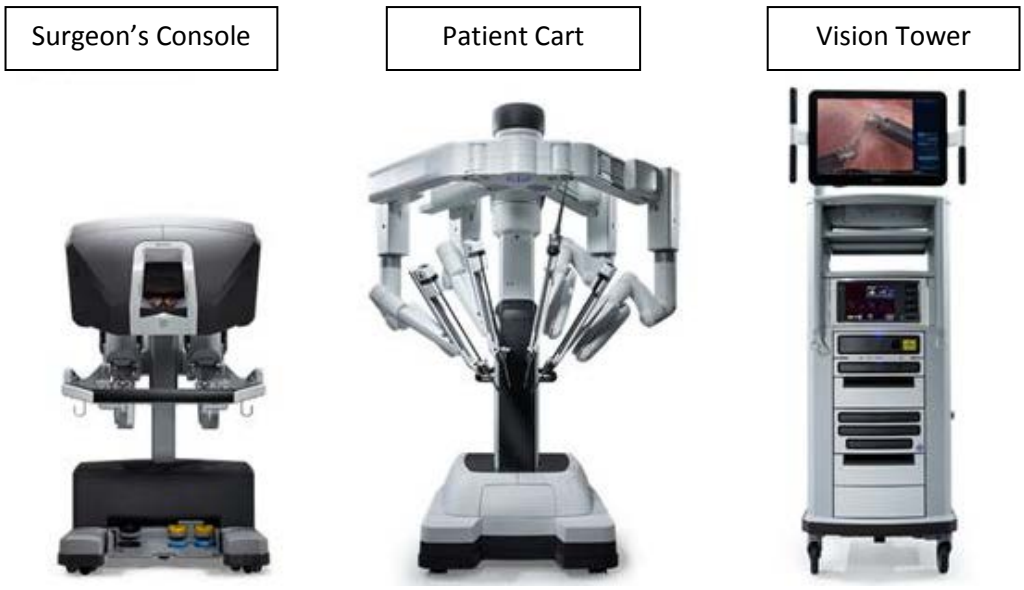

Figure 1: *da Vinci* Surgical System

The *da Vinci* System includes:

- mechatronics and computational algorithms that allow surgeons to intuitively control wristed laparoscopic instruments,
- 3D imaging that displays combined left and right eye images to the surgeon, and
- a suite of instruments and accessories that can perform the same surgical tasks as manual laparoscopy (e.g. scissors, needle drivers, cautery instruments).

The *da Vinci* System is not:

- an autonomous robot – it does not take any surgical action on its own, nor
- a clinical decision maker – there is no attempt to replace surgeon judgment.

As surgical robotics was more broadly adopted, the need for key technologies available in open and laparoscopic surgery was requested for the robotic product lines. This included vessel sealing, stapling, and single site instrument technology. The additional technology has recently expanded the *da Vinci* product offering and has allowed Intuitive Surgical to continue to support its customers' requests.

II. Summary of Significant Clinical Literature on *da Vinci* Assisted Surgery

The *da Vinci* System is a surgical tool that can be used for a variety of surgical procedures. By the end of 2014, over 3,000 systems were in clinical use worldwide, with approximately 570,000 procedures completed in 2014. Well more than 2.500.000 robotic assisted patients have received a robotic assisted da Vinci procedure. The majority of these would have otherwise received an invasive open procedure. The primary surgical specialties using the system in 2014 were gynecologic surgery, urologic surgery, general surgery, thoracic surgery, head and neck surgery (otherwise known as transoral robotic surgery or TORS), and cardiac surgery. The approximate breakdown in procedures for these specialties for 2014 worldwide is shown in **Table 2**.

Surgical Specialty	Approximate Procedures in 2014
Total	**570,000**
Gynecology	252,300
Urology	173,200
General Surgery	120,660
Thoracic	11,700
Head Neck (TORS)	6,800
Cardiac	4,600

Table 2: 2014 Breakdown of Procedures by Specialty

The peer-reviewed clinical literature on the *da Vinci* System is extensive and diverse. There are over 8,500 peer-reviewed clinical publications on the use of the *da Vinci* System across many specialties and patient populations with new publications on the *da Vinci* System releasing at a rate of approximately 150 per month. ISI-sponsored or supported[1] research constitutes less than 1% of these publications.

The data demonstrates that use of the da Vinci System compares favorably to both open and laparoscopic surgery across a variety of measures.

Please see the literature review regarding the comparative effectiveness of robotic assisted radical prostatectomy versus open radical prostatectomy below

In addition please find a separately attached literature overview with abstracts attached to the email.

[1] ISI sponsored or supported literature refers to studies to which ISI contributed funds or data analysis support for the study.

UROLOGY - Prostatectomy

Evidence summary for RARP versus ORP based on clinical evidence from RCTs, prospective comparative trials, meta-analysis and large and established real world database (2010 to 2014).

For detailed information on the references and literature search inclusion criteria please refer to the separate literature reference document.

Safety (Complications /Re-operation/Re-admissions)

The best available evidence consistently supports a superior RARP safety profile over ORP for a large variety of safety outcomes

- 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 favor of RALRP for readmission, ureteral injury, DVT, haematoma, lymphocele, anastomotic leakage, and wound infection, *Reference Tewari 2012.*

- A meta-analysis based on altogether 51 studies comparing RARP versus ORP demonstrates a reduced relative complication risks in favor of RARP when compared to ORP (RR RARP vs. ORP RR 0.74, CI 95% 0.56-1, p=0.047). *Reference Moran 2013.*

- 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 meta-analysis based on 12 included studies reported trends towards better overall complication rates in favor of robotic assisted prostatectomy but these were not statistically significant different. (OR=1.25; 95% CI 0.53 to 2.93; p=0.61; I2=94.7%). However, the inclusion of some studies such as for example Doumerc et al. which is comparing 502 ORP (5/502) patients with only 21 RARP (4/21) may raise significant concerns if the study results are confounded by learning curve factors, *Reference Novara 2012B.*
- A Swedisch nationwide wide prostate cancer database analysis demonstrated a lower 90 days re-admission rate in favor of robotic assisted prostatectomy when compared to either open or conventional laparoscopic surgery. Observed absolute differences were not statistically significantly different. (RARP 9% vs. ORP 10% vs. LRP 11%, p=ns). *Reference Frietheriksson 2014.*
- SEER retrospective database analysis (bivariate) of 5915 patients demonstrated statistically significant lower 90-day overall postoperative complications in favor of RARP vs ORP (RARP 26.0% vs 28.9%, p=0.01) and fewer but statistically not different 30 postoperative complications and 90 day readmission rates (RARP 22.2% and 5.5% vs ORP 23.8%, 5.9%, p = 0.1 and 0.5 respectively. 30 day readmission rates were almost similar (RARP 3.9% vs ORP 3.85, p=0.8). *Reference Gardiner 2014.*

- A large retrospective analysis (5471 patients) of the NSQIP database demonstrated statistically significant reduced RALRP re-admission rates when compared to RRP (RALRP 3.48 vs. RRP 5.47, p=0.002). The same study reports a strong reduction in overall complication rates in favor or robotic assisted surgery (RARLP 5.62% vs. RRP 23.25%, p<0.001). Reoperation rates did statistically not differ between both types of surgery (p=0.698). *Reference Pilecki 2013.*
- A systematic review and meta-analysis from India which included only 6 studies reported fewer perioperative complications. *Reference: Pan (2014*)
- A single center 150 patient prospective comparative analysis of RRP versus RARP demonstrated a reduced rate of major complication in favor of RARP (RRP and RALP were 28% and 7% (p = 0.025), respectively. Minor complication rates were not statistically significant different (p = 0.744). These results include the RARP learning curve. *Reference: Di Pierro (2011)*
- A large 3544 prospective comparative analysis of RARP versus ORP showed a reduced risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in favor of robotic assisted surgery in both patients with and without lymphnode dissection (LPND). The reduced DVT and PE risk in favor of RARP was most prominent in patients not undergoing LPND. *Reference: Tyritzis (2014).*
- An US NIS database comparative analysis of 20,424 surgical interventions (RARP versus ORP) demonstrated a statistically significantly reduced overall complication rate in favor of RARP (RARP 8.2% vs RRP 11.3%, p < 0.001). *Reference: Kim 2012.*
- A very large US NIS database comparative analysis (RARP versus ORP) of 77616 radical prostatectomies demonstrated a superior safety profile in favor of RARP. Both intra-operative complications as well as post-operative complications were statistically significant fewer in the RARP patient group compared to the open patient group (RARP 0.4% vs ORP 1.0%, OR 0.36, 95% CI 0.30-0.44, p < 0.001 and RARP 8.3% vs ORP 11.7% , OR 0.68, 95% CI 0.65 – 0.71) p <0.001 respectively. *Reference: Sammon 2012.*
- Results of a very large prospective controlled trial comparing RALP with RRP confirmed a strong short term safety profile in favor of RARP. Reoperation during initial hospital stay was more frequent after open surgery after adjusting for tumour characteristics and lymph node dissection (1.6% vs 0.7%, odds ratio [OR] 0.31, 95% confidence interval [CI 95%] 0.11-0.90). Men who underwent open surgery were more likely to seek healthcare (for one or more of 22 specified disorders identified prestudy) compared to men in the robot-assisted surgery group (p=0.03). It was more common to seek healthcare for cardiovascular reasons in the open surgery group than in the robot-assisted surgery group, after adjusting for non-tumor and tumor-specific confounders, (7.9% vs 5.8%, OR 0.63, CI 95% 0.42-0.94). The re-admittance rate was not statistically different between the groups. Reference: Wallerstedt 2015.

Length of stay

All analyzed studies consistently demonstrate a reduced length of stay in favor or RARP when compared to ORP. Magnitude of differences also varied by region

- 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.*

- A meta-analysis based on altogether 51 studies comparing RARP versus ORP demonstrates a reduced length of stay both when all studies are analyzed as well as when only European studies are being analyzed (RARP versus ORP -2 days, p<0.0001 and -2.1 days, p<0.0001 respectively). *Reference Moran 2013.*

- SEER retrospective database analysis (bivariate) of 5915 patients demonstrated a statistically significant shorter length of stay in favor of RARP when compared to ORP (RARP 1 day versus ORP 2 days, p<0.001). *Reference Gardiner 2014.*
- 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). Length of stay was 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. *Reference Trinh 2012.*
- Results of a very large prospective controlled trial comparing RALP with RRP confirmed a statistically significant reduction in length of stay in favor of RALP when compared to RRP (3.3 vs 4.1 days, p < 0.001). *Reference: Wallerstedt 2015.*
- A US NIS database comparative analysis of 20,424 surgical interventions (RARP versus ORP) demonstrated a statistically significantly reduced median length of hospital stay in favor of RARP (RARP 1d vs RRP 2d, p < 0.001). *Reference: Kim 2012.*
- A very large US NIS database comparative analysis (RARP versus ORP) of 77616 radical prostatectomies demonstrated a reduced length of stay in favor of RARP. This study reports the percentage of patients with LOS > 2days (RARP 12.9% vs. ORP 40.7%, OR 0.22 (0.21 – 0.22), p<0.001. Reference: *Sammon 2012.*

Oncological outcomes

A review of the included studies demonstrates a consistently strong oncological safety profile. All studies demonstrated that RARP had either a superior safety profile or a similar oncological safety profile when compared to ORP

- A meta-analysis based on altogether 51 studies comparing RARP versus ORP demonstrates fewer surgical margins for pT2 tumors in favor of RARP (RR 0.63, 95% CI 0.49-0.81, p<0.001). *Reference Moran 2013.*

- 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%) and comparative oncological safety profile 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*.

- Results of a large prospective controlled trial comparing RALP with RRP confirmed a similar oncological safety profile (Positive surgical margins: OR 1.09; 95% CI, 0.87-1.35), *Reference Haglind 2015.*
- A SEER retrospective database analysis (bivariate) of 5915 patients demonstrated a statistically significant difference in additional cancer therapy within 6 months after surgery as well as any time after surgery in favor of RARP (RARP 3.6% vs. ORP 6.3%, p<0.001 and respectively RARP 9.0% vs. 12.9%, p<0.001). *Reference Gardiner 2014.*
- A propensity score based SEER retrospective database analysis of 13,434 patients demonstrated a superior RARP versus ORP short to mid-term oncological safety profile based on less overall surgical margin rates and a reduced rate of post op oncological cancer treatment within 6, 12 and 24 months after surgery (RARP 13.6% vs. ORP 18.3% , <0.001; RARP 4.5% vs. 6.2%, p<0.001, RARP vs. ORP OR 0.73, p<0.001 and RARP vs. ORP OR 0.67, p<0.001 respectively. *Reference: Hu 2014*
- A systematic review and meta-analysis from India which included only 6 studies reported no differences in PSM rates. *Reference: Pan (2014)*
- A single center 150 patient prospective comparative analysis of RRP versus RARP demonstrated superior positive margin rates in favor of RARP (RRP 32% versus RARP 16%, p=0.002). These results include the RARP learning curve. *Reference Di Pierro 2011.*

Functional outcomes

The strong majority of analyzed studies demonstrated superior functional outcomes profile in favor of robotic assisted surgery. The remainer of the studies demonstrated similar functional outcomes with no studies favoring ORP

- 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.*
- Results of a large prospective controlled trial comparing RALP with RRP showed that fewer RALP patients were effected by erectile dysfunction when compared to RRP 12 months after surgery (70.4% RALP versus 74.7% RRP (OR 0.81; 95% CI, 0.66-0.98). Differences for urinary continence (OR 1.08; 95% CI, 0.87-1.34) were statistically non-significant. *Reference: Haglind 2015.*
- An double blind RCT with 422 patients of which 189 underwent open surgery, 115 robot-assisted laparoscopy, 88 conventional laparoscopy and 30 patients receiving “other” surgery demonstrates a statistically significant better erectile function (EF) recovery in favor of robotic assisted laparoscopy when compared to open surgery. The odds of achieving EF-recovery were

approximately twice as high in favor of robotic-assisted surgery (OR 2.42, CI 95% 1.24-4.72, p=0.029.

- A systematic review and meta-analysis from India which included only 6 studies statistically difference in potency favoring robotic assisted surgery over open surgery but no statistically significant difference with respect to urinary continence. Reference: Pan (2014)
- A meta-analysis based on altogether 51 studies comparing RARP versus ORP demonstrates improved functional outcomes for both sexual and urinary function favor of RARP (RR 1.60 CI 95% 1.33-1.93, p<0.0001 and RR 1.06, CI 95% 1.02-1.11, p<0.0009 respectively). Reference Moran 2013
- A single center 150 patient prospective comparative analysis of RRP versus RARP demonstrated improved continence at 3 month follow-up in favor of RALP (RRP 83% and RARP 95% (p = 0.003) and better but statistically not different continence rates in favor of RARP at 12 month follow-up (80% and 89% (p = 0.092). RARP patients benefited from improved potency rates at both 3 and 12 months follow-up. Among patients who were potent without phosphodiesterase type 5 inhibitors (PDE5-I) before RRP and RALP, recovery of erectile function with and without PDE5-Is was achieved in 25% (RRP) and 68% (RARP) at 3 mo postoperatively (p = 0.009) and in 26% (RRP) and 55% (RARP) 12 mo postoperatively (p = 0.009). These results include the RARP learning curve.
- A prospective comparative single center analysis of 180 patients demonstrated superior functional outcomes in favor of RARP versus RRP. The median time to continence was 16 days for RARP patients compared to 46 days for RRP patients (p = 0.007). RARP patients also scored better compared to RRP patients in both IPSS scores and almost all categories in the King´s Health Questionnaire. Reference: *Geraerts 2013.*

Transfusion / Bleeding

With the exception of one small outlier study from India, all analyzed studies demonstrated a consistently strong reduction in transfusion rates in favor of RARP versus ORP

- 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 Novara 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 transfusions (odds ratio [OR]: 0.34; 95% confidence interval [CI], 0.28–0.40), blood transfusion rates were RARP 2.4% and ORP 7.7% (p < 0.001), *Reference Trinh 2011.*

- Results of a large prospective controlled trial comparing RALP with RRP demonstrated that the robotic assisted surgery group had statistically significant less bleeding when compared to the RRP group (185ml vs. 683ml, p<0.001). *Reference: Wallerstedt 2015.*
- SEER retrospective database analysis (bivariate) of 5915 patients demonstrated a strong and statistically significant reduced rate of transfusions in the RARP group compared to the ORP patient group (RARP 1.9% vs. ORP 8.9%, p<0.01). *Reference Gardiner 2014.*
- A meta-analysis based on altogether 51 studies comparing RARP versus ORP demonstrates a reduced relative transfusion risk in favor of RARP (RR 0.63, 95% CI 0.49-0.81, p<0.001). *Reference Moran 2013.*
- A systematic review and meta-analysis from India which included only 6 studies reported no differences in transfusion. *Reference: Pan (2014)*
- A very large US NIS database comparative analysis (RARP versus ORP) of 77616 radical prostatectomies demonstrated statistically significant reduced transfusion rates in favor of RARP (RARP 2.0% versus 8.2%., OR 0.22, 95% CI 0.21-0.22, p < 0.001. *Reference: Sammon 2012.*

Mortality

Overall mortality rates were very low in both groups. RARP seems to trend towards lower mortality rates when compared to ORP

- 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.*
- A very large US NIS database comparative analysis (RARP versus ORP) of 77616 radical prostatectomies demonstrated statistically significant reduced mortality rate in favor of RARP. In both groups the mortality was low (RARP 0.0% vs ORP 0.1%, OR 0.3, 95% CI 0.05 – 0.30, p < 0.001. *Reference: Sammon 2012.*
- Results of a very large prospective controlled trial comparing RALP with RRP reports a 0% during hospital stay mortality rate in both RARP and ORP patient groups. *Reference: Wallerstedt 2015.*

Robotic assisted radical prostatectomy
HTA bibliography – National and state HTAs 2014 to 2010

Due to the highly dynamic development of new and improved quality of clinical research studies HTAs prior 2010 were excluded as there results are likely to be obsolete

A) UK NHS / Scottish NHS

- ***NICE Clinical Guideline Program – Prostate Cancer Update, 2014***
  - Intervention: RALP, LRP, OPEN
  - NICE recommendation:

- 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 cost effective by basing them in centres that are expected to perform at least 150 robot-assisted laparoscopic radical prostatectomies per year

- ***Health Technology Assessment - NIHR HTA Programme 201, Vol 16, Nr 41***
  - Intervention: RARP versus LRP
  - Reference: Ramsay, C. P., R.; Robertson, C.; Close, A.; Vale, L.; Armstrong, N.; Barocas, D.; Eden, C.; Fraser, C.; Gurung, T.; Jenkinson, D.; Jia, X.; Lam, T.; Mowatt, G.; Neal, D.; Robinson, M.; Royle, J.; Rushton, S.; Sharma, P.; Shirley, M.; Soomro, N. (2012). "Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer." Health Technology Assessment 16(41): 1-313.
  - Key findings (selected)
    - Outcomes were generally better for robotic than for laparoscopic surgery for major adverse events such as blood transfusion and organ injury rates and for rate of failure to remove the cancer (positive margin)
    - Probability outcome favours robotic prostatectomy. The predicted probability of a positive margin was 17.6% following robotic prostatectomy compared with 23.6% for laparoscopic prostatectomy.
    - The ICER in the base-case analysis (200 procedure per robot per year) was GBP 18,329 / QALY. If the base analysis is altered to a life time horizon, the incremental cost per QALY is GBP 1,436
  - Conclusions:
    - This study demonstrated that robotic prostatectomy had lower perioperative morbidity and a reduced risk of a positive surgical margin compared with laparoscopic prostatectomy although there was considerable uncertainty.
    - The modeling showed that robotic excess cost can be reduced if capital costs of equipment are minimized and by maintaining a high case volume for each robotic system of at least 100-150 procedures per year.

- ***Health Care Improvement Scotland - Open, laparoscopic and robot-assisted laparoscopic radical prostatectomy for localised prostate cancer – an update (2013)***

- Intervention: RALP, ORP, LRP
- Key findings (selected)
    - RALRP does take longer to perform than open surgery but is associated with less intra-operative blood loss, lower transfusion, shorter length of stay, and better functional outcomes. The evidence on oncology outcomes and complications is inconclusive
    - Studies comparing laparoscopic surgery with robot-assisted laparoscopic surgery report inconsistent results for operative time, length of stay, blood loos, transfusion, and oncology and functional outcomes. The evidence shows no difference in overall complication rates

B) CANADA

- ***Ontario Health Technology Advisory Committee (OHTAC 2014).***
- Reference:
    - Robotic-assisted minimally invasive prostatectomy: OHTAC recommendation [Internet]. Toronto: Queen's Printer for Ontario; 2014 January. 11 p. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ohtac-recommendations
        - Primary conclusions (selected)
            - Men (aged 40 to 75) who had RARP for prostate cancer in Ontario had better surgical outcomes than those who had RP by other methods
            - Patients who underwent robotic-assisted radical prostatectomy (RARP) had significantly fewer complications compared with those who had other forms of radical prostatectomy (RP). RARP patients requires statistically significant fewer blood transfusions (<0.8% vs. 11.4%, p<0.001) and had significantly fewer complications related to stricture and bladder neck contracture (4% vs. 12.1%; p<0.001)
            - The odds of having the composite measure (at least one of the following prostatectomy post surgical complication: blood transfusions, upper urinary tract complications, stricture and bladder neck contracture, urinary fistula, ureteric injury, gastrointestinal stoma creation, peritonitis, hospital readmission, death), were 1.45 times higher for the all other RP group compared to the RARP group (24.3% vs. 7.7%, respectively; p<0.001)
            - RARP outcomes improved over the study period, presumably as practitioners work through the learning curve and improve their skill with experience.
        - Decision determinants (selected)

- Based on decision determinant criteria, OHTAC weighed in favor of the safety of RARP in making its recommendation. RARP leads to fewer surgical complications than radical prostatectomy (RP) by other methods

- ***Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa, 2011***
  - Reference: Ho, C., et al. (2011). "Robot-Assisted Surgery Compared with Open Surgery and Laparoscopic Surgery: Clinical Effectiveness and Economic Analyses."
    - Procedures assessed:
      - Prostatectomies, Hysterectomies, Nephrectomies, Cardiac
    - Key message
      - Robotically assisted surgeries do improve a number of short-term patient outcomes
      - There are strategies that can help to decrease costs and maximize cost-effective use.

- ***Health Quality, O. (2010). "Robotic-assisted minimally invasive surgery for gynecologic and urologic oncology: an evidence-based analysis." Ont Health Technol Assess Ser 10(27): 1-118.***

OBJECTIVE: An application was received to review the evidence on the 'The Da Vinci Surgical System' for the treatment of gynecologic malignancies (e.g. endometrial and cervical cancers). Limitations to the current standard of care include the lack of trained physicians on minimally invasive surgery and limited access to minimally invasive surgery for patients. The potential benefits of 'The Da Vinci Surgical System' include improved technical manipulation and physician uptake leading to increased surgeries, and treatment and management of these cancers. The demand for robotic surgery for the treatment and management of prostate cancer has been increasing due to its alleged benefits of recovery of erectile function and urinary continence, two important factors of men's health. The potential technical benefits of robotic surgery leading to improved patient functional outcomes are surgical precision and vision. CLINICAL NEED: Uterine and cervical cancers represent 5.4% (4,400 of 81,700) and 1.6% (1,300 of 81,700), respectively, of incident cases of cancer among female cancers in Canada. Uterine cancer, otherwise referred to as endometrial cancer is cancer of the lining of the uterus. The most common treatment option for endometrial cancer is removing the cancer through surgery. A surgical option is the removal of the uterus and cervix through a small incision in the abdomen using a laparoscope which is referred to as total laparoscopic hysterectomy. Risk factors that increase the risk of endometrial cancer include taking estrogen replacement therapy after menopause, being obese, early age at menarche, late age at menopause, being nulliparous, having had high-dose radiation to the pelvis, and use of tamoxifen. Cervical cancer occurs at the lower narrow end of the uterus. There are more treatment options for cervical cancer compared to endometrial cancer, however

total laparoscopic hysterectomy is also a treatment option. Risk factors that increase the risk for cervical cancer are multiple sexual partners, early sexual activity, infection with the human papillomavirus, and cigarette smoking, whereas barrier-type of contraception as a risk factor decreases the risk of cervical cancer. Prostate cancer is ranked first in men in Canada in terms of the number of new cases among all male cancers (25,500 of 89,300 or 28.6%). The impact on men who develop prostate cancer is substantial given the potential for erectile dysfunction and urinary incontinence. Prostate cancer arises within the prostate gland, which resides in the male reproductive system and near the bladder. Radical retropubic prostatectomy is the gold standard treatment for localized prostate cancer. Prostate cancer affects men above 60 years of age. Other risk factors include a family history of prostate cancer, being of African descent, being obese, consuming a diet high in fat, physical inactivity, and working with cadium. THE DA VINCI SURGICAL SYSTEM: The Da Vinci Surgical System is a robotic device. There are four main components to the system: 1) the surgeon's console, where the surgeon sits and views a magnified three-dimensional image of the surgical field; 2) patient side-cart, which sits beside the patient and consists of three instrument arms and one endoscope arm; 3) detachable instruments (endowrist instruments and intuitive masters), which simulate fine motor human movements. The hand movements of the surgeon's hands at the surgeon's console are translated into smaller ones by the robotic device and are acted out by the attached instruments; 4) three-dimensional vision system: the camera unit or endoscope arm. The main advantages of use of the robotic device are: 1) the precision of the instrument and improved dexterity due to the use of "wristed" instruments; 2) three-dimensional imaging, with improved ability to locate blood vessels, nerves and tissues; 3) the surgeon's console, which reduces fatigue accompanied with conventional laparoscopy surgery and allows for tremor-free manipulation. The main disadvantages of use of the robotic device are the costs including instrument costs ($2.6 million in US dollars), cost per use ($200 per use), the costs associated with training surgeons and operating room personnel, and the lack of tactile feedback, with the trade-off being increased visual feedback. RESEARCH QUESTIONS: For endometrial and cervical cancers, 1. What is the effectiveness of the Da Vinci Surgical System vs. laparoscopy and laparotomy for women undergoing any hysterectomy for the surgical treatment and management of their endometrial and cervical cancers?2. What are the incremental costs of the Da Vinci Surgical System vs. laparoscopy and laparotomy for women undergoing any hysterectomy for the surgical treatment and management of their endometrial and cervical cancers. For prostate cancer, 3. What is the effectiveness of robotically-assisted radical prostatectomy using the Da Vinci Surgical System vs. laparoscopic radical prostatectomy and retropubic radical prostatectomy for the surgical treatment and management of prostate cancer?4. What are the incremental costs of robotically-assisted radical prostatectomy using the Da Vinci Surgical System vs. laparoscopic radical prostatectomy and retropubic radical prostatectomy for the surgical treatment and management of prostate cancer? RESEARCH METHODS: LITERATURE SEARCH: SEARCH STRATEGY: A literature search was performed on May 12, 2010 using OVID MEDLINE,

MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment for studies published from January 1, 2000 until May 12, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with unknown eligibility were reviewed with a second clinical epidemiologist, then a group of epidemiologists until consensus was established. The quality of evidence was assessed as high, moderate, low or very low according to GRADE methodology. INCLUSION CRITERIA: English language articles (January 1, 2000-May 12, 2010)Journal articles that report on the effectiveness or cost-effectiveness for the comparisons of interest using a primary data source (e.g. obtained in a clinical setting)Journal articles that report on the effectiveness or cost-effectiveness for the comparisons of interest using a secondary data source (e.g. hospital- or population-based registries)Study design and methods must be clearly describedHealth technology assessments, systematic reviews, randomized controlled trials, non-randomized controlled trials and/or cohort studies, case-case studies, regardless of sample size, cost-effectiveness studies EXCLUSION CRITERIA: Duplicate publications (with the more recent publication on the same study population included)Non-English papers. Animal or in-vitro studies Case reports or case series without a referent or comparison group studies on long-term survival which may be affected by treatment. Studies that do not examine the cancers (e.g. advanced disease) or outcomes of interest OUTCOMES OF INTEREST: For endometrial and cervical cancers, Primary outcomes: Morbidity factors- Length of hospitalization- Number of complications peri-operative factors- Operation time- Amount of blood loss- Number of conversions to laparotomy number of lymph nodes recovered. For prostate cancer, Primary outcomes: Morbidity factors- Length of hospitalization- Amount of morphine use/painPeri-operative factors- Operation time- Amount of blood loss- Number of transfusions- Duration of catheterization- Number of complications- Number of anastomotic strictures, Number of lymph nodes recovered, Oncologic factors- Proportion of positive surgical margins, Long-term outcomes- Urinary continence- Erectile function SUMMARY OF FINDINGS: Robotic use for gynecologic oncology compared to LAPAROTOMY: benefits of robotic surgery in terms of shorter length of hospitalization and less blood loss. These results indicate clinical effectiveness in terms of reduced morbidity and safety, respectively, in the context of study design limitations. The beneficial effect of robotic surgery was shown in pooled analysis for complications, owing to increased sample size. More work is needed to clarify the role of complications in terms of safety, including improved study designs, analysis and measurement. LAPAROSCOPY: benefits of robotic surgery in terms of shorter length of hospitalization, less blood loss and fewer conversions to laparotomy likely owing to the technical difficulty of conventional laparoscopy, in the context of study design limitations. Clinical significance of significant findings for length of hospitalizations and blood loss is low. Fewer conversions to laparotomy indicate clinical effectiveness in terms of reduced morbidity. Robotic use for urologic

oncology, specifically prostate cancer, compared to: RETROPUBIC SURGERY: benefits of robotic surgery in terms of shorter length of hospitalization and less blood loss/fewer individuals requiring transfusions. These results indicate clinical effectiveness in terms of reduced morbidity and safety, respectively, in the context of study design limitations. There was a beneficial effect in terms of decreased positive surgical margins and erectile dysfunction. These results indicate clinical effectiveness in terms of improved cancer control and functional outcomes, respectively, in the context of study design limitations. Surgeon skill had an impact on cancer control and functional outcomes. The results for complications were inconsistent when measured as either total number of complications, pain management or anastomosis. (ABSTRACT TRUNCATED)

C) EUROPE

- ***Health Information and Quality Authority, Ireland– HTA of robotic-assisted surgery in selected procedures (HIQA Jan 2012)***
    - Reference: O'sullivan, S. (2011). "HIQA Ireland Health technology assessment of robot-assisted surgery in selected surgical procedures."
    - The meta-analysis of the HIQA HTA is an update of the CADTH HTA (September 2011). It follows the same methodology and has been also partially advised by CADTH experts.
        - Procedures assessed:
            - Prostatectomies, Hysterectomies, Nephrectomies, Cystectomies, Pyleoplasty, GYN General, Head&Neck, Prolapse surgery, Cardiac
    - Advice
        - "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. Compared to conventional laparoscopic surgery generally, robot assistance is likely to be associated with less repetitive strain for surgeons, but the clinical benefits for patients would be marginal"
    - Cost Effectiveness
        - Incremental cost-effectiveness ratio: 26,647 EUR / QALY based on an annual steady state caseload of 200 procedures

D) Australia

- ***ASERNIP-S 2012, Health Policy Advisor Committee on Technology – Technology Brief, Robotic assisted Lung Resection (commissioned by Health PACT)***
    - http://www.health.qld.gov.au/healthpact/docs/briefs/WP126.pdf
    - Intervention: Lung Resection – RVATS, VATS, OPEN Thoracotomy

- Summary of findings
  - RVATS for the surgical treatment of suitable lung lesions appears to be at least as safe as the surgical alternatives, VATS and open thoracotomy. However, effectiveness data are primarily based on limited observational studies. While the da Vinci device is currently available worldwide, assistance in thoracic procedures has been reported in only a few centres, primarily in the USA and Italy. There is a significant learning curve for surgeons and costs are a concern. The observation to date is that RVATS is cost-saving as compared with open thoracotomy (primarily due to reduced hospital stay) but more costly than VATS; however, some of the technical limitations of VATS have been overcome with RVATS.

E) US

- Washington State Health Care Authority HTA
  - Gleitsmann, K. (2012). "Washington HCA Robotic Assisted Surgery HTA program." Gleitsmann, K., Bunker, K., Kriz, H., Ryan, K., Vandegriff, S., Liu, R., Thielke, A., & King, V. (2012). ; Robotic assisted surgery. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University