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Robot-assisted versus conventional laparoscopic radical prostatectomy – a systematic review

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Abstract

Background

There are conflicting evidence regarding safety and advantages of robot-assisted laparoscopic radical prostatectomies (RALRP) compared to conventional laparoscopic approach, as the number of robot-assisted prostatectomies continues to rise in USA and in most European countries, including Norway. The insufficient number of high quality randomized trials limited past systematic reviews to using the evidence from low quality non-randomized studies.

Objectives

The primary aim of the thesis is to compare effectiveness and safety of robot-assisted radical prostatectomies and conventional laparoscopic radical prostatectomies (LRP) using evidence based analyses. The secondary aim is to assess the current level of implementation of robotic surgical systems in prostate cancer treatment in Norwegian hospitals.

Method

A systematic review of studies that were comparing robot-assisted and conventional laparoscopic radical prostatectomy was conducted.

The Cochrane Central Register of Controlled Trials (CENTRAL), *MEDLINE*, and *EMBASE* were searched for randomized and non-randomized studies irrespective of language.

The methodological quality of the included studies was assessed by The Cochrane Collaboration's tool for assessing risk of bias. The data pooling was conducted separately for randomized trials and for non-randomized studies when possible. To explore a high level of heterogeneity when observed, an appropriate subgroup analyses were performed.

The level of implementation of robotic surgical systems in prostatectomies was assessed by an open-ended questionnaire sent to five Norwegian hospitals via email.

Results

Two randomized clinical trials and seven non-randomized comparative studies involving 2 193 participants were included in the review. Overall, the methodological quality of the non-randomized studies was low. Pooled data from two randomized trials revealed significantly higher number of potent patients in the RALRP group compared to LRP 12 months after surgery (RR 1.57, 95%CI 1.21 to 2.04, I^2=23%). The number of continent patients 12 months after surgery was also significantly higher in the RALRP group (RR 1.2, 95%CI 1.07 to 1.35, I^2=23%). The differences in the rates of complications, biochemical recurrence 12 months after surgery, and positive surgical margin were not statistically significant. The meta-analyses performed on the non-randomized studies were hampered by a high level of heterogeneity observed between the studies. RALRP was reported to be superior over LRP when performed by the transperitoneal approach, in terms of lower number of hospital days, lower rate of perioperative complications lower blood loss, and higher number of successful bilateral nerve sparing procedures. Pooled results from four comparative series showed that the patients in the RALRP group had significantly higher risk of experiencing postoperative bleeding compared to patients in the LRP group (RR 3.39, 95%CI 1.11 to 10.40).

Norwegian Radium Hospital in Oslo was the only institution who had answered the questionnaire. A total of 293 radical prostatectomies were performed in this hospital in 2011, and in all of them a robotic surgical system was used.

Conclusions

More randomized clinical trials are needed in order to fully assess the effectiveness and safety of RALRP. The procedure in the hands of experienced surgeon might be beneficial for younger and preoperatively potent patients. The potential benefits from the RALRP are likely to occur in high-volume institutions such as Norwegian Radium Hospital, with the additional costs that would very well exceed those from the open surgery.

Table of content

Background

Description of the condition

Prostate cancer was the second most frequently diagnosed cancer worldwide in 2008, with 899 000 new cases reported. Almost 75% of newly diagnosed prostate cancers were recorded in the developed countries. In the same year, the prostate cancer was attributable to 258 000 deaths worldwide, and it was the sixth leading cause of cancer deaths in men (GLOBOCAN 2008, 2010).

The increase in the prostate cancer incidence was observed during 1980s and 1990s worldwide (Hsing 2000, Quinn 2002). Between 1975 and 2010, 218% increase in the prostate cancer incidence was observed in United Kingdom (Cancer Research UK, 2013), with the rise of the incidence being the most rapid in late 1980s when the prostate specific antigen (PSA) testing was first introduced, and in late 1990s when the PSA testing started to increase in general practice (Melia 2001). The increase in the prostate cancer incidence was followed by increase in the survival, which was most likely due to earlier diagnosis of the disease that was made possible after the introduction of the PSA testing. The prostatic cancer mortality in the UK increased throughout 1980s, peaked in the early 1990s and declined to an average of 28 deaths per 100 000 recorded between 2008 and 2010 (Cancer Research UK, 2012 Feb). Evidence show that the prostate cancer incidence is stabilizing in US, and is followed by decrease in mortality rates (Center 2012).

Two different treatment strategies are used for treating localized prostate cancer. The first approach involves interventions with curative intent such as radical prostatectomy, radiotherapy, cryotherapy or therapy with ultrasound. During the radical prostatectomy, the entire prostate gland is removed along with some of the surrounding tissue. The second approach is observational, and it involves either active surveillance during which treatment is initiated if the progression of the disease has occurred, or "watchful waiting" during which only a palliative treatment is provided when the symptoms of the disease occur. The logic behind the observational approach is that the

most of the prostate cancers are slow growing tumors. Since the main portion of the prostate cancer patients is elderly, and prostate cancer often develops slowly, most of the elderly patients are more likely to die from other causes than the prostate cancer. However, there is still not enough evidence to support any of the proposed approaches (Hegarty 2012).

The gold standard for many years for radical prostatectomies was open radical surgery with a retropubic approach. The next step in the evolution of open radical prostatectomies was transfer to a field of minimally invasive surgeries (key hole surgeries), i.e. laparoscopic environment.

The first laparoscopic radical prostatectomy (LRP) was conducted in 1992, and as a novel minimally invasive procedure it showed some advantages over a gold standard - open retropubic radical prostatectomy, such as lower blood loss and complication rates, and decreased hospitalization and catheterization time (Ficarra 2009, Parsons 2008). However, due to difficulties in dissection and suturing, 2-dimensional visualization and compromising ergonomics, the method was in need of improvement. In 2000, the first robot-assisted laparoscopic radical prostatectomy (RALRP) was introduced as the attempt to resolve some of the issues from this type of minimally invasive surgeries. The use of robotic surgical systems for prostatectomies was most vigorous in the United States, where 67% of radical prostatectomies were robot-assisted (Lowrance 2012). The same trend began to be observed in Europe, as United Kingdom Prostate Cancer Advisory Group state that "robotic surgery for localized prostate cancer is an established therapy, and in most countries is now replacing conventional laparoscopic prostatectomy" (Anderson, 2012).

Description of the intervention

Both LRP and RALRP can be performed on the patients with localized prostate cancer, i.e. in selected $T_3N_0M_0$ stages based on TNM classification (Harmon 2008). Some precaution is needed in opting for either of the procedures if the following factors have been identified in the patient prior to surgery: neoadjuvant hormone therapy (Brown 2004), previous prostatic surgery

(Guillonneau 2003), and the history of prostatitis or previous major abdominal or pelvic surgery (Parsons 2002). Both LRP and RALRP can be performed either extraperitoneally or in transperitoneal fashion (Harmon 2008).

The LRP technique that was established at Montsouris involves a surgeon, an assistant and a scrub nurse (Harmon 2008). Five trocars are commonly used in both transperitoneal and extraperitoneal approaches, and they are positioned in either triangular or linear distribution. Two 5 mm trocars are reserved for the surgeon, while one 5 mm and one 10 mm are used by the assistant. The final 10 mm trocar is introduced at the umbilicus for the camera. The operative steps during a transperitoneal approach involve incision of the posterior vesical peritoneum, dissection of the space Retzius and the bladder neck, and selective dissection of the urethra. Final steps include performing a vesicourethral anastomosis after which the prostate is extracted. The extraperitoneal approach differs in a way that the incision of the peritoneum is avoided, thus decreasing the chance of gastrointestinal injuries (Harmon 2008). One of the steps that is performed between the previously mentioned when possible and indicated, is the dissection of the lateral surfaces of the prostate, in order to preserve neurovascular bundle. This step can either be performed unilaterally or bilaterally, and it is done to increase the chances of preserving erectile function postoperatively (Cancer Research UK 2012 Jul). However, if the cancer has advanced to tissue surrounding neurovascular bundle in a way that cannot be completely removed, the nerve sparing procedure is abandoned.

The RALRP technique that was described at Montsouris involves a three-armed robot, a surgeon, an assistant and a scrub nurse (Harmon 2008). A robotic surgical system consists of master and slave unit, connected by a computer-based system. The camera and the instrument arms are controlled by the slave unit which transmits surgeon's movement from the remote console (master unit). Two trocars are reserved for the assistant, but his role in the RALRP is limited to exposing the operative field, placing clips, and aiding in hemostasis. The RALRP

operative technique, after the insertion of trocars, does not differ from the technique used during a conventional laparoscopic radical prostatectomy (Harmon 2008).

A three-dimensional viewing, comfortable ergonomics that limits fatigue, and improved precision due to 7 degrees of freedom of the robotic arms and more accurate camera positioning are some of the advantages of RALRP over LRP (Ahlering 2004). In addition, the robotic surgical system allows filtering of hand tremor with motion scaling of 1:5 (Harmon 2008).

The lack of tactile sensation is the limitation that, although effects both interventions, is more pronounced during the robot-assisted prostatectomy, since during LRP some tactile feedback is preserved through instrument palpitation (Ahlering 2004, Harmon 2008).

Learning curve

A learning curve is described as the experience required to reach consistent performance of the procedure (Ahlering 2004). Some reports from the literature suggest that the learning curve for the laparoscopic prostatectomy is significantly reduced after the introduction of robotic surgical systems.

Patel et al. noted that for a surgeon with a significant experience in laparoscopic surgeries, 40 to 60 cases of LRPs were required to master the skill. However, for a surgeon with no prior experience in the laparoscopic procedures, the number of cases needed to achieve proficiency in laparoscopic prostatectomies rose to between 80 and 100 (Patel 2009). Ahlering et al. advocated the use of robotic surgical systems for this type surgery for training laparoscopically naive surgeons in a conclusion from their study. They stated that only 8 to 12 cases performed with robotic surgical systems were required to transfer one surgeon's skill to laparoscopic environment (Ahlering 2003). In the study by Menon et al, a single surgeon with no previous experience with either conventional or robot assisted prostatectomy, used daVinci® surgical system on 50 patients and different outcomes were compared to those from 50 pure laparoscopic prostatectomies performed by highly experienced operators. The authors reported no significant difference

between procedures in perioperative and postoperative outcomes and concluded that the robotic surgical systems can help a skilled "open" surgeon in mastering the skill of laparoscopic radical prostatectomy (Menon 2002).

Costs

The costs of acquiring robotic surgical system were estimated at $1.2 million, with an additional costs of $100 000 for a yearly maintenance and $1 500 per patient cost in disposable robotic instruments (Menon 2003). Bolenz et al. compared direct and component costs of RALRP, LRP and open radical prostatectomy in a study that included 643 patients. They reported that the median direct cost in their study was the highest for robot-assisted prostatectomy ($6 752), compared to conventional laparoscopic ($5 687) and open prostatectomy ($ 4 437). They further stated that the observed difference was mainly due to higher surgical supply costs of RALRP compared to LRP and open procedure, and costs of operating room. The authors concluded that the costs per patient who underwent robot-assisted prostatectomy, including the costs of the acquisition and maintenance of the system, would increase by $2 698 in the institution with an average 126 cases per year (Bolenz 2009). Previously, similar findings were reported by Lotan et al., who concluded that the RALRP could be competitive with LRP and open surgery only after significant decrease in the costs of device and maintenance, whereas Scales et al. stated that the equivalence in the costs between RALRP and open surgery reached in high cost hospitals and in institutions with a considerable number of prostatectomies being conducted (Lotan 2004, Scales 2005).

How the intervention might work

The functional outcomes after radical prostatectomy are found to be, along with a general health, the most important predictors of health-related quality of life in the patients who underwent the procedure (Finkelstein 2010). Moreover, urinary incontinence and erectile dysfunction were also significant determinants of satisfaction and regret of the patient after surgery (Schroeck 2008).

The continence and potency rates tend to differ between the surgical approaches. Frota et al. reported that the rate of continent patients after LRP was between 82% and 95% and between 95% and 96% after RALRP. In the same study the authors, based on the data obtained from several large series published, found that the potency rates after LRP were around 66%, while following RALRP between 38% and 64%.

The increased precision of robotic surgical systems, in the hands of an experience surgeon, might yield a higher number of successful bilateral nerve sparing procedures. The better preservation of neurovascular bundle surrounding the gland could improve erectile function of prostatectomy patients, increase the potency rates and shorten the time to potency. Moreover, the increase in precision could reduce the rate of the injuries of internal urethral sphincter, and ease the performing of vesicourethral anastomosis, thus increasing the continence rates and reducing the time to continence. The advantages of robotic surgical systems in improved ergonomics and precision, three-dimensional viewing, and reduction of fatigue and hand tremor could have an impact on important intraoperative and postoperative outcomes, such as estimated blood loss, transfusion rate, operative time and rate of complications. On the other hand, differences in reporting, patient age and comorbidities, disease severity, definition of outcomes and length of follow up may distort the comparison of functional outcomes from non-randomized studies.

Harmon et al. reported that, at Montsouris institute, the mean operative time was shorter in the RALRP series compared to LRP series, whit the similar results found in comparative series by Menon et al. Contradicting results were reported for the estimated mean blood loss. While at Montsouris institute the estimated blood loss was higher during RALRP, Menon et al. favored robot-assisted procedure and reported an average of 391 millilitres of blood lost in the LRP series compared to 391 millilitres in the RALRP group. Finally, the rate of complications between the series did not differ significantly, as reported by both authors (Harmon 2008, Menon 2005).

The length of hospital stay is determined by the intraoperative and early postoperative outcomes and could be interpreted as an early indication of patient's recovery. If RALRP is shown to have advantages over LRP in intraoperative and perioperative outcomes, this could also reflect on the length of hospital stay. However, Menon et al. state that the differences between the case series for this outcome failed to reach statistical significance (Menon 2005).

Regarding the oncological outcomes, the potential superiority of RALRP could reduce the rates of positive surgical margin (PSM), i.e. the rate of patients whose tumor is extending to the inked-surface or margin of the prostate after surgery. While Koutlidis et al. after comparing two series of patients, failed to find significant difference in the PSM rates between RALRP and LRP, Trabulsi et al. stated that the introduction of robotic surgical system in their institution radical prostatectomy program significantly reduced the PSM rates (Koutlidis 2012, Trabulsi 2008). The change in the rates of PSM could further reflect on the rates of the disease recurrence.

Finally, the costs of acquiring, maintenance and use of robotic surgical systems for prostatectomies compared to LRP are bound to be a significant financial burden to the institution which plans to introduce this type of surgery (Finkelstein 2010).

Why it is important to do this review

To this day, systematic reviews regarding benefits and safety of RALRP compared to LRP were limited to using and combining the data from non-randomized studies only (Ramsay 2012, Tewari 2012, Fiscara 2009), while the authors of the health technology assessment of robot-assisted surgery in selected surgical procedures published in Ireland combined non-randomised studies with a single RCT (Health Information and Quality Authority 2011). As some of the results from the present reviews are conflicting, it would be beneficial to search and identify high quality studies and use the data to try to resolve the controversies. Moreover, the systematic reviews regarding robotic surgical systems in other fields of surgery did not find any evidence that would support the use of the system in the respective fields (Gurusamy 2009, Meuffels 2011, Liu 2012).

As the number of robot-assisted prostatectomies continues to rise, it would be important to assess, by including the evidence from the high quality studies, safety and performance of the robotic surgical systems in prostatectomies.

The use of robotic surgical systems for prostatectomies in Norway - introduction

In 2010, 4 210 new cases of prostate cancer were diagnosed in Norway (approximately 30% of all new cancer cases in men). At the end of same year a total of 31 728 patients that lived with the prostate cancer were recorded, while 1 043 prostate cancer patients died. The incidence of prostate cancer increased from 3 328 cases that were recorded on average annually between 2001 and 2005, to 4 266 cases that were diagnosed on average every year between 2006 and 2010, with the incidence being the highest in 75-79 and 80-84 age groups. Between the same periods, the survival increased from 80.4% between 2001 and 2005 to 88.5% between 2006 and 2010 (Cancer Registry of Norway 2011).

Prostate cancer mortality has declined in Norway since 1996 and on average 1 050 persons died per year between 2004 and 2008, which made prostatic cancer accountable for 20% of cancer death in Norway in that period. The reason for the increase in incidence and survival are most likely due to a continuous increase in PSA screening and improvements in the treatment. Although, due to its poor test performance characteristics PSA screening is not recommended, in Norway it is still being used in a primary practice as a screening tool on non-symptomatic men (so-called "wild" screening). Moreover, the PSA screening was associated with an overdiagnosis (the diagnosis of the early stage tumor that would not progress to cause clinical symptoms) and overtreatment of the prostate cancer (the treatment of the disease that would not threaten patient's life) (Haldorsen 2011). The data from Norwegian Cancer Registry show that the number of prostatectomies has increased by 85% in the period between 2006 and 2009 (Sekretearіatet 2012). As a consequence of the increased demand for this treatment, a long waiting lines have become

common nowadays in Norwegian hospitals, and the demand for a new and more efficient prostatic cancer treatment becomes stronger and more frequent.

As the robotic surgical system is seen to be the next step in prostate surgeries it would be beneficial to assess how far have Norwegian hospitals have gone in implementing this high-end surgical procedure.

Objectives

The primary aim of the thesis is to compare safety and effectiveness of robot-assisted prostatectomies and conventional laparoscopic prostatectomies using evidence based analysis. The secondary aim is to assess the current level of implementation of robot assistants in prostate surgeries in Norwegian hospitals.

Methods

PRIMARY AIM

A systematic review of the studies that are comparing robot-assisted and conventional laparoscopic radical prostatectomy was performed.

Criteria for considering studies for this review

Types of studies

Randomized clinical trials (RCTs) comparing robot-assisted and conventional laparoscopic prostatectomies which reported on

at least one primary outcome, or a minimum of four secondary outcomes, or any combination of the primary and secondary outcomes were included in the review, irrespective of language. However, due to an insufficient number of RCTs as reported in some reviews (Fiscarra 2009, Ramsay 2012, Tewari 2012), the studies with a different designs, such as studies that were directly comparing two series of patients, are considered eligible to be included in the review if the criteria mentioned above were met. Studies that compared open radical prostatectomy with the RALRP, LRP or both, and conference abstracts were not considered eligible.

Types of participants

Male patients with clinically localized prostate cancer (clinical stage T1-T2-T3N_0M_0 according to TNM classification), that underwent either conventional or robot-assisted laparoscopic radical prostatectomy.

Types of interventions

Transperitoneal or extraperitoneal robot assisted versus transperitoneal or extraperitoneal conventional laparoscopic radical prostatectomy.

Types of outcome measures

Primary outcomes

-the evaluation of erectile function 3, 6 and 12 months after the surgery

- the evaluation of continence 3, 6 and 12 months after the surgery

- recurrence rate (biochemical indicators)

- recurrence rate (other indicators)

Secondary outcomes

Intraoperative and perioperative outcomes:

- operating time

- estimated blood loss

- transfusion rate

- complication rates

- conversion to open surgery

- hospital stay

- catheterization time

- number of nerve sparing procedures (unilateral/bilateral)

Pathological outcomes:

- positive surgical margin (PSM)

Other outcomes:

- costs

Search methods for identification of studies

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and *EMBASE* were searched for eligible studies irrespective of language, from inception to end of January 2013. *World Health Organization International Trials Registry Platform* was searched for the ongoing trials. The search strategies are presented in the Appendix 2.

Data collection and analysis

Selection of studies

The studies were included based on the criteria mentioned above.

Data extraction and management

The following items have been extracted from the included studies using extraction form.

- year, language and country of publication

- study design

- preoperative patient's characteristics

- inclusion and exclusion criteria

- surgical technique

- robotic surgical system used

- outcome measures

- information regarding methodological quality

Assessment of risk of bias in included studies

The methodological quality of the included studies was assessed by The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2008a). In total, six domains of bias were assessed: sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective outcome reporting and other potential threats to validity. Each study was judged of being at high, low or unclear risk of bias for each domain.

Adequate sequence generation

- *Low risk*, i.e. a judgment of YES*:* if a method used to generate the allocation concealment was described and the generation process was conducted by either using a random number table, using a computer generated randomization list, coin tossing, drawing of lots or other methods described as adequate in the Cochrane Handbook for Systematic Reviews of Interventions.

- *High risk*, i.e. a judgment of NO*:* if the study authors described a non-random component in the sequence generation process such as sequence generated by date of birth or hospital admission date, sequence generated by using clinical or hospital record number, allocation to treatment groups based on judgment of the clinician or patient's preference or any other method designated as inadequate in the Cochrane Handbook for Systematic Reviews of Interventions

- *Unclear risk:* if the randomization method was not described by study authors, or if there was insufficient information on the randomizations process to be able to make a clear judgment.

Adequate allocation concealment

- *Low risk*, i.e. a judgment of YES: The authors concealed allocation from both patients and investigators using methods designated as adequate in the Cochrane Handbook: central allocation (telephone or web-based), sequentially numbered, opaque, sealed envelopes.

- *High risk*, i.e. a judgment of NO*:* if the investigators were in any way familiar with the allocation sequence, e.g. open random allocation schedule was used, assignment envelopes were not properly guarded.

- *Unclear risk:* if there was insufficient information on the allocation concealment process.

Was the blinding performed?

A surgical trial does not allow blinding of health care provider (surgeon). However the blinding of the participants and the outcome assessors is possible (double blinding).

- *Low risk* i.e. a judgment of YES: Double blinding was performed with a low possibility of the blinding being broken.

- *High risk*, i.e. a judgment of NO*:* Blinding was not performed, single, incomplete or could have been broken.

- *Unclear risk:* if there was insufficient information to make a clear judgment.

Incomplete outcome data

- *Low risk* i.e. a judgment of NO: there were no post-randomization drop-outs; if the number of drop-outs has occurred, they were balanced between both intervention groups with similar reasons for dropping out; missing outcome data were unlikely to be affiliated to true outcome; missing data have been imputed using proper methods.

- *High risk*, i.e. a judgment of YES*:* imbalanced number of drop-outs or reasons for dropping out across intervention groups; inadequate method of missing data imputation; missing outcome data were likely to be affiliated to true outcome.

- *Unclear risk:* if there were no information about drop-outs or if the reasons of dropping out were unclear.

Selective outcome reporting

- *Low risk* i.e. a judgment of NO: If the study protocol was available and all of the outcomes specified in the protocol have been reported.

- *High risk,* i.e. a judgment of YES*:* If the study protocol was available and not all of the primary outcomes specified in the protocol have been reported; some of the outcomes have been reported incompletely; at least one of the primary outcomes was reported using measurements or methods that were not specified in the protocol; the outcome has been reported without being pre-specified in the protocol (unless the authors had a clear justification for the reporting).

- *Unclear risk:* if there was insufficient information to assess the risk of bias.

Other potential threats to validity

- *Low risk* i.e. a judgment of NO: the studies were apparently without other potential threats to validity.

- *High risk,* i.e. a judgment of YES*:* inadequate study design, extreme baseline imbalance; a study was stopped early (whether or not due to a result of a formal stopping rule), inadequate source of funding (e.g. robot manufacturer), surgeon's experience uneven between the procedures.

- *Unclear risk:* if there was insufficient information to make a clear judgment if there were any other potential threats to validity (e.g. some of the preoperative patients' characteristics were not compared).

Measures of treatment effect

Dichotomous outcomes

Risk Ratios (RR) were calculated along with 95% confidence intervals. If the calculated RR was > 1, the calculated risk of an event was higher for RALRP than for LRP. If the calculated RR was < 1, the calculated risk of an event was higher for LRP than for RALRP.

Continuous Outcomes

Mean differences were calculated along with 95% confidence intervals. In case when continuous outcomes were measured in different scales, a standardized mean difference was calculated.

Unit of analysis issues

No cluster-randomized trials or cross-over trials were included in the review.

Dealing with missing data

Study authors were contacted via email as a source for missing statistical data. If the response was not obtained, an available case analysis was executed.

If the study authors reported means of a continuous variable but failed to provide standard deviation (SD), the following method was used to calculate SD, if either standard error (SE) or *p* value were reported (Higgins 2008b):

(1) Extracting the *p* value and number of participants in each intervention arm

(2) Calculating the degrees of freedom (DF): $DF=N_R+N_L-2$, where N_R represents number of participants in the RALRP group and N_L number of participants in the LRP group

(3) Extrapolating the *t* value from a table of the *t* distribution by using the *p* value and DF.

(4) Calculating the standard error (SE): $SE = \frac{\mathrm{MD}}{t}$, where MD represents mean difference between the groups.

(5) Calculating the standard deviation (SD): $SD = \frac{\mathrm{SE}}{\sqrt{(1/\mathrm{NR}+1/\mathrm{NL})}}$

Assessment of heterogeneity

Heterogeneity was assessed by chi-squared test with the significance level designated at *p* value 0.1. To evaluate level of heterogeneity the I^2 statistics was used with the recommendations obtained from Cochrane Handbook for Systematic Reviews of Interventions. The values below

25% were considered as a low level of heterogeneity, between 25% and 50% as a moderate level, while the values above 50% were considered as a high level of heterogeneity and were further explored using subgroup analysis.

Assessment of reporting biases

In order to explore a publication bias, the construction of a funnel plot was planned, if the sufficient number of the studies was available. The assessment of possible asymmetry in the funnel plot which would indicate publication bias, was intended by using the test proposed by Egger et al (Egger 1997).

Data synthesis

Data synthesis was conducted using Review Manager v5.2.3 software package. For each outcome meta-analysis were conducted when possible. The meta-analyses were performed by pooling the results from included studies with similar study design, i.e. separate meta-analysis were conducted for RCTs and non-randomized studies. If the patient's characteristics, surgical technique, type of robot assistant, type of outcomes and timing of outcome measurements were similar a fixed-effect model was used. For pooling the data from the studies in which either clinical or methodological heterogeneity was observed, a random-effect model was applied.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis and was performed by grouping the studies by:

- different surgical approach (transperitoneal vs extraperitoneal)

- different robotic surgical system used

- number of surgeons involved in a study

- participants' preoperative clinical stage of tumors

If the studies included in the analysis could be grouped in several ways, one subgroup analysis was performed (e.g. two out of four studies with the transperitoneal approach are at the same time, the only two studies which involved more than one operator). The potential characteristics "overlapping" of the studies which were included in a subgroup analysis was reported in the results section of the review only if the heterogeneity was reduced below 50%.

SECONDARY AIM

To assess the level of implementation of robotic surgical systems in prostate cancer treatment, an open-ended questionnaire consisting of 8 questions were sent to five Norwegian hospitals via email (The Norwegian Radium Hospital, Oslo; St.Olav's Hospital, Trondheim; University Hospital of North Norway, Tromsø; Haukeland University Hospital, Bergen; Hospital of Southern Norway, Kristiansand). The questions in the questionnaire were used to explore the availability of robotic surgical systems in the institution, the year when the system was obtained, the way in which the system was procured, the frequency of the system utilization in radical prostatectomies, estimated costs compared to pure laparoscopic prostatectomies and the availability of quality registries regarding prostatic surgeries in the institution. The questionnaire is presented in Appendix 3.

Results

PRIMARY AIM

Description of studies

Descriptions of studies are available in *Characteristics of included studies* tables and *Characteristics of excluded studies* tables, Appendix 1.

Results of the search

A total of 725 references were obtained by electronic search - *The Cochrane Central Register of Controlled Trials* (14), *MEDLINE* (294), and *EMBASE* (417). The references were assessed by reading the titles and abstracts. Thirteen references were retrieved for more thorough assessment according to the criteria for inclusion, and 9 studies were finally included in the review. No ongoing trials were identified.

Included studies

Two randomized controlled trials (Asimakopoulos 2011, Porpiglia 2012), five retrospective (Joseph 2005, Hu, 2006, Rozet 2007, Hakimi 2008, Trabulsi 2011) and two prospective comparative series (Stolzenburg 2013, Gosseine 2009), met the eligibility criteria and were included in the review. One retrospective series compared contemporary series of patients (Rozet 2006) and four studies used historical series as a control (Hakimi 2009, Hu 2006, Joseph 2005, Trabulsi 2011).

Participants

Two RCTs included in the review enrolled a total of 232 patients with preoperative clinical stage T1 and T2.

Five retrospective and two prospective comparative series had available data for 1 963 patients. Preoperative clinical stage of the patients enrolled in comparative series differed between

the studies. Two studies included only patients in T1 and T2 stages (Joseph 2005, Gosseine 2009), while one study enrolled patients in T1, T2 and T3 stages (Hu 2006). Hakimi et al. included T2 and T3 clinical stage patients. Out of 266 participants in the study by Rozet et al, 265 were either in T1 or T2 stage, while one patient was in T3 preoperative stage. Stolzenburg et al. and Trabulsi et al. failed to provide data on preoperative clinical stage of participants in their study.

Inclusion end exclusion criteria if provided by the study authors were presented in *Characteristics of included studies tables*, Appendix 1.

Every included study reported mean age and mean PSA level of the participants in both intervention groups. Preoperative clinical stage of tumor was reported in all but two studies (Stolzenburg 2013, Trabulsi 2011), while patients' preoperative Gleason score, which is used as most commonly method of prostate cancer tissue grading and as a prognostic factor, was undisclosed in the study by Stolzenburg et al. The patients' average body mass index was reported in five studies (Asimakopoulos 2011, Gosseine 2009, Hu 2006, Porpiglia 2012, Rozet 2007), while mean American Society of Anesthesiologists (ASA) Scores, used to assess the physical status of patients before surgery, were presented in the studies by Rozet et al. and Porpiglia et al. The presence of comorbidities was reported in only one RCT (Asimakopoulos 2011), while two non-randomized studies included co-morbidities when assigning the patients in the different risk groups (Hu 2006, Rozet 2006). In addition Porpiglia et al. reported patients' mean prostate volume at transrectal ultrasonography, whereas Hu et al. reported on racial profile of the participants.

A preoperative rate of potent patients assessed by using IIEF questionnaire was reported in four studies (Asimakopoulos 2011, Hakimi 2009, Porpiglia 2012, Trabulsi 2011), while only Asimakopoulos et al. and Trabulsi et al. had presented the data on patients' preoperative continence, assessed by the IPSS questionnaire.

Intervention

One RCT used da Vinci® robotic surgical system (Asimakopoulos 2011). The type of robotic surgical system in the study by Porpiglia et al. remained undisclosed. The surgical approach was transperitoneal anterograde prostatectomy performed by a single surgeon in both RCTs.

The da Vinci® robotic surgical system was used in six comparative series (Gosseine 2009, Hakimi 2008, Rozet 2007, Stolzenburg 2013, Trabulsi 2011). Two remaining studies did not report the robotic system that was used (Joseph 2005, Hu 2006). An extraperitoneal approach was performed in three comparative series (Joseph 2005, Stolzenburg 2013, Rozet 2007). The remaining three series (Hu 2006, Gosseine 2009, Trabulsi 2011) used a transperitoneal approach while Hakimi et al. used this approach in 100% of RALRP and 77% of LRP patients.

The number of surgeons involved differed between the studies. A single operator performed surgeries in three series (Gosseine 2009, Hakimi 2008, Trabulsi 2011), Two, three and four surgeons were involved in the studies by Stolzenburg et al, Hu et al. and Rozet et al. respectively. One comparative series failed to provide data on the number of surgeons that had participated (Joseph 2005).

The surgeons participating in two RCTs have previous experience with both LRP and RALRP. In the study by Jospeh et al. the RALRP series consisted of the last 50 patients of 200 performed, indicating that the surgeon(s) were experienced with RALRP. Similarly, Rozet et al. reported that prior to 110 RALRPs included in the study, four surgeons had a total of 35 robot-assisted prostatectomies conducted. In other non-randomized studies, the surgeons involved did not have previous experience with robot-assisted prostatectomies.

The overview of previous experience of surgeons involved in the studies included is presented in the *surgeon's experience* table, Appendix 1.

Outcomes

Both RCTs have reported on three primary outcomes of which potency and continence were reported at 1, 3, 6 and 12 months after surgery. Length of hospital stay and intraoperative conversion to open surgery were the only secondary outcomes not reported by either trial, whereas Porpiglia et al. failed to report on transfusion rates.

Five non-randomized studies have reported on continence (Gosseine 2009, Joseph 2005, Hakimi 2009, Stolzenburg 2013, Trabulsi 2011). Potency rates were reported in four studies (Joseph 2005, Hakimi 2009, Stolzenburg 2013, Trabulsi 2011), whereas the study by Hakimi et al. was the only which have reported functional outcomes at each assessment point relevant to this review. Biochemical recurrence was reported in only two comparative series (Stolzenburg 2013, Hakimi 2009). The number of reported secondary outcomes differed between the studies with only number of nerve sparing procedures that was reported in all of the comparative series.

Continence and potency were self-reported by the patients involved. In all of the studies that reported on functional outcomes, The International Index of Erectile Function (IIEF) questionnaire was used for potency assessment, while the continence was assessed by the question regarding the number of pads used per day.

Costs and other indicators of disease recurrence were not reported by any of the studies included in the review.

The overview of the outcomes in included studies is presented in the *Characteristics of included studies* table, Appendix 1.

Excluded studies

Most of the studies were excluded after reading the title or the abstract of a study. The following studies were excluded after more thorough assessment.

Two retrospective comparative series were excluded, as they reported only a positive surgical margin as the outcome that was compared between the intervention groups (Koutlidis 2011, Trabulsi 2008).

A prospective non-randomized study was excluded since the primary aim of the study was to assess if a robotic surgical system is useful in learning the LRP technique (Menon 2002). Conventional laparoscopic prostatectomies in this study was performed or supervised by surgeons with an extensive experience in the procedure, whereas RALRPs were performed by a third surgeon with no previous experience with laparoscopic prostatectomies. The results of the perioperative and intraoperative outcomes were analyzed after 12 months. This baseline imbalance caused by a substantial inequality in surgeons' experience was likely to cause biased pooled estimates if the data from the study were used in the meta-analysis. Another prospective non-randomized study from the same authors was excluded due to the poor reporting of the outcomes, limited to effect estimates only. This would exclude this study from any meta-analysis conducted (Menon 2005).

Risk of bias in included studies

The risk of bias summary (Figure 1) provides an overview of the risk of bias in the included studies for each of the seven bias domains.

Allocation (selection bias)

Both RCTs (Asimakopoulos 2011, Porpiglia 2012) had adequate sequence generation method - a computer-generated randomization. However, none of the trials have reported on the allocation concealment method or if concealment was attempted.

Since seven other studies (Joseph 2005, Hu, 2006, Rozet 2007, Hakimi 2008, Gosseine 2009, Trabulsi 2011, Stolzenburg 2013) were non-randomized, they were all considered of being at high risk of selection bias.

Blinding (performance bias and detection bias)

None of the RCTs have reported if the patients were blinded. In one RCT (Asimakopoulos 2011) blinding of the outcome assessors was reported, while Porpiglia et al. failed to state if the blinding of the outcome assessors was performed.

The blinding of the patients was not performed in retrospective comparative series. In two prospective non-randomized studies, the authors did not state if the blinding of the participants or outcome assessors was attempted (Stolzenburg 2013, Gosseine 2009). It was not clear if the personnel that were acquiring data in the retrospective studies were blinded to the procedure that the patient underwent.

Incomplete outcome data (attrition bias)

One trial reported post-randomization drop-outs that were excluded from the analysis due to incompleteness of the data (2 patients in the LRP group and 9 in the RALRP group) or because bilateral nerve sparing procedure was not attempted (2 patients in the LRP group and 3 in the RALRP group, Asimakopoulos 2011). As the number of patients with incomplete data was not balanced between the groups, this trial is judged to be at high risk of attrition bias. The RCT by Porpiglia et al. excluded 10 patients in the RALRP group and 7 patients in the LRP group who underwent adjuvant therapy from the analysis regarding biochemical recurrence. As the reasons of the exclusions are stated and the number of excluded patients was similar between the groups, the study was judged to be at low risk of attrition bias.

One prospective comparative series have reported that postoperative questionnaires regarding continence were not available for 8% of the cases (Gosseine 2009), and it was judged to be at high risk of attrition bias. The rest of the comparative series had complete data reported for all participants.

Selective reporting (reporting bias)

No study protocol could be obtained for any of the studies included in the review. Therefore, it was not possible to assess if all the outcomes specified in the protocol were reported. In one RCT (Porpiglia 2012), the rate of blood transfusion was reported as an outcome in the method section of the paper but the results of this outcome were not published. Similarly, a mean hospital stay was reported as an outcome in one comparative series (Stolzenburg 2013), but the results remained unavailable. Furthermore, in the study by Stolzenburg et al. neither *p* values nor confidence intervals were reported when comparing patient's preoperative characteristics in two intervention groups. The same issue was observed in one retrospective comparative study (Hu 2006). In addition, Hu et al. failed to present *p* values or confidence intervals on the reported outcomes, stating only in narrative form if the observed difference was statistically significant or not. Finally, Trabulsi et al. failed to report the rate of potent patients in the LRP group.

For these reasons, the four studies are considered to be at high risk of reporting bias (Hu 2006, Porpiglia 2012, Stolzenburg 2013, Trabulsi 2011). The rest of the studies reported complete results of the outcomes that were specified in the method section.

Other potential sources of bias

The justification of sample size was reported in both RCTs. Neither of the studies was stopped early. One study have declared the source of funding (Porpiglia 2012) while the other did not, and it is considered that *the source of funding* bias was unclear in this trial (Asimakopoulos 2011). Both trials were free from surgeon's experience bias, as the operators involved had a substantial experience with both procedures.

The differences in the patients' characteristics, including the rate of preoperative co morbidities, between the intervention groups were not significant in the study by Asimakopoulos et al. Porpiglia et al. did not compare the patients in two groups by preoperative continence and pre-existing co morbidities, but they did compare ASA score between the groups, which is used to

measure preoperative physical status of the patient (Porpiglia 2012). In the same study there was a significantly higher number of patients with preoperative Gleason score of 7 in the RALRP group. However, as the difference in other preoperative characteristics between the groups was not significant, the study by Porpiglia et al. was judged as free of extreme baseline imbalance.

Patients' characteristics were described in every non-randomized study, with no apparent baseline imbalance between the intervention groups in five of them. In two studies it was not possible to determine if the patients were equally balanced between the groups as they did not report statistical data after comparing patients' characteristic (Hu 2006, Stolzenburg 2013).

Only two non-randomized studies compared more than five preoperative patients' characteristics (Hu 2006, Rozet 2006), while Stolzenburg et al. compared only mean age and mean PSA level. In three studies, the authors compared five patients' characteristics (Gosseine 2009, Hakimi 2009, Trabulsi 2011), whereas in the study by Joseph et al. four preoperative characteristics were compared between the intervention groups. Only two non-randomized studies indirectly compared existing co morbidities by comparing the number of patients in each risk group (Hu 2006, Rozet 2006). The small number of preoperative characteristics compared between the groups when observed does not necessarily imply that the baseline imbalance exists, but that there was not enough information to assess the risk of bias.

The source of funding remained undisclosed in six non-randomized studies, while Stolzenburg et al. reported no competing financial interests. All non-randomized studies reported on previous surgeon's experience. Four comparative series were judged to be at high risk from "surgeon experience bias", as the experience of the operators was favoring LRP in all of the studies (Hakimi 2009, Hu 2006, Rozet 2006, Stolzenburg 2013, Trabulsi 2011). In the study by Rozet et al. surgeon's experience with RALRP was limited to 35 initial cases, while Joseph et al. stated that the patients included in the study were the last 50 patients participating in the LRP and RALRP series, but failed to report if the same surgeon(s) were operating in both groups.

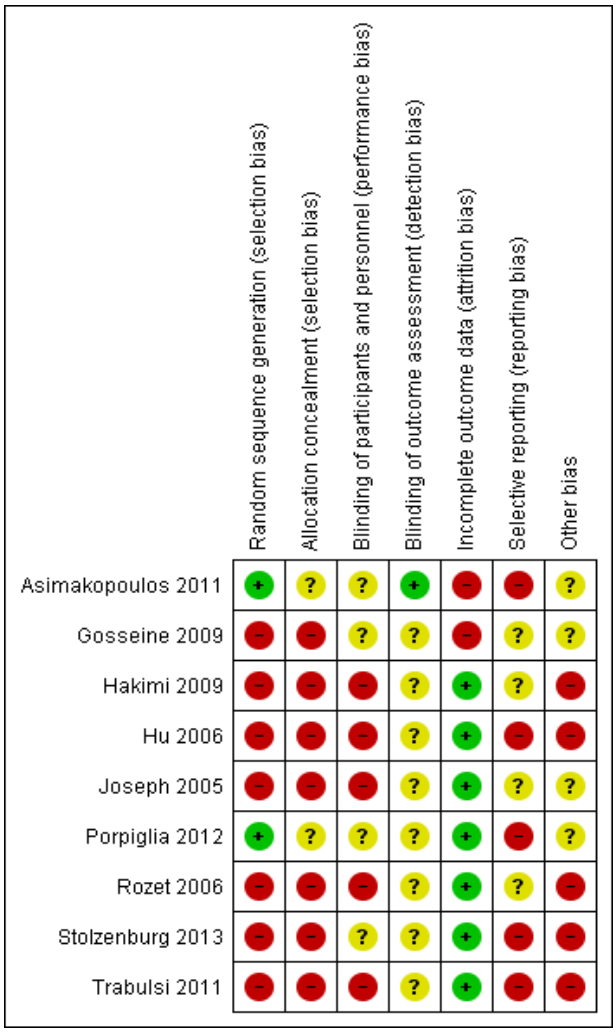

Figure 1 – The risk of bias summary:author's judgments about each risk of bias item for each included study

Effects of interventions

The results are presented as mean differences (MD) or risk ratio (RR) with 95% confidence intervals. The findings were summarized in the *Summary of findings table*, Appendix 1.

RANDOMIZED CONTROLLED TRIALS

Primary outcomes

Potency

By defining potency as ability to achieve intercourse (question 2 and 3 in the IIEF questionnaire), Asimakopoulos et al. found significantly higher number of potent patients in the RALRP group at each assessment point (3 months after surgery RR 3.46, 95%CI 2.09 to 5.74; 6 months after

surgery RR 4.76, 95%CI 2.42 to 9.37).One year after surgery, the patients which underwent robotic-assisted procedure had almost 2.5 times higher chances of achieving intercourse compared to those who underwent pure laparoscopic procedure (RR 2.43, 95%CI 1.63 to 3.63). Moreover, the authors reported that the time to capability for intercourse was significantly shorter in the RALRP group (MD -3.95 months, 95%CI -5.39 to -2.51).

Porpiglia et al. defined potent patient as those who scored more than 17 on the IIEF-5 questionnaire (with or without erectile aids). They included the patients who underwent either unilateral or bilateral nerve sparing procedure in the analyses, and found that the rate of potent patients was significantly higher in the RALRP group only at 12 months after surgery assessment point (3 months after surgery RR 1.50, 95%CI 0.92 to 2.44; 6 months after surgery RR 1.35, 95%CI 0.89 to 2.05). The only data that could be pooled was the number of patients who underwent a nerve-sparing procedure, and scored more than 17 points on the IIEF questionnaire 12 months after surgery. The meta-analysis revealed that after 12 months 70% of the patients in the RALRP group had an IIEF score of more than 17, compared with 44% in the LRP group (RR 1.57, 95%CI 1.21 to 2.04, I^2=0%, figure 2).

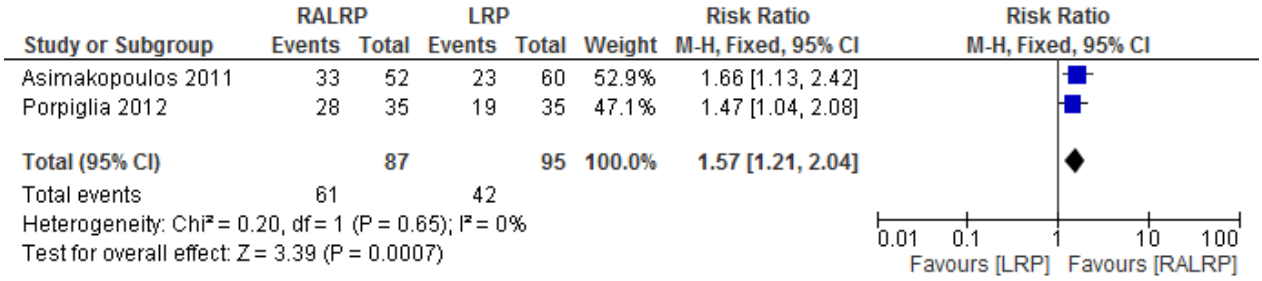

Figure 2 - Recovery of erectile function 12 months after surgery (IIEF-5 score > 17, patients who underwent either nerve-sparing procedure) - RCTs

Continence

Asimakopoulos et al. defined potency as no need to use of any protective pad, and did not find statistically significant difference in the number of continent patients between the intervention groups at any time point (3 months after surgery RR 1.09, 95% CI 0.84 to 1.42; 6 months after

surgery RR 1.18, 95% CI 0.99 to 1.41). They also reported not significant mean difference in the time to continence (MD -0.47 months, 95%CI -1.83 to 0.89). Contrary to these findings, Porpiglia et al., by defining continence as no use or use of one pad for safety, found statistical significance at each assessment point between the procedures, with the results favoring robot-assisted prostatectomy. Specifically, three months after surgery the rate of continent patients in the RALRP group was 80% compared to 61.6% of the continent patients in the LRP group (RR 1.30, 95% 1.02 to 1.64). At six months postoperatively 88.3% of the patients in the RALRP group and 73.3% of the patients in the LRP group were continent (RR 1.20, 95%CI 1.01 to 1.44).

Pooling of the results obtained 3 and 6 months after surgery was not possible due to different definitions of continence used in the studies, and would introduce obvious misclassification error. Nevertheless, both authors have presented separate data on the number of patients which did not use any pad, and the number of patients which used one pad for safety at 12 months assessment point, which allowed pooling the data at this time point only. However, Porpiglia et al. limited the data presented in this manner only to patients who did not start neoadjuvant therapy. The additional data for assessment points 3 and 6 months postoperatively could not be obtained from the authors.

The meta-analysis showed that 12 months after surgery 91.1% of the patients in the RALRP cohort were continent (defined as no need of use of any protective pad) compared to 76.1% of the patients in the LRP group (RR 1.2, 95%CI 1.07 to 1.35, I^2=23%, figure 3). However, at the same time point, no significant difference was found when the continence was defined as no use or use of one pad for safety, with a high level of heterogeneity observed between the studies (RR 1.12, 95% CI 0.96 to 1.30, I^2=66).

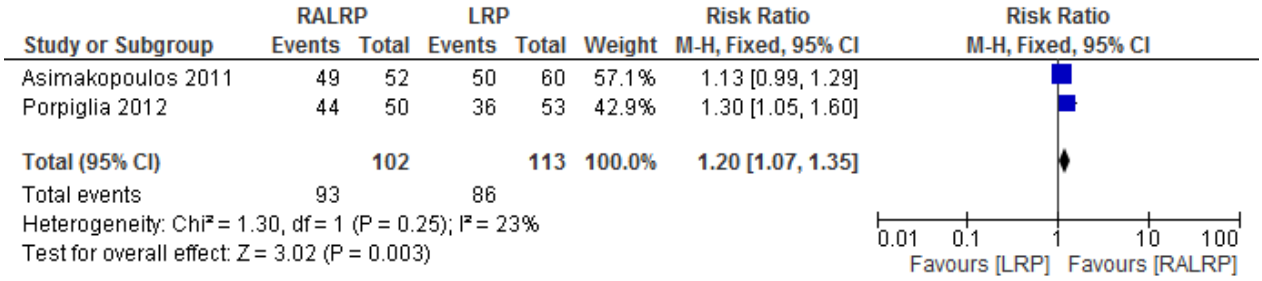

Figure 3 - Continence recovery 12 months after surgery (defined as no need for any protective pad) - RCTs

Biochemical recurrence

In both studies biochemical recurrence was defined as PSA levels after intervention higher than 0.2 ng/ml. A high level of heterogeneity was observed after the results were pooled (I^2=59%), and the random-effect model demonstrated not significant difference in the biochemical recurrence rate between the RALRP and LRP groups 12 months after surgery (RR 0.88, 95%CI 0.11 to 7.31).

Other indicators of recurrence

No other indicators of recurrence were reported.

Secondary outcomes

Operating time

Only one trial reported data on operating time that allowed pooling (Porpiglia 2012). In this trial the mean operative time between two groups did not differ significantly (MD 9,5 minutes, 95% CI -0.67 to 19.67). Asimakopoulos et al. failed to provide effect estimate or confidence intervals for this outcome, but stated that the mean operative time between the groups was insignificantly different.

Estimated blood loss

The mean blood loss did not differ significantly between the RALRP and LRP groups in the trial by Porpiglia et al. (MD -32.10 milliliters, 95% CI -81.36 to 17.16). The same conclusion

regarding the differences in the estimated blood loss was stated in the study by Asimakopoulos et al., but the data on effect estimates were not presented.

Length of hospital stay

None of the RCTs reported on this outcome.

Catheterization time

Pooled results from two trials revealed not significant mean difference between two groups (MD 0.13, 95%CI -0.55 to 0.81, I^2=1%).

Number of unilateral and bilateral nerve sparing procedures

One RCT included only patients who had bilateral nerve sparing procedure (Asimakopoulos 2011). Number of unilateral and bilateral nerve sparing procedures was not significantly different between the RALRP and LRP group in the study by Porpiglia et al (unilateral RR 1.2, 95%CI 0.73 to 1.98; bilateral RR 0.79, 95%CI 0.42 to 1.48).

Intraoperative conversion to open surgery

None of the RCTs reported on this outcome.

Transfusion rate

Porpiglia et al did not report on this outcome. Blood transfusion rate was not significantly different between the intervention groups in the study by Asimakopoulos et al (RR 0.16, 95%CI 0.01 to 3.11).

Complication rates (Clavien classification)

Both RCTs have used Clavien classification for recording and grading postoperative complications. Asimakopoulos et al. reported five cases of paravesical hematoma in each intervention group, and three more additional complications in LRP group (venous thromboembolism, bronchitis and epididymitis). In the study by Porpiglia et al., two urinary tract

infections were observed in the RALRP group and one in the LRP group. One case of urine leakage and wound infection was observed in each intervention group. Furthermore, one case of epididymitis, lymphoceles, ileus and transient hypoaesthesias of left arm, and two cases of acute urinary retention was observed in the RALRP group. One case of distal urethral stenosis, delirium, transient right leg edema and unknown origin fever were reported in the LRP group. After pooling the results, overall number of complications appeared to be higher in the RALRP group. The difference, however, was not significant (RR 1.60, 95%CI 0.81 to 3.15, I^2=0%).

Positive surgical margin

Pooled results from two RCTs revealed non-significant difference in favor of LRP in the overall rates of positive surgical margin (RR 1.40, 95%CI 0.81 to 2.42, I^2=0%) and in the distribution of PSMs among pathological stage T2 patients (RR 0.86, 95%CI 0.36 to 2.06, I^2=0%). A borderline insignificant difference was found in the PSM rate in relation to pathological stage T3, with the higher rate observed in the RALRP group (RR 1.93, 95%CI 0.97 to 3.84, I^2=0%, figure 4)

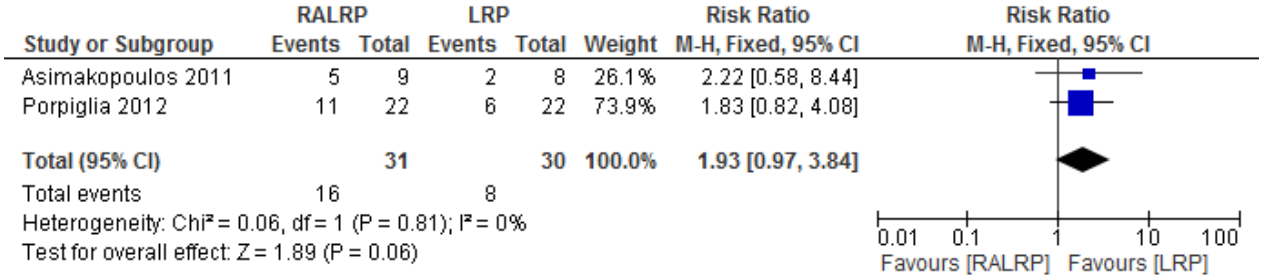

Figure 4 - Positive surgical margin among pathological stage T3 patients - RCTs

Costs

None of the RCTs reported on the measures of the resource use.

Publication bias

Due to an insufficient number of studies, the funnel plot was not constructed.

NON-RANDOMISED STUDIES

Primary outcomes

Potency

Similarly to RCTs, the potency in non-randomized studies was self-reported by the patients by using the IIEF questionnaire.

Only two studies have reported the results in a way that allowed pooling (Hakimi 2009, Stolzenburg 2013). The rate of patients who underwent either nerve sparing procedure (unilateral or bilateral), and that were able to achieve intercourse 3 months after surgery was higher in the RALRP group, but the difference failed to reach statistical significance (RR 1.61, 95%CI 0.90 to 2.87, I^2=0%). Here, it should be noted that the number of unilateral and bilateral nerve sparing procedures did not differ significantly between the intervention groups in the studies that were included in the meta-analysis (Hakimi 2009, Stolzenburg 2013). Jospeh et al. stated that the data regarding potency rate in their study were immature, and that 3 month after surgery 36% of the patients in the LRP group and 46% of the patients in the RALRP group had spontaneous erections.

Hakimi et al. reported potency rates 6 and 12 months after surgery. The difference in the rates of potent patients who underwent unilateral or bilateral nerve sparing procedure was not significantly different between the RALRP and LRP groups (unilateral 6 months RR 1.07, 95%CI 0.34 to 3.36; unilateral 12 months RR 1.43, 95%CI 0.53 to 3.86; bilateral 6 months RR 1.36, 95%CI 0.95 to 1.95; bilateral 12 months RR 1.08, 95%CI 0.85 to 1.37). Trabulsi et al. failed in reporting the number of potent patients in the LRP group at each assessment point. However, they stated that the rate of potent patients with nerve sparing procedure 24 months after surgery was 82% in the RALRP group, compared to 62% in the LRP cohort (RR 1.31, 95% CI 0.95 to 1.80).

Continence

Hakimi et al. and Joseph et al. defined continence as no need of use of any protective pad, and reported data which allowed pooling. The meta-analysis showed that the rate of patients who did

not use any protective pad 3 months after surgery was not significantly different between the intervention groups with observed high level of heterogeneity (RR 1.06, 95%CI 0.83 to 1.36, I^2=67%). Hakimi et al. reported that the rate of continent patients was also non-significantly different 6 and 12 months after surgery (6 months RR 1.14, 95%CI 0.93 to 1.41; 12 months RR 1.04, 95%CI 0.95 to 1.15). Although Gosseine et al. used the same outcome measure, the results from this study could not be included in the meta-analysis, since the authors did not report the distribution of patients lost to follow-up between the RALRP and LRP groups, making the total number of the patients in each group that were included in the analysis impossible to deduce. The logistic regression performed in this study favored RALRP but the odds ratio was not statistically significant (OR (robot no vs yes) 2.09; 95%CI 0.86 to 5.48).

Stolzenburg et al. and Trabilsi et al. defined continent patients as those who did not use at all or used one pad for safety. After pooling the results, the difference between the groups 3 months after surgery was not significant (RR 1.09, 95%CI 0.93 to 1.29), with a low level of heterogeneity (I^2=0%), which makes these results probably more reliable than the results from the meta-analysis above.

Biochemical recurrence

The results from two studies that reported on this outcome (Hakimi 2009, Stolzenburg 2013) were not combined since PSA levels were measured at different time points. In both studies biochemical recurrence was defined as PSA levels after intervention higher than 0.2 ng/ml. Hakimi et al. found no statistically significant difference in the rate of biochemical recurrence between intervention groups, at a mean follow-up of 48 months in the LRP group and 17 months in the RALRP group (RR 0.80, 95%CI 0.22 to 2.86). Stolzenburg et al. assessed the rate of recurrence 3 months after surgery with statistically insignificant higher rates of recurrence in the RALRP group (RR 1.50, 95%CI 0.55 to 4.06).

Other indicators of recurrence

None of the studies reported on other indicators of recurrence

Secondary outcomes

Operating time

The results from five studies could be included in the meta-analysis (Hakimi 2009, Gosseine 2009, Rozet 2006, Stolzenburg 2013, Trabulsi 2011). Jospeh et al. reported mean values for both groups, but failed to report confidence interval or standard deviation, and only stated that the means were not significantly different. Hu et al. reported median which can not be used as the effect estimate in the RevMan software package.

Pooled results showed no significant difference in the mean operating time between the groups (MD -5.87 minutes, 95%CI -26.91 to 15.17) with a high level of heterogeneity (I^2=89%). A subgroup analysis was conducted in order to explore the heterogeneity. The mean operating time in the studies that used transperitoneal approach was not significantly different between RALRP and LRP groups (MD -30.26 minutes, 95%CI -64.46 to 3.95) with the level of heterogeneity being reduced to 76%. The heterogeneity was explained after pooling the results from the studies which included only the patients with T1 or T2 preoperative clinical stage (Rozet 2006, Gosseine 2009), with non-significant difference being observed (MD 4.95 minutes, 95%CI -1.62 to 11.53, I^2=0%).

Estimated blood loss

Six studies presented data that allowed meta-analysis (Hakimi 2009, Gosseine 2009, Rozet 2006, Stolzenburg 2013, Jospeh 2005, Trabulsi 2011), while Hu et al. reported only median blood loss for both groups. No significant difference in the estimated blood loss was observed between the groups after pooling the results, with a level of heterogeneity of 85% (MD -19.92 milliliters, 95%CI -91.39 to 51.56). The heterogeneity was explained after grouping the studies by the number of surgeons involved. The first subgroup analysis included three studies in which one

operator performed surgeries, and which were at the same time the only studies with a transperitoneal surgical approach (Gosseine 2009, Hakimi 2009, Trabulsi 2011). The estimated blood loss was significantly higher in the LRP group (MD -75.20 milliliters, 95%CI -115.81 to -34.58, I^2=0%, figure 5).

Contrary to this finding, a subgroup analysis involving the studies in which more than one surgeons performed the procedures (Rozet 2006, Stolzenburg 2013), showed significantly higher blood loss in the RALRP group (MD 58.28 millilitres, 95%CI 25.15 to 91.41, I^2=0%).

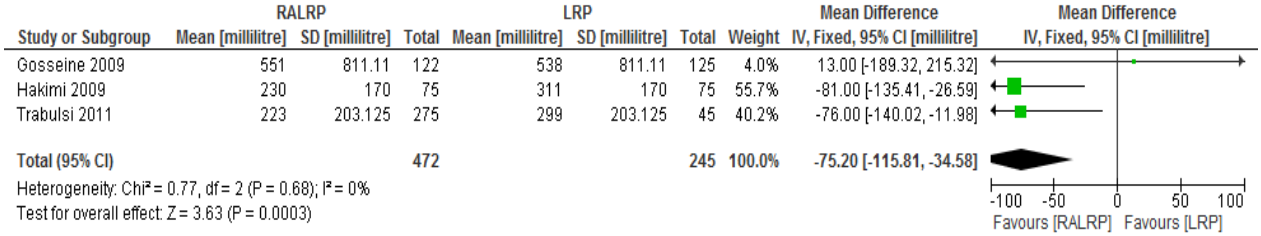

Figure 5 - Estimated blood loss - Subgroup of comparative series with transperitoneal surgical approach [milliliter]

Length of hospital stay

Three studies have reported on this outcome in a way that allowed meta-analysis (Rozet 2006, Gosseine 2009, Hakimi 2009). Trabulsi et al reported mean values for both groups, but failed to provide additional data which would allow the inclusion of the results in the analysis. The meta-analysis showed no significant difference in the mean length of hospital stay, with a high level of heterogeneity being revealed (MD -0.73 days, 95%CI -1.88 to 0.42, I^2=87%). The observed heterogeneity was explained by a subgroup analysis of the studies that used transperitoneal surgical approach (Gosseine 2009, Hakimi 2009), which at the same time, were single-surgeon studies, with the significantly lower number of hospital days in the RALRP group (MD -1.32 days, 95%CI -1.81 to -0.83, I^2=0%).

Catheterization time

Three studies reported on this outcome (Rozet 2006, Stolzenburg 2013, Gosseine 2009). A high level of heterogeneity necessitate the use of random-effect model, which revealed no significant difference in the length of catheter drainage between the groups (MD -0.15 days, 95%CI -0.93 to 0.64, I^2=74%). The reduction of the heterogeneity was observed after separate analysis of the studies that used extraperitoneal surgical approach (Rozet 2006, Stolzenburg 2013), with the difference remaining not significant (MD 0.26 days, 95%CI -0.22 to 0.73, I^2=0%). The studies by Rozet et al. and Stolzenburg et al. were also the studies which involved more than one operator.

Number of unilateral and bilateral nerve sparing procedures

Number of unilateral nerve sparing procedures did not differ between the RALRP and LRP group, after pooling the results from six comparative series (RR 1.03, 95%CI 0.80 to 1.33, I^2=31%).

A high level of heterogeneity was observed after data on number of bilateral procedures were summarized, with the borderline significantly higher rate of bilateral procedures being conducted in the RALRP group (RR 1.17, 95%CI 1.01 to 1.34, I^2=70%). Subgroup analysis of comparative series with a transperitoneal surgical approach (Gosseine 2009, Hakimi 2009, Hu 2006, Trabulsi 2011) reduced heterogeneity to 0%, with the rate of bilateral procedures remaining significantly higher in the RALRP group (RR 1.19, 95%CI 1.10 to 1.28, figure 6). The heterogeneity was also diminished after grouping the studies which included T3 preoperative clinical stage patients (Hakimi 2009, Hu 2006). The difference in the number of bilateral nerve sparing procedures in this subgroup was again significantly higher among RALRP patients (RR 1.20, 95%CI 1.10 to 1.31, I^2=0).

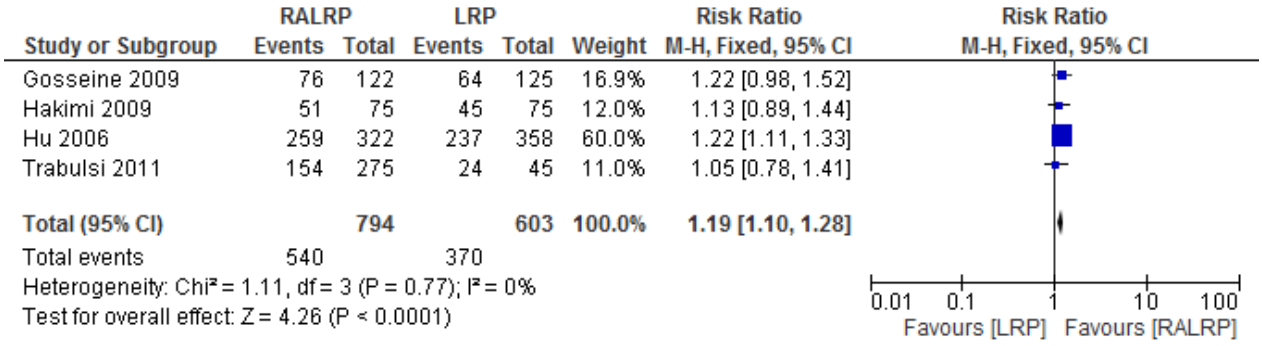

Figure 6 - Number of bilateral nerve sparing procedures - Subgroup of comparative series with a transperitoneal surgical approach

Intraoperative conversion to open surgery

The results from the three studies were summarized (Hakimi 2009, Hu 2006, Trabulsi 2011). No significant difference was observed in the rates of intraoperative conversion to open surgery between the groups (RR 0.20, 95%CI 0.01 to 2.80, I^2=64%). The level of heterogeneity was reduced to moderate after the analysis of the studies which included T3 preoperative clinical stage patients (RR 0.53, 95%CI 0.10 to 2.97, I^2=44%)

Transfusion rate

Four studies were included in the meta-analysis (Hu 2006, Rozet 2006, Gosseine 2009, Trabulsi 2011), while Stolzenburg et al. reported 0% transfusion rate in both groups. A borderline high level of heterogeneity was observed, with a non-significant difference in the rate of transfusion between the groups (RR 0.64, 95%CI 0.26 to 1.60, I^2=51%). The heterogeneity was reduced to 5% after grouping the studies which had more than one surgeon (Hu 2006, Rozet 2006), with the significantly lower rate of transfusion in the RALRP group (RR 0.45, 95%CI 0.21 to 0.97).

Complication rates

The differences in the rates of specific conditions between two groups are presented in the *Summary of findings* table, Appendix 1. The only significant difference observed was in the rates of postoperative bleeding. Pooled results from four studies (Hakimi 2009, Hu 2006, Rozet 2006, Stolzenburg 2013) revealed that the participants in the RALRP group were at 3.4 times higher risk

of postoperative bleeding compared to the participants in the LRP group (RR 3.39, 95%CI 1.11 to 10.40, I^2=0%, figure 7).

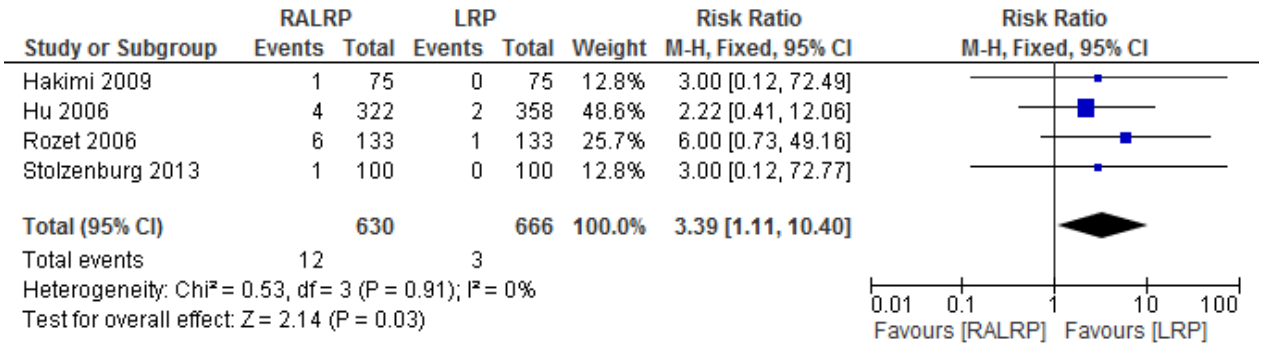

Figure 7 - Postoperative bleeding - Comparative series

Moreover, large differences between the groups in the number of cases were found in three additional outcomes. However, in each of the outcomes the differences failed to reach statistical significance. The risk of deep vein thrombosis had a wide confidence interval and was not significant after pooling the results from two studies (Hakimi 2009, Hu 2006: RR 4.24, 95%CI 0.48 to 37.44, I^2=0%). However, pooled results from the same two studies revealed that the patients in the RALRP group apparently had a non-significant lower risk to suffer from bladder neck contracture compared to LRP group (RR 0.33, 95%CI 0.09 to 1.17, I^2=0%). Hakimi et al. and Rozet et al. reported the number of pulmonary embolus cases in each group, again with non-significant findings and wide confidence intervals (RR 0.33, 95%CI 0.03 to 3.18, I^2=0%).

The difference in the number of other specific conditions was also insignificant between the RALRP and LRP groups - symptomatic lymphocoele (Hakimi 2009, Hu 2006, Stolzenburg 2013: RR 0.63, 95% CI 0.20 to 2.01, I^2=0%); urinary tract sepsis (Hakimi 2009, Rozet 2006: RR 1.80 95%CI 0.39 to 8.36, I^2=0%); urinary retention (Hakimi 2009, Hu 2006, Rozet 2006: RR 0.77, 95%CI 0.42 to 1.42, I^2=0%); wound infection/abscess (Rozet 2006, Stolzenburg 2013: RR 1.67, 95%CI 0.22 to 12.52, I^2=0%); ileus (Hakimi 2009, Hu 2006: RR 0.90, 95%CI 0.19 to 4.40, I^2=52%).

The overall perioperative complication rate was not significantly different after pooling the results from three studies which used Clavian classification to address complication rates (Hakimi, 2009, Hu 2006, Rozet 2006), with a high level of heterogeneity being observed (RR 0.92, 95%CI 0.37 to 2.33, I^2=87%). After a subgroup analysis of the studies which had T3 preoperative clinical stage patients included and at the same time used transperitoneal approach (Hakimi 2009, Hu 2006), the heterogeneity was reduced to 0%. The same analysis revealed that the patients who underwent the RALRP procedure had 50% of the risk of those who underwent pure laparoscopic prostatectomy to experience some perioperative complication (RR 0.55, 95%CI 0.41, 0.74).

Positive surgical margin

The overall rate of PSM did not differ significantly between the groups after pooling the results from three studies (Hakimi 2009, Rozet 3006, Stolzenburg 2013, Trabulsi 2011; RR 1.10 95%CI 0.81 to 1.50, I^2=0%). Rozet et al., Stolzenburg et al. and Trabulsi et al. also reported positive surgical margins separately for T2 and T3 pathological stage patients. The observed difference in the PSM rates was also insignificant among patients with pathological stage T2 tumor (RR 1.18, 95%CI 0.78 to 1.79, I^2=40%). The results from the study by Trabulsi et al. could not be included in analysis which was comparing the PSM rates for pathological stage T3, since the authors have presented combined PSM rates for T3 and T4 stages. Pooled results from two remaining studies failed to reach statistical significance (RR 1.12, 95%CI 0.57 to 2.20, I^2=0%).

Costs

None of the studies reported on the costs.

Publication bias

The rule of thumb proposed in the paper by Sterne et al., is that no test for assessing a funnel plot symmetry should be attempted if the number of studies is lower than 10, as the power of the test would be too low to differentiate chance from real asymmetry. Furthermore, if there is a high level of heterogeneity between the studies, than the number of the studies should be substantially more

than 10 in order to have meaningful results from testing funnel plot symmetry (Sterne 2011). As the number of the non-randomized studies in this review was lower than 10, with significant heterogeneity observed between the studies, Egger's test was not attempted.

Finally, any attempt of making a meaningful conclusion regarding publication bias based on a visualization of the funnel plot would have been hampered by a poor methodological quality of the studies, and by a high level of heterogeneity between them, as these could be the actual reasons of the funnel plot asymmetry (Egger 1997, Sterne 2011).

The results from the assessment of the use of robotic surgical system in the prostate cancer treatment in Norwegian hospitals

Only Norwegian Radium Hospital in Oslo provided the feedback. In this institution, a robotic surgical system is used from 2004 when it was received as a gift from a third party. In 2011, total of 293 radical prostatectomies were conducted in the Norwegian Radium Hospital, and all of them were robot-assisted. No cost estimates of robot-assisted radical prostatectomies were conducted in the institution. Norwegian Radium Hospital has implemented a quality registry regarding prostate surgeries.

Discussion

Summary of main results

Although two high quality studies were included in the review, their insufficient number allowed the inclusion of non-randomized studies. Based on recommendations from Cochrane Handbook for Systematic Reviews of Interventions, no attempt was made to combine the evidence from different study designs (Reeves 2008).

Two RCTs and seven non-randomized studies (five retrospective and two prospective) which compared series of patients were included in the review (2 195 participants). Out of five retrospective studies, four used the historical LRP series were as a control, and only one compared contemporary series of patients.

Concerning the potency 12 months after surgery, the meta-analysis conducted on two RCTs revealed that the robot-assisted prostatectomy had advantage over conventional laparoscopic procedure. Unfortunately, due to the differences in potency definition in two studies, no conclusions on which procedure was superior could be drawn at 3 and 6 months after surgery.

It should be noted that the Asimakopoulos et al. presented data for the patients with bilateral nerve sparing procedure, as these were the patients who were included in the analysis for each outcome. Porpiglia et al. presented data regarding potency rates for the nerve-sparing cohort consisting of 35 patients, with both unilateral and bilateral nerve sparing procedure.

Asimakopoulos et al. argued that inclusion of bilateral nerve sparing patients only could interfere with the results and that "the observed clinical difference (in erectile function) might not be real". For that reason they conducted a sensitivity analysis assuming "the most adverse scenario", in which all of the excluded patients from the LRP group were assumed as potent and all the excluded patients randomized in the RALRP group as unable to achieve intercourse. The difference in the rates of potent was reduced as expected but it still significantly favored robot-

assisted prostatectomy. This type of intention to treat analysis was not attempted in the study by Porpiglia et al. However, the potency rate reported by the patients who underwent non-nerve sparing procedure is usually zero (Dubbelman 2006). Since the number of nerve sparing procedures performed in the study by Porpiglia et al. was equal between the groups (25), and that these patients most likely would not experience the event, the change in the effect estimates, if the intention to treat analysis was performed based on the clinical judgments, would be insignificant.

Some caution is needed when interpreting the definition of potency used in the RCTs. The IIEF-5 questionnaire is validated and the definition of potency as scoring more than 17 points was commonly used in previous studies (Fiscarra 2011, Fiscarra 2006). However, scores between 17 and 21 are referred to as mild erection dysfunction, and only those with a score higher than 21 are considered as patients without any erectile dysfunction (Rosen 1999). It was only in the study by Asimakopoulos et al. the number of patients who preoperatively scored more than 26 points and continued to present the score above 26 after surgery, was compared between the intervention groups, with the RALRP procedure shown to be superior.

The possible advantage of robot-assisted prostatectomy over conventional laparoscopic procedure regarding the potency rates could be due to increased precision of robotic surgical system used, which might resulted in better preservation of the periprostatic neural tissue and the neurovascular bundle.

The issue with the difference in defining the outcome was again observed when data synthesis was attempted on the continence rates. The difference in defining continence between the trials limited the assessment to only one year after surgery. Again, the robot-assisted procedure was shown to be superior over human-assisted, when the continence was define as no need for of any protective pad. By adding as continent the patients who had used one pad for security reasons only, the difference in the rates of continent patients was no longer significant, with the analysis being hampered by the high level of heterogeneity.

The rate of patients with a biochemical recurrence was not significantly different between the RALRP and LRP groups.

Similarly to potency rates, the intention to treat analysis was not performed in the study by Porpiglia et al, as they excluded 17 patients from the analysis regarding the rate of biochemical recurrence, as those were the patients who started neoadjuvant therapy. The same authors also failed to include those patients when presenting the data regarding continence rate 12 months after surgery in a way that allowed pooling. Unlike for the erectile function outcome, Asimakopoulos et al. also failed to attempt intention to treat analysis for continence and biochemical recurrence, hence the possibility of the change in the effect estimates if the sensitivity analyses that would include excluded patients, were performed.

The differences in intraoperative, perioperative and pathological outcomes between the intervention groups were not statistically significant after pooling the available data from the RCTs.

The importance of interpreting the results from the meta-analysis which included non-randomized studies with a caution can not be stressed enough, due to studies' poor methodological quality, high risk of bias, and high level of heterogeneity between the studies.

In the meta-analyses of non-randomized studies neither type of prostatectomy was superior for any of the primary outcomes. Similarly to RCTs, most comparative series did not have the same definitions of potency and continence, while in some, the outcomes were evaluated at different time points (biochemical recurrence). This caused the meta-analysis of potency and continence rate to be limited to only a few studies and to 3 months after surgery.

One comparative series that was included in the meta-analysis of erectile function did not give a clear definition of potency (Stoltenburg 2013). The authors used validate IIEF questionnaire but failed to report above which score was a patient classified as potent, and the information needed could not be obtained from the authors. However, the definition they provided (ability to

achieve an erection satisfactory for intercourse) was equal as the potency definition given in the study by Hakimi et al, who, in addition, provided threshold score above which a patient was considered potent, which was considered sufficient to combine the results from these two studies.

The high level of heterogeneity between the comparative series hampered the assessment of most of the secondary outcomes, which was an expected issue when combining the results from non-randomized studies. The Cochrane Non-Randomized Studies Method Group recommends that when the high level of heterogeneity is observed between non-randomized studies, the interpretation of the results from meta-analysis should be avoided (Reeves 2008).

The random-effect model was applied and subgroup analyses were conducted in order to explore the sources of heterogeneity when possible. The subgroups were formed based on the number of surgeons involved in the study, transperitoneal or extraperitoneal surgical approach, and the inclusion of the patients with a T3 preoperative clinical stage of the tumor. The study by Eden et al. showed that there were significant difference in the perioperative and functional outcomes between the transperitoneal and extraperitoneal approach (Eden 2004). The separate analysis of the studies which in addition involved T3 clinical stage patients was conducted, since the severity and progress of the disease in these patients could make a difference when combined with the studies which had only T1 and T2 clinical stage patients. The differences in the individual techniques between the surgeons are bound to happen in the multi-surgeon studies that might interfere with the potential "real" differences between the surgical approaches. As this is something that does not occur in the studies which involve single surgeon, the difference in the number of operators could be the source of heterogeneity.

Overall, the meta-analyses conducted on the studies with the transperitoneal surgical approach revealed that, when conducted in this fashion, RALRP appeared to be superior over LRP in terms of lower number of hospital days, lower rate of perioperative complications and lower estimated blood loss. Moreover, transperitoneal RALRP yielded more bilateral nerve sparing

procedures compared to transperitoneal LRP, which might be due to a higher precision of robotic surgical system. These findings, however, differ from the results from two RCTs, in both which surgeries were performed in transperitoneal fashion. Related to rate of transfusions, the RALRP was favorable in those studies which involved more than one surgeon.

Some caution is required when interpreting the results from the subgroup analyses. By definition this is an observational investigation of the differences between studies. As such, it is often confounded by other study-level characteristics and sometimes even the observed differences between studies are not due to the subgroup's classification (Deeks 2008). Furthermore, for some of the outcomes, the included studies could have been grouped by several characteristics. If the heterogeneity was reduced, it became impossible to explore which study-level characteristic was "responsible" for the reduction. For example, the substantial heterogeneity observed after pooling the data on mean hospital stay was reduced to 0% after separate analysis of the studies which used transperitoneal surgical approach. At the same time those studies were the only one which had single surgeon involved. It is, therefore, impossible to conclude due to which study characteristic, if any, the heterogeneity was diminished. The subgroup analyses in most cases were limited to only two or three studies. This requires that the results should be interpreted with caution, since there might not be sufficient number of studies in the subgroup analyses to draw useful conclusion, even when the heterogeneity was reduced to 0% (Deeks 2008).

The study by Hakimi et al was designated as a study with a transperitoneal surgical approach, even though 17 out of 150 procedures were conducted in a extraperitoneal fashion (all of them were LRP), and as such was used in a subgroup analysis. The possibility exists that the reduction of the heterogeneity when observed in these analysis could have been due to a confounding effect of some other study level characteristic, or that the transperitoneal surgical approach was not the reason of the reduction in the first place. A similar issue was observed in the studies by Stolzenburg et al. and Jospeh et al. Stolzenburg et al used extraperitoneal approach in all but a high risk patients (PSA>20 ng/ml), but failed to report on how many patients underwent

transperitoneal prostatectomy. Since this study was included in the subgroup of studies with the extraperitoneal surgical approach, this could be the reason why the heterogeneity was not reduced significantly in any of the analyses that were grouping the studies by this characteristic. Moreover, Joseph et al. used extraperitoneal approach in all but two patients. However, it is unlikely that these two patients with a different approach could introduce bias in the change of heterogeneity when the study was included in the subgroup analyses of the studies conducted in the extraperitoneal fashion.

Finally, the study by Rozet et al. included the patients with the preoperative classified tumor as either T1 or T2 with the exception of one with T3 stage tumor. As this one patient's characteristic was unlikely to cause biased changes in the heterogeneity if observed, the study was classified as the study which included T1-T2 preoperative clinical stage patients in the subgroup analyses.

Only one significant result was found regarding specific complications. The meta-analysis conducted on four comparative series, revealed that the use of robot surgical system in prostatectomies would four-fold increase the risk of postoperative bleeding compared to human-assisted laparoscopic prostatectomy. This surprising result might be due to a significant difference in the surgeons' experience with the two procedures. Specifically, in all of the studies that were included in the analysis, surgeon(s) had prior experience only with LRP (Hakimi 2009, Hu 2006, Stolzenburg 2013), whereas the surgeons involved in the study by Rozet et al. have had a limited RALRP experience. The previously acquired skills with LRP could have made a difference in the rates of postoperative bleeding. Furthermore, the observed difference could be a consequence of potential baseline imbalance between the groups of patients and underlining confounder, as, for example, Stolzneburg et al. used only two preoperative characteristics to compare the groups.

Moreover, the differences in surgeons' experience between the studies, along with the obvious methodological differences and quality, could be the possible explanation for the

differences in functional outcomes between RCTs and non-randomized studies from this review. Both surgeons involved in RCTs had substantial experience with RALRP, while the experience of the surgeons from the non-randomized studies, which reported on this outcome, was rather limited.

Overall completeness and applicability of evidence

The studies included in the review were performed in five different countries (France, Germany, Italy, UK, USA). This diversity strengthens the applicability of the results presented. It should be noted, however, that both RCTs originated from Italy.

The applicability of the findings might be reduced by the fact that the procedures were performed by a highly experienced operators in most of the studies, who already had several hundreds of LRPs conducted, while in both RCTs the surgeons had a substantial experience with RALRP as well. Since the number of hospitals with such an experienced personal is limited, it is clear how this could affect the generalizability of the findings from the review. In addition, both RCTs and three non-randomized studies had only one surgeon involved, and the caution is needed when applying the results from these studies to other surgeons.

As non-randomized studies were at high risk of selection bias, this hampered the applicability of the evidence from these studies.

Incomplete data reporting was observed in some of the studies. The common issue was that the authors failed to report either confidence intervals, *p* values, standard error, or even the effect size of an outcome, and limited the report of their findings to only narrative form. This made impossible to include those studies in meta-analyses. Furthermore, several studies failed to report on the robotic surgical system that was used. Therefore, subgroup analyses that grouped studies by the robotic surgical system that was used could not be conducted.

Quality of the evidence

Although two randomized controlled trials represent high-quality studies included in the review, they were not free of bias. Selective outcome reporting was observed in the study by Asimakopoulos et al., in which 16 already randomized patients were excluded from the analyses, whereas Porpiglia et al excluded the patients who underwent adjuvant therapy from the biochemical recurrence comparison. The sample size justification was presented in both RCTs, but these were still relatively small studies. Neither of the RCTs was double-blinded.

The inclusion of non-randomized trials in the review could be justified by a small number of RCTs being identified (Reeves 2008). However, seven comparative series that were included are considered to be of poor methodological quality and highly susceptible to biased estimates. When assessing the quality of the comparative studies and level of evidence in their systematic review, in which were compared open, laparoscopic and robot-assisted radical prostatectomy, Fiscarra et al. designated retrospective comparative series as level of evidence 3b if contemporary series of patients were compared, and level of evidence 4 if historical series were used as a control. Prospective series were judged as a level of evidence 2b, whereas RCTs were level of evidence 1a (Fiscarra 2009).

Poor reporting made it difficult to properly assess the risk of bias for several domains and it was a common problem for both RCTs and non-randomized studies.

All retrospective studies are considered to be at high risk of selection bias. The blinding of the study personnel to a type of intervention and the outcome results, during the process of patient selection, would be preferred in the retrospective studies, and none of the retrospective studies have reported if this was attempted. If the blinding did not occur, this could result in selection bias. The risk of bias might have been attenuated in the studies who stated that they were comparing initial or last patients in the LRP and RALRP group (Hakimi 2006, Jospeh 2005, Trabulsi 2009). It should be noted, however, that the blinding of this sort would be difficult to

perform. Although the type of intervention could be masked by some sort of coding (e.g. RALRP-1, LRP-0), there could be some other indicators in the medical records that would have revealed the surgical approach a patient had undergone.

The studies by Stolzenburg at al. and Gosseine et al. were prospective, but no randomization process was attempted

Although, neither of the retrospective studies reported if the patients were blinded to type of procedure, it is reasonable to assume that they were familiar with a surgical approach through a consent form. It can be argued that, as the procedures in the retrospective comparative series were completed prior to enrolment of the studies, the blinding the patients to a type of laparoscopy in the consent form was not performed.

Similarly to RCTs, all the non-randomized studies had small sample size and were underpowered.

Matching of the patients in non-randomized studies is one way of adjusting for potential confounders (Reeves 2008). Inadequate matching results in the baseline imbalance which is most likely to cause biased effect estimates. Moreover, if the matching of the patients by only few characteristics might be insufficient to properly adjust for confounders. The baseline imbalance was not an issue in any of the non-randomized studies based on the data reported by the authors. However, only Hu et al. and Rozet et al. compared more than 5 preoperative patients' characteristics and these were the only non-randomized studies in which existing co morbidities was one of the features compared. If the baseline imbalance caused by difference between the groups in the preoperative co morbidities or/and any other combination of non-reported characteristics was present, the quality of evidence obtained from these studies would be severely undermined. Therefore, the possibility of biased estimates in each of the primary and secondary outcomes reported by non-randomized studies can not be excluded.

The point of concern is an uneven experience in robot-assisted and conventional laparoscopic prostatectomies observed in most of the non-randomized studies. Four studies have involved surgeons with previous experience with the LRP and no experience with the RALRP (Hakimi 2009, Hu 2006, Stolzenburg 2013, Trabulsi 2011), while Rozet et al. excluded initial 35 RALRPs performed in their institutions.

The observed imbalance in surgeons' experience between the groups might result in biased estimates for some of the outcomes favoring LRP. However, the lower performance of the RALRP due to a lack of experience would probably be limited to initial cases, as the previous experience with the LRP would shorten the learning curve for the RALRP.

In three non-randomized studies, the series were performed by several surgeons. Therefore, the variations across the intervention groups in those studies might be the result of individual differences between the surgeons' techniques rather than between surgical approaches. It can be argued that the risk of bias might be attenuated, as the same team of surgeons was performing on both series of patients in all three studies (Hu 2006, Rozet 2006, Stolzenburg 2013).

Finally, Joseph et al. failed to report if the same surgeon or team of surgeons were conducting both RALRPs and LRPs which preceded the robot-assisted series. If that was not the case, it would severely reduce the quality of evidence obtained from the analysis in which this study was included.

Potential biases in the review process

Although the search strategy was comprehensive and without restrictions such as language, the possibility remains that some of the studies remained unidentified.

The search of the literature, selection of studies, data extraction and assessment of bias in the included studies was conducted by a single author. Since it is recommended that at least two

authors are involved in these processes (Higgins 2008b), the risk of bias can not be excluded in any of three steps mentioned.

The Cochrane Collaboration's tool for assessing risk of bias is used primarily for assessing a methodological quality of RCTs. However, in this review, the tool was also used to assess the risk of bias in the non-randomized studies as well. Although Deeks et al. in their systematic review regarding instruments for methodological quality assessment of non-randomized studies, suggested that the Downs and Black instrument (Downs 1998) and the Newcastle-Ottawa scale (Wells 2008) were the most useful when assessing the risk in non-randomized studies, they also stated that these tools were more appropriate for case-control and cohort studies. This left the Cochrane's risk of bias tool as the instrument that was easiest to apply to non-randomized studies in this review, and it was previously used in the systematic reviews by Ramsay et al. which had included studies with a similar design (Ramsay 2012).

Most of the studies reported *range* when presenting the results of continuous outcomes. As the derivation of SD from the range is not recommended in Cochrane Handbook for Systematic Reviews of Intervention, the method described in the *Dealing with missing data* portion of the review was applied. It is important to underline that this method provides only one value that is an estimate of SD. The same estimated SD is applied to the mean value of a continuous outcome in both intervention groups, and is likely to differ from the true value.

Moreover, the standard deviations of *estimated blood loss* outcome obtained by this method were unusually high in some studies. Although this could be nothing more that the reflection of large differences between the patients or/and individual procedures, an imprecise SD can not be excluded. The reason for the imprecision might be due to the imprecise or even incorrect *p* values or means reported by the study authors. As a consequence, the studies with a large SD were given a lower weight compared to the studies with a small SD, when fixed-effect model was applied, which could result in biased pooled estimates. Another possible explanation

could be the experience of the surgeon. Specifically, one of the studies with a high SD deviation of *estimated blood loss* was by Gosseine et al. which involved single surgeon with no prior experience with either procedure. It would be expected that the blood loss was higher during early procedures compared to later, hence the higher standard deviation compared to studies which involved more experienced operators.

Agreements and disagreements with other studies or reviews

To my knowledge this is the first systematic review on this topic in which results from the high-quality studies (RCTs) were combined.

The authors of Health technology assessment (HTA) of robot-assisted surgery in selected surgical procedures was recently published in Ireland (Health Information and Quality Authority 2012). In the section regarding robotic prostatectomies, the authors of the HTA combined results from nine studies in order to compare RALRP to LRP. They found non-significant difference between the procedures and high level of heterogeneity in oncological outcomes (PSM), sexual function, urinary function at 3 and 12 months after surgery, estimated blood loss, transfusion rate, complication rate, operative time and conversion to open surgery rates. The only significant difference was reported in length of hospital stay and urinary function 6 months after surgery, in which the robot-assisted prostatectomy was found to be superior. The difference in the results between the HTA and the present review is probably due to different criteria regarding inclusion and exclusion of the studies. Moreover, the difference could also arise from the HTA authors' decision to combine results from non-randomized studies and one RCT (Asimakopoulos 2011). As this is something that is not recommended in the Cochrane Handbook for Systematic Reviews of Interventions, it was not attempted in this review.

Tewari et al. used the data from seven non-randomized studies to compare open, conventional laparoscopic and robot-assisted prostatectomy. They found that the RALRP was superior compared to other two procedures in the terms of shorter length of hospital stay, lower

estimated blood loss and reduced perioperative complication rates. The authors, however, used a complex statistical model (propensity adjustment) to adjust for the possible differences in the patients' characteristics between the intervention groups that are common in non-randomized studies. The use of the model along with possible differences in the study selection criteria could be the reason of the differences in the results between the present review and the review by Tewari et al (Tewari 2012).

Fiscarra et al performed a systematic review in which they were comparing open, pure laparoscopic and robot-assisted prostatectomy. They included four comparative series in order to explore differences between RALRP and LRP and found non-significant differences in the mean operative time, complication rates, erectile function, urinary continence and positive surgical margin rate (Fiscarra 2009).

Finally, in the recent systematic review by Ramsay et al., the robot-assisted prostatectomy was found to be superior over LRP with regard to positive surgical margin. The difference in these findings between the reviews might be due to a methodology that was incorporated in the study by Ramsay et al. Specifically, in addition to studies that were directly comparing RALRP and LRP, the authors have also included studies which were comparing open prostatectomy to either RALRP and/or LRP. The studies were included in a mixed-treatment comparison model which was used to assess the relative effectiveness of robotic and laparoscopic radical prostatectomy. This approach yielded significantly larger number of studies to be included in the review. However, no differences were found in cancer-related and dysfunction outcomes (Ramsay 2012).

None of the above mentioned studies attempted any of the subgroup analyses performed in the present review.

The use of robotic surgical systems for prostatectomies in Norwegian hospitals

Even after several attempts, only Norwegian Radium Hospital in Oslo answered the questionnaire. In 2011, 293 radical prostatectomies were performed in this hospital and robotic surgical system,

procured as a gift, was used in each procedure. Some additional information regarding the use of robotic systems in Norwegian hospitals were available from the report regarding robotic surgeries by Norwegian National Council for Priority Setting in Health Care from August 2012.

Currently, there is no national strategy for the implementation of robotic surgical systems in Norwegian hospitals. However, at the time the report was published, 8 robotics surgical systems were operational in the hospitals and the procurements of 3 additional units were planned. The robotic systems used at St.Olav's Hospital in Trondheim, University Hospital of North Norway in Tromsø, Telemak Hospital and Aker University Hospital were public procurements. The units at Haukeland University Hospital in Bergen, Stavanger University Hospital and two units at Norwegian Radium Hospital in Oslo were acquired as gifts from the third party.

The total number of robot-assisted prostatectomies performed in Norway is increasing. In 2009, 409 procedures were recorded, while in 2010 a total of 493 RALRPs were performed. A 60% increase is observed in the number of RALRPs performed between 2010 and 2011, reaching 787 cases as recorded in 2011. From 2006 to 2009 the increase of the total number of prostatectomies by 85% was followed by the increase in the number of RALRPs by 170%. In 2011 more than 50% of total number of prostatectomies was performed with robotic surgical systems. (Sekretearіatet 2012).

The abrupt increase in robotic surgeries in 2011 was not limited to prostatectomies only, as it was observed in the gynaecological, renal and gastrointestinal surgeries as well.

The authors of the report further notice that, based on the data from the Irish health technology assessment report. The additional costs of RALRP are predicted to be 23 000 Norwegian kroner compared to open prostatectomy and 27 750 Norwegian kroner compared to conventional laparoscopic procedure (Sekretearіatet 2012). The findings from Beolenz et al. suggest that the additional costs are mainly due to a higher surgical supply costs and costs of operating room. Therefore, even in the hospitals which procured their robotic surgical systems as a

third part donations, the additional costs of RALRP are still a significant financial burden compared to conventional laparoscopic and open prostatectomy.

A potential benefits from the RALRP are more likely to occur in high-volume hospitals. Eastham et al. found that the postoperative morbidity of the patients who underwent radical prostatectomies was lower in hospitals with a high number of prostatectomies conducted compared to low-volume institutions (Eastham 2008). This is probably due to difficulties that the surgeons in low-volume hospitals encounter in conducting necessary number of procedures to master the skill. Even though the use of robotic surgical systems significantly shortens the time needed to transfer the skills from open surgery to laparoscopic environment as stated before (Ahlering 2003, Menon 2002, Patel 2009), it is to assume that the benefits of robot-assisted radical prostatectomies are first to appear in the institutions which perform high number of the procedures.

From the information available from the questionnaires and the National Council for Priority Setting in Health Care's report, the number of the robot-assisted radical prostatectomies in 2011, shared between all the hospitals which had the robotic surgical system with the exception of Norwegian Radium Hospital in Oslo was 494. As no other hospital answered the questionnaire, it was not possible, by using this method, to determine how this number of robot-assisted prostatectomies was distributed between them.

No cost comparison between RALRP and LRP was conducted in Norwegian Radium Hospital. However, the results from the study by Scales et al. suggested that at least 10 cases of RALRP in the generalist setting and 15 cases at specialist centers are required for RALRP to become cost equivalent to open prostatectomy (Scales 2005). Moreover, Lotan et al. have reported, by using the data from 2004, that operating time decrease to 161 minutes would make LRP cost competitive to open surgery. However, no individual decreases in operating time or length of hospital stay would make RALRP reach cost equivalence with the open surgery. They

further state that at 2004 costs of technology, in the institution in which robotic surgical system was procured as a donation and it is used for 300 prostatectomies yearly, the costs of robotic equipment should decrease for more than $1 000 per case in order to reach cost equilibrium with the open surgery (Lotan 2004).

Given the results from the studies by Scales et al. and Lotan et al., and that in Norwegian Radium Hospital less than 6 of robot-assisted prostatectomies were conducted on average per week in 2011, this might overshadow the potential benefits regarding operative, functional and pathological outcomes benefits from RALRP. However, it should be noted that the date from two studies mentioned above are from 2004 and 2005, thus making it somewhat unreliable nowadays as the costs of the technology would decrease in time. This, again, emphasize the importance for each institution to have at least some internal cost-effectiveness or cost-benefit analysis before procuring the robotic-surgical system.

Finally, it would be beneficial for the institutions to establish the quality registries regarding prostatectomies which could be used to further assess the benefits from the RALRP in functional outcomes compared to both conventional laparoscopic and open prostatectomy.

Conclusion

Implications for practice

Based on the results from the RCTs, there are no evidence that robot-assisted laparoscopic prostatectomy has any significant advantages over human-assisted procedure when it comes intraoperative, perioperative and pathological outcomes. The data from functional outcomes, however, revealed that RALRP could be beneficial if performed by the surgeon with a substantial experience with the procedure, and on younger and preoperatively potent patients, due to its better erectile function outcomes 12 months after surgery compared to conventional laparoscopic procedure. Moreover, the higher continence rate in the RALRP group one year after surgery indicates that this procedure could improve quality of life to a larger number of prostatic cancer patients. In order to support these conclusions, more high quality studies are necessary.

The high level of heterogeneity between non-randomized studies and their poor methodological quality significantly limited the usefulness of the evidence acquired from these studies. Although the heterogeneity was reduced after conducting a subgroup analysis and the evidences of superiority of the transperitoneal RALRP over transperitoneal conventional LRP appeared, this was far from sufficient to make a firm conclusion about effectiveness and safety of RALRP compared to LRP.

With 293 RALRPs performed in 2011, Norwegian Radium Hospital is one of the leading hospitals in Norway regarding this field of surgery. Although the number of performed cases in the institution is sufficient for a surgeon to master the skill, which would allow for the benefits from the RALRP to be fully exploited, the additional costs of the procedure might still be substantial financial burden.

Implications for research

More randomized controlled trials that would compare robot-assisted and conventional laparoscopic prostatectomies are required.

It is necessary that the authors of future trials report complete both statistical data and data regarding methodology. It is further important for the authors to apply the same definition of functional outcomes such as continence, in order to avoid misclassification error when conducting a meta-analysis. A further assessment of specific adverse effects is also required. It would be beneficial that the future studies would involve surgeons with a sufficient experience in both procedures.

Although some previous studies have unequivocally favored LRP over RALRP regarding total costs, it would be beneficial for a future studies to include this outcome. It is reasonable to assume that the costs of acquiring and maintenance of robotic surgical systems would decrease, as it is the case with any other new technology. This would allow further economic evaluation through a cost-effectiveness analysis, and could give answer on how viable would it be to implement robotic surgical system for this specific procedure in the future. Furthermore, the comparison of disease-free survival time would be beneficial to evaluate a long-term benefits from RALRP compared to LRP.

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Appendix 1

Characteristics of included studies (ordered alphabetically)

ASIMAKOPOULOS 2011

Methods	Randomized controlled trial
Participants	128 patients were randomized in two intervention groups (64 patients in each arm). Inclusion criteria: age<=70 years; Gleason score <=7; clinically organ-confirmed disease (cT1-cT2); total serum PSA<=10 ng/ml; Normal preoperative continence, IIEF-6>=17 and normal IPSS. Exclusion criteria: Preoperative incontinence or moderate-to-severe erectile dysfunction (IIEF<17); neoadjuvant therapy; any previous prostatic, urethral, or bladder neck surgery; positive MRI for extracapsular extension; no bilateral nerve sparing. Tumor clinical stage: T1, T2 Setting: Policlinico Tor Vegata, Rome, Italy
Interventions	The transperitoneal anterograde RALRP and LRP performed by a single surgeon. In all of the procedures bilateral nerve sparing intrafascial dissection was attempted. Robotic surgical system: daVinci®
Outcomes	Primary: comparing the erectile function at different time points between the LRP and RALRP groups. Secondary: continence outcomes, complication rates, length of catheter drainage, positive surgical margin rate, mean operative time, blood loss, blood transfusion rate, the rate of complications, prostate volume, tumor volume, pathologic GS, pathologic stage, PSM, PSA measurements. Potency assessment: IIEF-6 questionnaire sent 12 months after surgery; telephone interview regarding capability of intercourse at 1,3,6 and 12 months after surgery.

	Potency definition: IIEF-6 score above 17 (with or without phosphodiesterase type 5 inhibitors) or capability of intercourse Contency assessment: telephone interview at 1,3,6 and 12 months after surgery Contency definition: no leakage or no need of use of any protective pad
Notes	Only patients with a bilateral nerve sparing procedure included in the analysis.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Low risk	Blinding of the outcome assessors performed
Incomplete outcome data (attrition bias)	High risk	Post-randomisation drop-outs that were excluded from the analysis due to an incompleteness of the data.
Selective reporting (reporting bias)	High risk	No study protocol available. The results of mean operative time and estimated blood loss presented only in narrative form, without any figures being presented.
Other bias	Unclear risk	Source of funding was not declared

GOSSEINE 2009

Methods	A prospective study comparing series of patients
Participants	The initial125 patients who underwent LRP match-paired with the initial 122 patients who underwent RALRP between March 2004 and April 2007. Inclusion criteria: not presented Exclusion criteria: not presented

	Tumor clinical stage: T1, T2 Setting: Service d'urologie, hôpital Bichat—Claude-Bernard, AP—HP, faculté de médecine Denis-Diderot, université Paris-VII, groupe hospitalo-universitaire Nord, 46, rue Henri-Huchard, 75018 Paris, France
Interventions	The transperitoneal RALP and LRP performed by a single surgeon. Robotic surgical system: da Vinci®
Outcomes	Continence rate, intraoperative complication rate, operative time, blood loss, transfusion rate, preservation of neurovascular bundles rate, length of hospitalization, postoperative catheterization time, continence rate Potency assessment: not reported as an outcome Continence assessment: via International prostate symptom score (IPSS) and The International Continence Society (ICSmale) questionnaires 6 and 12 months after surgery. Continence definition: no need for any protective pad.
Notes	None

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Randomisation not attempted.
Allocation concealment (selection bias)	High risk	See above.
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	High risk	In 8% of the cases postoperative questionnaires regarding continence were not available.
Selective reporting (reporting bias)	Unclear risk	No study protocol available.
Other bias	Unclear risk	Source of funding not reported, only five preoperative patients' characteristics compared, preoperative co morbidities not compared.

HAKIMI 2009

Methods	A retrospective study comparing series of patients.
Participants	75 patients, the last of more than 300 who underwent LRP (from 2001 to 2005) match-paired with the initial 75 patients who underwent RALRP (after 2005). Inclusion criteria: not presented Exclusion criteria: not presented Tumor clinical stage: T2, T3 Setting: Department of Urology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA.
Interventions	100% of RALRP and 77% of LRP were conducted transperitoneally by a single surgeon. 23% of LRP were performed in an extraperitoneal fashion. Robotic surgical system: daVinci®
Outcomes	Continence and potency rates, complication rates, operative time, blood loss, open surgery conversion, preservation of neurovascular bundles rate, length of hospitalization, PSM, biochemical recurrence. Potency assessment: All patients who underwent nerve sparing procedure answered on questions 2 and 3 of IIEF questionnaire at 3,6 and 12 months after surgery Potency definition: able to achieve and maintain erection satisfactory for intercourse with or without oral phosphodiesterase-5 inhibitors more than one half of the time (score of >=3 on the IIEF questionnaire). Continence assessment: At 3,6 and 12 months after surgery via questionnaire regarding the number of pads used per day. Continence definition: no leakage and no need for any protective pad.
Notes	Historical series used as a control

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The study is judged to be at risk of selection bias due to its retrospective design.
Allocation concealment (selection bias)	High risk	See above.
Blinding of participants and personnel (performance bias)	High risk	Blinding of the participants not performed.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Low risk	Complete data reported for all of the participants.
Selective reporting (reporting bias)	Unclear risk	No study protocol available.
Other bias	High risk	Surgeon's experience uneven between the procedures, source of funding not reported, only five preoperative patients' characteristics compared, preoperative co morbidities not compared.

HU 2006

Methods	A retrospective study comparing series of patients.
Participants	358 patients who underwent LRP performed, from October 2000 to January 2003 match-paired with 322 patients who underwent RALRP, from June 2003 to June 2004. Inclusion criteria: not presented Exclusion criteria: neoadjuvant hormonal therapy Tumor clinical stage: T1, T2, T3 Setting: Urologic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

Interventions	The transperitoneal RALRP and LRP performed by three surgeons. Robotic surgical system: not reported
Outcomes	Preservation of neurovascular bundles rate, vascular, bowel ureteral and obturator nerve injury, infectious complications, blood loss, operative time, blood transfusion rate, reoperation rate and its causes, incidences of myocardial infarction, deep vein thrombosis, cerebrovascular accidents, urine leakage, urine retention, ileus, anastomotic stricture, other self-limited complications, operative time, estimated blood loss, number of perioperative and intraoperative complications by surgeon. Potency assessment: not reported as an outcome Contency assessment: not reported as an outcome
Notes	Historical series used as a control.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	The study is judged to be at risk of selection bias due to its retrospective design.
Allocation concealment (selection bias)	High risk	See above.
Blinding of participants and personnel (performance bias)	High risk	Blinding of the participants not performed.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Low risk	Complete data reported for all of the participants.
Selective reporting (reporting bias)	High risk	No study protocol available. The results of the statistical analysis of preoperative patients' characteristics comparisons and of each outcome were incomplete.
Other bias	High risk	Surgeon's experience uneven between the procedures, source of funding not reported, not possible to assess if the distribution of the patients was balanced according to their characteristics between the intervention groups.

JOSEPH 2005

Methods	A retrospective study comparing series of patients.
Participants	The last 50 patients who underwent LRP match-paired with the last 50 patients who underwent RALRP; LRP series completed before RALRP series (unknown time period) Inclusion criteria: not presented Exclusion criteria: not presented Tumor clinical stage: T1, T2 Setting: Section of Laparoscopic and Robotic Surgery, Department of Urology, University of Rochester Medical Center, Rochester, New York, USA and Institute of Urology, University College London, UK.
Interventions	The extraperitoneal RALRP and LRP with the exception of two patients (unknown number of surgeons). Robotic surgical system: not reported
Outcomes	Mean surgical time, blood loss, preservation of neurovascular bundles rate, urinary continence, potency Potency assessment: 3 months after surgery via IIEF-5 questionnaire Potency definition: spontaneous erection Continence assessment: Continence assessed immediately, 4, 8, 12, and >12 weeks after surgery and verified by the absence of urinary leakage on Valsalva manoeuvre or coughing after catheter removal. Continence definition: no leakage and no need for any protective pad.
Notes	Historical series used as a control.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	The study is judged to be at risk of selection bias due to its retrospective design.
Allocation concealment (selection bias)	High risk	See above.

Blinding of participants and personnel (performance bias)	High risk	Blinding of the participants not performed.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Low risk	Complete data reported for all of the participants.
Selective reporting (reporting bias)	Unclear risk	No study protocol available.
Other bias	Unclear risk	Source of funding not reported, not stated if the same surgeon(s) were performing in both intervention groups, only five preoperative patients' characteristics compared, preoperative co morbidities not compared.

PORPIGLIA 2012

Methods	Randomized controlled trial
Participants	120 patients were randomized in two intervention groups (60 patients in each arm). All patients were aged 40-75 years. Inclusion criteria: prostatic cancer patients - T1-T2N0M0 clinically staged according to TNM classification 2009. Exclusion criteria: previous radiation therapy, hormonal therapy, and/or transurethral resection of the prostate. Tumor clinical stage: T1, T2 Setting: San Luigi Gonzaga hospital, Turin, Italy
Interventions	The transperitoneal anterograde RALRP and LRP performed by a single surgeon. When possible, unilateral or bilateral nerve-sparing procedure and extended lymph node dissection were performed. Robotic surgical system: not reported
Outcomes	Primary: the evaluation of continence 3 months after surgery. Secondary: the evaluation of continence at different end-points, the recovery of erectile

	function, operative time, preservation of neurovascular bundles rate, blood loss, transfusion rate, the mean hospital stay, the mean postoperative catheterization time, the rate of complications, prostate volume, tumor volume, pathologic GS, pathologic stage, PSM, PSA measurements, the biochemical recurrence-free survival rate. Potency assessment: Potency assessed in patients who underwent nerve sparing procedures 1,3,6 and 12 months after surgery using IIEF-5 questionnaire. Potency definition: IIEF-5 score above 17 (with or without phosphodiesterase type 5 inhibitors). Contency assessment: evaluation at catheter removal, 48 hours later, 1, 3,6, and 12 months after surgery by using a single question from the Expanded Prostatic Index Composite questionnaire: "How many pads of adult diapers per day did you usually use to control leakage?" Continence definition: not use of any pad, or use of one pad for safety reasons.
Notes	None

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow up, except for 17 patients limited to biochemical recurrence analysis. Study flow diagram presented.
Selective reporting (reporting bias)	High risk	No study protocol available. A blood transfusion rate reported as an outcome in the method section, but the results were not published.
Other bias	Unclear risk	Preoperative co morbidities and continence not compared.

ROZET 2006

Methods	A retrospective study comparing series of patients.
Participants	133 patients who underwent LRP match-paired with the initial 133 patients who underwent RALRP, from May 2003 to May 2005. Inclusion criteria: not presented Exclusion criteria: not presented Tumor clinical stage: T1, T2 and one patient in LRP group with T3 stage Setting: Department of Urology, Institut Montsouris, Paris, France
Interventions	The extraperitoneal RALRP and LRP performed by four surgeons. Robotic surgical system: daVinci®
Outcomes	Operative time, mean blood loss, preservation of neurovascular bundles rate, transfusion rate, length of hospital stay and bladder catheterization, rate of complications, pathological GS, pathological stage, PSM. Potency assessment: not reported as an outcome Continence assessment: not reported as an outcome
Notes	None

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	The study is judged to be at risk of selection bias due to its retrospective design.
Allocation concealment (selection bias)	High risk	See above.
Blinding of participants and personnel (performance bias)	High risk	Blinding of the participants not performed.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Low risk	Complete data reported for all of the participants.

Selective reporting (reporting bias)	Unclear risk	No study protocol available.
Other bias	High risk	Surgeon's experience uneven between the procedures, source of funding not reported.

STOLZENBURG 2013

Methods	A prospective study comparing series of patients.
Participants	100 patients from among the last 208 who underwent LRP match-paired with the initial 100 patients who underwent RALRP, from July 2011 to January 2012. Inclusion criteria: not presented Exclusion criteria: not presented Tumor clinical stage: not stated Setting: Department of urology and Clinical Trial Centre Leipzig, Univerzity of Leipzig, Leipzig, Germany.
Interventions	Mainly extraperitoneal RALRP and LRP performed by two surgeons. Transperitoneal approach used for high risk patients. Robotic surgical system: daVinci®
Outcomes	Potency rate, continence rate, operative time, mean blood loss, mean hospital stay, transfusion rate, length of bladder catheterization, preservation of neurovascular bundles rate, rate of rectal/visceral injuries, wound infections, urinary infections, urinary retentions and pulmonary embolism, pathological GS, pathological stage, PSM, PSA at three months. Potency assessment: 3 months after surgery, IIEF questionnaire was sent to patients who underwent nerve sparing procedure. Potency definition: able to achieve an erection satisfactory for intercourse Continence assessment: A questionnaire was sent 3 months after surgery. Continence assessed by a number of pads over a 24-hour period.

	Continence definition: not used any pad, or used one pad for safety reasons.
Notes	None.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Not attempted.
Allocation concealment (selection bias)	High risk	See above.
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	Complete data reported for all of the participants.
Selective reporting (reporting bias)	High risk	No study protocol available. Mean hospital stay reported as an outcome in the method section, but the results were not published. The results of the statistical analysis of preoperative patients' characteristics comparisons were not reported
Other bias	High risk	Surgeon's experience uneven between the procedures, not possible to assess if the distribution of the patients was balanced according to their characteristics between the intervention groups, only two preoperative patients' characteristics compared, preoperative co morbidities not compared.

TRABULSI 2011

Methods	A retrospective study comparing series of patients.
Participants	the final 45 patients who underwent LRP (from 2000 to 2005) match-paired with the initial 275 patients who underwent RALRP (after 2005) Inclusion criteria: not presented Exclusion criteria: not presented

	Tumor clinical stage: not stated Setting: Department of Urology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA.
Interventions	The transperitoneal RALRP and LRP performed by a single surgeon. Robotic surgical system: daVinci®
Outcomes	Potency and continence rates, Pathologic Gleason score, Pathologic tumor stage, PSM, number of BNS procedures, mean operative time, estimated blood loss, number of open conversions, rate of blood transfusion, mean hospital length of stay. Potency assessment: IIEF questionnaire sent 3, 6, 12 and 24 months after surgery Potency definition: able to attain and maintain an erection satisfactory for intercourse with or without the use of phosphodiesterase-5 inhibitors Continence assessment: IPSS questionnaire sent 3,6 and 12 months after surgery. Continence definition: no leakage or pad use for social protection only.
Notes	Historical series used as a control.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	The study is judged to be at risk of selection bias due to its retrospective design.
Allocation concealment (selection bias)	High risk	See above.
Blinding of participants and personnel (performance bias)	High risk	Blinding of the participants not performed.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Low risk	Complete data reported for all of the participants.
Selective reporting (reporting bias)	High risk	No study protocol available. The rate of potent patients in the LRP group not reported.
Other bias	High risk	Surgeon's experience uneven between the procedures, source of funding not reported, only five preoperative patients'

		characteristics compared, preoperative co morbidities not compared.

Surgeon's experience in the included studies

Author and year	Number of surgeons involved	Surgeons' experience prior to beginning of a study
Asimakopoulos 2011	1	More than 600 LRPs and 100 RALRPs performed.
Gosseine 2009	1	No previous experience with either procedure.
Hakimi 2009	1	More than 300 LRPs performed no previous experience with RALRP.
Hu 2006	3	LRP series preceded RALRP series.
Joseph 2005	N/A	LRP series preceded RALRP series - last 50 out of 78 LRPs and last 50 of 200 RALRPs included in the study.
Porpiglia 2012	1	More than 900 LRPs and more than 300 RALRPs performed (around 80 LRPs and 70 RALRPs per year).
Rozet 2006	4	5 year experience of each surgeon with LRP, previous experience with RALRP limited to 35 cases.
Stolzenburg 2013	2	Each surgeon performed more than 1 000 LRPs, no previous experience with RALRP.
Trabulsi 2011	1	More than 200 LRPs performed, no previous experience with RALRP.

Summary of findings table

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect estimate	Level of heterogeneity
1.1 Recovery of erectile function 12 months after surgery (IIEF-5 score > 17, patients who underwent either nerve-sparing procedure) - RCTs	2	182	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.21, 2.04]	0%
2.1 Continence recovery 12 months after surgery (defined as no need for any protective pad) - RCTs	2	215	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.07, 1.35]	23%

2.2 Continence recovery 12 months after surgery (defined as no need for any protective pad or use of one pad for seurity) - RCTs	2	215	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.96, 1.30]	66%
3.1 Biochemical recurrence 12 months after surgery (defined as PSA>0.2 ng/ml) - RCTs	2	215	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.11, 7.31]	59%
4.1 Mean catheterization time - RCTs [Days]	2	232	Mean Difference (IV, Fixed, 95% CI [Days])	0.13 [-0.55, 0.81]	1%
5.1 Overall complication rate (Clavian classification) - RCTs	2	232	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.81, 3.15]	0%
6.1 Positive surgical margin - RCTs	2	230	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.81, 2.42]	0%
6.2 Positive surgical margin (pathological stage T2) - RCTs	2	171	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.36, 2.06]	0%
6.3 Positive surgical margin (pathological stage T3) - RCTs	2	61	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [0.97, 3.84]	0%
7.1 Recovery of erectile function 3 months after surgery (ability to achieve an erection satisfactory for intercourse, patients who underwent either nerve-sparing procedure) - Comparative series	2	235	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.90, 2.87]	0%
8.1 Continence rate 3 months after surgery (defined as no need for any protective pad) - Comparative series	2	250	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.83, 1.36]	67%
8.2 Continence rate 3 months after surgery (defined as no need for any protective pad or use of one pad for security) - Comparative series	2	520	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.93, 1.29]	0%
9.1 Mean operating time - Comparative series [minutes]	5	1183	Mean Difference (IV, Random, 95% CI [minutes])	-5.87 [-26.91, 15.17]	89%
9.2 Mean operating time - Subgroup of comparative series with extraperitoneal surgical approach [minutes]	2	466	Mean Difference (IV, Random, 95% CI [minutes])	15.40 [-3.75, 34.54]	90%
9.3 Mean operating time - Subgroup of comparative series with transperitoneal surgical approach [minutes]	3	717	Mean Difference (IV, Random, 95% CI [minutes])	-30.26 [-64.46, 3.95]	76%

9.4 Mean operating time - Subgroup of comparative series with preoperative clinical stage T1-T2 patients [minutes]	2	513	Mean Difference (IV, Fixed, 95% CI [minutes])	4.95 [-1.62, 11.53]	0%
10.1 Estimated blood loss - Comparative series [millilitre]	6	1283	Mean Difference (IV, Random, 95% CI [millilitre])	-19.92 [-91.39, 51.56]	85%
10.2 Estimated blood loss - Subgroup of comparative series with extraperitoneal surgical approach [millilitre]	3	566	Mean Difference (IV, Random, 95% CI [millilitre])	17.10 [-87.63, 121.84]	86%
10.3 Estimated blood loss - Subgroup of comparative series which included T1-T2 preoperative clinical stage patients [millilitre]	3	613	Mean Difference (IV, Random, 95% CI [millilitre])	0.40 [-138.57, 139.36]	77%
10.4 Estimated blood loss - Subgroup of comparative series in which more than one operators performed surgeries [millilitre]	2	466	Mean Difference (IV, Fixed, 95% CI [millilitre])	58.28 [25.15, 91.41]	0%
10.5 Estimated blood loss - Subgroup of comparative series with transperitoneal surgical approach [millilitre]	3	717	Mean Difference (IV, Fixed, 95% CI [millilitre])	-75.20 [-115.81, -34.58]	0%
11.1 Mean hospital stay - Comparative series [days]	3	663	Mean Difference (IV, Random, 95% CI [days])	-0.73 [-1.88, 0.42]	87%
11.2 Mean hospital stay - Subgroup of comparative series with transperitoneal surgical approach [days]	2	397	Mean Difference (IV, Fixed, 95% CI [days])	-1.32 [-1.81, -0.83]	0%
11.3 Mean hospital stay - Subgroup of comparative series which included T1-T2 preoperative clinical stage patients [days]	2	513	Mean Difference (IV, Random, 95% CI [days])	-0.36 [-2.03, 1.30]	90%
12.1 Mean catheterization time - Comparative series [days]	3	713	Mean Difference (IV, Random, 95% CI [days])	-0.15 [-0.93, 0.64]	74%
12.2 Mean catheterization time - Subgroup of comparative series with extraperitoneal surgical approach [days]	2	466	Mean Difference (IV, Fixed, 95% CI [days])	0.26 [-0.22, 0.73]	0%
13.1 Number of unilateral nerve sparing procedures - Comparative series	6	1643	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.80, 1.33]	31%
13.2 Number of bilateral nerve sparing procedures - Comparative	7	1963	Risk Ratio (M-H, Random,	1.17 [1.01,	70%

series			95% CI)	1.34]	
13.3 Number of bilateral nerve sparing procedures - Subgroup of comparative series with transperitoneal surgical approach	4	1397	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.10, 1.28]	0%
13.4 Number of bilateral nerve sparing procedures - Subgroup of comparative series with extraperitoneal surgical approach	3	566	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.79, 1.84]	88%
13.5 Number of bilateral nerve sparing procedures - Subgroup of comparative series which included T1-T2 preoperative clinical stage patients	3	613	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.88, 1.86]	89%
13.6 Number of bilateral nerve sparing procedures - Subgroup of comparative series which included T3 preoperative clinical stage patients	2	830	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.10, 1.31]	0%
13.7 Number of bilateral nerve sparing procedures - Subgroup of comparative series in which one operator performed surgeries	3	717	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.99, 1.32]	0%
13.8 Number of bilateral nerve sparing procedures - Subgroup of comparative series in which more than one operator performed surgeries	3	1146	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.88, 1.29]	75%
14.1 Intraoperative conversion to open surgery - Comparative series	3	1150	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 2.80]	64%
14.2 Intraoperative conversion to open surgery - Subgroup of comparative series which included T3 preoperative clinical stage patient	2	830	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.10, 2.97]	44%
14.3 Intraoperative conversion to open surgery - Subgroup of comparative series in which one operator performed surgeries	2	470	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.00, 24.05]	82%
15.1 Transfusion rate - Comparative series	4	1513	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.26, 1.60]	51%
15.2 Transfusion rate - Subgroup of comparative series with transperitoneal surgical approach	3	1247	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.47, 1.97]	47%
15.3 Transfusion rate - Subgroup of comparative series with preoperative clinical stage T1-T2	2	513	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.11, 6.16]	82%

15.4 Transfusion rate - Subgroup of comparative in which more than one operator performed surgeries	2	946	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.21, 0.97]	5%
15.5 Transfusion rate - Subgroup of comparative series in which one operator performed surgeries	2	567	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.13, 6.75]	71%
16.1 Symptomatic lymphocoele - Comparative series	3	1030	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.20, 2.01]	0%
16.2 Postoperative bleeding - Comparative series	4	1296	Risk Ratio (M-H, Fixed, 95% CI)	3.39 [1.11, 10.40]	0%
16.3 Pulmonary embolus - Comparative series	2	416	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.18]	0%
16.4 Urinary tract sepsis - Comparative series	2	416	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.39, 8.36]	0%
16.5 Deep vein thrombosis - Comparative series	2	830	Risk Ratio (M-H, Fixed, 95% CI)	4.24 [0.48, 37.44]	0%
16.6 Bladder neck contracture - Comparative series	2	830	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.09, 1.17]	0%
16.7 Urinary retention - Comparative series	3	1096	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.42, 1.42]	0%
16.8 Ileus - Comparative series	2	830	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.19, 4.40]	52%
16.9 Wound infection/abscess - Comparative series	2	466	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.22, 12.52]	0%
16.10 Total perioperative complication rates (Clavian classification) - Comparative series	3	1096	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.37, 2.33]	87%
16.11 Total perioperative complication rates (Clavian classification) - Subgroup of comparative series with transperitoneal surgical approach	2	830	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.41, 0.74]	0%
16.12 Total perioperative complication rates (Clavian classification) - Subgroup of comparative series in which more than one operator performed surgeries	2	946	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.26, 4.15]	93%
17.1 Positive surgical margin	4	936	Risk Ratio (M-	1.10	0%

(overall) - Comparative series			H, Fixed, 95% CI)	[0.81, 1.50]	
17.2 Positive surgical margin (pathological stage T2) - Comparative series	3	608	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.78, 1.79]	40%
17.3 Positive surgical margin (pathological stage T3) - Comparative series	2	106	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.57, 2.20]	0%

Appendix 2

Search strategies

1. CENTRAL

#1 MeSH descriptor Laparascopy explode all trees

#2 laparoscop*

#3 (#1 OR #2)

#4 MeSH descriptor Prostatic Neoplasms explode all trees

#5 “prostate cancer” OR “cancer of prostate” OR “prostatic neoplasms”

#6 (#5 OR #6)

#7 MeSH descriptor Prostatectomy explode all trees

#8 prostatect* OR “retropubic prostatectomy” OR “suprapubic prostatectomy” OR “prostate resection” OR “radical prostatect*” OR “extraperitoneal prostatect*” OR “transperitoneal prostatect*”

#9 (#7 OR #8)

#10 Mesh descriptor Robotics explode all trees

#11 “remote operations” OR “robot*-assisted” OR “robot*” OR robotics OR telerobotics OR “da vinci” OR “computer-assisted “OR “computer assisted”

#12 (#10 OR #11)

#13 (#3 AND #6 AND #9 AND #12)

2. MEDLINE

#1 laparoscop* [tw] OR surgery, laparoscopic surgery [MeSH]

#2 Prostatectomies [MeSH] OR prostatect* [tw] OR “prostate resection” [tw] OR Prostatectomy, Retropubic [MeSH] OR Prostatectomy, Suprapubic [MeSH] OR “retropubic prostatectomy” [tw] OR “suprapubic prostatectomy” [tw] OR “radical prostatect*” [tw] OR “extraperitoneal prostatect*” [tw] OR “transperitoneal prostatect*” [tw]

#3 Cancer, Prostate [MeSH] OR “prostate cancer” [tw] OR “cancer of prostate” [tw] OR “prostatic neoplasms” [tw]

#4 Robotics [MeSH] OR “remote operation*” [tw] OR “robot-assisted” [tw] OR robot* [tw] OR telerobotics [tw] OR “da vinci” [tw] OR “computer-assisted“ [tw] OR “computer assisted” [tw]

#5 randomi?ed controlled trial [pt] OR randomi?ed clinical trial [pt] OR controlled clinical trial [pt] OR controlled clinical trials, randomized [Mesh] OR clinical trial [MeSH] OR clinical trial [pt] OR random allocation [MeSH] OR method, single blind [MeSH] OR method, double blind [MeSH] OR “clinical trial” [tw] OR “controlled trial” [tw] OR random* [tw] or retrospectiv* [tw] OR prospectiv* [tw] OR prospective study [Mesh] OR retrospective study [Mesh]

#6 (#1 AND #2 AND #3 AND #4 AND #5)

3. EMBASE

#1 laparoscop*/tw OR laparoscopic surgery/exp

#2 Prostatectomy/ exp OR prostate surgery/exp OR retropubic prostatectomy/tw OR suprapubic prostatectomy/tw OR prostatect*/tw OR prostate resection/tw OR radical prostatect*/tw OR extraperitoneal prostatect*/tw OR transperitoneal prostatect*/tw

#3 cancer prostate/exp OR prostate cancer/tw OR cancer of prostate/tw OR prostatic neoplasms/tw

#4 robotics/exp OR remote operation*/tw OR robot-assisted/tw OR robot*/tw OR telerobotics/tw OR da vinci/tw OR computer-assisted/tw OR computer assisted/tw

#5 randomi?ed controlled trial/pt OR randomi?ed clinical trial/pt OR clinical trial/pt OR randomized controlled trials/exp OR retrospective study/exp OR prospective study/exp OR controlled clinical trial/exp OR single-blind/tw OR single blind/tw OR double-blind/tw OR double blind/tw OR clinical trial/tw OR controlled trial/tw OR random*/tw retrospectiv*/tw OR prospectiv*/tw

#6 (#1 AND #2 AND #3 AND #4 AND #5)

Appendix 3

Questionnaire

1. Does Your institution have any type of robotic surgery systems?

2. If yes, when was the system obtained?

3. Was the system purchased or was it a gift from the third party?

4. Is the system used for radical prostatectomies in Your institution?

5. If yes, how many robot-assisted radical prostatectomies are conducted per day and in the last year (on average)?

6. In Your institution, how many percent of radical prostatectomies conducted in the last year were retropubic radical prostatectomy (open surgery), pure laparoscopic radical prostatectomy (human-assisted) and robot-assisted radical prostatectomy respectively?

7. Do You have any cost estimates of robot-assisted radical prostatectomies compared to pure laparoscopic surgeries?

8. Does Your institution have some type of quality registries regarding prostate surgeries?