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ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Robotic Surgical System for Radical Prostatectomy: A Health Technology Assessment

KEY MESSAGES

Prostate cancer is the second most common cancer in men in Canada. It forms in the prostate gland of the male reproductive system and often grows very slowly. However, in some patients, prostate cancer grows more quickly and causes symptoms or even death.

One of the possible treatments for prostate cancer is to surgically remove the prostate gland. This is known as radical prostatectomy. It can be performed in an open, laparoscopic, or robot-assisted approach. The open approach is the traditional surgical approach and involves a large incision. In contrast, laparoscopic and robot-assisted approaches are minimally invasive and performed through small keyhole incisions. The robot-assisted approach is the newest method. It uses a surgical robotic system with arms that the surgeon controls to perform the radical prostatectomy.

We reviewed the evidence to evaluate the effectiveness, safety, and cost-effectiveness of the robotic surgical system for radical prostatectomy compared with the open and laparoscopic approaches.

We found that, compared with open radical prostatectomy, the robotic surgical approach improves some perioperative outcomes, such as the length of the hospital stay and blood loss. However, results were generally not significant or inconclusive for functional outcomes, such as urinary and sexual function, and for cancer-related outcomes.

Patients may prefer the robot-assisted method, particularly if their surgeon recommends it as a better treatment.

There was generally no difference in outcomes for the robotic surgical approach and the laparoscopic approach to radical prostatectomy.

Our economic analysis showed that compared with open radical prostatectomy, the costs of using the robotic system are high while the health benefits are small. Thus, robot-assisted radical prostatectomy does not appear to be cost-effective in Ontario. If its adoption continues to rise, this would lead to a considerable increase to the provincial budget.

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ABSTRACT

Background

Prostate cancer is the second most common type of cancer in Canadian men. Radical prostatectomy is one of the treatment options available with a curative aim, and it involves removing the prostate gland and surrounding tissues. In recent years, robot-assisted radical prostatectomy has been increasingly used.

We set out to determine the clinical effectiveness and safety of the robotic surgical system for radical prostatectomy (robot-assisted radical prostatectomy) compared with the open and laparoscopic surgical methods. We also assessed the cost-effectiveness of robot-assisted versus open radical prostatectomy in patients with clinically localized prostate cancer in Ontario.

Methods

We performed a literature search and included prospective comparative studies that examined robot-assisted versus open or laparoscopic radical prostatectomy for prostate cancer. The outcomes of interest were perioperative, functional, and oncological. The quality of the body of evidence was examined according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group criteria.

We also conducted a cost-utility analysis with a 1-year time horizon. The potential long-term benefits of robot-assisted radical prostatectomy for functional and oncological outcomes were also evaluated in a 10-year Markov model in scenario analyses. In addition, we conducted a budget impact analysis to estimate the additional costs to the provincial budget if the adoption of robot-assisted radical prostatectomy were to increase in the next 5 years.

A needs assessment determined that the published literature on patient perspectives was sufficient for this technology and direct patient engagement would not add great value.

Results

Compared with the open approach, we found robot-assisted radical prostatectomy reduced length of stay and blood loss (moderate quality evidence) but had no difference or inconclusive results for functional and oncological outcomes (low to moderate quality evidence). Compared with laparoscopic radical prostatectomy, robot-assisted radical prostatectomy had no difference in perioperative, functional, and oncological outcomes (low to moderate quality evidence).

Compared with open radical prostatectomy, robot-assisted prostatectomy was associated with higher costs ($6,234) and a small gain in quality-adjusted life-years (QALYs) (0.0012). The incremental cost-effectiveness ratio (ICER) was $5.2 million per QALY gained. However, if robot-assisted radical prostatectomy were assumed to have substantially better long-term functional and oncological outcomes, the ICER would be $83,921 per QALY gained. The annual budget increase was estimated to be $0.8 million to $3.4 million over the next 5 years.

Conclusions

Robot-assisted radical prostatectomy provides no difference in functional and oncological outcomes compared with open and laparoscopic approaches. However, compared with open radical prostatectomy, the costs of using the robotic system are high while the health benefits are small.

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BACKGROUND

Health Condition

Prostate cancer is the second most common cancer (after non-melanoma skin cancers) and the third leading cause of death among Canadian men. It has been estimated that, in Canada, prostate cancer accounted for 21% of all new cancer cases (21,600) and 10% of all cancer deaths (4,000) in men in 2016.[1] In Ontario, men have a 15.4% lifetime probability of developing prostate cancer,[2] and the incidence among all new cancer cases in 2012 was 21.6%.[3]

Prostate cancer arises within the prostate gland of the male reproductive system. The function of the prostate is to secrete a fluid that constitutes semen. Most prostate cancers are asymptomatic and slow growing. Symptoms usually appear if the prostate cancer is quite advanced locally, and may include a weak or interrupted flow of urine, frequent or trouble with urination, and painful ejaculation. Urinary symptoms are almost always owing to the coexisting condition of benign enlargement of the prostate (benign prostatic hyperplasia).

Prostate cancer typically affects men over the age of 60 years. Risk factors that have been associated with the development of prostate cancer are family history, African descent, obesity, a high-fat diet, and physical inactivity. The 5-year survival rate is high for prostate cancer, at around 96%.[4]

Clinical Need and Target Population

Since clinically localized prostate cancer usually causes no symptoms, early detection tests have been developed to identify prostate cancer while it remains confined to the prostate. Most patients are referred to a urologist because they have abnormal results on their digital rectal examination or an elevated prostate-specific antigen (PSA) level. Prostate-specific antigen is a protein produced by prostate cells that can be measured in the blood and is normally present at low levels. Higher PSA levels may indicate prostate cancer or other noncancerous prostate conditions such as benign prostatic hyperplasia or prostatitis (an inflammation of the prostate).

If prostate cancer is suspected in patients, a needle biopsy is performed to confirm the diagnosis. Positive biopsies are scored using the Gleason system, which typically grades biopsies from 6 to 10 (6 being well-differentiated, 7 moderately differentiated, and 8–10 poorly differentiated). Gleason scores ≤ 6 are uncommon for detected tumours. A less well-differentiated prostate cancer indicates a more aggressive tumour (high-grade prostate cancer).

Tumour stage is also used for prognosis and refers to the degree in which the tumour has involved the prostate gland or has spread. Tumour stage generally ranges from T1 to T4[5]:

- T1: tumour is too small to be seen on imaging scans or felt during examination, but can be found incidentally during a biopsy or surgery
    - T1a: tumour is in ≤ 5% of tissue taken
    - T1b: tumour is in > 5% of tissue taken
    - T1c: tumour is found by biopsy after an elevated PSA level was detected
- T2: tumours are confined within the prostate gland
    - T2a: tumour is in ≤ 50% of one lobe
    - T2b: tumour is in > 50% of one lobe
    - T2c: tumour is in both lobes

- T3: tumour has extended through the capsule that surrounds the prostate
    - T3a: tumour has gone through the capsule without invading the seminal vesicles
    - T3b: tumour has invaded the seminal vesicles
- T4: tumour has invaded structures or tissues near the prostate other than the seminal vesicles (e.g., bladder neck, rectum, pelvic wall)

The Gleason score and tumour stage are used to predict outcomes for prostate cancer. By using the PSA, Gleason score, and tumour stage, risk stratification schemes have been developed that are significantly associated with biochemical recurrence (elevated PSA levels after radical prostatectomy) and mortality owing to prostate cancer. Different risk stratification systems exist with slight variations in categorical definitions.[6] However, patients are generally grouped as low, intermediate, or high risk. Below is a risk stratification from D'Amico et al,[7] the first proposed three-group stratification for radical prostatectomy (and radiotherapy):

- Low risk: PSA ≤ 10 ng/mL and Gleason score ≤ 6 and T1–T2a
- Intermediate risk: PSA 10–20 ng/mL and/or Gleason score 7 and/or T2b and not low-risk
- High risk: PSA > 20 ng/mL or Gleason score 8–10 or clinical stage ≥ T2c

Current Treatment Options

Current standard treatment options for prostate cancer are watchful waiting, active surveillance, surgery (radical prostatectomy), radiation therapy, and hormone therapy. The differences between prostate cancer incidence and mortality indicate that many patients may not benefit from immediate treatment (such as surgery) of localized prostate cancer, such as those patients diagnosed with early-stage low-grade prostate cancer. Patients who forgo immediate therapy may opt for watchful waiting or active surveillance. In watchful waiting, there is no treatment for the prostate cancer. Instead the focus is on managing quality of life and other illnesses. In active surveillance, instead of immediate treatment, patients are actively monitored to provide treatment if the cancer is likely to progress, thereby reducing treatment-related complications if the cancer is not likely to progress.

Radical treatments with a curative aim consist of radical prostatectomy and radiation therapy. In selecting potential candidates for radical prostatectomy, surgeons consider:

- Life expectancy
- The natural history of the diagnosed prostate cancer
- The ability of radical prostatectomy to cure the prostate cancer
- The morbidity of radical prostatectomy
- Patient choice

Radical prostatectomy is generally performed on patients with localized prostate cancer (stage ≤ T2) and a life expectancy greater than 10 years. Patients with poorer prognostic factors, such as locally advanced prostate cancer (stage T3a), a Gleason score > 8, and a PSA level > 20 ng/mL, may also be offered radical prostatectomy. However, they will likely need further treatments.

Radical prostatectomy involves removing the prostate and the surrounding tissues and seminal vesicles. It is performed via one of four surgical approaches:

1. Open retropubic: the operation is performed through a primary incision through the pubic area
2. Open perineal: the operation is performed through a primary incision in the perineum (a rarely performed approach compared with open retropubic prostatectomy)
3. "Conventional" laparoscopic (referred to in this report as "laparoscopic radical prostatectomy"): this is a minimally invasive approach in which the operation is performed through keyhole incisions in the abdomen; a video camera is inserted to help the surgeon view the prostate
4. Robot-assisted laparoscopic (referred to in this report as "robot-assisted radical prostatectomy"): this is similar to the laparoscopic approach; however, a surgeon manipulates robotic arms of a surgical system that are inserted into the small incision points

Depending on tumour characteristics and a patient's sexual function, either nerve-sparing radical prostatectomy (to preserve erectile function) or non-nerve-sparing radical prostatectomy is commonly performed. Pelvic lymphadenectomy (the removal of lymph nodes in the pelvis) can be performed concurrently and is generally reserved for patients with a higher risk of lymph node involvement.

The laparoscopic approach was introduced in the 1990s and gained acceptance through advances in medical technology. However, laparoscopic radical prostatectomy did not disseminate widely because it is technically difficult to perform. In the early 2000s, with the advent of robotic surgery technology, the option emerged to use a robotic surgical system for radical prostatectomy (i.e., robot-assisted radical prostatectomy).

Technology

The da Vinci Surgical System is the only robotic surgical system that is available for clinical use in Canada. It has four main components:

1. A surgeon's console, where the surgeon sits and views a magnified three-dimensional image of the surgical field
2. A patient side cart, which consists of three instrument arms and one endoscope (a tubular optical instrument for viewing the inside of the body)
3. Detachable instruments, which are used to simulate a person's fine motor movements
4. A three-dimensional vision system

The main procedural advantages of using the robotic system are improved dexterity, its precision, three-dimensional imaging, and its ergonomic design for surgeons. A potential disadvantage is that while it helps the surgeon accurately manipulate tissue, the surgeon experiences only visual feedback and none of the touch experienced in laparoscopic and open radical prostatectomies.

Costs include the initial cost of the robotic surgical system, annual maintenance, training for surgeons and operating room personnel, and disposable instruments.

The overall goals of laparoscopic and robot-assisted radical prostatectomy are to maintain the benefits of minimally invasive surgery, while maximizing:

- Cancer control

- Urinary continence—the ability to voluntarily control the release of urine
- Erectile function—the ability to develop or maintain an erect penis during sexual activity

Laparoscopic radical prostatectomy is indicated for men who have intermediate- to high-risk prostate cancers that appear localized to the gland. Relative contraindications to robot-assisted radical prostatectomy, based on surgeon experience, include extensive prior intra-abdominal surgery and anatomical features that pose difficulty for the robotic system. If a surgeon has a lot of experience with the system, these factors may not have such a big effect.

Compared with the open retropubic approach that is performed through a 6- to 8-cm incision, robot-assisted radical prostatectomy involves multiple incisions ranging from only 5- to 12-mm in diameter.

Of note, the introduction of robot-assisted radical prostatectomy also serves as a gateway for other robot-assisted surgeries (e.g., partial nephrectomy).

Regulatory Information

The first generation of the da Vinci Surgical System has been licensed by Health Canada since 2001 as a Class IV medical device. In 2010, Health Canada approved the use of the third generation, the da Vinci Si. In 2010 and 2012, it also approved new components, categorized as Class II medical devices. The da Vinci Surgical Systems are intended to be used by trained physicians in an operating room environment for a wide range of surgeries, including urologic, gynecologic, cardiac, colorectal, oropharyngeal, thoracic, and general surgeries. The latest version of the surgical system, the da Vinci Xi, was approved by Health Canada in July 2016; however, no systems have been purchased in Canada as of this writing. The da Vinci Surgical Systems are marketed internationally, with about 3,500 systems installed worldwide as of 2015.

The US Food and Drug Administration (FDA) approved the da Vinci Surgical System for use in 2000. However, in February 2016, the administration published a guidance document to "assist industry in following appropriate human factors and usability engineering processes to maximize the likelihood that new medical devices will be safe and effective for the intended users, uses, and use environments."[8] The recommendations contained within the document hope to support manufacturers in improving the design of the device. The goal is to ensure that the user interface is designed to eliminate or reduce errors that could cause harm or degrade medical treatment.

In addition, the Food and Drug Administration included robotic surgery devices in a 2016 draft document that listed the highest-priority devices for a review of human factors (e.g., device design input, verification, and validation; usability engineering).[9] This guidance informed manufacturers that human factors data should be included in their premarket submissions for particular medical devices. The administration believes these device types have clear potential for serious harm resulting from errors.

Patient Values and Preferences

Patient preference is integral to the decision-making process for prostate cancer treatment. Patients may prefer the minimally invasive nature of robot-assisted radical prostatectomy compared with open radical prostatectomy because there are fewer surgical scars, a faster recovery, and decreased perioperative outcomes (see the Outcomes of Interest section).[10,11] Based on data from the United States, patients with a higher socioeconomic status are more

likely to undergo minimally invasive radical prostatectomy (laparoscopic or robot-assisted). These patients may be more informed about all surgical options, be willing to undergo a newer treatment modality, and seek out minimally invasive prostatectomy if it is not offered locally.[12] A shorter hospital stay and less time off work may be especially appealing to these patients.[12]

It has also been suggested that marketing and promotional language unrelated to presentation of potential risks and benefits may influence patients to prefer robot-assisted over open radical prostatectomy.[13] Media coverage and online marketing for robot-assisted radical prostatectomy are also more widespread,[14] although there is the potential for inaccurate information from online sources.[15,16]

Data from the United States have also shown that patients who undergo robot-assisted radical prostatectomy may be more likely to regret their decision, possibly because their expectations were too high owing to its innovative nature.[17] Patients undergoing robot-assisted surgery were found to have higher expectations for a significantly shorter hospital stay, earlier return to physical activity, and earlier return of potency than those undergoing open radical prostatectomy.[18] Baseline functional outcomes, age, and peri- and postoperative outcomes were independent predictors of patients' satisfaction and decision regret following robot-assisted radical prostatectomy.[19,20]

A Canadian study by Davison et al[21] examined decision regret using the Decision Regret Scale to measure distress and remorse at 1 year postsurgery. However, in contrast with US findings, the authors found scores were low for the robot-assisted and open groups and that results did not differ significantly between them.

Canadian and International Contexts

Robot-assisted prostatectomy is currently publicly funded through the quality-based procedure pathway for prostate cancer. However, funding rates for robot-assisted and open radical prostatectomy are the same and are determined through the Ontario Ministry of Health and Long-Term Care's case costing methodology (provincial cost per weighted case × institution's case mix index). The choice of open or robot-assisted radical prostatectomy is determined by the treating surgeon.

The da Vinci Surgical Systems that are currently in use in Ontario and their associated maintenance fees have been purchased through charitable donations or have come from within a hospital's budget. Experts have told us that in 2016, there were 10 Ontario hospital centres (located in London, Toronto, Hamilton, Ottawa, and Windsor) that owned at least one da Vinci Surgical System. London Health Sciences Centre was designated as the exclusive national training centre for robotic surgery by the manufacturer of the da Vinci Surgical System, Intuitive Surgical Inc.

Since robot-assisted surgery is available in only a limited number of urban teaching hospital centres, potential pressure to centralize robotic surgery may make it harder for some patients to access this surgery. However, given the technical challenges of robot-assisted radical prostatectomy, maximizing surgeons' caseloads may help them overcome the learning curve and improve outcomes.

Other than Ontario, as of 2016 only three provinces had hospital centres with at least one da Vinci Surgical System: Alberta (Edmonton and Calgary), Quebec (Montreal and Quebec City), and British Columbia (Vancouver). In total, there were 25 (21 clinical systems, 4 research

systems) da Vinci Surgical Systems in Canada installed in 2014. In provinces where robot-assisted radical prostatectomy is currently available, the provincial fee codes do not distinguish between laparoscopic and robot-assisted radical prostatectomy. The fees are the same for the two procedures, and there is no extra user fee for robot-assisted radical prostatectomy.

Experts also told us that in 2015, more than 3,500 robot-assisted surgical procedures were performed in Canada. Of these procedures, 64% were urologic surgeries (more than 80% were radical prostatectomies), with gynecologic surgeries being the second most common type of procedure, at 25%. In Ontario, the volume of robot-assisted radical prostatectomies was 828 cases (1,909 cases in Canada).

According to experts, the adoption of robot-assisted surgery has been slower in Canada than in the United States, with about 70% of radical prostatectomies still performed using the open procedure versus less than 15% in the United States. In the United States, funding for robot-assisted radical prostatectomy is covered by the Centers for Medicare and Medicaid Services (CMS) under the same code as laparoscopic radical prostatectomy. This agency reimburses hospitals at the same rate, regardless of surgical approach. Most private insurers also do not pay an additional fee for robot-assisted radical prostatectomy.[22] However, a study among privately insured younger patients suggests hospitals may receive more per case for minimally invasive radical prostatectomy than open radical prostatectomy.[23]

Some US studies have also discussed that hospitals may want to use robotic surgery regularly to improve its cost-effectiveness. This may lead to wider indications for robot-assisted prostatectomy, where alternative surgery or nonsurgical interventions might actually be preferable.

In other comparable jurisdictions such as the United Kingdom and Australia, the adoption of robot-assisted radical prostatectomy has also been higher than in Canada. In the United Kingdom, 2013 data showed an approximately even proportion of robot-assisted versus non-robot-assisted radical prostatectomy procedures.[24] According to experts, in Australia in 2015, 58% of radical prostatectomies were performed with robotic assistance. Of note, both the United Kingdom and Australia have a two-tiered hospital system (public and private), with a much higher installation of the da Vinci Surgical System in the private system.

Without robotic assistance, performing laparoscopic radical prostatectomy is technically challenging, with a steep learning curve. The advanced skills required to perform laparoscopic radical prostatectomy have limited its widespread use.

In contrast, it has been proposed that robot-assisted radical prostatectomy can be mastered by most prostate surgeons, although Ontario data are lacking. However, part of the mandate of academic surgeons in Ontario is to train the next generation of surgeons. This includes providing critical analysis of innovative technologies such as robot-assisted surgery, which makes up the majority of performed radical prostatectomies in the developed world (e.g., the United States, Europe excluding the United Kingdom and Ireland, Australia, Japan, and Korea).

Research Questions

Our health technology assessment endeavoured to answer the following questions:

- What are the effectiveness and safety of robot-assisted radical prostatectomy for prostate cancer, compared with:

  - Open retropubic radical prostatectomy?
  - Conventional laparoscopic radical prostatectomy (without robotic assistance)?
- What is the evidence on the cost-effectiveness of robot-assisted radical prostatectomy compared with open retropubic radical prostatectomy in men with clinically localized prostate cancer?
- From the perspective of the Ontario Ministry of Health and Long-Term Care, what is the cost-effectiveness of robot-assisted versus open retropubic radical prostatectomy in patients with clinically localized prostate cancer?
- What is the potential budget impact in Ontario of publicly funding robot-assisted radical prostatectomy for localized prostate cancer treatment?
- What are the needs, priorities, and preferences for those with lived experience in determining the type of radical prostatectomy they receive? How do these factors influence a patient's decision-making process?

CLINICAL EVIDENCE REVIEW

Objective

This study aimed to assess the effectiveness and safety of robot-assisted radical prostatectomy compared with open retropubic radical prostatectomy (referred to in this report as "open radical prostatectomy") and laparoscopic radical prostatectomy for prostate cancer.

Methods

Research questions were developed by Health Quality Ontario in consultation with experts in the topic area.

Sources

We performed a literature search on April 21, 2016, using Ovid MEDLINE, Ovid MEDLINE In-Process, Ovid Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), and Centre for Reviews and Dissemination (CRD) Health Technology Assessment, for studies published from January 1, 2006, to April 21, 2016.

Search strategies were developed by medical librarians using controlled vocabulary (i.e., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist (McGowan, 2016). Database auto-alerts were created in Ovid and monitored for the duration of the HTA review.

Literature Screening

A single reviewer reviewed the abstracts and, for those studies meeting the eligibility criteria, we obtained full-text articles. We also examined reference lists for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 2006, and April 21, 2016
- Randomized controlled trials (RCTs), prospective comparative nonrandomized studies, and systematic reviews
- Studies comparing robot-assisted radical prostatectomy with laparoscopic or open radical prostatectomy for prostate cancer

Exclusion Criteria

- Animal and in vitro studies
- Editorials, commentaries, conference abstracts, nonsystematic reviews, noncomparative and retrospective studies (e.g., case reports, case series, registry studies, or studies involving the use of administrative data)
- Studies of robot-assisted, laparoscopic, or open radical prostatectomy for salvage treatment

- Studies of simple prostatectomy, open perineal radical prostatectomy, or minimally invasive radical prostatectomy (where laparoscopic and robot-assisted radical prostatectomy cannot be distinguished)
- Studies that compare different techniques for one type of radical prostatectomy (e.g., nerve-sparing versus non-nerve-sparing robot-assisted radical prostatectomy)
- Studies that do not report the outcomes of interest, or where the outcomes of interest cannot be extracted

Outcomes of Interest

Perioperative outcomes of interest were:

- Operative time
- Length of hospital stay
- Estimated blood loss
- Transfusion rates
- Duration of indwelling catheterization
- Rates of hospital readmission
- Complication rates

Functional outcomes included:

- Urinary function
- Erectile function
- Health-related quality of life
- Pain
- Time to mobilization or return to work or activity

Oncological outcomes were:

- Positive surgical margin rates
- Biochemical (PSA) recurrence-free rates

Data Extraction

We extracted relevant information on study characteristics; the study population, details of the intervention, comparator(s), and outcomes of interest (PICO); and risk-of-bias items. We collected information about the:

- Source (e.g., primary author, year, country)
- Methods (e.g., study design, inclusion and exclusion criteria, patient assignment, patient population characteristics, details of the intervention and comparator[s], number of surgeons, surgeon experience, length of follow-up)

- Outcomes (e.g., differences in patient characteristics between groups, definition of outcomes of interest, details on outcome assessment and measurement, data time points, loss to follow-up)

Statistical Analysis

We performed an analysis of individual studies using Review Manager v. 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Summary measures were expressed as the mean difference for continuous data using the inverse-variance method and risk ratio for dichotomous data using the Mantel-Haenszel method. A random effects model was used according to the Cochrane handbook.[25] We also examined graphical displays of the forest plots. We considered a *P* value of ≤ .05 statistically significant for the overall effect estimate. Where data pooling was considered inappropriate in the case of considerable heterogeneity (I^2 > 75%), we summarized the data narratively.

Quality of Evidence

We examined the quality of the body of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.[26] The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Expert Consultation

Between March 2016 and October 2016, we solicited expert consultation on robot-assisted radical prostatectomy. Consulted experts included physicians in the specialty areas of urology, oncology, and surgery and a health economics researcher in prostate cancer. Their role was to refine the clinical review plan, contextualize the evidence, and confirm the volume of robot-assisted radical prostatectomy. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Literature Search

The database search yielded 4,553 citations published between January 1, 2006, and April 21, 2016. After removing duplicates, we reviewed titles and abstracts to identify potentially relevant articles. We obtained the full texts of these articles for further assessment. Thirty-three studies (two RCTs and 31 nonrandomized studies) met the inclusion criteria. We hand-searched the reference lists of the included studies, along with health technology assessment websites and other sources, to identify additional relevant studies. After the search date, we included another RCT[27] found through Ovid auto-alerts.

Figure 1 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

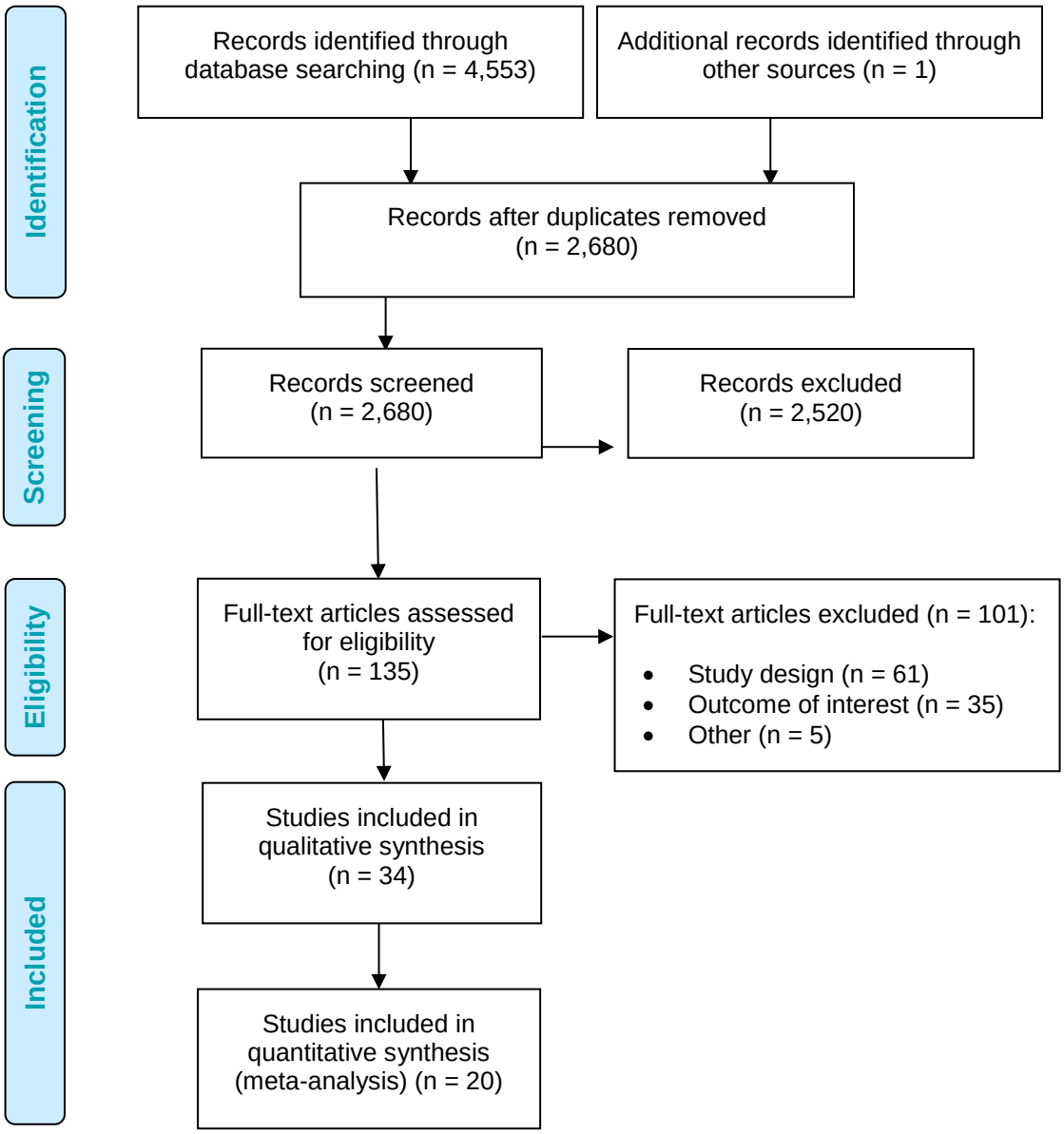

Figure 1: PRISMA Flow Diagram for the Clinical Evidence Review

Source: Adapted from Moher et al.[28]

Systematic Reviews

Numerous systematic reviews and meta-analyses have been conducted comparing robot-assisted radical prostatectomy with open or laparoscopic approaches (Table A21 in Appendix 5). However, they varied in their study inclusion criteria, included studies, and methods of analyses.

In 2010 the Medical Advisory Secretariat conducted a systematic review on robot-assisted surgery for gynecologic and urologic cancers in Ontario.[29] It found that compared with open radical prostatectomy, the clinical benefits of robot-assisted radical prostatectomy included

reduced lengths of hospital stay, blood loss, transfusion rates, and positive surgical margin rates; and improved erectile function. When compared with the laparoscopic approach, robot-assisted radical prostatectomy reduced blood loss and transfusion rates. However, all included studies were nonrandomized, and surgeon skill was noted to have an impact on functional and oncological outcomes.

None of the health technology assessments or systematic reviews published restricted study design to prospective comparative studies. Typically the authors mixed prospective and retrospective nonrandomized studies in their quantitative analyses. The majority of the published reviews contained literature search end dates from 2011 or earlier, therefore excluding more current literature. However, all of the studies noted limitations within the evidence base for robot-assisted radical prostatectomy. As such, authors usually advised that conclusions be interpreted with caution given the heterogeneity (diversity) within the evidence.

In these reviews, perioperative outcomes such as reduced length of hospital stay, blood loss, transfusion rate, and complication rate were the most consistently reported that favoured the robot-assisted approach compared with open surgery. Increased operative time was also noted for the robot-assisted approach. The results were inconsistent for continence, potency, and positive surgical margin rates. Some results favoured the robot-assisted approach, while others found no difference or inconclusive results. Some reviews also suggested faster recovery of functional outcomes for the robot-assisted approach. When a significant difference for positive surgical margin rates was found, it was typically a reduction favouring robot-assisted radical prostatectomy in patients with pT2 cancer but not pT3 cancer. No reviews found significant differences in biochemical recurrence rates between robot-assisted and open radical prostatectomy.

Differences in outcomes between robot-assisted and laparoscopic radical prostatectomy were generally less apparent.

Since the reviews did not fit our specific inclusion criteria, or there were concerns of recency, we undertook an evaluation of primary studies.

Study Characteristics of Included Primary Studies

We found only two RCTs[30,31] for robot-assisted versus laparoscopic radical prostatectomy, and one RCT[27] for robot-assisted versus open radical prostatectomy. In the latter, results were available for only a 3-month interim period. Tables 1 and 2 summarize the study characteristics of the included RCTs and prospective comparative studies. Two studies included patients from the same study population, and both were included because they reported some different outcomes of interest.[32,33]

The studies involved one to nine surgeons (or stated “multiple” surgeons) who, prior to the start of the trial, had varying amounts and types of surgical experience (e.g., transition from either open or laparoscopic radical prostatectomy to robot-assisted prostatectomy). Some studies did not report surgeon number or experience. The surgical technique, including nerve-sparing status, also differed between studies.

Follow-up in the studies varied from postsurgery to 3 years, with the majority of the studies having a follow-up duration of 1 year or less. Studies also inconsistently reported pelvic floor training after the radical prostatectomy, rehabilitation for continence recovery, and medication use for erectile dysfunction. Some stated that patients were encouraged to perform training or

rehabilitation or given medication to treat erectile dysfunction to use as required. Others did not mention any type of postsurgery care.

These variations resulted in a heterogeneous (diverse) body of evidence. Because of the clinical and significant statistical heterogeneity, we primarily summarized the results for outcomes in tabular and narrative formats and used graphics to show the inconsistency of the data. Where possible, we presented the meta-analysis results when the I^2 statistic was < 75%. However, the results were unadjusted, and we could not factor in other patient- and surgeon-important factors (e.g., patient risk level, surgeon experience, and surgical technique).

Appendix 2 presents the results of the risk-of-bias assessment for the included RCTs (using Cochrane's Risk of Bias tool) and prospective comparative nonrandomized studies (using the Risk of Bias in Non-randomized Studies—of Interventions tool), along with the results of the methodology checklist. Because of the nature of the nonrandomized studies, many had moderate to serious risks of bias for the pre-intervention phase of the Risk of Bias in Non-randomized Studies—of Interventions tool, under the items of potential confounders and patient selection. For the postintervention domain, we found moderate risks of bias primarily within outcome measurement owing to the use of nonstandardized methods of measurement. For the included RCTs, randomization primarily addressed most of the pre-intervention risks of bias present in the included nonrandomized studies, such as significant differences between baseline patient and tumour characteristics.

Tables 1 and 2 present study characteristics for robot-assisted radical prostatectomy compared with the open approach or with laparoscopic radical prostatectomy.

Table 1: Randomized Controlled Trials on Robot-Assisted Versus Open or Laparoscopic Radical Prostatectomy

Author, Year	Country	Patient Eligibility	Surgeon	Comparators	Main Outcomes	Follow-Up
Robot-assisted vs. open radical prostatectomy						
Yaxley et al, 2016[27]	Australia	Inclusion: age 35–75 years, newly diagnosed clinically localized prostate cancer; no previous history of head injury, dementia, or psychiatric illness; no concurrent other cancer; estimated life expectancy ≥ 10 years Exclusion: evidence of nonlocalized prostate cancer, PSA > 20 ng/mL, previous laparoscopic hernia repair, previous pelvic radiotherapy or major pelvic surgery, another malignancy within past 5 years	1 surgeon > 200 RARPs 1 surgeon > 1,500 ORPs	RARP ORP	Primary: urinary continence, erectile function, oncological outcomes Secondary: pain, physical and mental functioning, fatigue, bowel function, prostate cancer distress, psychological distress, time to return to work	24 months (3-month interim results reported)
Robot-assisted vs. laparoscopic radical prostatectomy						
Asimakopoulos et al, 2011[31]	Italy	Inclusion: age ≤ 70 years, clinically organ-confined prostate cancer (clinical stage T1–T2), Gleason score ≤ 7, total serum PSA ≤ 10 ng/mL, normal preoperative continence, IIEF-6 ≥ 17, and normal IPSS Exclusion: preoperative incontinence or moderate to severe erectile dysfunction (IIEF-6 < 17); neoadjuvant therapy; any previous prostatic, urethral, or bladder neck surgery; positive MRI results for extracapsular extension; no bilateral nerve sparing	1 surgeon (> 300 RARPs, > 900 LRPs)	RARP LRP	Primary: erectile function, continence at 12 months Secondary: perioperative outcomes, complication rate, oncological outcomes	12 months
Porpiglia et al, 2013[30]	Italy	Inclusion: age 40–75 years, T1-T2N0M0, any prostate size Exclusion: previous radiation therapy, hormonal therapy, transurethral resection of the prostate	1 surgeon (> 100 RARPs, > 600 LRPs)	RARP LRP	Primary: continence at 3 months Secondary: continence at different times, perioperative results, rate of PSM, recovery of erectile function	12 months

Abbreviations: IIEF, International Index of Erectile Function Questionnaire; IPSS, International Prostate Symptom Score; LRP, laparoscopic radical prostatectomy; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; ORP, open radical prostatectomy; PSM, positive surgical margin; RARP, robot-assisted radical prostatectomy; TNM, tumour staging (tumour, lymph node, metastasis).

Table 2: Nonrandomized Prospective Comparative Studies for Robot-Assisted Versus Open or Laparoscopic Radical Prostatectomy

Author, Year	Country	Patient Eligibility	Surgeon	Comparators	Main Outcomes	Follow-Up
Robot-assisted vs. open and laparoscopic radical prostatectomy						
Ball et al, 2006[34]	United States	Newly diagnosed prostate cancer; all patients were candidates for surgical intervention	7 surgeons (2 performing RARP; 3, ORP; 2, LRP)	82 RARPs 135 ORPs 125 LRPs	Health-related quality of life	36 months
Robot-assisted vs. open radical prostatectomy						
Bier et al, 2016[35]	Canada	Patients with clinically localized prostate cancer undergoing radical prostatectomy	1 surgeon	128 RARPs 174 ORPs	Return to work, return to normal daily activity	12 months
Breyer et al, 2010[36]	United States	Biopsy-confirmed prostate cancer	At least 3 surgeons	293 RARPs 695 ORPs	Bladder neck contracture incidence	12 months
Carlsson et al, 2010[37]	Sweden	Inclusion: clinically localized clinical T1–T2 prostate cancer Exclusion: no previous treatment for prostate cancer, no history of neoadjuvant or adjuvant hormonal therapy	9 surgeons (6 performing RARP) Varying experience	1,253 RARPs 485 ORPs	Adverse events or complications	24 months
Davison et al, 2014[21]	Canada	Inclusion: clinically localized clinical T1–T2 prostate cancer Exclusion: no previous treatment for prostate cancer, no history of neoadjuvant or adjuvant hormonal therapy	4 surgeons (2 performing RARP; 2, ORP)	78 RARPs 73 ORPs	Health-related quality of life	12 months
Di Pierro et al, 2011[38]	Switzerland	Patients with prostate cancer undergoing radical prostatectomy and pelvic lymph node dissection	4 surgeons (1 performing RARP; 3, ORP)	75 RARPs 75 ORPs	Oncological outcomes, urinary continence, erectile function, complications,	12 months
Doumerc et al, 2010[39]	Australia	Inclusion: patients with prostate cancer undergoing radical prostatectomy Exclusion: first 50 cases of RARP, patients with factors increasing surgical difficulty	1 surgeon (learning curve)	212 RARPs 502 ORPs	Operative outcomes	Up to 18 months
Farnham et al, 2006[40]	United States	Clinically localized prostate cancer	1 surgeon	176 RARPs 103 ORPs	Blood loss, perioperative hematocrit, transfusion requirements	14 months

Author, Year	Country	Patient Eligibility	Surgeon	Comparators	Main Outcomes	Follow-Up
Ficarra et al, 2009[41]	Italy	Clinically localized prostate cancer	6 surgeons (2 with > 50 RARPs each, 4 with > 400 ORPs each)	103 RARPs 105 ORPs	PSM, surgical time, blood loss, transfusion rate, complications, urinary continence, time to catheter removal, length of hospital stay	12 months
Fode et al, 2014[42]	Denmark	Patients with biopsy-proven localized prostate cancer, undergoing radical prostatectomy	9 surgeons (4 performing RARP and ORP; 3, ORP only; 2, RARP only)	585 RARPs 453 ORPs	PSM, potency, continence, complications	12 months
Fracalanza et al, 2008[43]	Italy	Clinically localized prostate cancer	4 surgeons (1 with > 50 RARPs, 3 with >300 ORPs)	35 RARPs 26 ORPs	Acute phase reaction, operative time, length of hospital stay, PSM	Post-RP
Geraerts et al, 2013[32]	Belgium	Inclusion: localized or locally advanced prostate cancer Exclusion: cognitive problems, non-Dutch speaking, simultaneously planned for salvage procedure or other surgery of pelvic region	3 surgeons (1 with > 150 RARPs, 1 with > 3,000 ORPs, 1 with > 50 RARPs and 700 ORPs)	64 RARPs 116 ORPs	Primary: time to continence, cumulative continence incidence Secondary: point prevalence of continence	12 months
Haglind et al, 2015[44,a]	Sweden	Patients with prostate cancer undergoing radical prostatectomy, age < 75 years, ability to write or read Swedish, clinical stage T1–T3, no sign of distant metastasis, PSA < 20 ng/mL, surgeon with ≥ 100 procedures	Multiple surgeons	1,847 RARPs 778 ORPs	Continence, sexual function, perioperative outcomes	12 months
Ham et al, 2008[45]	South Korea	Prostate cancer without distant metastasis	1 surgeon (199 ORPs, 223 RARPs)	35 early RARPs, 188 late RARPs 89 early ORPs, 110 late ORPs	Continence, sexual function	12 months
Hong et al, 2010[46]	South Korea	Patients with American Society of Anesthesiologists physical status I or II	2 surgeons (1 with > 180 RARPs; 1 with ORP experience)	26 RARPs 26 ORPs	Perioperative outcomes, complications (venous gas embolism)	Post-RP

Author, Year	Country	Patient Eligibility	Surgeon	Comparators	Main Outcomes	Follow-Up
Kim et al, 2011[47]	South Korea	Patients with prostate cancer undergoing radical prostatectomy	1 surgeon	528 RARPs 235 ORPs	Continence, sexual function, perioperative outcomes	24 months
Kordan et al, 2010[48]	United States	Patients with clinically localized prostate cancer undergoing radical prostatectomy and lymphadenectomy	4 surgeons (1 performing RARP; 2, ORP; 1, both)	830 RARPs 414 ORPs	Primary: transfusion Secondary: PSM, estimated blood loss, change in hematocrit	Post-RP
Loeb et al, 2010[49]	United States	Patients with prostate cancer undergoing radical prostatectomy	1 surgeon	152 RARPs 137 ORPs	Primary: benign prostate glands at bladder neck margin	Post-RP
Lott et al, 2015[50]	Brazil	Patients with prostate cancer undergoing radical prostatectomy	8 surgeons (2 performed RARP; they had no previous laparoscopic experience but had > 10 years' ORP experience. 2 performed ORP and had robotic experience. 4 had an average of 25 years' experience with RP)	50 RARPs 34 ORPs	Primary: urinary continence, erectile function Secondary: histological outcomes	12 months
Ludovico et al, 2013[51]	Italy	Inclusion criteria: clinically localized prostate cancer (clinical < T2b), PSA < 10 ng/mL, Gleason score < 7, life expectancy > 10 years, preoperative IIEF score > 25, EHS of 4, in a stable relationship Exclusion: other neoplasm, lower urinary tract or major concomitant diseases, previous abdominal surgery, urinary incontinence, or erectile dysfunction treated with phosphodiesterase type 5 inhibitors or intracorporeal injection of prostaglandin E1	1 surgeon (> 50 RARPs)	82 RARPs 48 ORPs	Primary: potency recovery rate Secondary: continence, PSM, complications	12 months
Miller et al, 2007[52]	United States	Clinically localized prostate cancer (T1–T2)	Not reported	42 RARPs 120 ORPs	Health-related quality of life	6 weeks

Author, Year	Country	Patient Eligibility	Surgeon	Comparators	Main Outcomes	Follow-Up
Nelson et al, 2007[53]	United States	Patients with prostate cancer undergoing radical prostatectomy	Not reported	629 RARPs 374 ORPs	Length of hospital stay, readmission rates, unscheduled clinical visits, complications	Not specified
O'Malley et al, 2006[54]	Australia	Inclusion criteria: patients with prostate cancer undergoing radical prostatectomy Exclusion criteria: patients treated early in learning curve	1 surgeon	102 RARPs 102 ORPs	PSM, learning curve	3 months
Philippou et al, 2012[55]	UK	Patients with prostate cancer undergoing radical prostatectomy	1 surgeon (> 50 ORPs)	50 RARPs 50 ORPs	Oncologic outcomes, sexual function and urinary continence, perioperative parameters, complications	3 months
Thompson et al, 2013[56]	Australia	Patients with prostate cancer undergoing radical prostatectomy	1 surgeon (> 3,000 ORPs)	837 RARPs 674 ORPs	PSM, health-related quality of life	12 months
Wallerstedt et al, 2015[33,a]	Sweden	Patients with prostate cancer undergoing radical prostatectomy, age < 75 years, ability to write or read Swedish, clinical stage T1–T3, no sign of distant metastasis, PSA < 20 ng/mL, surgeon with ≥ 100 procedures	Multiple surgeons	1,847 RARPs 778 ORPs	Perioperative, complications, readmission rates	3 months
Wood et al, 2007[57]	United States	Patients with prostate cancer undergoing radical prostatectomy	1 surgeon	117 RARPs 89 ORPs	Perioperative, oncological, functional, health-related quality of life	6 months
Robot-assisted vs. laparoscopic radical prostatectomy						
Asimakopoulos et al, 2013[58]	Italy	Inclusion: age ≤ 70 years, clinical T1c–cT2, PSA < 10 ng/mL, biopsy Gleason score < 7; fully continent, potent, and candidates for bilateral nerve-sparing radical prostatectomy Exclusion: history of neoadjuvant treatment for prostate cancer, clinical or MRI suspicion for locally advanced prostate cancer	1 surgeon	136 RARP 91 LRP	Primary: pentafecta (potency, urinary continence, no perioperative complications, negative surgical margins, and no BCR) Secondary: preoperative or prognostic factors predicting pentafecta	Up to 3 years

Author, Year	Country	Patient Eligibility	Surgeon	Comparators	Main Outcomes	Follow-Up
Berge et al, 2013[59]	Norway	Patients with localized prostate cancer undergoing radical prostatectomy	4 surgeons	210 RARPs 210 LRPs	Health-related quality of life	36 months
Ploussard et al, 2009[60]	France	Patients with prostate cancer undergoing radical prostatectomy	3 surgeons (1 performing RARP; 2, LRP)	83 RARPs 205 LRPs	Operative time, short-term postoperative complications	Not specified
Ploussard et al, 2014[61]	France	Patients with prostate cancer undergoing radical prostatectomy	At least 5 surgeons (3 senior surgeons performed most of the LRPs; 2 senior surgeons performed RARPs and had experience with > 100 LRPs)	1,009 RARPs 1,377 LRPs	Perioperative, functional, oncological	24 months
Willis et al, 2012[62]	United States	Clinically localized prostate cancer (≤ T2)	1 surgeon (had performed 250 LRPs; new to RARP)	121 RARPs 161 LRPs	Perioperative, oncological, functional, health-related quality of life	12 months

Abbreviations: BCR, biochemical recurrence; EHS, Erection Hardness Score; LRP, laparoscopic radical prostatectomy; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; PSM, positive surgical margin; ORP, open radical prostatectomy; RARP, robot-assisted radical prostatectomy; RP, radical prostatectomy; T, tumour stage.
[a]Haglind et al[44] and Wallerstedt et al[33] reported different outcomes of interest for the same study population.

Robot-Assisted Versus Open Radical Prostatectomy

The following section presents the results for robot-assisted versus open radical prostatectomy.

Operative Time

One RCT and 12 nonrandomized studies reported operative time. Results for operative time between robot-assisted and open radical prostatectomy showed significant heterogeneity among studies when mean operative time was pooled (I^2 = 98%) (Table A5). The range for operative time was large, from a median or mean of 125 to 330 minutes for robot-assisted surgery and 103 to 280 minutes for open surgery.

Different definitions for "operative time" were used, from total operative time to skin-to-skin time (i.e., the time from incision to finishing suturing). However, despite differences in measurement, the general trend was a significant decrease in operative time in favour of the open approach in the nonrandomized studies, which may be explained by the extra setup time required for the robot-assisted approach. In contrast, the RCT by Yaxley et al[27] showed a significant increase in operative time for the open approach (for both operative time and surgery time). Among the nonrandomized studies, only Hong et al[46] showed no difference between groups, and Philippou et al[55] found results favouring robot-assisted radical prostatectomy.

A learning curve also exists between operative time and surgeon experience. Doumerc et al[39] noted that operative time for robot-assisted radical prostatectomy decreased with experience, and continued to decrease over the study period, with about 110 cases needed to achieve an operative duration of less than 3 hours.

Table 3 presents the GRADE evidence profile for operative time.

Length of Hospital Stay

One RCT and 11 nonrandomized studies reported on length of hospital stay, which varied from a mean or median of 1 day to 6 days. This may be explained by differences in postoperative care between hospitals. For example, Nelson et al found that patients undergoing robot-assisted or open radical prostatectomy can be treated on the same clinical pathway and that a targeted hospital discharge date of postoperative day 1 can be achieved in the majority of patients.[53] Likely for this reason, of the nonrandomized studies, it is the only one that reports a length of stay of about 1 day for both robot-assisted and open radical prostatectomies. All other studies, including the RCT, found a significant reduction in length of stay with robot-assisted prostatectomy. We did not pool the data because of considerable statistical heterogeneity between studies (I^2 = 100%).

Table A6 presents the results, and Table 4 shows the GRADE evidence profile for length of hospital stay.

Table 3: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Operative Time

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
12 non-RCTs	Serious limitations (−1)[b]	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences.
[b]GRADE starts at low for nonrandomized studies. Differences in baseline patient characteristics and surgeon experience between groups may impact operative time.
[c]One study showed results favouring robot-assisted radical prostatectomy,[55] while another study showed no difference between groups.
[d]Differences affected by variations in room setup and personnel between hospital centres.

Table 4: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Length of Hospital Stay

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
11 non-RCTs	Serious limitations (−1)[b]	No serious limitations[c]	Serious limitations (−1)[d]	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences.
[b]GRADE starts at low for nonrandomized studies. Differences in baseline clinical factors may impact length of hospital stay.
[c]Differences in hospital discharge pathways likely account for large variability in mean/median lengths of hospital stay between studies; however, almost all studies still show significance for reduced length of stay for the robot-assisted group.
[d]Generalizability concerns from centres where length of stay is not reflective of average Ontario times.

Estimated Blood Loss

One RCT and 16 studies reported estimated blood loss for robot-assisted versus open radical prostatectomy. Estimated blood lost was measured either categorically or, most often, as a continuous variable. All studies showed significantly less estimated blood loss for robot-assisted radical prostatectomy (Table A7). There were large variations in blood loss between groups, ranging from a mean or median of 100 mL to over 400 mL for robot-assisted surgery. The reported mean or median blood loss in the open group was typically higher, at around 500 mL to over 1300 mL.

Fode et al found that, along with a low prostate volume ($P < .001$), non-nerve-sparing surgery ($P < .001$), and surgeon ($P < .001$), robot-assisted radical prostatectomy was a predictor of low perioperative blood loss in multivariable analysis. There was a relative risk of 2.89 (95% confidence interval [CI] 2.52–3.3, $P < .001$) between the open and robot-assisted groups.[42]

Table 5 presents the GRADE evidence profile for estimated blood loss.

Transfusion Rates

The differences in transfusion rates between robot-assisted and open radical prostatectomy are presented in Figure 2. These rates are from one RCT and 11 nonrandomized studies. While the RCT[27] did not find any significant differences between groups, the nonrandomized studies showed significant and nonsignificant decreases in transfusion rates with robot-assisted radical prostatectomy.

Low hematocrit levels are triggers for transfusion. Farnham et al[40] found that differences in the discharge hematocrit (36.8% for robot-assisted versus 32.8% for open, $P < .001$) and the mean perioperative change in hematocrit (8.0% decrease for robot-assisted versus 10.7% decrease for open, $P < .001$) were significant between robot-assisted and open groups. Kordan found similar results: a change in hematocrit of 10% (8–12%) in open and 7% (6–9.5%) in robot-assisted surgery ($P < .001$).[48] However, in the study by Philippou et al,[55] the decrease in postoperative hematocrit was lower in the open group (4.19 ± 2.21%) than in the robot-assisted group (8.51 ± 3.67%, $P < .001$).

Kordan et al[48] further investigated whether robot-assisted radical prostatectomy was associated with a lower transfusion rate than the open approach. On univariate analysis, the robot-assisted approach, estimated blood loss ≥ 500 mL, and a change in hematocrit ≥ 10% were the only significant predictors of transfusion. In an exploratory multivariate model (limited to only 21 transfusion events), they found that robot-assisted radical prostatectomy was the only significant predictor of reduced need for transfusion (odds ratio [OR] 0.23, 95% CI 0.09–0.58, $P = .002$). The likelihood of transfusions was not associated with surgeon for the group as a whole, and there was a trend of decreasing likelihood of transfusion with the advancing calendar year because of the increasing volume of robot-assisted radical prostatectomies.

Table 6 presents the GRADE evidence profile for transfusion rates.

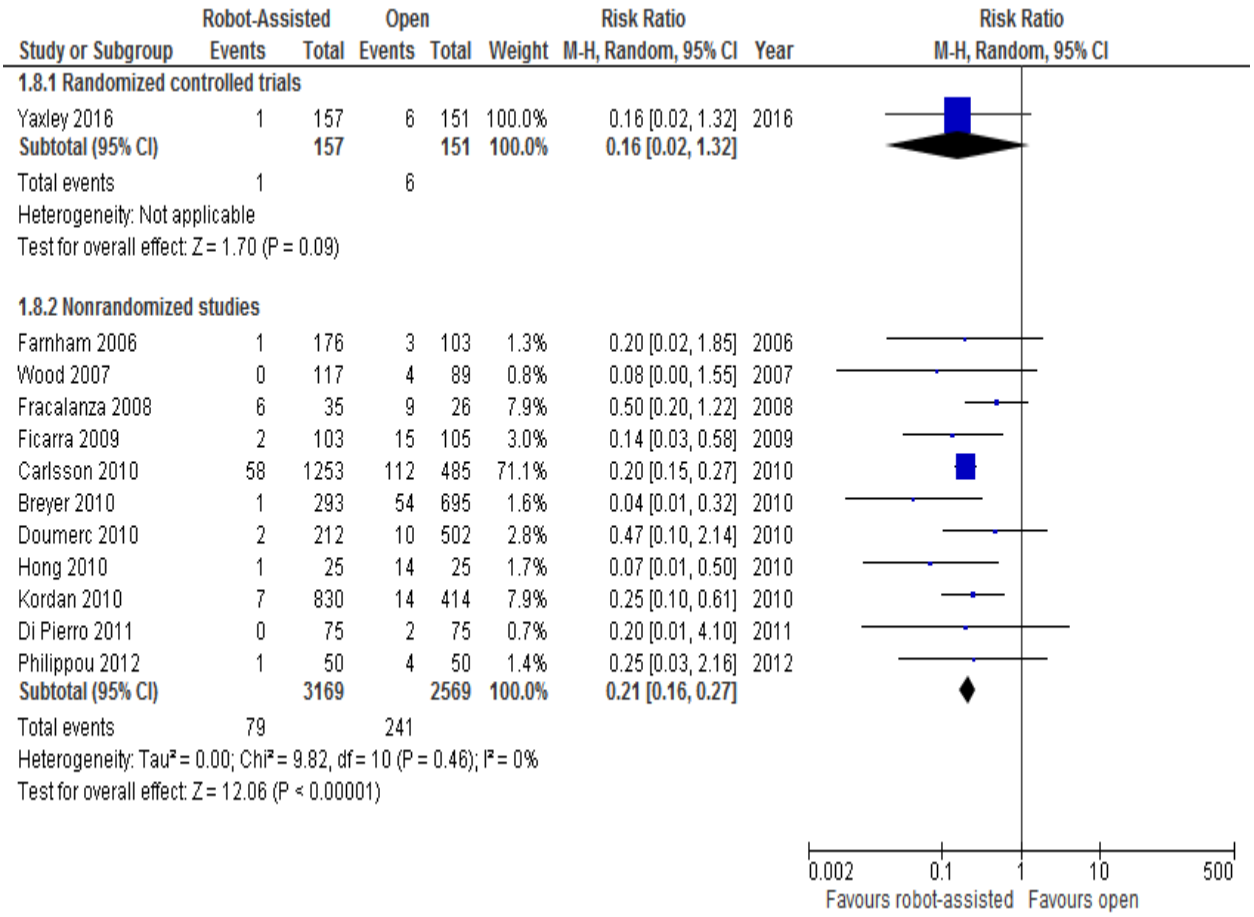

Figure 2: Transfusion Rates for Robot-Assisted Versus Open Radical Prostatectomy

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
Sources: Data from Yaxley et al, 2016,[27] Farnham et al, 2006,[40] Wood et al, 2007,[57] Fracalanza et al, 2008,[43] Ficarra et al, 2009,[41] Kordan et al, 2010,[48] Doumerc et al, 2010,[39] Hong et al, 2010,[46] Carlsson et al, 2010,[37] Breyer et al, 2010,[36] Di Pierro et al, 2011,[38] and Philippou et al, 2012.[55]

Table 5: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Estimated Blood Loss

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	Large magnitude of effect (+1)	⊕⊕⊕ Moderate
16 non-RCTs	Serious limitations (−1)[b]	No serious limitations[c]	No serious limitations	Serious limitations (−1)[a]	Undetected	Large magnitude of effect (+1)	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences. Large variability within data in nonrandomized studies. Difficulties in accurately measuring blood loss.
[b]GRADE starts at low for nonrandomized studies. Differences in clinical characteristics between groups may affect outcome.
[c]While results all significantly favour robot-assisted radical prostatectomy for reduced blood loss, large differences in blood loss amount between studies may be impacted by clinical characteristics and surgeon experience between groups.

Table 6: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Transfusion Rates

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
11 non-RCTs	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences. Studies had differences in postoperative hematocrit thresholds that would trigger the requirement of transfusion.
[b]GRADE starts at low for nonrandomized studies. Differences between groups in patient characteristics and surgeon experience.

Duration of Indwelling Catheterization

Table A8 shows the results for the one RCT and seven nonrandomized studies reporting on the duration of indwelling catheterization for robot-assisted versus open radical prostatectomy. Generally, shorter durations were found for the robot-assisted radical prostatectomy group, with a range of 3 to 12 days for robot-assisted surgery and 6 to 11 days for open surgery. The wide range of results is likely because of different hospital protocols and procedures for removal time.

Di Pierro et al[38] measured catheter-free rates at days 10 and 15, and while the rates favoured the robot-assisted group, no *P* values were reported to show significance. This study was one of only two studies that evaluated prolonged catheterization (> 10 days after surgery), with no significant difference found between robot-assisted and open procedures. Doumerc et al[39] also noted prolonged catheterization in the open group; however, they did not report values for significance.

In contrast to the nonrandomized studies reporting significantly shorter durations for indwelling catheterization duration for robot-assisted radical prostatectomy, in the recently published RCT there was no difference between groups.[27]

Table 7 presents the GRADE evidence profile for indwelling catheterization.

Rates of Hospital Readmission

One RCT and two nonrandomized studies examined rates of hospital readmission (Table A9).

Nelson et al[53] found no significant differences between robot-assisted and open approaches for readmission or unscheduled clinical or emergency room visits. The authors found that readmission rates or unscheduled hospital visits are necessary in a small percentage of patients treated with an early discharge program.

The most common cause for readmission of patients who had undergone robot-assisted radical prostatectomy was ileus (obstruction of movement in the intestine), at 3.2%.[53] Other causes of readmission were port hernia, rectal injury, postoperative hemorrhage, clot retention, and urinary tract infection. For unscheduled visits, the most common causes were clot retention (1.5%), urinary leakage/urinoma, and other unspecified reasons.

For the open surgery group, the most common cause of readmission was also ileus, at 2.5%.[53] Deep vein thrombosis, lymphocele, and fever were the other causes. For unscheduled visits, the most common causes were wound infection (1.4%), ileus (1.6%), and unspecified other reasons.

Yaxley et al[27] and Wallerstedt et al[33] similarly found no significant differences between groups at 3 months. Wallerstedt et al[33] investigated predictors of patient-reported readmission to hospital. Factors that significantly increased the risk of readmission included the preoperative PSA level, lymph node dissection, prostate weight, clinical tumour stage, tumour stage of the prostatectomy specimen, the Gleason score of the pathology specimen, and a history of mental disorder. The most common causes of readmission for robot-assisted radical prostatectomy were infection (2%) and surgical reasons (3%). In the open group, the most common causes were infection (1.3%), cardiovascular issues (1.2%), and surgical reasons (1.9%).

Table 8 presents the GRADE evidence profile for rates of hospital readmission.

Table 7: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Indwelling Catheterization Duration

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
7 non-RCTs	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences.
[b]GRADE starts at low for nonrandomized studies. Differences in baseline patient characteristics may impact outcome.
[c]Outcome is impacted by differences in hospital procedures or protocols for actual duration.

Table 8: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Hospital Readmission Rates

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
2 non-RCTs	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences.
[b]Nonrandomized studies start at low GRADE. Readmission rates may be impacted by differences in baseline patient characteristics and other comorbid conditions.

Complication Rates

Table A10 presents the reported complications from one RCT and 14 nonrandomized studies. Common complications were nerve or rectal injury, ileus, bladder neck contracture (narrowing of the connection between the bladder and urethra owing to scarring), and anastomotic stricture (a narrowing of the anastomotic suture line). When grouped using the Clavien or Dindo classification of surgical complications, most complications were minor (grades I and II). Mortality was rare for both procedures.

In general, the nonrandomized studies showed significant reductions in overall rates of complications for robot-assisted radical prostatectomy. However, the RCT found borderline nonsignificant differences for overall complicate rates between groups (P = .052).[27]

Carlsson et al[37] specifically examined complications in robot-assisted and open radical prostatectomy. Clavien grade IIIb to grade V complications were more common in the open group (12.9%) than in the robot-assisted group (3.7%). Among late postoperative complications (> 30 days to 15 months), Carlsson et al found that bladder neck contractures were treated more often in the open group (4.5%) than in the robot-assisted group (0.2%) (P < .001). Also, more patients needed surgery because of postoperative incontinence in the open group (2.2% vs. 0.5% robot-assisted, P < .01).

Breyer et al[36] examined bladder neck contracture and found that patients were diagnosed at a median of 2.5 months (range 1–13.5 months) in the open group and 6 months (3–24 months) in the robot-assisted group. Life table analysis showed that the rates for being free of bladder neck contracture at 18 months were 97% for open and 99% for robot-assisted surgery (log-rank P = .13). The authors performed a Cox proportional hazards regression analysis of patients who underwent open radical prostatectomy, covarying for year of surgery, age, biopsy Gleason grade, and PSA level at diagnosis. They found that earlier year of surgery (hazard ratio 0.51, 95% CI 0.34–0.79) and higher PSA level at diagnosis (hazard ratio 1.03, 95% CI 1.01–1.06) were significantly associated with bladder neck contracture. In the robot-assisted group, none of the covariates were significantly associated with bladder neck contracture.

Hong et al[46] evaluated the incidence of intraoperative venous gas embolism and found a significantly increased rate in the open radical prostatectomy group.

Table 9 presents the GRADE evidence profile for complication rates.

Urinary Function

One RCT and 12 nonrandomized studies compared results for urinary function after robot-assisted versus open radical prostatectomy. We performed a meta-analysis for unadjusted dichotomous continence outcomes (e.g., continent or incontinent) (Figure 3). Pooled data showed large statistical heterogeneity (I^2 = 73%). Definitions for dichotomous outcomes were primarily the use of pads or absence of leakage, with definitions varying slightly between studies, from strictly pad free (0 pads) to 0 or 1 pad per day.

Additional details of urinary outcomes are presented in Table A11. The RCT found no significant differences in urinary continence at 3 months.[27] Four studies also reported on time to continence, with three studies showing significantly faster continence recovery with robot-assisted radical prostatectomy.

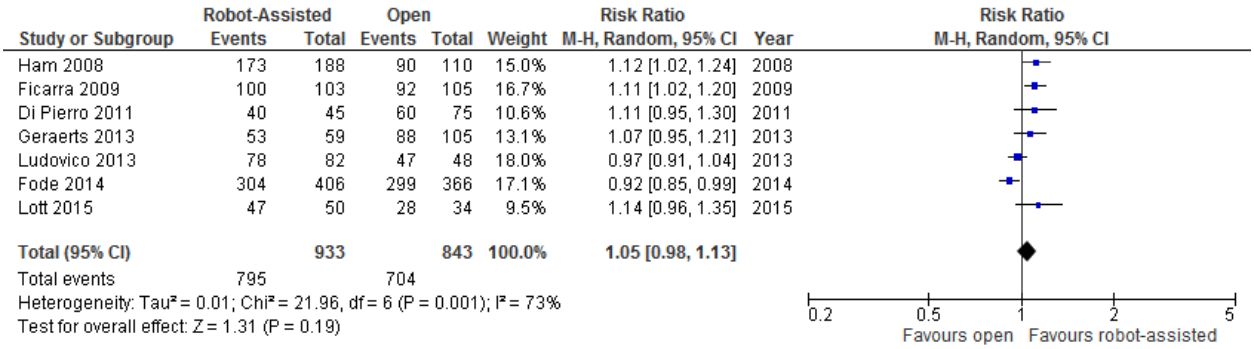

Figure 3: Urinary Continence Outcomes for Robot-Assisted Versus Open Radical Prostatectomy at 12 Months

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
Sources: Data from Ham et al, 2008,[45] Ficarra et al, 2009,[41] Di Pierro et al, 2011,[38] Ludovico et al, 2013,[51] Geraerts et al, 2013,[32] Fode et al, 2014,[42] and Lott et al, 2015.[50]

Four nonrandomized studies adjusted for potential confounders. After correction for covariates, Geraerts et al[32] found the difference in time to continence was significant (hazard ratio 1.522, 95% CI 1.027–2.255, *P* = .036). In addition, younger men, men with positive surgical margins, and men without preoperative incontinence achieved continence sooner. A comparison of time to continence between groups with a sufficient number of patients (intermediate risk and/or bilateral nerve-sparing) still showed a faster return of continence after robot-assisted radical prostatectomy, but the effect was smaller and nonsignificant (hazard ratio > 1.2, *P* > .05). The robot-assisted group also had significantly fewer voiding symptoms than the open group at 1 month (*P* = .01) and 3 months (*P* = .04) after surgery. At 12 months, patients in the open group were more physically limited and took more precautions to avoid a urine leak than did those in the robot-assisted group (*P* = .01 and *P* = .01, respectively).

In contrast, in a study by Haglind et al, at 12 months, 366 men (21.3%) who underwent robot-assisted radical prostatectomy were incontinent, as were 144 men (20.2%) in the open group.[44] When adjusting for confounders, the results were not significant (OR 1.08, 95% CI 0.87–1.34).

Davison et al[21] also found that urinary domain scores in the Expanded Prostate Cancer Index Composite (EPIC) did not differ significantly between the two groups at baseline, 6 months, or 12 months postsurgery after adjustment.

Similarly, Fode et al[42] found no difference in the proportion of patients in the robot-assisted or open group who had undergone surgical treatment for incontinence (*P* = .4). The authors noted, however, that patients who had undergone open radical prostatectomy had an increased chance of subjective continence at 12 months (OR 2.6, *P* = .01), with the opposite effect seen in the robot-assisted group. On multivariate analysis, the type of surgery remained an independent predictor of regaining continence (subjective assessment) at 12 months (*P* = .01). Significant predictors of subjective continence were a low preoperative Danish Prostatic Symptom Score (*P* = .004), younger age at surgery (*P* = .02), and unilateral or bilateral nerve-sparing surgery compared with non-nerve-sparing surgery (*P* = .03).

Tables 10 and 11 present the GRADE evidence profiles for urinary function at 3 and 12 months, respectively.

Table 9: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Complication Rates

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
14 non-RCTs	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Few studies powered to detect differences, in particular between individual complications.
[b]Nonrandomized studies start at low GRADE. Differences in baseline patient characteristics between groups may impact types of complication and rates.

Table 10: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Urinary Function at 3 Months

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	Serious limitation (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
12 non-RCTs	Serious limitations (−1)[b]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]No intention-to-treat analysis. Interim 3-month data analysis.
[b]Nonrandomized studies start at low GRADE. Differences in baseline patient, cancer, or surgeon characteristics may impact continence outcomes. Most studies did not adjust for possible confounding.
[c]Use of nonvalidated and possibly subjective outcome measures in some studies for dichotomous urinary outcomes. Nonstandardized reporting and different tools used makes it difficult to directly compare studies.

Table 11: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Urinary Function at 12 Months

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
12 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Nonrandomized studies start at low GRADE. Differences in baseline patient, cancer, or surgeon characteristics between groups may impact urinary function.
[b]Even when adjusted for differences in baseline characteristics between groups, results were inconsistent.
[c]Use of nonvalidated or nonstandardized assessments for dichotomous outcomes.

Erectile Function

One RCT and 11 nonrandomized studies reported results comparing erectile function after robot-assisted versus open radical prostatectomy. We performed a meta-analysis for unadjusted dichotomous erectile function outcomes (e.g., potent or impotent) (Figure 4). Outcome results were primarily determined by a single question asking patients if they experienced erections sufficiently firm for sexual intercourse.

Table A12 presents additional details for erectile function outcomes. The RCT found no significant differences in erectile function at 3 months.[27] One study showed that time to potency was significantly less in the robot-assisted group.[47]

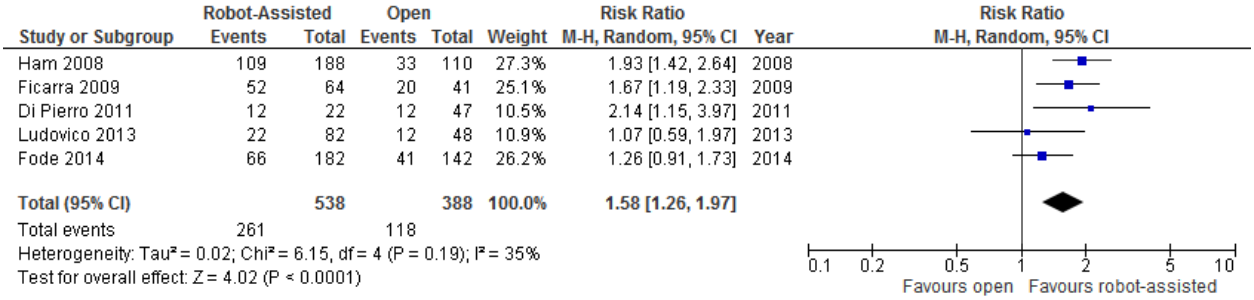

Figure 4: Erectile Function Outcomes for Robot-Assisted Versus Open Radical Prostatectomy at 12 Months

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
Sources: Data from Ham et al, 2008,[45] Ficarra et al, 2009,[41] Di Pierro et al, 2011,[38] Ludovico et al, 2013,[51] and Fode et al, 2014.[42]

Considering only patients undergoing bilateral nerve-sparing surgery, at ≥ 12 months of follow-up Ficarra et al[41] found that 49% in the open group and 81% in the robot-assisted group were potent ($P < .001$). Similarly, when evaluating only patients aged < 65 years and with a Charlson score of ≤ 2, they found that 58% in the open group and 84% in the robot-assisted group were potent ($P < .01$).[41]

Di Pierro et al[38] considered patients who were potent without phosphodiesterase type 5 (PDE5) inhibitors before robot-assisted or open radical prostatectomy. They found recovery of erectile function with or without PDE5 inhibitors, respectively, was achieved in 25% and 68% at 3 months postoperatively ($P = .009$) and in 26% and 55% at 12 months postoperatively ($P = .009$).

When adjusting for nerve-sparing status and the use of PDE5 inhibitors, Davison et al[21] found significant within-subject differences in mean scores across time for both the Expanded Prostate Cancer Index Composite sexual summary and sexual bother domains ($P < .001$). ("Sexual bother" is the level of interference or annoyance caused by limitations in sexual function.) However, the sexual summary and sexual bother domains were not significantly different between groups at 6 or 12 months. Patients who had either one or two nerves spared reported an overall higher mean sexual quality of life score than those with no (or unknown) nerves spared. Similar results were seen for patients who used a PDE5 inhibitor versus patients with no use of PDE5 inhibitors.

Kim et al[47] evaluated factors impacting functional outcomes. In a multivariate analysis, younger age and a longer preoperative membranous urethral length (as seen on magnetic resonance

imaging of the prostate) were significant independent factors for the prognosis of continence recovery. Younger age, surgical method (robot-assisted vs. open), and higher preoperative serum testosterone were independent prognostic factors for potency recovery. The extent of nerve sparing (unilateral vs. bilateral) did not make difference to potency outcome. When the preoperative serum testosterone level was ≥ 3.9 ng/mL, potency recovery at 12 months could be expected (OR 2.1, $P < .001$).

Fode et al[42] found on univariate analysis that there was no statistically significant difference between groups in the proportions of potent patients at 3 and 12 months ($P = .08$ and $P = .16$, respectively). However, significantly more patients in the robot-assisted group had regained potency at 6 months ($P = .02$). There was no difference in the use of PDE5 inhibitors or other erection aids in sexually active patients at any point during follow-up. Multivariate analyses showed no difference between groups for potency rates among sexually active patients at 3 months ($P = .16$), 6 months ($P = .11$), or 12 months ($P = .7$). A high preoperative score on the International Index of Erectile Function Questionnaire (IIEF-5; $P = .001$), younger age at surgery ($P = .03$), and nerve sparing ($P < .001$) were all independent predictors of regained potency at 12 months.

In another study, Geraerts et al[32] found that after adjustment the odds ratio for any erectile dysfunction was 0.80 (95% CI 0.64–1.00). Classification by the various definitions of “erectile dysfunction” did not substantially affect the odds ratios. When adjustments were made for preoperative clinical tumour characteristics, the odds ratio was 0.74 (95% CI 0.59–0.95); for neurovascular preservation, the odds ratio was 0.75 (95% CI 0.58–0.96); and for lymph node dissection, the odds ratio was 0.78 (95% CI 0.61–1.00).

Bier et al[35] found there were no significant differences in robot-assisted or open groups for time between surgery and first postoperative sexual activity ($P = .63$), or for time between surgery and satisfaction with sexual life ($P = .85$).

Tables 12 and 13 present the GRADE evidence profiles for erectile function at 3 and 12 months, respectively.

Table 12: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Erectile Function at 3 Months

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
11 non-RCTs	Serious limitations (−1)[b]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]No intention-to-treat analysis. Interim 3-month data analysis.
[b]Nonrandomized studies start at low GRADE. Differences in baseline patient, cancer, or surgeon characteristics between groups may impact erectile function. Some studies did not adjust for possible confounding. Even when adjusted, results were inconsistent, showing both significant and nonsignificant results.
[c]Use of nonvalidated or nonstandardized assessments for dichotomous outcomes.

Table 13: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Erectile Function at 12 Months

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
11 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Nonrandomized studies start at low GRADE. Differences in baseline patient, cancer, or surgeon characteristics between groups may impact erectile function.
[b]Even when adjusted for differences in baseline characteristics between groups, results were inconsistent.
[c]Use of nonvalidated or nonstandardized assessments for dichotomous outcomes.

Health-Related Quality of Life

One RCT and another nonrandomized study measured generic health-related quality of life (Table A13).

Miller et al[52] found that patients in the robot-assisted radical prostatectomy group demonstrated significantly greater physical quality of life compared with those in the open group ($P < .001$). However, mental quality of life was not significantly related to operative condition ($P < .13$).

The RCT found no significant differences between groups at 6 or 12 weeks for the Short-Form 36 Health Survey mental function, Expanded Prostate Cancer Index Composite bowel domain, or Revised Impact of Events Scale.[27] Minor differences were found between groups for the Short-Form 36 Health Survey at 6 weeks and the Hospital and Depression Scale (HADS) at 12 weeks.

Table 14 presents the GRADE evidence profile for health-related quality of life.

Pain

All three studies (one RCT and two nonrandomized studies) examining pain after robot-assisted and open radical prostatectomy found no difference in pain between groups at the latest time point reported (Table A14). However, the RCT noted significantly reduced short-term pain favouring robot-assisted radical prostatectomy at 24 hours and 1 week postsurgery. These results were for pain during activities and when experiencing worst pain, but not while resting.[27]

Wallerstedt et al[33] examined pain at various parts of the body (operation wound, lower abdomen, upper abdomen); however, they found no significant difference between groups at the 3 month follow-up.

Wood et al[57] examined pain and discomfort at 2 and 6 weeks postsurgery (overall pain, and also pain in the abdomen, bladder, and flank). They found no significant differences between the robot-assisted and the open groups for overall and site-specific pain.

Table 15 presents the GRADE evidence profile for pain.

Table 14: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Health-Related Quality of Life

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
1 non-RCT	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences.
[b]Nonrandomized studies start at low GRADE. Differences in baseline patient characteristics between groups may impact recovery and thus health-related quality of life scores.

Table 15: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Pain

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
2 non-RCTs	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences. Individual patient factors and additional medication may affect pain tolerance.
[b]Nonrandomized studies start at low GRADE. Differences in patient characteristics may affect outcome.

Time to Mobilization or Return to Work or Activity

One RCT and three nonrandomized studies evaluated time to mobilization (e.g., movement or limited physical activity), or return to work or (full or normal) activity.

The RCT found no significant differences in return-to-work outcomes at 3 months postsurgery among those who were employed full or part time.[27] Similarly, investigators found no significant difference between groups in length of time away from work (robot-assisted group: mean 42.71 days, 95% CI 30.98–54.45; open group: mean 42.71 days, 95% CI 41.09–53.30; *P* = .49).

Bier et al[35] found patients felt affected in their work for a median time of 2 months for both robot-assisted and open groups (*P* = .67, range < 1 to > 8 months). The median time to pursue their hobbies again without feeling restricted was 3 months after surgery in both groups (*P* = .71, range < 1 to > 8 months), and to completely pursue work and hobbies again was 4 months (*P* = .73, range < 1 to > 8 months).

Wood et al[57] similarly did not find significant differences for:

- Median time to normal activity: robot-assisted group, 9 days (range 1–30 days), versus open group, 7 days (range 7–45 days); *P* = .57
- Median time to 100% activity: robot-assisted group, 21 days (range 6–52), versus open group, 28 days (range 7–45 days); *P* = .95
- Time to driving: robot-assisted group, 13 days (range 4–44), versus open group, 14 days (range 1–31); *P* = .15

In comparison, Fracalanza et al[43] found a significant difference for average time to mobilization and resumption of oral feeding favouring robot-assisted radical prostatectomy (robot-assisted, 1 day, versus open, 1.2 days, *P* < .001).

Table 16 presents the GRADE evidence profile for time to mobilization or return to work or activity.

Table 16: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Time to Mobilization or Return to Work or Activity

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
3 non-RCTs	Serious limitations (−1)[b]	Serious limitations (−1)[c]	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences. No standardized method for measurement.
[b]Nonrandomized studies start at low GRADE. Differences in baseline patient characteristics between robot-assisted and open prostatectomy groups may impact time to mobilization or return to work or activity.
[c]One study found a significant difference favouring robot-assisted radical prostatectomy for time to mobilization.

Rates of Positive Surgical Margins

One RCT and 15 nonrandomized studies reported on rates of positive surgical margins. The results for unadjusted rates are presented below for all patients within studies (Figure 5) and, where available, for patients with stage pT2 (Figure 6) or pT3 cancer (Figure 7). When we analyzed results by the overall positive surgical margin rates, we found considerable heterogeneity (I^2 = 78%). As a result, we have not shown summary estimates. When we analyzed subgroups pT2 and pT3, the heterogeneity reduced to an I^2 of 40% and 59%, respectively, likely owing to controlling for tumour characteristics.

In the RCT, no difference was found in the overall rates of positive surgical margins for robot-assisted versus open prostatectomy.[27] The majority of the nonrandomized studies showed significant or nonsignificant reductions in rates, favouring robot-assisted radical prostatectomy. When comparing pT2 and pT3 subgroups, there was a general trend in favour of a nonsignificant reduction in positive surgical margins for robot-assisted radical prostatectomy in patients with pT2 cancer. The opposite was seen in patients with pT3 cancer, where a nonsignificant trend favoured open radical prostatectomy.

Doumerc et al[39] investigated the effect of learning curve (surgeon experience). They found that the overall rate of positive surgical margins for robot-assisted surgery declined as surgeon experience increased. A learning curve effect was also noted in pT2 cancers. However, rates between pT2 and pT3 remained statistically different at the end of the trial. The authors noted this may have been because of the low number of cases available for analysis, or because the learning curve had not yet been overcome.

Fode et al,[42] using univariate analyses, also examined the learning curve. They found that compared with robot-assisted prostatectomy, open radical prostatectomy had a relative risk of positive surgical margins of 1.56 (95% CI 1.23–1.99, $P < .001$). However, on multivariate analyses, with stratification for tumour characteristics, patient characteristics, and the surgeon, the type of surgery did not affect the surgical margins ($P = .96$). A large tumour volume ($P < .001$), pathological tumour stage ($P = .005$), and a small prostate volume ($P = .04$) were independent predictors of positive surgical margins.

Thompson et al[56] also examined the learning curve, and found that in T2 disease, the odds of a positive surgical margin were 6.19 times higher (95% CI, 1.20–31.80) for robot-assisted than open radical prostatectomy. However, this lowered after 108 robot-assisted radical prostatectomies had been performed, and plateaued at around 400 to 500 procedures. At the end of the study, after 866 cases, the odds of a positive surgical margin were 55% lower for the robot-assisted surgery compared with the open approach (OR 0.45, 95% CI 0.22–0.92).

Table 17 presents the GRADE evidence profile for positive surgical margin rates.

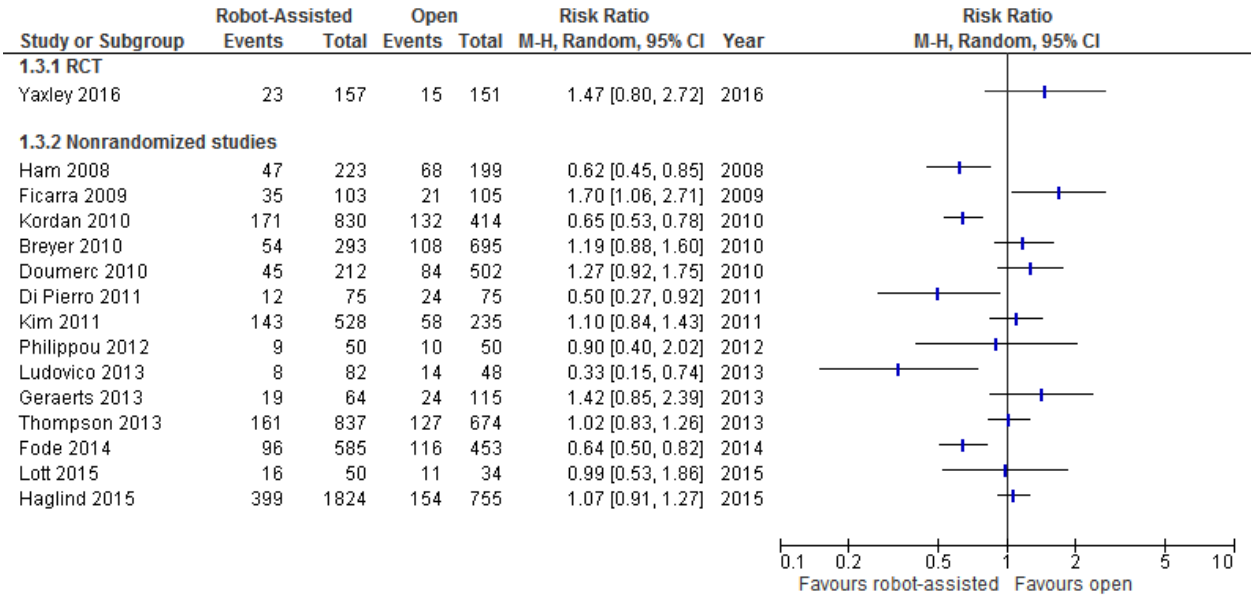

Figure 5: Overall Positive Surgical Margin Rates for Robot-Assisted Versus Open Radical Prostatectomy

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
Sources: Data from Yaxley et al, 2016,[27] Ham et al, 2008,[45] Ficarra et al, 2009,[41] Kordan et al, 2010,[48] Breyer et al, 2010,[36] Doumerc et al, 2010,[39] Di Pierro et al, 2011,[38] Kim et al, 2011,[47] Philippou et al, 2012,[55] Ludovico et al, 2013,[51] Geraerts et al, 2013,[32] Thompson et al, 2013,[56] Fode et al, 2014,[42] Lott et al, 2015,[50] and Haglind et al, 2015.[44]

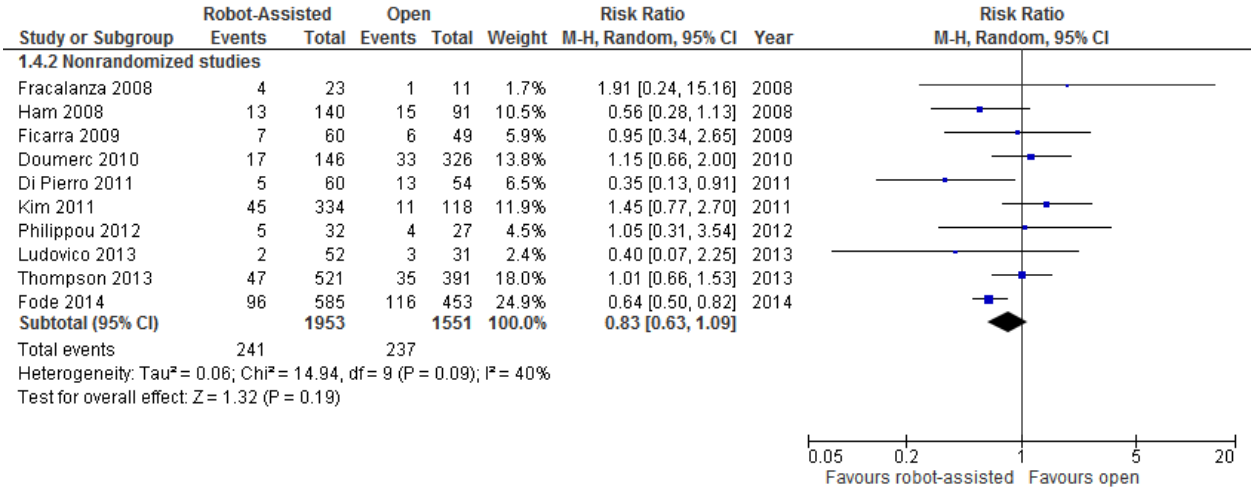

Figure 6: Positive Surgical Margin Rates in Cancer Stage pT2 for Robot-Assisted Versus Open Radical Prostatectomy

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
Sources: Data from Fracalanza et al, 2008,[43] Ham et al, 2008,[45] Ficarra et al, 2009,[41] Doumerc et al, 2010,[39] Kim et al, 2011,[47] Di Pierro et al, 2011,[38] Philippou et al, 2012,[55] Ludovico et al, 2013,[51] Thompson et al, 2013,[56] and Fode et al, 2014.[42]

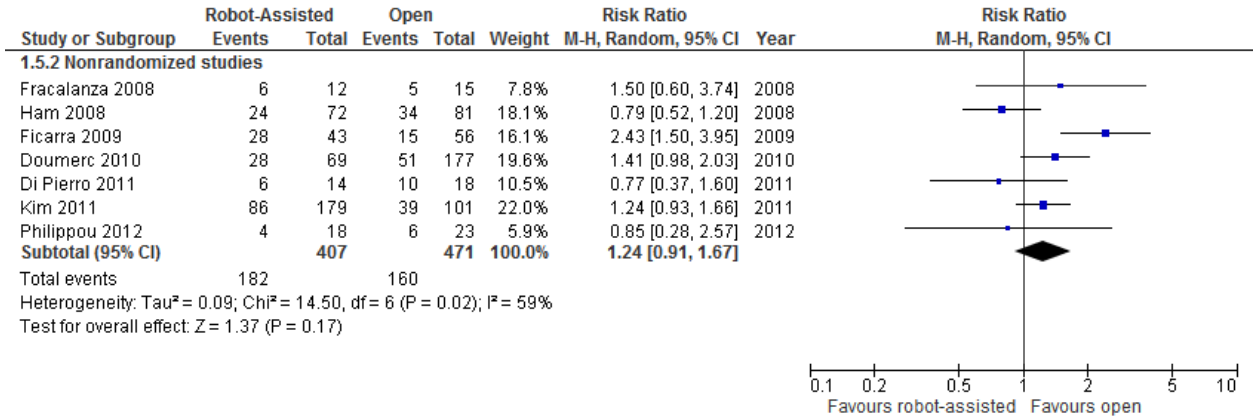

Figure 7: Positive Surgical Margin Rates in Cancer Stage pT3 for Robot-Assisted Versus Open Radical Prostatectomy

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
Sources: Data from Fracalanza et al, 2008,[43] Ham et al, 2008,[45] Ficarra et al, 2009,[41] Doumerc et al, 2010,[39] Di Pierro et al, 2011,[38] Kim et al, 2011,[47] Philippou et al, 2012.[55]

Table 17: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Positive Surgical Margin Rates

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Undetected	None	⨁⨁ Low
15 non-RCTs	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Undetected	None	⨁ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Surrogate outcome for patient-important outcome of cancer-free survival or cancer-specific mortality. Impact of potential differences in pathological assessment of positive surgical margins.
[a]Not powered to detect differences.
[c]Nonrandomized studies start at low GRADE. Differences in baseline patient, tumour, or surgeon characteristics between groups may affect outcome.
[d]Inconsistency in results in both direction of effect and significance between studies.

Biochemical Recurrence-Free Rates

Three nonrandomized studies reported biochemical recurrence-free rates (the absence of elevated PSA levels after radical prostatectomy; Table A15). Di Pierro et al[38] found no difference between biochemical recurrence-free rates at 3 or 12 months, as did Philippou et al[55] at 12 months. Meanwhile, Breyer et al[36] found significant differences between groups at 3 years, favouring open radical prostatectomy.

No studies reported information on cancer-free survival rates.

The RCT[27] will be evaluating biochemical recurrence rates between groups; however, longer-term results that include biochemical recurrence have yet to be published.

Table 18 presents the GRADE evidence profile for biochemical recurrence-free rates.

Table 18: GRADE Evidence Profile for Robot-Assisted Versus Open Radical Prostatectomy for Biochemical Recurrence-Free Rates

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
3 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Nonrandomized studies start at low GRADE. Unadjusted differences in baseline patient, tumour, or surgeon characteristics may affect outcome.
[b]One study showed significant results favouring the open group, while other two studies showed no difference.
[c]Surrogate (substitute or proxy) outcome for patient-important outcome of cancer-free survival or cancer-specific mortality. There is an issue with the biological relevancy of the outcome, and the ability to detect true prostate cancer recurrence in patients.
[d]Unpowered to detect differences.

We found two RCTs[30,31] and five prospective comparative nonrandomized studies[58-62] comparing robot-assisted versus laparoscopic radical prostatectomy. An additional study[34] included a laparoscopic comparison in addition to robot-assisted versus open radical prostatectomy. No prospective comparative studies were found that examined readmission rate, pain, or return to mobilization or work.

Asimakopoulos et al[58] authored the only study that examined the pentafecta of outcomes for (bilateral nerve-sparing) radical prostatectomy: potency, urinary continence, absence of perioperative complications, negative surgical margins, and no biochemical recurrence. Recently proposed by Patel et al,[63] the pentafecta builds upon a trifecta of outcomes (potency, continence, and biochemical recurrence-free progression after surgery) and is a composite outcome measure for radical prostatectomy.

Of the 140 patients who did not achieve pentafecta, 90 (64%) missed a single parameter, with a significant difference between laparoscopic (80%) and robot-assisted (53%) groups (P = .007).[58] Through regression analysis, Asimakopoulos et al[58] found these significant independent factors were associated with pentafecta: lower age (OR 0.94, 95% CI 0.9–1.0, P = .04), lower pathological stage (OR 0.24, 95% CI 0.1–0.7, P = .006), and robot-assisted radical prostatectomy (OR 1.9, 95% CI 1.0–3.5, P = .04).

Operative Time

Mean operative time between robot-assisted and laparoscopic radical prostatectomy was reported in two RCTs and four nonrandomized studies (Figure 8).

In their RCT, Asimakopoulos et al[31] found no difference in mean operative time between the two surgeries (actual results and P value not reported). The RCT by Porpiglia et al[30] also found no difference.

A nonrandomized study reported reduced mean operative time for robot-assisted surgery, at 128.9 minutes versus 175.5 minutes for laparoscopic surgery (P < .001).[61] However, the results provided could not be meta-analyzed.[61] Operative time was less in the other nonrandomized studies, favouring robot-assisted radical prostatectomy.[59,60,62]

A nonrandomized study by Ploussard et al[60] examined factors impacting operating room time. The authors found that while total operative time was not significantly different between groups, compared with laparoscopic radical prostatectomy:

- The installation step was longer for robot-assisted surgery (33.2 ± 15.8 minutes vs. 24.0 ± 12.1 minutes, P < .01)
- Actual skin-to-skin time was reduced for robot-assisted surgery (145.6 ± 34.4 minutes vs. 164.7 ± 49.1 minutes, P < .01)

If lymphadenectomy was performed, this increased the average operative time by 15 minutes for the laparoscopic group (P = .1) and 30 minutes for the robot-assisted group (P = .01).[60]

Table 19 presents the GRADE evidence profile for operative time.

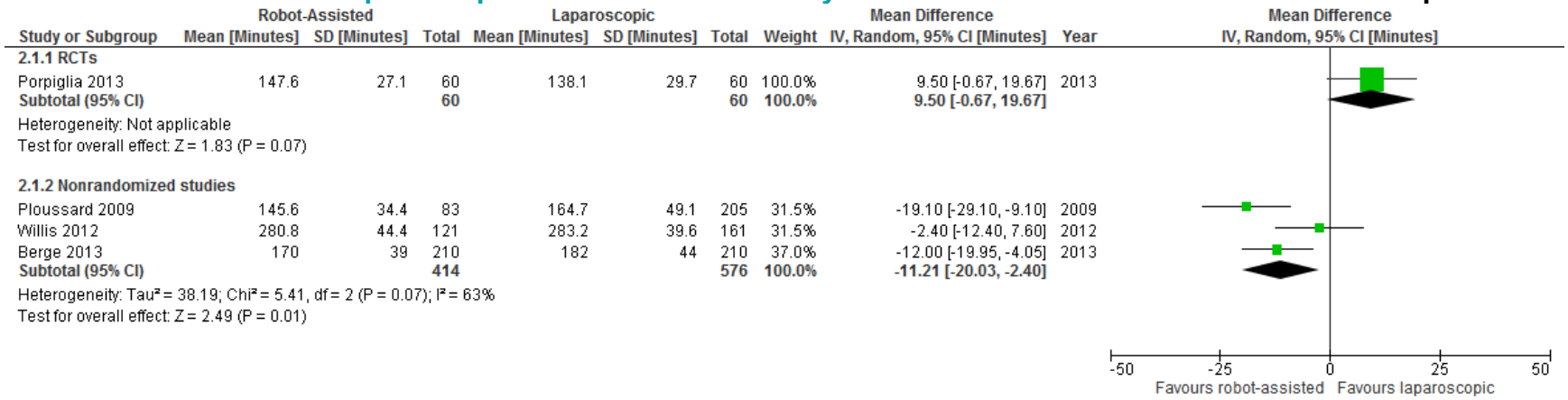

Figure 8: Mean Operative Time for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation.
Sources: Data from Porpiglia et al, 2013,[30] Ploussard et al, 2009,[60] Willis et al, 2012,[62] and Berge et al, 2013.[59]

Table 19: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Operative Time

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
2 RCTs	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
4 non-RCTs	Serious limitations (−1)[b]	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences.
[b]GRADE starts at low for nonrandomized studies. Differences in baseline patient characteristics and surgeon experience between groups may impact operative time.
[c]Significant and nonsignificant reductions favouring the robot-assisted group.
[d]Generalizability concerns because of differences in hospital discharge pathways.

Length of Hospital Stay

Length of hospital stay was reported in two RCTs and two nonrandomized studies. No difference was found in any of the studies (Figure 9). The lengths of hospital stay ranged from 2.2 to 4.6 days for the robot-assisted group, and 2.1 to 4.8 days for the laparoscopic group.[31,60,62,64]

Table 20 presents the GRADE evidence profile for length of hospital stay.

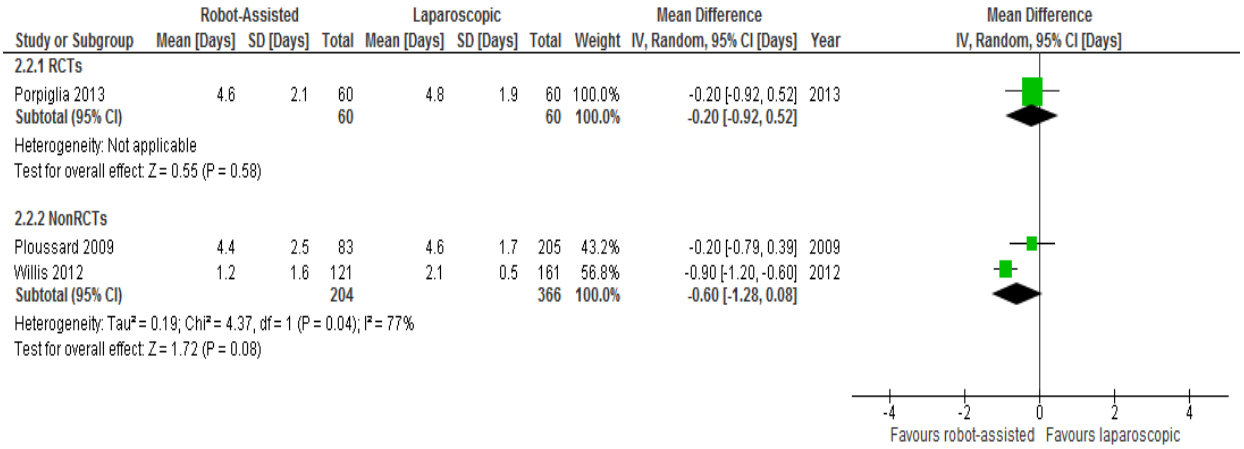

Figure 9: Length of Hospital Stay for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation.
Sources: Data from Porpiglia et al, 2013,[30] Ploussard et al, 2009,[60] and Willis et al, 2012.[62]

Estimated Blood Loss

One RCT and three nonrandomized studies reported estimated blood loss (Table A16). The RCT by Porpiglia et al[30] found no significant differences between groups, whereas the nonrandomized studies found a significant reduction favouring the robot-assisted group.[59,60,62] However, there was large variability within groups, ranging from an average blood loss of 148 to 469 mL in the robot-assisted group, to 203 to 889 mL in the laparoscopic group.

Table 21 presents the GRADE evidence profile for estimated blood loss.

Table 20: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Length of Hospital Stay

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
2 RCTs	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
2 non-RCTs	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences.
[b]GRADE starts at low for nonrandomized studies. Differences in baseline patient characteristics and patient factors potentially impact length of hospital stay.
[c]Generalizability concerns for results from centres where length of stay is not reflective of average Ontario times.

Table 21: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Estimated Blood Loss

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (–1)[a]	Undetected	None	⊕⊕⊕ Moderate
3 non-RCTs	Serious limitations (–1)[b]	No serious limitations	No serious limitations	Serious limitations (–1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences. Difficulties in accurately measuring blood loss.
[b]GRADE starts at low for nonrandomized studies. Differences in baseline patient characteristics and surgeon experience may impact estimated blood loss.

Transfusion Rates

One RCT and three nonrandomized studies examined transfusion rate. Only one large study found reduced transfusion rates favouring laparoscopic radical prostatectomy[61] (Figure 10). In contrast with open radical prostatectomy, both robot-assisted and laparoscopic radical prostatectomy are minimally invasive procedures conducted through keyhole incisions. This likely explains the similarities in outcomes.

Table 22 presents the GRADE evidence profile for transfusion rate.

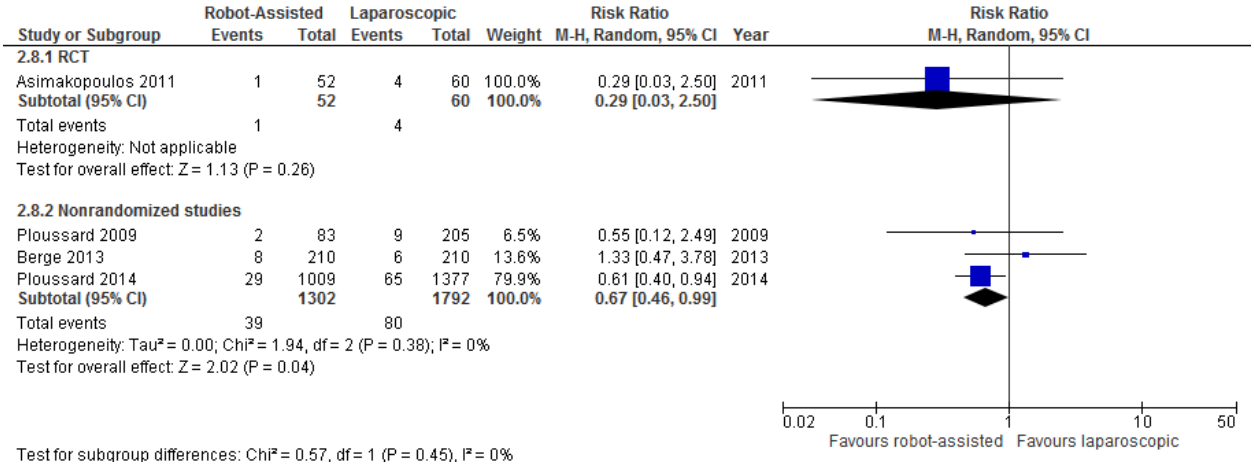

Figure 10: Transfusion Rates for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
Sources: Data from Asimakopoulos et al, 2011,[31] Ploussard et al, 2009,[60] Berge et al, 2013,[59] and Ploussard et al, 2014.[61]

Table 22: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Transfusion Rates

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
3 non-RCTs	Serious limitations (−1)[b]	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences.
[b]GRADE starts at low for nonrandomized studies.
[c]One large study showed a significant reduction in transfusion rate favouring the robot-assisted group.
[d]Potential differences in postoperative hematocrit levels that trigger transfusion.

Duration of Indwelling Catheterization

The duration of indwelling catheterization was reported in two RCTs and one nonrandomized study. All found nonsignificant differences between robot-assisted and laparoscopic radical prostatectomy (Figure 11).

Table 23 presents the GRADE evidence profile for indwelling catheterization duration.

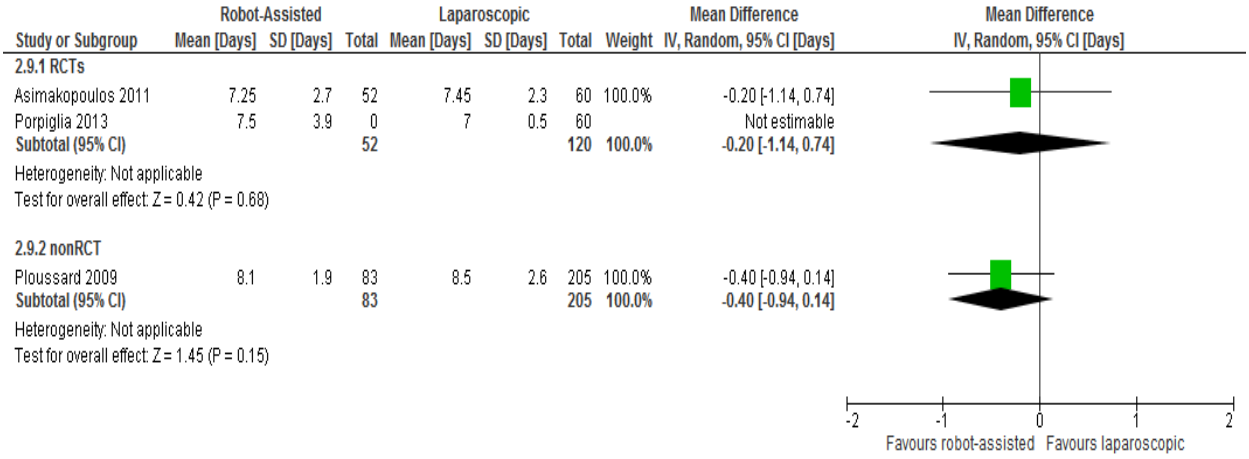

Figure 11: Indwelling Catheterization Duration for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation.
Sources: Data from Asimakopoulos et al, 2011,[31] Porpiglia et al, 2013,[30] and Ploussard et al, 2009.[60]

Complication Rates

Complication rates were reported in both RCTs and three nonrandomized studies (Table A17). None of the studies found any differences in total complication rate between the two groups, and they did not report any deaths. The most common complications were “paravesical” hematoma, urinary infection, retention, and anastomotic leakage or stenosis. Complication rates ranged from 0% to 16.6% in the robot-assisted group and 0% to 11.6% in the laparoscopic group.

Table 24 presents the GRADE evidence profile for complication rates.

Table 23: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Indwelling Catheterization Duration

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
2 RCTs	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
1 non-RCT	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Not powered to detect differences.
[b]GRADE starts at low for nonrandomized studies. Differences in baseline patient characteristics may affect duration.
[c]Generalizability of results may be limited because of differences between health system contexts.

Table 24: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Complication Rates

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
2 RCTs	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕⊕⊕ Moderate
3 non-RCTs	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Studies not powered to detect differences, in particular between individual complications.
[b]Nonrandomized studies start at low GRADE. Differences in baseline patient characteristics between groups may impact type of complication and rates.

Urinary Function

Two RCTs and four nonrandomized studies reported results on urinary function (Table A18).

Of the RCTs, Porpiglia et al[30] found results that favoured laparoscopic radical prostatectomy at all time points (3, 6, and 12 months using the Expanded Prostate Cancer Index Composite questionnaire). Step-wise regression analysis also showed that the laparoscopic approach was associated with continence at 3 months after surgery ($P = .03$).[30] However, the other RCT showed no significant difference between groups in continence rates at 3, 6, or 12 months, or time to continence.[31]

Berge et al[59] found no difference for urinary function at 3, 12, or 36 months using the University of California—Los Angeles Prostate Cancer Index questionnaire, even when stratifying for nerve-sparing status (no, unilateral, or bilateral nerve-sparing).

Willis et al[62] also found no difference in continence rates based on the Expanded Prostate Cancer Index Composite urinary summary score or pad usage.

Ploussard et al[61] found significant findings for robot-assisted radical prostatectomy at 3 months and 24 months (absence of pad use), but results were not significant at 6 months. However, in their univariable analysis, the rate of continence was significantly in favour of the robot-assisted approach at each postoperative visit ($P < .001$). In their multivariable analysis, the only factor independently associated with a better continence recovery was age ($P = .002$) at each time point. Surgical experience, nerve-sparing surgery, and surgical approach were not independent predictors for short- or long-term continence recovery. Surgical treatment for persistent incontinence was also more frequent in the laparoscopic group compared with the robot-assisted group ($P < .001$). Use of the Macroplastique injection, adjustable continence therapy balloon, suburethral sling, or artificial sphincter was reported respectively in 3, 10, 17, and 13 cases in the laparoscopic group versus 0, 2, 5, and 0 cases in the robot-assisted group.

Table 25 presents the GRADE evidence profile for urinary function.

Table 25: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Urinary Function

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
2 RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
4 non-RCTs	Serious limitations (−1)[c]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]No intention-to-treat analysis.
[b]Inconsistent (nonsignificant vs. significant) results.
[c]Nonrandomized studies start at low GRADE. Differences in baseline patient, cancer, or surgeon characteristics may impact continence outcomes without adjustment.
[d]Use of nonvalidated and possibly subjective outcome measures in some studies for dichotomous urinary outcomes. Nonstandardized reporting makes it difficult to directly compare studies.

Erectile Function

Two RCTs and four nonrandomized studies reported on erectile function, with inconsistent results (Table A19).

Asimakopoulos et al[31] found significant results favouring robot-assisted radical prostatectomy for scores at 3, 6, and 12 months compared with baseline on the International Index of Erectile Function Questionnaire (IIEF-6):

- Mean IIEF-6 change in score per patient
- Rates of return to baseline IIEF-6 score
- Rates of patients affected by severe dysfunction

The RCT by Porpiglia et al[30] found significant improvement at only 12 months, not at the 3- and 6-month time points.

In comparison, Berge et al[59] found no significant difference using the University of California–Los Angeles Prostate Cancer Index for sexual function. However, their analysis was limited to patients who received nerve-sparing radical prostatectomy.

Using the Expanded Prostate Cancer Index Composite, Willis et al[62] found significant differences for sexual function at only 12 months, not at 3 or 6 months.

In a univariable analysis, Ploussard et al[61] found that the rate for potency significantly favoured robot-assisted radical prostatectomy at each postoperative visit. This difference remained significant in a subgroup of patients undergoing bilateral nerve-sparing preservation ($P < .001$). In their multivariable analysis, age ($P = .001$), nerve-sparing surgery ($P = .033$, OR 3.9), and robot-assisted approach ($P = .045$, OR: 5.9) were significant independent predictors of potency recovery 12 months after surgery. These factors were also associated with potency at each medical visit during follow-up. Surgical experience, the surgeon, and the date of intervention were not associated with potency return. When examining potency using IIEF-5 scores, the scores were significantly better in the robot-assisted group at each time point after surgery.

According to Asimakopoulos et al,[58] potency was the most difficult outcome in the pentafecta to achieve. However, the single question used to assess potency was not a validated question, although the authors reported a good correlation between the question's definition and the validated patient-derived IIEF score. The authors reported similar results for the other pentafecta outcomes (continence, absence of perioperative complications, negative surgical margins, and no biochemical recurrence) for pT3 disease.

Table 26 presents the GRADE evidence profile for erectile function.

Health-Related Quality of Life

One nonrandomized study reported on generic health-related quality of life.[59] Berge et al[59] used the 12-Item Short-Form Health Survey (SF-12) physical and mental component summaries through a mailed questionnaire approach. The authors found no significant difference at any time point (3, 12, and 36 months) between the mean scores for robot-assisted and laparoscopic radical prostatectomy. Similarly, there was no difference in the two groups' scores in the University of California–Los Angeles Prostate Cancer Index bowel function and bowel bother domains.

At the 36-month follow-up, the authors found:

- Better urinary function and lower preoperative comorbidity were associated with better mental health
- Surgical method, sexual function score at 36 months, the status of positive surgical margins, tumour stage, preoperative PSA level, body mass index, and age were not associated with better mental health[59]

Table 27 presents the GRADE evidence profile for health-related quality of life.

Table 26: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Erectile Function

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
2 RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
4 non-RCTs	Serious limitations (−1)[c]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]No intention-to-treat analysis.
[b]Inconsistent (nonsignificant vs. significant) results.
[c]Nonrandomized studies start at low GRADE. Differences in baseline patient, cancer, or surgeon characteristics may impact potency outcomes without adjustment.
[d]Use of nonvalidated and possibly subjective outcome measures in some studies for dichotomous potency outcomes. Nonstandardized reporting within studies makes it difficult to directly compare studies.

Table 27: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Health-Related Quality of Life

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
1 non-RCT	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Nonrandomized studies start at low GRADE. Differences in baseline patient characteristics between groups may impact recovery and thus health-related quality of life scores.
[b]Not powered to detect differences.

Rates of Positive Surgical Margins

Two RCTs and four nonrandomized studies reported on rates of positive surgical margins. Only one study showed lower positive surgical margin rates for laparoscopic radical prostatectomy[61]; the others found no difference (Figure 12). When subgrouped by pT2 or pT3 stage, this difference disappeared (Figures 13 and 14).

Asimakopoulos et al[31] found no difference in the location of focal positive surgical margins (*P* = .59).

Another study found the presence of locally advanced disease exposed patients to a statistically higher risk of positive surgical margin (9.7% for pT2 vs. 25% for pT3 cancer, *P* = .01).[58] The authors also found that a positive surgical margin was significantly related to biochemical recurrence both in the entire cohort (*P* = .003) and in the robot-assisted cases (*P* = .017).[58]

Berge et al[59] reported no differences in positive surgical margins for pT2 and pT3 groups between nerve- and non-nerve-sparing groups for each technique.

Ploussard et al[61] found the following:

- Classic prognostic factors—PSA, tumour stage, and Gleason score—were significantly associated with positive surgical margins
- Prostate volume was inversely correlated with a risk for positive surgical margins (*P* = .004)
- In multivariable analysis, robot-assisted radical prostatectomy was not associated with an increased positive surgical margin rate
- Positive surgical margin rate was significantly reduced for the robot-assisted approach in pT2 cancers, an independent factor associated with better oncologic control of margins in organ-confined disease (*P* = .030, OR 0.396)
- In pT3 cancers, the type of surgical approach did not affect the rate of surgical margins in multivariable analysis (*P* = .619)
- Only the PSA level and surgical experience were independent predictors of positive surgical margins in pT3 cancers (*P* < .001 and *P* < .001, respectively)

Table 28 presents the GRADE evidence profile for positive surgical margin rates.

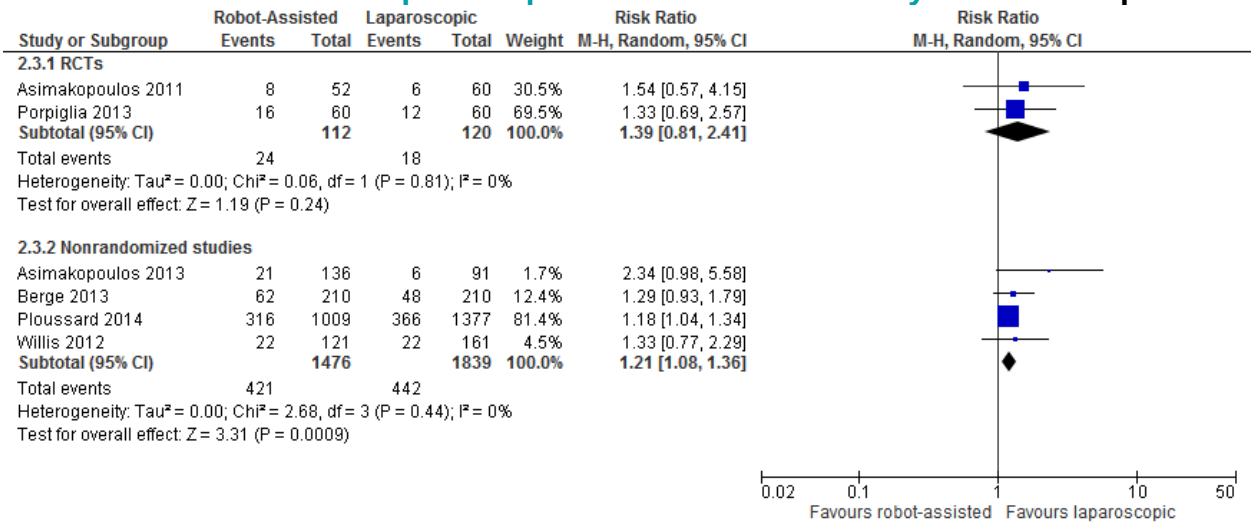

Figure 12: Overall Positive Surgical Margin Rates for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; RCT, randomized controlled trial.
Sources: Data from Asimakopoulos et al, 2011,[31] Porpiglia et al, 2013,[30] Asimakopoulos et al, 2013,[58] Berge et al, 2013,[59] Ploussard et al, 2014,[61] and Willis et al, 2012.[62]

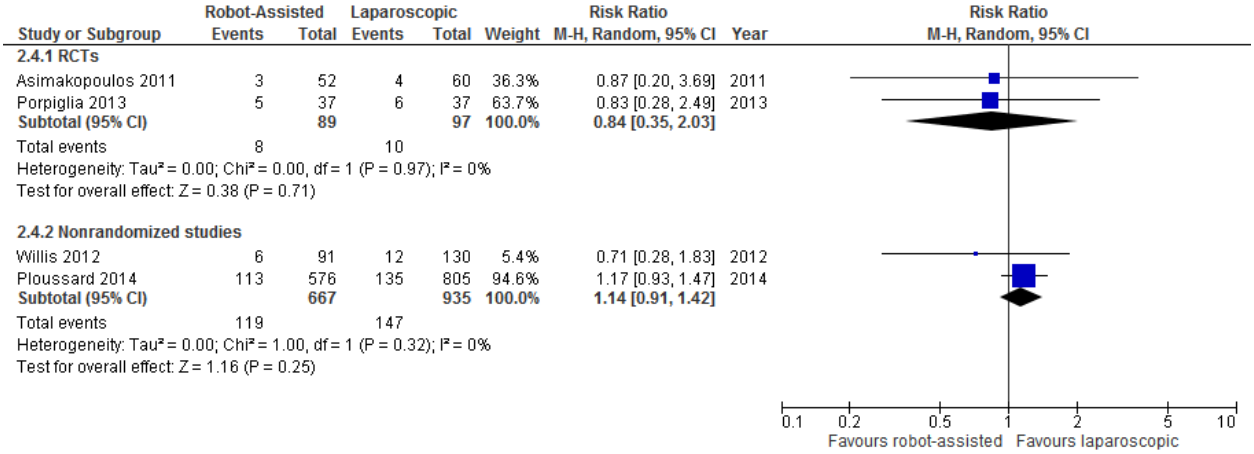

Figure 13: Positive Surgical Margin Rates in pT2 Cancer for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; RCT, randomized controlled trial.
Sources: Data from Asimakopoulos et al, 2011,[31] Porpiglia et al, 2013,[30] Willis et al, 2012,[62]and Ploussard et al, 2014.[61]

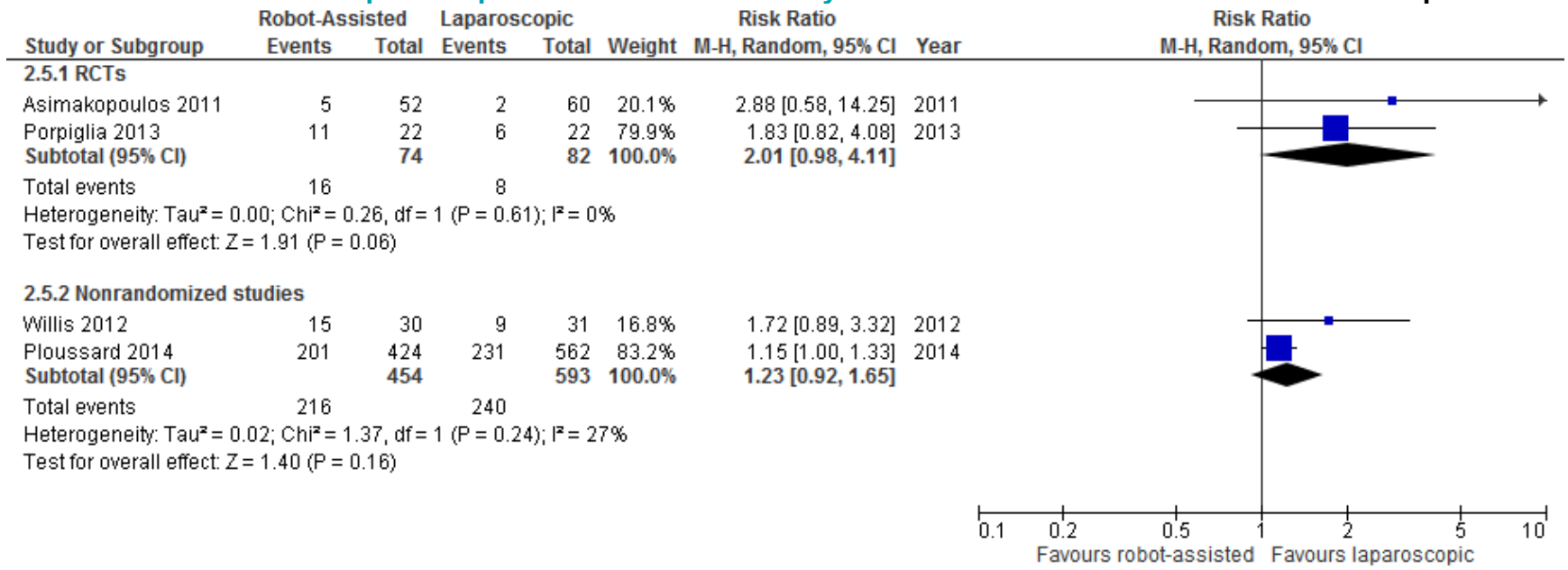

Figure 14: Positive Surgical Margin Rates in pT3 Cancer for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; RCT, randomized controlled trial.
Sources: Data from Asimakopoulos et al, 2011,[31] Porpiglia et al, 2013,[30] Willis et al, 2012,[62] and Ploussard et al, 2014.[61]

Table 28: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Positive Surgical Margin Rates

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
2 RCTs	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Undetected	None	⊕⊕ Low
4 non-RCTs	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Surrogate outcome for patient-important outcome of cancer-free survival or cancer-specific mortality. Impact of potential differences in method of pathological assessment of positive surgical margin.
[b]Not powered to detect differences.
[c]Nonrandomized studies start at low GRADE. Differences in baseline patient, tumour, or surgeon characteristics between groups may affect outcome.
[d]Inconsistency in significance of results.

Biochemical Recurrence-Free Rates

Four studies (two RCTs and two nonrandomized studies) reported biochemical recurrence-free rates. All found nonsignificant differences between the two groups (Table A20).

Table 29 presents the GRADE evidence profile for biochemical recurrence-free rates.

Table 29: GRADE Evidence Profile for Robot-Assisted Versus Laparoscopic Radical Prostatectomy for Biochemical Recurrence-Free Rates

# Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
2 RCTs	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Undetected	None	⨁⨁ Low
2 non-RCTs	Serious limitations (−1)[c]	No serious limitations	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Undetected	None	⨁ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Surrogate outcome for patient-important outcome of cancer-free survival or cancer-specific mortality. There was a potential issue of the biological relevancy of the outcome in some patients, and the ability to detect true prostate cancer recurrence.
[b]Unpowered to detect differences.
[c]Nonrandomized studies start at low GRADE. Unadjusted differences in baseline patient or tumour characteristics may affect the outcome.

Guidelines

We also found four guidelines with recommendations on robot-assisted radical prostatectomy (Appendix 6).[65-68] Two were general guidelines for prostate cancer that included recommendations on robot-assisted radical prostatectomy,[66,68] while the other two were specific to robot-assisted surgery.[65,67] One of the latter guidelines consisted of recommendations from the Pasadena Consensus Panel on robot-assisted radical prostatectomy.[67]

These guidelines indicated that each approach (open, laparoscopic, and robot-assisted) produces similar results and that surgeon experience is crucial in achieving good outcomes. They concluded that there is limited evidence to suggest the superiority of one approach over another for perioperative, functional, and oncological outcomes.[65,68]

Discussion

Canada has been slower than the United States to adopt robot-assisted radical prostatectomy (about 70% of radical prostatectomies are still performed using the open procedure versus less than 15% in the United States). However, the current trend is increased yearly adoption. Despite the continued adoption, studies from Canadian centres are limited and either exist in robot-assisted radical prostatectomy case series or have retrospective study designs.[69-73]

Four Canadian studies were found, but were excluded because of their retrospective design.[69,71-73] They generally did not find differences between robot-assisted and open radical prostatectomy outcomes (select perioperative and functional outcomes).

No published studies from Ontario were found through the literature search. A 2013 unpublished report from the Institute for Clinical Evaluative Sciences (excluded based on publication status) examined preliminary provincial data comparing surgical outcomes for robot-assisted versus open or laparoscopic radical prostatectomy. It included four hospital centres with a total of 646 robot-assisted radical prostatectomy cases and 17,065 open and laparoscopic cases. While the study found reduced length of stay and complication rates favouring robot-assisted radical prostatectomy, the data were based on early robot-assisted radical prostatectomy in Ontario, and patient groups were noted to have baseline differences.

Study Population

Many of the included prospective comparative nonrandomized studies had significant differences in baseline (presurgery) patient characteristics. The authors did not adequately adjust for these differences when reporting outcome results. In general, when significant baseline differences occurred, they showed that patients who underwent open radical prostatectomy were typically older with more high-risk features (e.g., higher average preoperative PSA levels, higher Gleason score, more advanced clinical stage). If not properly adjusted for, this may result in selection bias since patients in the open radical prostatectomy group may naturally experience worse outcomes because of their older age and higher risk status.

While there are no absolute contraindications for robot-assisted radical prostatectomy, depending on the surgeon's level of expertise and comfort level, anatomic differences such as a large prostate, high body mass index, and previous abdominal surgery may influence the surgeon to perform open rather than robot-assisted radical prostatectomy.

In the RCTs, baseline patient and tumour characteristics were balanced by specific patient eligibility criteria (e.g., age, no other comorbid conditions, life expectancy) and randomization. In contrast, some of the nonrandomized studies did not specify any inclusion or exclusion criteria, other than including patients who were candidates to undergo radical prostatectomy.

Surgical Technique

The evolution of and differences in surgical techniques may influence outcomes.

The nerve-sparing technique is meant to preserve sexual function; however, it may lead to higher positive surgical margin rates, according to our experts. Among some of the included studies, there were significant differences in nerve-sparing status between robot-assisted versus open procedures, with the open group using the nerve-sparing approach less often.

Not all details of the surgical technique were available in the included studies, which made exploring surgical technique difficult. When information was available, the techniques varied between studies.

A study[74] has also found large heterogeneity in surgical techniques for robot-assisted radical prostatectomy.

Study Design

While we excluded retrospective studies in this review, they comprise the majority of the evidence base for radical prostatectomy, in the form of comparative and noncomparative (case series) studies.

Studies of recent large administrative databases have shown favourable outcomes for robot-assisted radical prostatectomy compared with open radical prostatectomy. These include reduced lengths of stay, blood loss, risk of positive surgical margins, use of radiation therapy, 30-day mortality, and complications.[75-78] Retrospective comparative studies were excluded in this review because of potential methodological limitations and biases in the retrospective study design (such as selection bias for patients included in each surgical group). However, they typically have larger sample sizes because the historical database allows investigators to find relevant patients through various years of follow-up. Administrative databases in particular are not useful in accurately evaluating functional outcomes, but they may provide some insight on health care resource use, including readmission rates and the need for secondary procedures.

The majority of the included studies had a follow-up time of 1 year or less. This does not adequately address longer-term oncological outcomes between different radical prostatectomy approaches. Longer follow-up is also required for functional outcomes, as it has been suggested that continence and erectile function may continue to improve for 2 to 3 years postsurgery.[79,80] We also note that currently the highest level of evidence for robot-assisted versus open radical prostatectomy is from an RCT[27] that has only short term outcomes (3-month interim results). Therefore, currently there are no reported long-term outcomes (1 year or longer) available from an RCT.

Two RCTs were terminated because of slow recruitment and low enrolment.[81,82] One with low recruitment aimed to evaluate robot-assisted versus open and laparoscopic radical prostatectomy. Important reasons for failure to recruit patients included these[83]:

- Too much personal bias of the surgeons and research nurses for one approach over the other
- Surgeons who perform robot-assisted radical prostatectomy did not feel they could present all surgical options with equipoise (i.e., they did not feel all options are equally effective)
- There was a market-led bias for patients seeking specific surgeons for particular approaches

In contrast, there was more success obtaining earlier RCT evidence comparing robot-assisted versus laparoscopic radical prostatectomy,[30,31] likely because they are both minimally invasive and therefore easier to recruit and randomize patients.

Surgeon Experience and Learning Curve

It has been suggested that surgeon experience (i.e., where surgeons lie on the learning curve) is the central factor in improving outcomes, rather than the surgical approach itself.[84,85] While large international multicentre studies are usually desirable for generalizability of results, surgeon experience is a difficult factor to adjust for in systematic reviews and meta-analyses since the number of cases needed to overcome the learning curve is uncertain. A recent systematic review found the learning curve ranged from 250 to 1,000 cases for open radical prostatectomy, and from 200 to 750 cases for the laparoscopic approach.[86] In comparison, the learning curve for robot-assisted radical prostatectomy was reported to be 40 cases at a minimum, with significant reductions in operative time, blood loss, and complication rates after 100 procedures.[86]

Given this uncertainty in defining surgeon experience and the lack of adequate reporting in some of the included studies, we could not adequately analyze the effect of surgeon experience on the included outcomes of interest.

The experience of a single centre may be difficult to extrapolate to other centres, especially when high-volume centres with very experienced surgeons are involved, such as in the RCT comparing robot-assisted and open radical prostatectomy. The clinical experts we consulted noted that few surgeons in Ontario have performed large caseloads of open radical prostatectomy; thus, the results for the open radical prostatectomy group may not be generalizable to the Ontario context.

Also, it has been suggested that low-volume institutions experience inferior outcomes relative to the highest-volume centres, irrespective of radical prostatectomy approach.[87] Similarly, surgeons' days off between robot-assisted radical prostatectomies may have resulted in increased blood loss and operative time.[88]

Assessment of Outcomes

Some of the results of the perioperative outcomes of interest do not reflect current practice in other countries or health care systems. Outcomes such as length of hospital stay, operative time, and indwelling catheterization duration may depend on context.

For example, in Ontario, patients are typically discharged 2 to 3 days following radical prostatectomy (robot-assisted or open), while lengths of stay of 5 or more days were seen in some of the included studies. Length of stay is also sensitive to changes in factors such as patient personality, pain threshold, and partner anxiety. Efforts toward early discharge pathways

for open radical prostatectomies have also narrowed the potentially larger differences in length of stay between groups.

Definitions of "operative time" differed within the studies, from total operative time (including preparation time and the induction of anaesthesia) to skin-to-skin time (incision to closure).

The duration of indwelling catheterization may also vary by hospital protocols. Prolonged catheterization is likely a better measure of clinically significant differences between groups. However, very few included studies reported prolonged catheterization duration.

Our experts noted that transfusion rates are subject to differences in transfusion triggers and thresholds—hemoglobin or hematocrit below a certain level. Patients who undergo open radical prostatectomy may be discharged with low hemoglobin levels, so postoperative hematocrit levels may be a better measure for transfusion-related differences between groups. However, this information was rarely reported in the included studies.

Some studies reported instead specific steps of the radical prostatectomy procedure. Authors typically did not provide details of the surgical setup and staff personnel, which, in addition to patient and tumour characteristics, may impact operative time. Lasser et al[89] suggested that using consistent nonphysician staff may reduce presurgical preparation time and therefore overall operative time for robot-assisted procedures.

Outcomes following radical prostatectomy may also be measured in a composite manner: in the classic trifecta of potency, continence, and no biochemical recurrence,[90] or in the more recently proposed pentafecta,[63] which adds negative surgical margins and no perioperative complications. These composite measures are important for patients since they represent an ideal result. However, the differences in reporting composite outcomes are highly variable because of how the individual outcomes are defined.[91]

There is also a lack of standardization in reporting functional outcomes. The reported continence and potency results were obtained through either questionnaires or telephone interviews, which carry a risk of response bias. Most studies also derived single questions from validated questionnaires. Taken separately, these questions were not validated (although authors usually noted there was good correlation between the two). Some dichotomous (yes/no) outcomes for function differed in their definitions and introduced an element of subjectivity.

The assessment of erectile function lacked uniformity and encompassed different factors: partial recovery, adequate rigidity, ability for intercourse, and overall sexual satisfaction. In addition, potency rates need to be correlated with age, preoperative function, oncological outcomes, surgical technique, and the use of medication to achieve erections.

Some studies specified the use of phosphodiesterase type 5 (PDE5) inhibitor regimens in the first few postoperative months, with PDE5 inhibitor use then reduced to an as-needed basis. However, men may continue using PDE5 inhibitors after achieving excellent postoperative erectile function, for various reasons: ease of obtaining an erection, confidence boost after months of erectile dysfunction, or assured erection.

Few studies collected data on partners of patients and frequency of sexual relations.

Reports of continence rates were more consistent, with most studies using safety pad usage for measurement. However, the number of safety pads used may differ based on their absorbency and how frequently patients opted to change them.

Postoperative care for incontinence was inconsistently reported as well. Some studies reported patients receiving instruction on pelvic floor rehabilitation and training, but most studies did not mention this.

There may also be discrepancies between urologists' and patients' perceptions of urinary incontinence after robot-assisted radical prostatectomy. Urologists may underestimate how much incontinence affects patients' health-related quality of life.[92,93] It is recommended that common validated prostate-specific or generic questionnaires, as well as objective data collection, be used for functional and health-related quality of life outcomes in particular. This would minimize biases.

Positive surgical margins and biochemical recurrence are reported as indications of cancer control. While they are associated with prostate cancer progression and provide information on prognosis, they are not discrete patient-important outcomes. Instead, they act as surrogates for future cancer-free survival and cancer-specific mortality rates. A systematic review on positive surgical margins after radical prostatectomy found that their long-term impact is highly variable and largely influenced by other risk modifiers.[94]

Pathologist assessment of surgical margins varies with experience and expertise; interpretation can be difficult. This may result in overdiagnosis of positive surgical margin status.[95]

Positive surgical margin rates vary with surgeon experience and cancer stage, volume, and grade. They can range widely from less than 10% to greater than 30% for radical prostatectomy. Also, patients with extracapsular extension (pT3—the cancer has spread beyond the prostate capsule) can have an increased risk of positive surgical margins, depending on the extracapsular extension and how much of the neurovascular bundle or tissue around the prostate the surgeon removes.

Study authors highlighted that biochemical recurrence is not necessarily cancer specific. Benign tissue left during apical dissection or to preserve the bladder neck may mimic biochemical recurrence.[31] A better indication of cancer control may be the need for secondary cancer treatment; however, this information was limited in the included studies.

Furthermore, there are various definitions of biochemical recurrence in the literature, ranging from a single PSA measurement of a certain threshold (e.g., > 0.2 ng/mL or > 0.4 ng/mL) to combinations of consecutive PSA measurements.[96] While the included studies often defined biochemical recurrence as two consecutive PSA levels > 0.2 ng/mL, some studies accepted a single PSA measurement of > 0.2 ng/mL as an indication of biochemical recurrence.

Ultimately, given the relatively short follow-up durations within studies and the natural progression of prostate cancer, the impact of any radical prostatectomy approach on cancer-free survival or cancer-related mortality could not be determined from positive surgical margins and biochemical recurrence.

Ongoing Studies

We searched the World Health Organization's International Clinical Trials Registry Platform for relevant ongoing comparative studies on robot-assisted radical prostatectomy (Appendix 7). Nine ongoing studies were found, ranging from RCTs on robot-assisted versus laparoscopic radical prostatectomy to prospective nonrandomized studies comparing robot-assisted with open or laparoscopic radical prostatectomy. From the search, it seems there is no RCT registered on robot-assisted versus open radical prostatectomy like the one by Yaxley et al.[27] However, these upcoming studies are all prospective and will contribute valuable information to the current evidence base, which is primarily retrospective with methodological limitations.

According to PROSPERO, an international prospective register of systematic reviews, there are currently two ongoing systematic reviews related to robot-assist radical prostatectomy (Appendix 7). One systematic review is evaluating how the surgical approach (robot-assisted or open radical prostatectomy) impacts positive surgical margins. The other is investigating robotic surgery in urology and includes only RCTs on the topic.

When searching the Cochrane Database of Systematic Reviews, we found a published Cochrane protocol on open and laparoscopic (specifically robot-assisted) radical prostatectomy for localized prostate cancer. However, we did not find a published review in the Cochrane Database.

Summary

To address the uncertainty and limitations in the evidence, more prospective comparative studies are required that adequately adjust for differences in clinical characteristics between groups. These are particularly needed for the Ontario context, given the increased adoption of robot-assisted surgery in the province.

Conclusions

The body of evidence was heterogeneous for clinical and surgeon characteristics. There were a limited number of RCTs evaluating the comparative effectiveness of robot-assisted versus open or laparoscopic radical prostatectomy. These RCTs also had methodological limitations, which may have affected their findings. The conclusions below are based on the best-quality evidence available.

When comparing robot-assisted with open radical prostatectomy, we found:

- No differences in short-term urinary and erectile functions at 3 months (moderate quality) and inconclusive findings for long-term results (very low quality)
- No differences in pain, health-related quality of life, or return to work or activity (low to moderate quality)
- No difference in positive surgical margins (low quality)
- Inconclusive results for biochemical recurrence (very low quality)
- Reduced operative times favouring robot-assisted prostatectomy (moderate quality)
- Reduced lengths of hospital stay and estimated blood loss favouring robot-assisted prostatectomy (moderate quality)
- No differences in transfusion rates, indwelling catheterization duration, or hospital readmission rates (moderate quality)

- No difference in complication rates (in the RCT; moderate quality), and a reduction in complications favouring robot-assisted surgery (in the nonrandomized studies; very low quality)

When comparing robot-assisted with laparoscopic radical prostatectomy, we found:

- Inconclusive results for urinary and erectile functions (low quality)
- No difference in health-related quality of life (very low quality)
- No differences in positive surgical margins and biochemical recurrence (low quality)
- No differences in operative times, lengths of hospital stay, estimated blood loss, transfusion rates, indwelling catheterization duration, or complication rates (moderate quality)

ECONOMIC EVIDENCE REVIEW

Objective

This analysis aimed to review the published economic evidence on the cost-effectiveness of robot-assisted radical prostatectomy versus open radical prostatectomy in patients with clinically localized prostate cancer.

Methods

Sources

We performed an economic literature search on April 22, 2016 for studies published from January 1, 2006, to the search date. The search was developed using the clinical search strategy with an economic filter applied. See Clinical Evidence, Literature Search above, for methods used, and Appendix 1 for literature search strategies, including all search terms. The search was updated monthly through the AutoAlert function in Ovid until September 1, 2016. We also reviewed reference lists of the included economic literature for any additional relevant studies not identified through the systematic search.

Literature Screening

A single reviewer reviewed the titles and abstracts. For studies likely to meet the inclusion criteria from the title and abstract screening stage, we obtained the full-text articles and performed further assessment for eligibility.

Inclusion Criteria

- Studies comparing robot-assisted radical prostatectomy versus open radical prostatectomy in patients with clinically localized prostate cancer
- English-language full-text publications
- Studies published between January 1, 2006, and April 22, 2016
- Cost-utility analyses with at least 1 year of follow-up

Exclusion Criteria

- Reviews
- Abstracts, letters, and editorials
- Unpublished studies

Outcomes of Interest

- Costs
- Quality-adjusted life-years (QALYs)
- Incremental cost and incremental effectiveness
- Cost per QALY gained

Data Extraction

A single reviewer conducted the preliminary data extraction, applying the inclusion criteria. For studies containing several comparators, we extracted only the results for the comparison of robot-assisted radical prostatectomy versus open radical prostatectomy. We mainly extracted the following information:

- Source (i.e., first author, country, year of publication)
- Population, perspective, and time horizon
- Interventions and comparators
- Outcomes (e.g., health outcomes, costs, cost-effectiveness)

If we had questions about a publication, we contacted the authors.

Appraisal of Study Applicability

We determined the usefulness of each included cost-utility study for decision-making by applying a modified methodology checklist for economic evaluations developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom. The original checklist is used to inform the development of clinical guidelines by NICE.[97] We modified the wording of the questions to make it Ontario specific. The original NICE checklist was separated into two sections: one for applicability and one for methodological quality. We used only the first section for our review. Using this checklist, we deemed studies directly applicable, partially applicable, or not applicable to our research questions.

Results

Literature Search

The database search yielded 362 citations (after we removed duplicates) published between 2006 and April 22, 2016. After the formal search date, we also obtained 24 unique results from the monthly AutoAlert function in Ovid. We excluded a total of 375 articles based on information in the title and abstract. We obtained 11 full-text articles that were potentially relevant for further assessment. Figure 15 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

We excluded eight studies because they:

- Compared robot-assisted radical prostatectomy versus laparoscopic radical prostatectomy[98-100]
- Compared robot-assisted radical prostatectomy versus mixed procedures of open and laparoscopic radical prostatectomy[101]
- Did not report QALYs as an outcome[102]
- Had major flaws in the estimation of QALYs[103]
- Were economic review articles only[104,105]

Finally, we included three studies from the United States,[106] Denmark,[107] and Australia.[108]

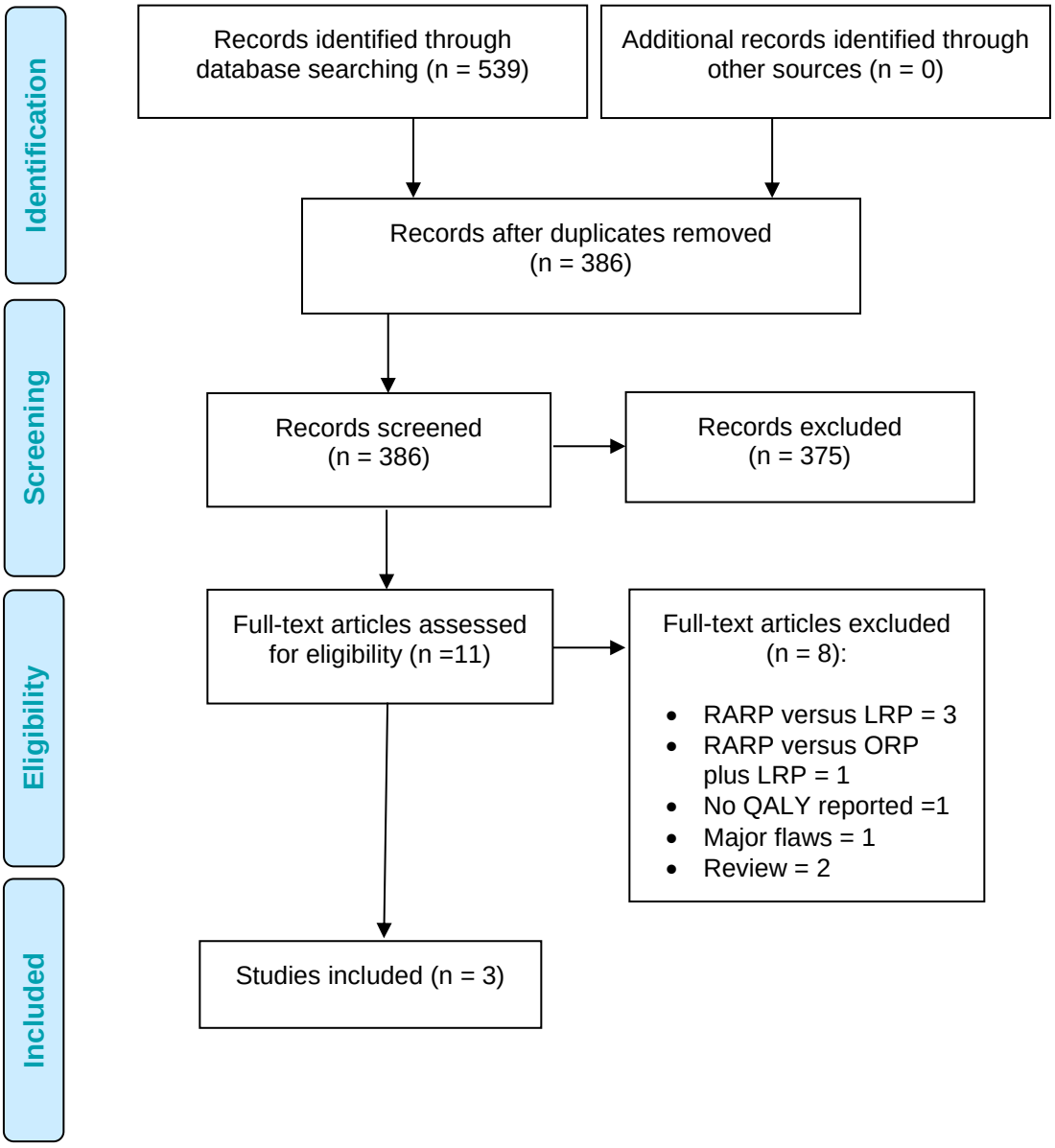

Figure 15: PRISMA Flow Diagram for the Economic Evidence Review

Source: Adapted from Moher et al, 2009.[28]
Abbreviations: LRP, laparoscopic radical prostatectomy; ORP, open radical prostatectomy; QALY, quality-adjusted life-year; RARP, robot-assisted radical prostatectomy.

Study Applicability of the Included Studies

After reviewing the three cost-utility studies using the quality appraisal checklist, we found the results of these studies were not applicable to the publicly funded health care system in Ontario. These studies were considered not applicable because the estimates of treatment effects were based on earlier clinical evidence,[106-108] the studies were not conducted from the perspective of Ontario or the Canadian public payer,[106-108] or the cost of purchasing the robotic system was not included.[106]

The complete results of the quality appraisal checklist applied to all the included full-text articles can be found in Appendix 8.

Review of Included Economic Studies

Table 30 provides a summary of the three included cost-utility analyses, from the United States,[106] Denmark,[107] and Australia.[108] The studies' results were inconsistent. Cooperberg et al[106] concluded that open radical prostatectomy was dominated by robot-assisted radical prostatectomy in three patient subgroups: men with localized prostate cancer at low, intermediate, or high risk. In contrast, Hohwu et al[107] found that robot-assisted radical prostatectomy was dominated by open radical prostatectomy. The Australian study[108] showed that robot-assisted radical prostatectomy was more likely to be cost-effective if its effect on sexual function was considered ($37,420 per QALY, in 2005 Australian dollars [AUD]). However, it was not cost-effective when only its effect on urinary continence was considered ($450,200 AUD per QALY).

Table 30: Results of the Economic Literature Review—Summary

Author, Year, Country	Study Details	Population	Interventions/ Comparators	Results			
				Health Outcomes	Costs	Includes Acquisition Cost of Robot?	Cost-Effectiveness ($/QALY)
Cooperberg et al, 2013, United States[106]	**Type of economic analysis:** CUA **Study design:** Decision-analytic model **Perspective:** Payer (insurance payments) **Time horizon:** Lifetime	Men with clinically localized, low-, intermediate-, or high-risk prostate cancer	1. RARP 2. ORP	**Primary outcome:** QALYs **Total QALYs[a]:** 1. 11.3; 10.5; 9.3 2. 11.3; 10.4; 9.2 **Discount rate:** 3%	**Currency, cost year:** USD, 2009 **Total costs[a]:** 1. $19,901; $28,017; $35,014 2. $20,245; 428,589; $36,279 **Discount rate:** 3%	No	ICER: ORP was dominated by RARP in low-, intermediate-, and high-risk groups
Hohwu et al, 2011, Denmark[107]	**Type of economic analysis:** CUA **Study design:** economic evaluation alongside cohort-control study **Perspective:** Societal **Time horizon:**1 year	Men aged 50–69 years with clinically localized prostate cancer	1. RARP 2. ORP	**Primary outcome:** QALYs gained (difference in utility between baseline and 1 year for each group) **Total QALYs gained[b]:** 1. 0.0103 2. 0.0116	**Currency, cost year:** EUR, 2008 **Total direct costs:** 1. €8,369 2. €3,863 **Discount rate:** 3% for estimating the equivalent annual cost of robotic system	Yes	ICER: RARP was dominated by the ORP
Medical Services Advisory Committee, 2006, Australia[108]	**Type of economic analysis:** CUA **Study design:** Decision-analytic model **Perspective:** Public payer **Time horizon:** 10 years	Men with clinically localized prostate cancer	1. RARP 2. ORP	**Primary outcome:** QALYs **Total QALYs[c]:** 1. 6.76; 6.93 2. 6.66; 6.92 **Discount rate:** 5%	**Currency, cost year:** AUD, 2005 **Total costs[c]:** 1. $17,562; $17,388 2. $13,820; $12,886 **Discount rate:** 5%	Yes	RARP was associated with an ICER of $37,420 AUD per QALY based on sexual function, and of $450,200 AUD per QALY based on urinary continence

Abbreviations: AUD, Australian dollar; CUA, cost-utility analysis; EUR, Euro; ICER, incremental cost-effectiveness ratio; NA, not applicable; ORP, open radical prostatectomy; QALY, quality-adjusted life-year; RARP, robot-assisted radical prostatectomy.

[a]Results are presented for patients with low-risk, followed by intermediate-risk, and then high-risk prostate cancer.

[b]Authors did not use the common definition of QALY gained, but reported that "the difference in the derived utility weight between baseline and 1 year constitutes the gained QALYs for each group."[107]

[c]Results are presented for analysis based on sexual function followed by that based on urinary continence.

Discussion

There are some methodological concerns for all three economic studies included in this review. Cooperberg et al[106] conducted a cost-utility analysis from the perspective of a US payer. They compared numerous primary treatment options (including radiation therapy and surgery) for men with localized prostate cancer at low, intermediate, or high risk. The authors found that for all risk groups, open radical prostatectomy was dominated by robot-assisted radical prostatectomy. However, when we evaluated the study, we found that the differences in QALYs between the two treatments were relatively small in each risk level.

In addition, Cooperberg et al[106] assumed that the direct medical costs of robot-assisted radical prostatectomy were the same as those for the traditional laparoscopic approach. This study also did not include the capital cost of the robotic surgical system and its disposables since those costs were not paid by insurance companies in the United States. Given the excess cost of the equipment, consumables, and maintenance associated with robotic surgery, the generalizability of the results of this analysis to the Canadian context was limited.

Hohwu et al[107] estimated the cost-utility over 1 year for robot-assisted versus open radical prostatectomy in Denmark from a societal perspective. The acquisition cost (amortized over 5 years and assuming an average of 110 procedures per year) and cost of the maintenance contract were included. The authors estimated that patients who underwent robot-assisted radical prostatectomy had a loss of 0.001 QALYs at incremental direct costs of €4,506 (in 2008 Euros). Therefore, robot-assisted surgery was dominated by open radical prostatectomy in the first year postsurgery.

However, when using the other outcome, "successful radical prostatectomy" (PSA < 0.2 ng/mL, urinary continence, and erectile function), the results favoured robot-assisted radical prostatectomy (34% versus 27%), with a corresponding incremental cost of €64,343 per successful operation.[107] This suggests an inconsistency between clinical outcomes and QALYs gained by robot-assisted radical prostatectomy.

In 2006, the Medical Services Advisory Committee of Australia assessed the clinical evidence and economic implications of robot-assisted radical prostatectomy.[108] The authors compared the cost of robot-assisted versus open radical prostatectomy. In the study's appendix, the authors conducted an "indicative cost-utility analysis" since there was an absence of robust comparative effectiveness data. The cost-utility analysis comparing robot-assisted to open radical prostatectomy over 10 years was conducted from the perspective of the publicly funded health care system.

Under the assumption that the only observable differences in long-term patient outcomes between robot-assisted and open radical prostatectomy were sexual function and urinary continence, the authors used utilities associated with these conditions to adjust patients' quality of life over their lifetime.[108] Because of a lack of combined health-related utility data, the authors ran two decision-analytic models: one based on data for sexual function and one based on data for urinary continence. The results showed that robot-assisted radical prostatectomy was cost-effective when considering its effect on sexual function ($37,420 AUD per QALY). However, it was not cost-effective when considering its effect on only urinary continence ($450,200 AUD per QALY).

These results should be interpreted with caution. The QALY in this cost-utility analysis was derived from a single observational study published in 2003.[109] In this study, robot-assisted

radical prostatectomy showed large health benefits in continence, erections, and intercourse over open radical prostatectomy. These large benefits were not observed in most other studies. Also, the estimated differences in the blood infusion rate (2% in robot-assisted versus 35% in open radical prostatectomy) and length of stay (2 days in robot-assisted radical prostatectomy versus 7.5 days in open radical prostatectomy) in this study[108] were much greater than those in most Canadian hospitals at present.[69,110] Overall, the results of this study were not applicable to the Canadian health care system.

Two Canadian cost studies showed that compared with open radical prostatectomy, there was an increased hospitalization cost for robot-assisted radical prostatectomy of $2,893 and $3,860 CAD per patient, respectively.[29,111] However, both studies were conducted more than 5 years ago, and several cost components need to be updated to reflect current costs. For example, in the study by the Canadian Agency for Drugs and Technologies in Health (CADTH),[111] the costs (in US$) for acquisition of the robotic system, maintenance, and consumables need updating. Also the US to Canadian dollar exchange rate has increased significantly (from $1 USD = $1.02 CAD in 2011 to $1 USD = $1.32 CAD in 2016). This would lead to a substantial increase in costs related to using robotic surgery in Canada. In addition, this report did not include the 5% federal tax for purchasing robotics and disposables from outside Canada. Nor did it include the overhead cost of using a robotic system, which is about 30% of the capital cost, according to experts' estimates. Finally, the new generation of robotic system and its disposable may be more expensive.

Conclusions

The systematic review identified three cost-utility analyses on robot-assisted versus open radical prostatectomy for patients with localized prostate cancer. Results ranged from robot-assisted radical prostatectomy being dominant to being dominated, and none of the studies were applicable to the health care system in Ontario.

PRIMARY ECONOMIC EVALUATION

The first RCT comparing robot-assisted versus open radical prostatectomy was published online in July 2016.[27] The study demonstrated that robot-assisted and open radical prostatectomy have similar outcomes in urinary function, sexual function, positive surgical margin rates, and the Short-Form 36 Health Survey (physical and mental domains) responses after 12 weeks. The clinical evidence review section of this report includes results from this same RCT.

Recognizing that this RCT provides a higher level of evidence than previously published nonrandomized studies for robot-assisted versus open radical prostatectomy, we primarily based our model parameters on the short term data reported in the RCT, where available. We then developed a primary economic evaluation for the Ontario context.

Objective

This study aimed to assess the cost-effectiveness (i.e., the incremental cost per QALY gained) of robot-assisted versus open radical prostatectomy in patients with clinically localized prostate cancer in Ontario.

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards statement.[112]

Type of Analysis

We conducted a cost-utility analysis comparing robot-assisted versus open radical prostatectomy in patients with clinically localized prostate cancer in Ontario.

Target Population

The target population in our model was 60-year-old males who are newly diagnosed with clinically localized prostate cancer, with no concurrent cancer or other major comorbidities, and with an estimated remaining life expectancy of over 10 years. We focused on patients with low or intermediate risk of cancer progression since, in Ontario, robot-assisted radical prostatectomy is generally performed in these patients.[73]

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health and Long-Term Care.

Interventions

We compared open radical prostatectomy with robot-assisted radical prostatectomy performed using the da Vinci Surgical System. This is the only robotic surgical system licensed for use in Canada. We excluded laparoscopic radical prostatectomy as a comparator since it is uncommonly performed in Ontario. (According to data from IntelliHealth Ontario, its total volume in 2015 was 98 cases, about 4% of the total radical prostatectomies performed in Ontario.)

Discounting and Time Horizon

We discounted future costs and QALYs (i.e., greater than 1 year) to present values, and we applied an annual discount rate of 5% to both costs and QALYs, following the guidelines for economic evaluations from the Canadian Agency for Drugs and Technologies in Health.[113]

The results of the clinical review did not find high-quality evidence suggesting differences in long-term outcomes between robot-assisted and open radical prostatectomy. Thus, we used a 1-year time horizon in our base case analysis and a 10-year time horizon for the scenario analyses.

Main Assumptions

To simplify the model, we made the following assumptions:

- In the base case, there are some benefits for health-related quality of life for robot-assisted radical prostatectomy within 1 year, but no differences in functional and oncological outcomes between robot-assisted and open radical prostatectomy at 1 year postsurgery
- For one of the scenario analyses, we assumed robot-assisted is better than open prostatectomy in functional and oncological outcomes, and we explored the cost-effectiveness of the two treatments in the long-term time horizon
- The Surgical Pain Score and Expanded Prostate Cancer Index Composite are adequate to measure patients' health-related quality of life after a radical prostatectomy. We derived the average utility values for the short-term analysis from these measures
- There are no perioperative mortalities for either treatment
- Except in patients who have progressed to the metastatic state, the mortality risk of patients in other health states is the same as that of the general Canadian age- and sex-specific population. This is because prostate cancer is a low-risk cancer; the 5-year relative survival ratio (observed survival of cancer patients compared with the expected survival of the general population) is high, at 0.98 to 0.99[114]
- Resource use (e.g., operating room time, length of stay) of robot-assisted and open radical prostatectomy from the RCT is applicable to the Ontario context[27]
- Capital costs of the da Vinci Surgical System are fixed and are based on the da Vinci Si HD. In addition, we included the 5% federal tax for purchasing the robotic surgical system, service contract, and disposable items
- Service contract costs for the da Vinci Surgical System and costs of disposables remain constant over time, and there are no cost differences between hospitals
- The exchange rate between Canadian and US dollars is constant

None of these assumptions altered our primary goal.

Model Structure

In the base case analysis, a decision-analytic model was constructed to compare the costs and utilities of patients treated with robot-assisted or open radical prostatectomy within a 1-year time horizon, without considering disease progression. Costs and utilities were estimated separately (see the Model Parameters section, below).

In the scenario analyses, we constructed a Markov decision-analytic model to capture prostate cancer progression and the economic outcomes of patients undergoing open or robot-assisted radical prostatectomy in the long-term (Figure 16). We used a yearly cycle in the model. Patients would receive either robot-assisted or open radical prostatectomy at time zero. The model includes a 1-year transition period after the radical prostatectomy. At the end of the first year, patients would move to a recurrence-free health state, a local progression health state (i.e., biochemical recurrence), or death. After the first year (i.e., from the second cycle), patients would remain in the same health state or move in a one-way trajectory from recurrence free to recurrence and metastasis.

The costs and utility values in the first year were estimated based on the results from the base case, plus the cost and the QALY loss owing to urinary or sexual dysfunction. The health utility and cost in the second year or later were estimated based on patients' cancer stages and possible urinary and sexual dysfunction.

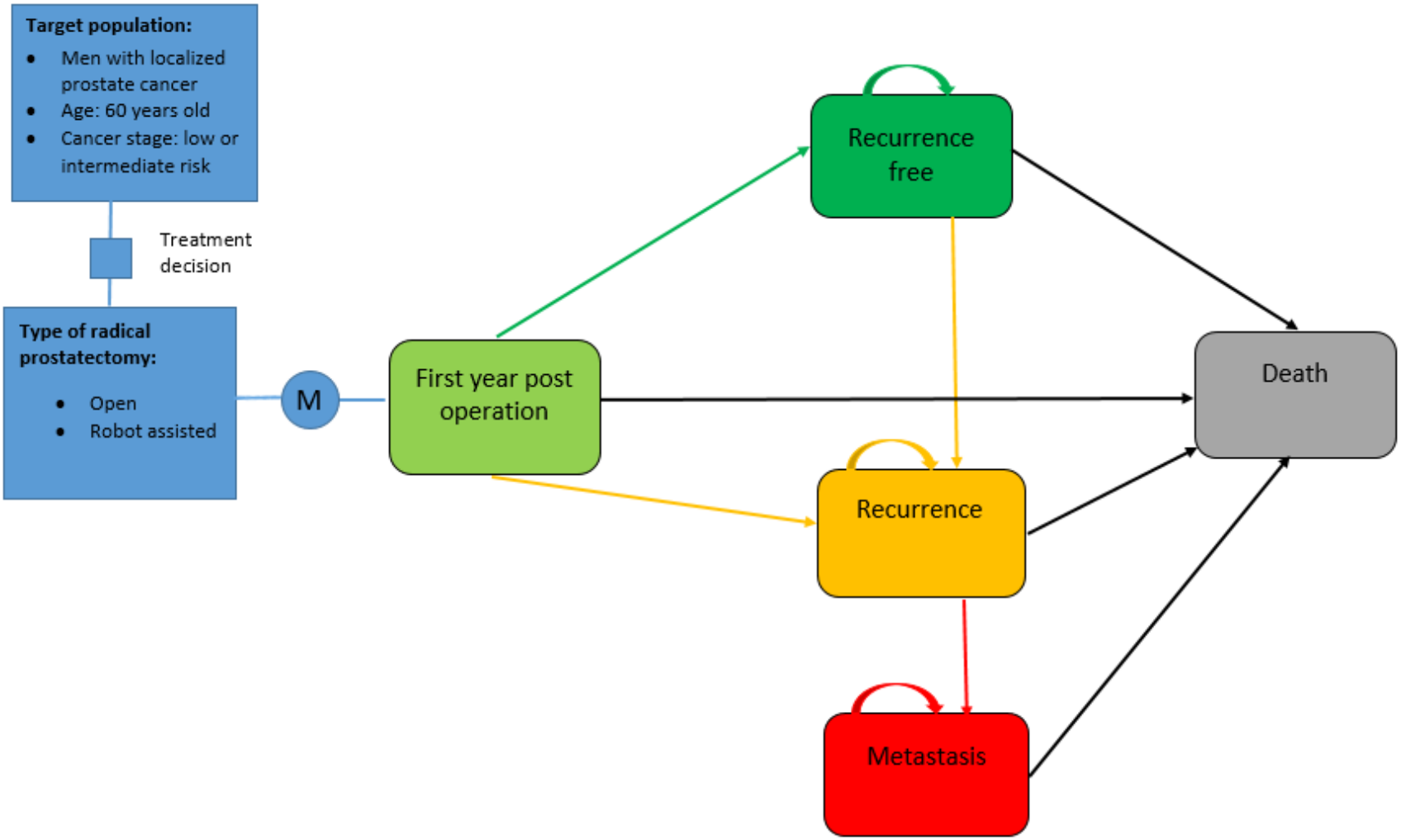

Figure 16: Markov Decision-Analytic Model for Scenario Analyses

Abbreviation: M, Markov model.

Model Parameters

We obtained the model parameters from several published studies. When necessary, we contacted the authors to clarify questions or request additional data regarding their publications.[115] These inputs—utilities, costs, and clinical outcomes—are provided below.

Utility Parameters

Overview

Utilities represent a person's preference for certain health outcomes, such as being able to walk. These are often measured on a scale of 0 (death) to 1 (full health). Since Yaxley et al[27] did not report utility values, we estimated the baseline utility (before the radical prostatectomy) from the literature, and derived utility changes postsurgery from the pain and Expanded Prostate Cancer Index Composite scores reported in the RCT. Figure 17 outlines the process we used to estimate utilities at different follow-up times. Table 31 shows the utility values we used in our analysis.

Utilities at baseline (0.97) and 1 year post-prostatectomy (0.94) were obtained from Krahn et al,[116] who measured quality-of-life changes in a cohort of Toronto men with newly diagnosed, localized prostate cancer. They measured utilities using the Patient-Oriented Prostate Utility Scale (PORPUS).[116] This instrument is more sensitive than generic instruments to detecting small changes in quality of life in early prostate cancer.[117,118] The decrease in utility from baseline to 1 year (−0.03)[116] showed that patients had not fully recovered at 1 year after radical prostatectomy.

We assumed that patients undergoing robot-assisted or open radical prostatectomy would have the same utility at baseline and 1 year. However, we expected utility to be different during the recovery process since Yaxley et al[27] found patients had slightly different pain and functional outcomes (based on actual reported results and not statistical inference). Two studies reported the relationship between utility change and changes in pain and functional scores (i.e., the coefficient).[115,119] Thus, the utility values at day 1, day 7, week 6, and week 12 were estimated by subtracting the decrease in utility at given follow-up time points from the baseline value (0.97). In the following sections, we discuss the details for estimating utility change at different time points.

We calculated the QALY in the first year as the area under the utility curve at 1 year following each treatment.

Since we used various sources to derive the utilities, we examined the logical consistency of the calculated utility value at each time point (i.e., face validity). For example, postsurgery utility values would be the lowest on the first day following surgery and would gradually increase over time in both groups. Also, we would expect the utility of the open radical prostatectomy group to be lower than that of the robot-assisted radical prostatectomy group in a short period postsurgery, since open radical prostatectomy is a more invasive and painful treatment and has a higher risk of perioperative complications and needing blood transfusions.[27]

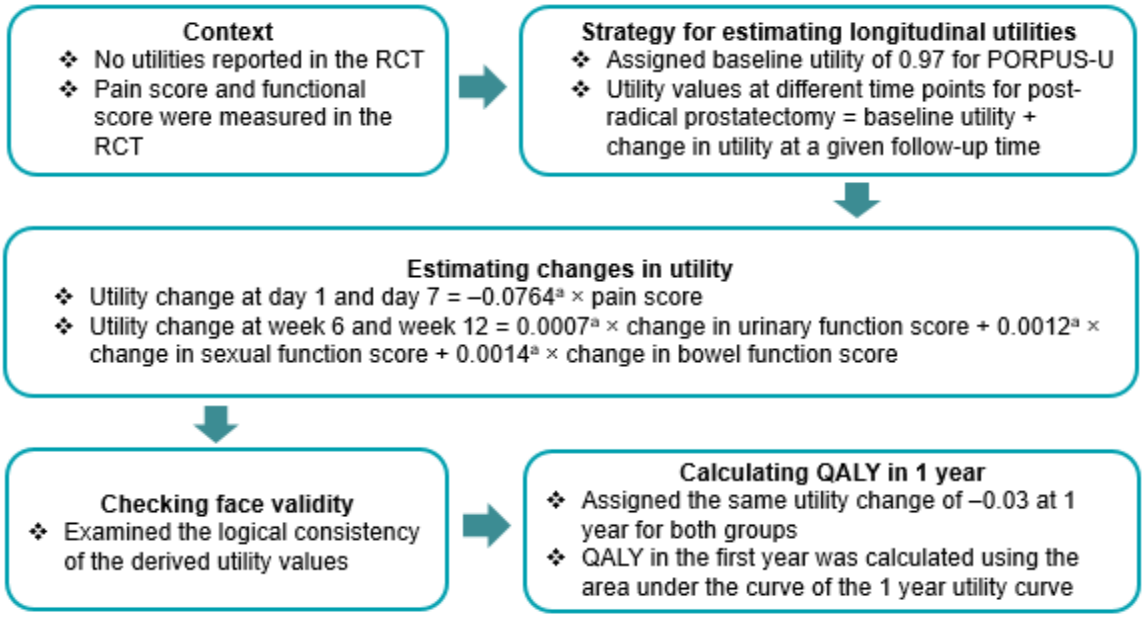

Figure 17: Process of Estimating Utility Values and QALYs

Abbreviations: PORPUS-U, Patient-Oriented Prostate Utility Scale—Utility; QALY, quality-adjusted life-year; RCT, randomized controlled trial.
[a]Coefficient from statistical models in published articles (Krahn et al, 2013,[115] and Xie et al, 2016[119]).
Source: RCT data from Yaxley et al, 2016.[27]

Table 31: Utilities Used in the Economic Model

Health State	Mean (95% CI)	Distribution for Probabilistic Sensitivity Analysis	Reference
Utility in the first year			
Pre-treatment (baseline)	0.97	Fixed value	Krahn et al[116]
Utility change in RARP arm			
1 day	−0.1406 (−0.1539, −0.1272)[a]	Pain score: normal (4.60, 0.1786)[b]	Calculated[27,119]
7 days	−0.0767 (−0.0873, −0.0660)[a]	Pain score: normal (2.51, 0.1607)[b]	Calculated[27,119]
6 weeks	−0.0524 (−0.0607, −0.0423)[a]	Normal for EPIC urinary, sexual, and bowel domains[c]	Calculated[27,115]
12 weeks	−0.0326 (−0.0391, −0.0246)[a]	Normal for EPIC urinary, sexual, and bowel domains[c]	Calculated[27,115]
1 year	−0.03 (−0.05, −0.01)	Normal (−0.03, 0.01)	Krahn et al[116]
Utility change in ORP arm			
1 day	−0.1782 (−0.1938, −0.1624)[a]	Pain score: normal (5.83, 0.2015)[b]	Calculated[27,119]
7 days	−0.0975 (−0.1078, −0.0872)[a]	Pain score: normal (3.19, 0.1454)[b]	Calculated[27,119]
6 weeks	−0.0469 (−0.0543, −0.0378)[a]	Normal for EPIC urinary, sexual, and bowel domains[c]	Calculated[27,115]
12 weeks	−0.0333 (−0.0401, −0.0248)[a]	Normal for EPIC urinary, sexual, and bowel domains[c]	Calculated[27,115]
1 year	−0.03 (−0.05, −0.01)	Normal (−0.03, 0.01)	Krahn et al[116]
Utility in the second year or later			
Recurrence free	0.94	NA	Krahn et al[116]
Recurrence	0.83	NA	Naik et al[120]
Metastasis	0.78	NA	Naik et al[120]
Utility change because of secondary surgeries for urinary incontinence	–0.0361[d]	NA	Krahn et al[115]
Utility change because of sexual dysfunction in the second and third years	–0.0581[e]	NA	Krahn et al[115]

Abbreviations: CI, confidence interval; EPIC, Expanded Prostate Cancer Index Composite; NA, not applicable; ORP, open radical prostatectomy; RARP, robot-assisted radical prostatectomy.

[a]Since the utility change was calculated from two or more variables, we used a Monte Carlo simulation to estimate 95% CIs.

[b]Distribution of the coefficient of the pain/discomfort domain in EuroQoL—Five Dimensions (EQ-5D-5L): normal (–0.0764, 0.0022).[119]

[c]Distribution of the coefficient for EPIC domains: urinary—normal (0.000722, 0.000117); sexual—normal (0.001162, 0.000101); and bowel—normal (0.001365, 0.000164).[115]

[d]We assumed that the secondary surgeries for urinary incontinence would result in a 50-point reduction in the urinary domain of the Prostate Cancer Index, and that the utility reduction would last for 1 year.

[e]We assumed that sexual dysfunction would result in a 50-point reduction in the sexual domain of the Prostate Cancer Index.

Days 1 and 7 After Surgery

We estimated the utility change at days 1 and 7 after surgery by using the pain score during normal activities (measured by the Surgical Pain Scale, from 0 to 10) from the RCT[27] since there was no Expanded Prostate Cancer Index Composite score measured at days 1 and 7. In a recently published article on the valuation of a five-level version of the EuroQoL—Five Dimensions (EQ-5D-5L) for Canada, the authors reported that the coefficient of the pain/discomfort domain was −0.0764 in the linear term in the main effect model.[119] We assumed

that the minimum and maximum values in the 10-level Surgical Pain Scale would be equivalent to those in the pain/discomfort domain of EQ-5D-5L (with 0 and 10 in the Surgical Pain Scale corresponding to 1 and 5 in the EQ-5D-5L, respectively). We also assumed the spacing between two consecutive levels would be distributed evenly for each instrument. The change in pain score from the Surgical Pain Scale would be divided by 2.5, which approximates to the change in the pain/discomfort domain in EQ-5D-5L. Assuming "no pain" at baseline (0 in the Surgical Pain Scale), we used the formula below to estimate the utility change at day 1 and day 7,[27,119] relative to baseline utility:

EQ-5D-5L Utility Change = −0.0764 × (Surgical Pain Score During Normal Activities ÷ 2.5)

Weeks 6 and 12 After Surgery

We also estimated the utility reduction at weeks 6 and 12. We extracted the Expanded Prostate Cancer Index Composite scores for the urinary, sexual, and bowel domains at time 0, week 6, and week 12 from the single RCT[27] and calculated the score changes in each domain at 6 weeks and 12 weeks relative to time 0. As obtained through multiple regression analyses by Krahn et al,[115] one unit change of Prostate Cancer Index score in the urinary domain, sexual domain, or bowel domain corresponded to a mean utility change of 0.00072, 0.001162, or 0.001365, respectively. We then used the following formula to approximate the utility change at 6 weeks and 12 weeks, compared with baseline:

PORPUS-U Change at a Given Time Point = 0.000722 × Change in EPIC Urinary Function + 0.001162 × Change in EPIC Sexual Function + 0.001365 × Change in EPIC Bowel Function,

where EPIC is the Expanded Prostate Cancer Index Composite and PORPUS-U is the Patient-Oriented Prostate Utility Scale—Utility.

It should be noted that Yaxley et al[27] reported the results using the Expanded Prostate Cancer Index Composite, whereas Krahn et al[115] used the results of the Prostate Cancer Index in their multiple regression. Since the Expanded Prostate Cancer Index Composite and Prostate Cancer Index have the same scale from 0 to 100 and considerable correlations, especially for urinary and sexual function domains,[121,122] we made the assumption that the coefficients from the Prostate Cancer Index could also be applied to the Expanded Prostate Cancer Index Composite.

More Than 1 Year After Surgery

We assumed that patients' long-term utility values were associated with patients' oncological and functional outcomes (up to 3 years). The health utilities were 0.94, 0.83, and 0.78 for patients in the recurrence-free, recurrence, and metastasis health states, respectively.[116,120] (Note: We did not find an appropriate Patient-Oriented Prostate Utility Scale—Utility source for recurrence and metastasis. Thus, the utilities for recurrence and metastasis were based on the EQ-5D-5L method.) We also estimated the utility reduction owing to specific reasons such as sexual dysfunction (Table 31).

Cost Parameters

Costs are reported in 2016 Canadian dollars (CAD), unless otherwise indicated.[123]

Capital Investment, Service Contract, and Disposables

Experts provided the 2016 purchasing price of the da Vinci Surgical System, as well as the costs for service and its disposables (Table 32).

The capital cost associated with the robotic system included the costs of the base and accessories and a one-time cost for upgrading the operating room. The average total cost of a da Vinci Si Surgical System was estimated to be $3.1 million USD: $2.4 million USD for the base, $500,000 USD for accessories, and $200,000 USD for the start-up reusable equipment (e.g., three-dimensional vision system).

According to the manufacturer, the base of the robotic system costs $1.7 million to $3 million USD. We used an average of $2.4 million USD considering both the quoted price and any potential discount.

The da Vinci Si Surgical System also offers accessories such as a second console, skills simulator, fluorescence imaging starter kit, and vessel sealer starter kit. The total quoted cost of those options (one of each) was slightly over $1,000,000 USD. We used $500,000 USD as the average cost, assuming that a hospital would purchase only a few of these additional options.

According to consulted experts, the indirect (overhead) cost for the hospital of using robotics was estimated to be about 30% of the capital cost. Hospitals often need to upgrade the operating room to conduct robotic-assisted surgeries because there are higher operating room standards for robotic surgeries.[111] Thus, we assumed that the total indirect cost for a hospital was $1,000,000 CAD for the whole service life of a robotic system.

In addition, the annual service and maintenance fee of the robotic system was $220,000 USD. The quoted cost of disposables for a typical procedure was $2,825 USD. We used $2,500 USD per procedure in our base case analysis, considering a potential discount.

Since these costs are in US dollars, we converted them into Canadian dollars using the average exchange rate from January to August 2016 ($1 USD = $1.32 CAD).[124] There is also a 5% federal tax for purchasing medical devices and services through a hospital in Canada. We calculated the equivalent annual cost of the capital investment of purchasing a robotic surgical system under a few assumptions:

- The service lifespan of the da Vinci Si Surgical System is 9 (base case) years
- There is no residual value at the end of the surgical system's service life
- There is no cost to dispose of the surgical system

We present the capital and annual costs of using robotics in Table 32.

Table 32: Costs of the da Vinci Si Surgical System

Description	USD in 2016	CAD in 2016
Capital cost		
Base of da Vinci Si Surgical System	$2,400,000	$3,337,310[a]
Options of da Vinci Si Surgical System	$500,000	$695,273[a]
Start-up reusable equipment (in total)	$200,000	$278,109[a]
Hospital's overhead cost	NA	$1,000,000
Equivalent annual cost of total capital cost and hospital's overhead cost at different service lifespan		
5 years	NA	$1,226,636
7 years	NA	$917,793
9 years	NA	**$747,162**
12 years	NA	$599,181
Service/maintenance cost (per year)	$220,000	$305,920[a]
Disposable costs for prostatectomy (per procedure)	$2,500	$3,476[a]

[a]Calculated using an exchange rate of $1 USD = $1.32 CAD (the average exchange rate from Jan–Aug 2016), plus 5% federal tax for purchasing medical devices and services.

We used the following formula to estimate the attributable cost per procedure of using the robotic system (not including disposable costs):

Attributable Cost per Procedure = (Equivalent Annual Cost + Annual Service Fee)
÷ Expected Number of Robot-Assisted Surgeries per Year per Robotic Surgical System

According to experts, in Ontario in 2015, there were 10 da Vinci Surgical Systems used for 1,616 robotic-assisted surgeries (including 828 prostatectomies, 294 hysterectomies, and 123 lobectomies). On average, one robotic system is used for 162 surgeries per year. We expect that the overall volume of robotic-assisted surgeries will continue to increase in the next few years. Thus, we assumed 200 robot-assisted surgeries conducted per robotic system per year in Ontario as the base case (about 24% higher than that in 2015).

We also conducted sensitivity analyses under different assumptions for the service lifespan of the robotic system and the volume of robot-assisted surgeries (Table 33). The attributable cost and the costs of disposables are the total cost related to using the da Vinci Surgical System.

Table 33: Attributable Cost per Procedure Related to Using the da Vinci Surgical System

	Attributable Cost per Procedure ($CAD) by Different Volume per Robotic System per Year		
Service Life of the System	**n = 162**	**n = 200**	**n = 300**
5 years	9,460	7,663	5,109
7 years	7,554	6,119	4,079
9 years	6,501	**5,265**	3,510
9 years, without the capital cost of purchasing the system[a]	2,757	2,233	1,489
12 years	5,587	4,526	3,017

[a]Although there was no capital cost for purchasing the robotic system (e.g., a donated system), there were $1,000,000 in overhead costs for the hospital plus an annual service fee of $305,920 per year.

Hospitalization Costs

We estimated the hospitalization costs of robot-assisted and open radical prostatectomy using the unit price multiplied by the use of health care resources, such as the operating room time, length of stay, recovery room time, blood transfusion rate, and readmission rate. Thus, the hospitalization cost estimates included the hospitalizations for radical prostatectomy treatment and readmission owing to complications.

The resources used for the two treatments were based on the single RCT,[27] and the unit prices were obtained from earlier cost comparison studies at McMaster University's Institute of Urology,[125] McGill University Health Centre,[126] and the Ontario Schedule of Benefits.[127] Clinical experts verified our estimations for these unit prices. We assumed that the hospitalization cost was the total cost of two prostatectomy treatments in the first month (Table 34). Costs for the remaining 11 months were estimated to be $2,746 for both groups, based on the Ontario cohort.[128]

We noticed that in the RCT,[27] the Canadian data for operating room times and lengths of the hospital stay showed considerable differences. Thus, we used the local data for the operating room time and length of hospital stay in the scenario analyses. Based on the Ontario Case Costing Initiative from Ontario Ministry of Health and Long-Term Care, we estimated that on average the lengths of hospital stay were 2.6 days for robotic surgery and 3.1 days for open surgery, and the direct operating room costs were $2,793 for robotic surgery and $2,589 for open surgery. (Operating room time was not available.) The Ontario hospitalization costs of robot-assisted and open radical prostatectomy were then reduced to $8,079 and $16,511, respectively.

Based on the national statistics from Canadian Institute for Health Information,[110] the median hospital stays were 2 days for robotic surgery and 3 days for open surgery, and operating room times were 3.67 hours for robotic surgery and 2.85 hours for open surgery. Using these data, the hospitalization costs of robot-assisted and open radical prostatectomy were $9,028 and $17,785, respectively.

Long-Term Cost in Patients with Prostate Cancer

We also estimated the long-term health care costs of patients following radical prostatectomy. We used only those costs in the scenario analyses for the Markov model. Based on data from Krahn et al,[128] we estimated that the yearly costs for the recurrence-free, recurrence, and metastasis health states after prostatectomy were $2,996, $7,854, and $19,110, respectively.

In addition, we estimated the cost of secondary treatments using data from one teaching hospital in Ontario: artificial urinary sphincter insertion ($14,047.50) and urethral sling placement ($4792.5) for incontinence. We estimated the annual cost for erectile dysfunction therapy was $479.[129]

Table 34: Hospitalization Cost of Robot-Assisted and Open Radical Prostatectomy, Including Readmission

		RARP[a]		ORP[a]	
Health Care Resource	**Unit Price, $[a]**	**Resource Use, Mean (95% CI)**	**Cost, $**	**Resource Use, Mean (95% CI)**	**Cost, $**
Robotic equipment and service contract	—	—	5,265	—	NA[b]
Consumables and disposables	—	—	3,476[c]	—	273
Operating room	1,278/hour[125]	4.10 (3.96, 4.24)[27]	5,241	4.67 (4,57, 4.77)[27]	5,971
Recovery room	221/hour[130]	1.80 (1.64, 1.96)[27]	397	1.79 (1.40, 2.18)[27]	394
Surgical bed	1,037/day[125]	1.55 (1.41, 1.96)[27]	1,607	3.27 (3.03, 3.51)[27]	3,390
Surgeon fees	—	—	1,508[127,c,d]	—	1,081[127,c,d]
Anaesthesia	15/unit[127]	10.00[127]	150	10.00[127]	150
Blood transfusion	757/transfused patient[125]	0.01 (0, 0.03)[27]	8	0.04 (0.01, 0.08)[27]	30
Readmission[e]	4,334[125,127,130]	0.05 (0.02, 0.1)[27]	217	0.08 (0.04, 0.13)[27]	347
Total average costs	—	—	**17,869**	—	**11,636**

Abbreviations: CI, confidence interval; ORP, open radical prostatectomy; RARP, robot-assisted radical prostatectomy.

[a]In the probabilistic sensitivity analysis, we used the fixed values for the unit price and gamma distributions for the resource uses for both groups. All costs are in 2016 Canadian dollars.

[b]Although there are equipment-related costs for ORP, the surgical equipment is often not solely dedicated for ORP. In the long-term, the attributable cost of equipment for ORP is likely to be small, assuming that the service life of the equipment is long and the volume of (different types of) surgeries is large. Since this cost is relatively small and difficult to quantify, we have excluded it from this analysis.

[c]We used the ± 25% of the point estimate in the deterministic sensitivity analysis, and assumed the standard error is 20% of the point estimate in the probabilistic sensitivity analysis.

[d]The Ontario Schedule of Benefits[127] includes the cost for the surgical assistant service (8 units for RARP and 6 units for ORP).

[e]We assumed that one readmission would consume 1 hour of operating room time, 2 hours of recovery room time, 2 days of hospitalization, and a professional fee of 50% of the ORP cost ($4,334 total).

Parameters of Functional and Oncological Outcomes Favouring Robot-Assisted Radical Prostatectomy in the Scenario Analyses

The recently published RCT concluded that there were no significant differences in oncological and functional outcomes between the two treatments at 12 weeks.[27] Our present clinical review (based on prospective comparative studies) found similar findings for these outcomes at 1 year. However, many retrospective nonrandomized studies (e.g., those using administrative databases) showed results favouring robot-assisted radical prostatectomy.[131] Also, according to expert opinion, the benefit of robot-assisted radical prostatectomy may not be adequately captured in the evidence included in our report.

Thus, we made more favourable assumptions for robot-assisted radical prostatectomy in the scenario analyses. We created the Markov model to capture the long-term outcomes. In the Markov model, the probabilities of cancer progression in open radical prostatectomy were obtained from the validated model for prostate cancer.[132] Since the clinical review showed inconclusive results for biochemical recurrence, we used an assumed risk ratio of 0.85 for biochemical recurrence for robot-assisted versus open radical prostatectomy.

The rate of secondary surgeries owing to urinary incontinence in open radical prostatectomy was based on a large cohort in Ontario: about 2.8% and 1.1% of patients underwent artificial urinary sphincter and urethral sling placement, respectively.[133] We assumed that the risk ratio of secondary surgeries was 0.5 favouring robot-assisted radical prostatectomy because we did not identify published evidence of these surgeries after the robotic surgery.

In addition, there are few published data comparing sexual function outcomes between these two prostatectomies in Ontario. For simplicity, we extracted data from the time-to-potency curve for both treatments in an observational study with a 30-month follow-up.[47] This study showed a large benefit of robot-assisted radical prostatectomy on sexual function.

All the parameters for the long-term model are presented in Table 35.

Table 35: Long-Term Clinical Outcomes for Scenario Analyses Favouring Robot-Assisted Radical Prostatectomy

Description	Mean	References
Oncological outcomes		
Annual transition probability from recurrence-free to local recurrence for patients with low- or intermediate-risk cancer in the ORP group[a]	0.03	Sanyal et al[129,132]
Risk ratio of recurrence, RARP versus ORP	0.85	Assumption[b]
Annual transition probability from biochemical recurrence to metastatic castration-resistant prostate cancer for both groups	0.07	Sanyal et al[132]
Mortality in different health states		
Recurrence free or local recurrence	Same as for age- and sex-specific general population in Canada	Assumption
Age, years		
55	0.00481	Padavano et al[134]
60	0.00791	Padavano et al[134]
61	0.00846	Padavano et al[134]
62	0.0087	Padavano et al[134]
63	0.00994	Padavano et al[134]
64	0.01136	Padavano et al[134]
65	0.01161	Padavano et al[134]
66	0.01306	Padavano et al[134]
67	0.01452	Padavano et al[134]
68	0.01595	Padavano et al[134]
69	0.01713	Padavano et al[134]
Metastatic castration-resistant prostate cancer	0.27	Sanyal et al[132]
Functional outcomes: urinary incontinence		
Artificial urinary sphincter insertion in the ORP group per year (up to 3 years)	0.94%	Nam et al[133]
Urethral sling placement in the ORP group per year (up to 3 years)	0.37%	Nam et al[133]
Risk ratio of surgical interventions owing to urinary incontinence in the RARP group	0.5	Assumption

Description	Mean	References
Functional outcomes: sexual dysfunction		
Patients with sexual dysfunction in the RARP group[c]		
Year 1	0.67	Kim et al[47]
Year 2	0.3	Kim et al[47]
Year 3	0.08	Kim et al[47]
Patients with sexual dysfunction in the ORP group[c]		
Year 1	0.93	Kim et al[47]
Year 2	0.55	Kim et al[47]
Year 3	0.31	Kim et al[47]

Abbreviations: CI, confidence interval; ORP, open radical prostatectomy; RARP, robot-assisted radical prostatectomy.

[a]The recurrence rates vary greatly in published data for various reasons. We used the value 0.03 annually from the validated model by Sanyal et al.[129,132]

[b]Two of the prospective comparative studies showed no significant difference for biochemical recurrence between groups.[38,55] A third study by Breyer et al[36] showed ORP had a statistically significant lower risk of recurrence at 3 years. Thus, we made a hypothetical risk ratio to favour RARP.

[c]We extracted data on the proportion of potent patients at 6, 18, and 30 months in the Kaplan-Meier curve to represent the estimates of the sexual function in years 1, 2, and 3, respectively.

Analysis

Using the parameters above, we estimated the health care costs and QALYs of robot-assisted and open radical prostatectomy. We conducted a base case analysis using the best available point estimates. We applied Ontario and Canadian data regarding lengths of hospital stay and operating room times in the scenario analyses. We also conducted deterministic sensitivity analyses (e.g., changing from the mean to the upper and lower limit 95% CIs of the variables) to assess the impact of key variables on the incremental cost-effective ratio (ICER), and probabilistic sensitivity analyses to assess parameter uncertainty.

Also, we conducted additional analyses to examine the cost-effectiveness of robot-assisted versus open radical prostatectomy in scenarios favouring robot-assisted radical prostatectomy. First, we used the 1-year model, which is the same as the base case but excluded the capital cost of the robotic system. We then applied the upper limits of the 95% CIs of the longitudinal utilities to estimate QALYs in the robot-assisted radical prostatectomy group. Next, we applied functional and oncological outcomes that favoured robot-assisted radical prostatectomy in the Markov model.

We conducted all analyses using SAS version 9.4 (SAS Institute, Cary, North Carolina) for the 1-year model and TreeAge Pro 2016 (TreeAge Software, Williamstown, Massachusetts) for the Markov model.

Generalizability

The findings of this economic analysis cannot be generalized to all patients with localized prostate cancer. They may however be used to guide decision-making about the specific patient populations in Ontario addressed in the studies we evaluated.

Expert Consultation

Throughout the development of this model, we solicited expert consultation. The expert advisors reviewed the model structure and inputs to confirm that the information we used reasonably reflected the clinical context for prostate cancer in Ontario. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Base Case Analysis

Table 36 presents the base case results for our analysis. Compared with open radical prostatectomy, robot-assisted radical prostatectomy was associated with higher costs ($6,104 per patient) and small QALYs gained (0.0012). The associated ICER was $5.2 million per QALY gained. Based on a willingness to pay of $100,000 per QALY or lower, robot-assisted radical prostatectomy was not cost-effective compared with open radical prostatectomy.

Table 36: Results of the Base Case Analysis for the Cost-Utility Analysis, Robot-Assisted Versus Open Radical Prostatectomy

Strategy	Average Total Costs, $[a,b]	Incremental Cost, $[a,b]	Average Total QALYs[a]	Incremental QALYs[a]	Incremental Cost-Effectiveness Ratio, $[a,b]/QALY gained
ORP	14,369	—	0.9284	—	—
RARP	20,604	6,234	0.9296	0.0012	5,200,894

Abbreviations: ORP, open radical prostatectomy; QALY, quality-adjusted life-year; RARP, robot-assisted radical prostatectomy.
[a]Numbers may appear inexact because of rounding.
[b]All costs are 2016 Canadian dollars.

Deterministic Sensitivity Analysis

We examined several factors that could affect the ICER values of robot-assisted versus open radical prostatectomy. Figure 18 presents the results of the one-way sensitivity analysis. The blue and orange bars illustrate the ICERs at lower and upper limits of the respective variables. The main variables that influenced the cost-effectiveness included the utility changes after 12 weeks or 1 year of surgery for both groups, the service life of robotic system, the volume of surgeries per robotic system, and the cost of disposables for robot-assisted radical prostatectomy.

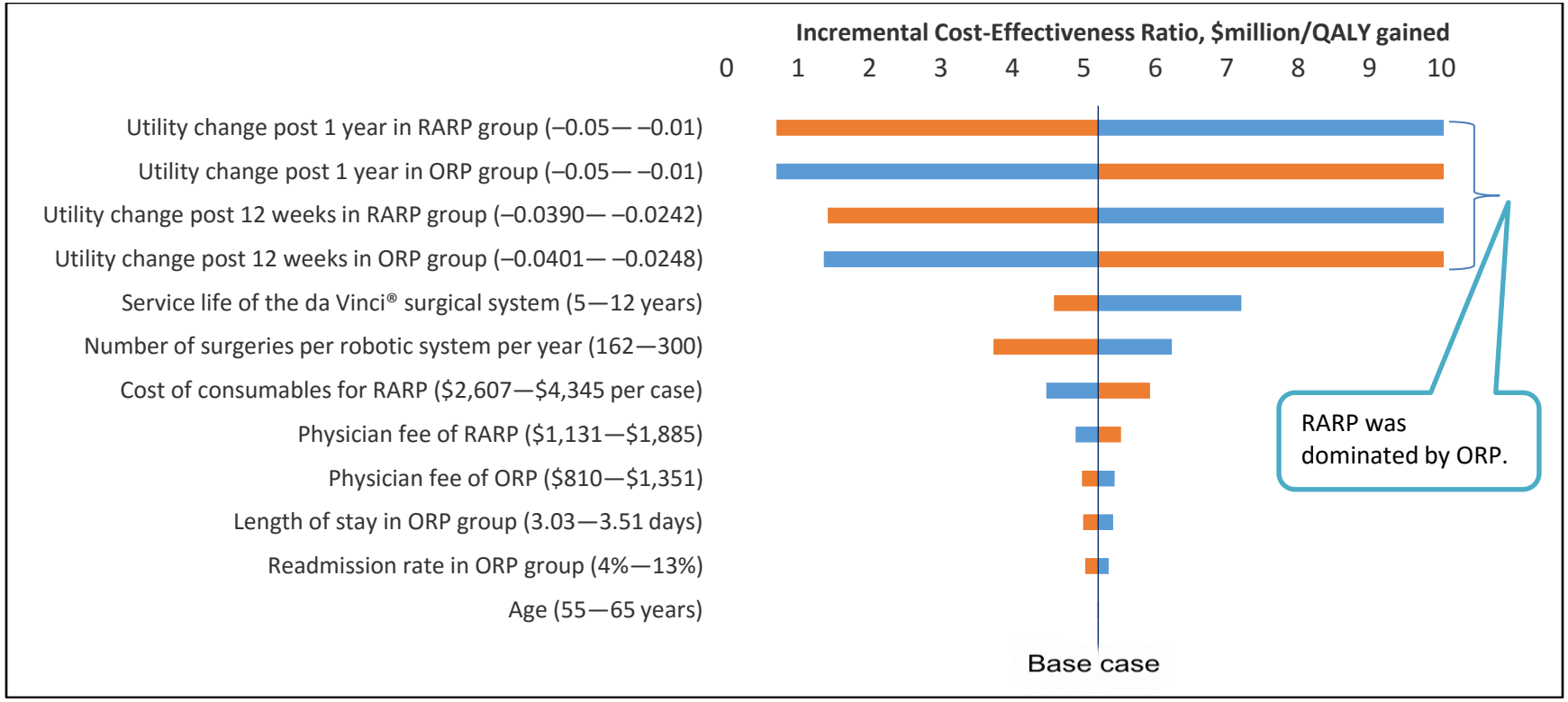

Figure 18: Tornado Diagram of One-Way Sensitivity Analysis, Robot-Assisted Versus Open Radical Prostatectomy[a]

Abbreviations: ORP, open radical prostatectomy; QALY, quality-adjusted life-year; RARP, robot-assisted radical prostatectomy.
[a]All costs are in 2016 Canadian dollars. For each variable, the blue and orange bars show the incremental cost-effectiveness ratios at lower and upper limits, respectively.

Probabilistic Sensitivity Analysis

We conducted a probabilistic sensitivity analysis using the same 1-year model as the base case, and we assigned the parameters with probabilistic distributions instead of point estimates. Figure 19 illustrates the incremental cost and incremental QALYs calculated for each simulation of the probabilistic sensitivity analysis for robot-assisted versus open radical prostatectomy.

The results of the Monte Carlo simulations are consistent with those of the base case. Compared with open radical prostatectomy, the median incremental cost of robot-assisted radical prostatectomy is $6,164 (quartile 1: $5,279; quartile 3: $7,102), and the median QALY gained is 0.0012 (quartile 1: 0.0002; quartile 3: 0.0026). All simulated results are above the threshold line, indicating robot-assisted radical prostatectomy has very little to no chance of being cost-effective at a willingness-to-pay threshold of $100,000 per QALY gained.

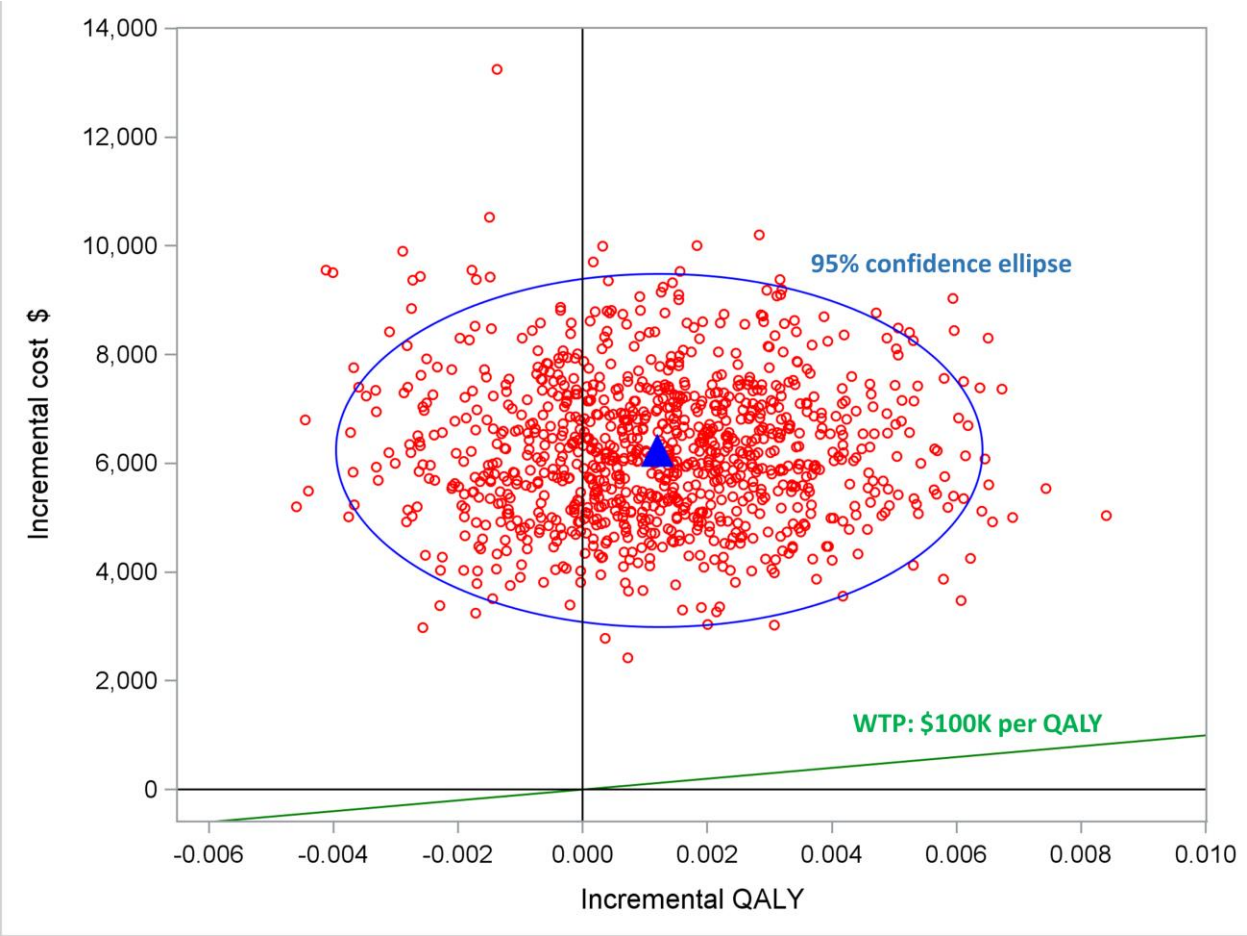

Figure 19: Incremental Cost and QALYs of Robot-Assisted Versus Open Radical Prostatectomy[a]

Abbreviations: ORP, open radical prostatectomy; QALY, quality-adjusted life-year, RARP, robot-assisted radical prostatectomy.
[a]The triangle indicates the base case scenario. Each circle surrounding the triangle represents a single result from the simulation, presenting the incremental effects and incremental costs of RARP relative to ORP. The green diagonal line shows the willingness-to-pay threshold of $100,000 per QALY.

Scenario Analyses

Table 37 presents the results of our various scenario analyses. Assuming that the QALYs of both treatments were the same as those in base case, we used the local length of stay data and operating room time data to recalculate the costs in the scenario analyses. When we used the Ontario data, the incremental cost for the robotics treatment increased to $8,432 and the associated ICER was $7.0 million per QALY gained. When we used the Canadian statistics, the incremental cost for the robotics treatment increased to $8,757 with an associated ICER of $7.3 million per QALY gained.

We also conducted various scenario analyses that favoured robot-assisted radical prostatectomy. When we used the upper limits of the 95% CIs of the longitudinal utility data in the robot-assisted radical prostatectomy group, we got a much higher QALY gained (0.0138). If we also excluded the capital cost for purchasing the robotic system (i.e., assuming the robotic system was donated), the incremental cost was reduced to $3,224 and the associated ICER was $234,339 per QALY gained. In addition, if we excluded the capital cost of adopting the robotic surgical system and the maintenance fee (i.e., to estimate the cost-effectiveness of additional cases using the robotic surgical system), the ICER was $808,708 per QALY gained.

We also created the Markov model to capture the potential health benefits of robot-assisted radical prostatectomy in the long term. If we assumed that it can provide sexual and urinary benefits compared with open radical prostatectomy for 3 years, robot-assisted radical prostatectomy had a much greater QALY gained (0.0419). If we assumed that it can lead to a lower risk of cancer recurrence, robot-assisted radical prostatectomy had a 0.0213 QALY gained over 10 years compared with open radical prostatectomy. Under assumptions that it can provide both functional and oncological benefits compared with open radical prostatectomy, the ICER was $83,921 per QALY gained.

Table 37: Results of Scenario Analyses for the Cost-Utility Analysis, Robot-Assisted Versus Open Radical Prostatectomy

Scenario	Incremental Cost, $[a] (RARP vs. ORP)	Incremental QALYs[a] (RARP vs. ORP)	Incremental Cost-Effectiveness Ratio, $[a]/QALY Gained
Using local data for operating room time and length of hospital stay			
Ontario data	8,432	0.0012	7,034,376
Canadian national statistics	8,757	0.0012	7,305,690
1-year model (under assumptions favouring RARP)			
Excluding the capital cost of purchasing the robotic system[b]	3,224	0.0012	2,689,882
Using the upper limits of 95% CI for utility values in days 1, 7, 42, 84, and 365 in the RARP group	6,234	0.0138	453,095
Excluding the capital cost of purchasing the robotic system[b] and using upper limits of 95% CI for utility values in the RARP group	3,224	0.0138	234,339
Excluding the capital cost of using the robotic system and maintenance service fee[c]	969	0.0012	808,708
Excluding the capital cost of using the robotic system and maintenance service fee[c] and using upper limits of 95% CI for utility values in the RARP group	969	0.0138	70,454
Long-term model (under assumptions favouring RARP)			
RARP with favourable functional outcomes in 3 years	5,899	0.0419	140,700
RARP with favourable oncological outcomes in 10 years	5,542	0.0213	260,127
RARP with favourable functional outcomes in 3 years and favourable oncological outcomes in 10 years	5,206	0.062	83,921

Abbreviations: CI, confidence interval; ORP, open radical prostatectomy; QALY, quality-adjusted life-year; RARP, robot-assisted radical prostatectomy.
[a]Note: some numbers may appear inexact because of rounding.
[b]Although there was no capital cost for purchasing the robotic system (e.g., a donated system), there was $1,000,000 CAD in overhead costs for the hospital and an annual service fee of $305,920 CAD per year.
[c]This analysis included only the cost of the disposables for the robotic system; it excluded the cost of the base, options, and start-up equipment of robotic system, the annual service fee, and hospital's overhead cost.

Discussion

Likelihood of Robot-Assisted Radical Prostatectomy Being Cost-Effective

Our economic evaluation showed that compared with open radical prostatectomy, robot-assisted surgery had substantially higher costs and slightly greater QALYs, resulting in a very high ICER. Results were robust in the one-way and probabilistic sensitivity analyses. When using Ontario and Canadian data for the lengths of stay and operating room times, we found the ICERs were even higher than those in the base case. In probabilistic sensitivity analysis, almost all simulated results were beyond the commonly used willingness-to-pay threshold in Ontario (Figure 19).

We also explored the likelihood of robot-assisted radical prostatectomy being cost-effective in several scenarios that favoured it. For example, after we excluded the capital cost of purchasing the robotic surgical system, the ICER decreased substantially from $5.2 million per QALY in the base case to $2.7 million per QALY. However, this is still significantly higher than the commonly accepted threshold in Canada. Increasing the volume of robotic-assisted radical prostatectomies and the service life of the surgical system would also reduce the ICER, but it would still be higher than $2.7 million per QALY. More importantly, the large volume would lead to a greater budget increase.

The results in our long-term model showed that the ICER would be $83,921 per QALY gained if robot-assisted radical prostatectomy had more favourable oncological and functional outcomes, relative to open radical prostatectomy. The clinical review found either no difference or inconclusive results for functional and oncological outcomes between robot-assisted and open radical prostatectomy. Thus, we applied a hypothetical benefit for robot-assisted radical prostatectomy in the long-term model.

Also, oncological outcomes and functional outcomes may be negatively correlated, depending on the width of the neurovascular bundle resection. For example, the nerve-sparing procedure may be associated with a higher positive surgical margin rate but better functional outcomes.

We did not conduct a scenario analysis for patients with a high risk of cancer progression since, in Ontario, robot-assisted radical prostatectomy is commonly used for patients with low- or intermediate-risk cancer. However, the results in our 1-year base case model would be applicable for patients with high-risk cancer, under the assumption that there is no difference in oncological outcomes between the two groups.

Since the RCT found that both treatments resulted in the same length of time away from work,[27] we did not conduct analyses for productivity loss.

Magnitude of Clinical Benefit of Robot-Assisted Radical Prostatectomy in Canada

Since the high ICER in the present study is largely driven by the small QALY gained from robot-assisted radical prostatectomy, we explored the potential magnitude of its clinical benefit. There are several published studies comparing robot-assisted and open radical prostatectomy in Canada. The comparative studies in British Columbia and Alberta showed that robotic-assisted and open radical prostatectomy have small differences in clinical outcomes.[69,135-137]

Gagnon et al[69] analyzed 200 consecutive robotic-assisted radical prostatectomies by one surgeon (after a learning curve of 70 cases) and 200 consecutive open radical prostatectomies by another surgeon.[69] The authors concluded that both treatments had comparable lengths of stay, transfusion rates, positive surgical margin rates, and rates of postoperative urinary incontinence. However, compared with open radical prostatectomy, robot-assisted radical prostatectomy was associated with[69]:

- A higher 90-day postoperative complication rate: 22% versus 11.5%, $P = .007$
- A longer operative time: skin to skin, 234 versus 114 minutes, $P < .001$
- A higher cost: incremental cost of $5,629 per procedure

We identified three conference abstracts involving a cohort of 1,019 consecutive patients (815 undergoing robot-assisted versus 204 open radical prostatectomy) with clinically localized prostate cancer in Alberta.[135-137] However, we did not find a full-text publication of this study. In

this cohort, patients in both groups had comparable short-term surgical outcomes (complications within 90 days of surgery) and oncologic outcomes (biochemical recurrence-free survival and positive surgical margins). However, robot-assisted radical prostatectomy was associated with an increased chance of achieving pentafecta (defined as no biochemical recurrence, continent, potent, negative surgical margins, and no complications) at 12 months. The authors also found that the surgeon significantly impacted the clinical outcomes.[135]

Also, a retrospective study by Rush et al[73] of Ontario's population showed that after adjusting for potential confounders, robot-assisted and open radical prostatectomy did not result in clinically significant differences in health-related quality of life, as measured by the Patient-Oriented Prostate Utility Scale.

In addition, although there were no statistics available to compare the surgical outcomes of the two treatments in Canada, the risks of unplanned readmission within 30 days postsurgery were similar, at 3.8% for open radical prostatectomy and 3.9% for robot-assisted radical prostatectomy (fiscal years 2009/10–2011/12).[110]

Since robot-assisted radical prostatectomy is presently used only in select teaching hospitals in Canada, it is appropriate to limit the comparison of robot-assisted to open radical prostatectomy within high-volume teaching hospitals. In recent years, the improvements of surgical techniques in open radical prostatectomy and anaesthesia have substantially reduced the risk of surgical complications and decreased the lengths of hospital stay.[69,138,139] Thus, the historical benefits of robot-assisted radical prostatectomy (e.g., the lower surgical complication rates and shorter lengths of stay) have narrowed over time.[138] Also, in high-volume hospitals such as Duke University Medical Center, the transfusion rates of both treatments were also comparable.[138]

Pierorazio et al[139] found that, excluding the "off-pathway" patients (e.g., those experiencing ileus, urine leak, anemia, or re-exploration for bleeding), the average length of stay for all radical prostatectomies was reduced from 7.7 days in 1991 to 1.6 days in 2010 at Johns Hopkins University. Both procedures showed comparable complication rates and lengths of stay (1.87 days for open radical vs. 1.96 days in robot-assisted prostatectomy) since 2005.

In summary, the clinical data in Canada suggest that the difference in various outcomes between the two procedures is very small. The historical benefit of robot-assisted radical prostatectomy has narrowed over time because of the improvements in open techniques as well as contemporary patient-management strategies.

Study Strengths

Our study has the following strengths:

- We estimated the costs and QALYs based on the most recent RCT comparing these treatments. This is considered higher-quality evidence compared with earlier observational studies
- We captured the temporary health-related quality of life benefit immediately after robot-assisted radical prostatectomy
- Our 1-year model and long-term Markov model explored the uncertainty of the potential benefits of robot-assisted radical prostatectomy in various scenarios

Study Limitations

The following limitations should be noted when interpreting the findings of this analysis:

- Cost estimates for both treatments were largely derived from a single RCT from Australia with 12 weeks' (short term) follow-up
- Utilities of these treatments were not available in the RCT; thus, we derived the estimates of longitudinal utility values using indirect methods
- No high-quality evidence was available to allow for the comparison of sexual function, urinary function, or oncological outcomes of treatments in long-term follow-up
- We did not control for the effect of surgeons' skills

Conclusion

The cost of using the robotic surgical system is high, while the health benefit is small. Therefore, robot-assisted radical prostatectomy does not appear to be cost-effective in patients with clinically localized prostate cancer.

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis to estimate the cost burden of continuing public funding of robot-assisted radical prostatectomy at an increased adoption over the next 5 years. All costs are reported in 2016 Canadian dollars.

Objective

This study aimed to assess the budget impact of purchasing robotic surgical systems and continuing public funding of the robot-assisted radical prostatectomy procedure at an increased adoption in men with clinically localized prostate cancer. We conducted this assessment within the context of the Ontario Ministry of Health and Long-Term Care.

Methods

Target Population

The target population was men with newly diagnosed, clinically localized prostate cancer who were eligible for radical prostatectomy.

We estimated the volume of robot-assisted radical prostatectomy in next 5 years based on data from IntelliHealth Ontario. This database showed that the total volume of radical prostatectomy procedures was in decline from 2011 to 2013 but stabilized in 2014 and 2015 (Table 38). However, the volume of robot-assisted radical prostatectomy has constantly been on the rise. In 2015, it reached a total of 816 procedures (34% of the total volume of all radical prostatectomies).

Based on the trends in the database, we assumed that in the next 5 years, the volume of total procedures and laparoscopic procedures would be fixed at 2,400 and 48 cases (2%), respectively. And we assumed the adoption of robot-assisted radical prostatectomy would gradually increase to 40% in year 1, 45% in year 2, 50% in year 3, 55% in year 4, and 60% in year 5.

In practice, patients' characteristics are not identical for robot-assisted and open radical prostatectomy. In Ontario, open radical prostatectomy is performed in patients with various risk profiles, while robot-assisted radical prostatectomy is typically used for patients with a low or intermediate risk of cancer progression.[73] Open radical prostatectomy is performed in teaching hospitals and community health centres. But robot-assisted radical prostatectomy is generally conducted exclusively in teaching hospitals. We therefore think it is reasonable to assume that robot-assisted surgery can replace open radical prostatectomy in some instances.

In Canada, Alberta has the highest proportion of robot-assisted radical prostatectomy procedures: about 60% in fiscal years 2011/12 and 2012/13.[140] Based on these data, we estimated its adoption in Ontario would be as high as 60% in year 5.

Table 39 shows the expected volumes of robot-assisted radical prostatectomy in Ontario in the next 5 years.

Table 38: Volumes of the Different Types of Prostatectomy Procedures Performed in Ontario

Year	RARP	ORP	LRP	Total
2011	229[a]	2,695	335[a]	3,259
2012	456[a]	2,199	242[a]	2,897
2013	692	1,704	157	2,553
2014	756	1,539	110	2,405
2015	816	1,492	98	2,406

Abbreviations: RARP, robot-assisted radical prostatectomy; ORP, open radical prostatectomy; LRP, laparoscopic radical prostatectomy.
[a]Estimated number. RARP has had a unique procedure code since 2012 in Ontario. Prior to 2012, RARP shared the same code with LRP. Thus, IntelliHealth data do not distinguish between LRP and RARP in 2012 or before 2012. The volume of RARP in 2011 and 2012 was obtained from experts. The volume of LRP in 2011 and 2012 was estimated by subtracting RARP from the total volume of LRP plus RARP.
Note: the volumes of RARP from 2013 to 2015 from the two sources (IntelliHealth Ontario and experts) were slightly different.

Table 39: Expected Volumes of Robot-Assisted Radical Prostatectomy in the Next 5 Years in Ontario

	Expected Number of Patients				
Type of Prostatectomy	Year 1 (40% RARP)	Year 2 (45% RARP)	Year 3 (50% RARP)	Year 4 (55% RARP)	Year 5 (60% RARP)
Total radical prostatectomies	2,400	2,400	2,400	2,400	2,400
RARP	960	1,080	1,200	1,320	1,440
ORP	1,392	1,272	1,152	1,032	912
LRP	48	48	48	48	48

Abbreviations: LRP, laparoscopic radical prostatectomy; ORP, open radical prostatectomy; RARP, robot-assisted radical prostatectomy.

Resources and Canadian Costs

Based on the undiscounted results from our base case economic evaluation model, we estimated the health care cost of two treatments in the first year. (We did not apply discounting in estimating the equivalent annual cost of capital investment of the robotic system.) The costs included the purchase costs of the da Vinci Surgical System and its service contract, the hospital's overhead costs for using robotic system, costs for disposables, hospitalization costs, physician fees, and the costs of perioperative complications. More details of the cost components included are presented in the primary economic analysis.

Analysis

We explored the budget impact of publicly funding robot-assisted radical prostatectomy, using an increased adoption compared with the 2015 rate of 34%. We assumed that open and robot-assisted radical prostatectomy do not have any difference in cost after 1 year postsurgery.

The estimated costs of both treatments in the first year in base case and scenario analyses are summarized in Table 40. In scenario one, we used the local resource use data in Ontario. In scenario two, we excluded the cost of the robotic system, assuming it was donated. In scenario three, we excluded all capital costs related to using the robotic surgical system and the cost of maintenance, assuming that those costs are fixed for a hospital in the next few years,

regardless of the volume of robotic surgeries, and that no new robotic systems are purchased in hospitals in Ontario.

The budget impact analysis was conducted using Excel 2013 (Microsoft, Redmond, Washington).

Table 40: Estimated 1-Year Per-Patient Cost for Robot-Assisted and Open Radical Prostatectomy[a]

Scenario	RARP, $[b]	ORP, $[b]
Base case: including the cost of purchasing the robotic system and cost for maintenance[a]	19,819	14,369
Scenario analysis 1: using the length of stay and operating room data for the Ontario population[a]	18,461	10,814
Scenario analysis 2: excluding the cost of purchasing robotic system[c]	17,424	14,369
Scenario analysis 3: excluding the capital cost of using robotic system and cost for maintenance	15,339	14,369

Abbreviations: ORP, open radical prostatectomy; RARP, robot-assisted radical prostatectomy.
[a]Not applying discounting in estimating the equivalent annual cost of the capital investment of the robotic system.
[b]All costs are in 2016 Canadian dollars. Some numbers may appear inexact because of rounding.
[c]Although excluding the capital cost of robotic system, it included the hospital's overhead cost and cost for annual maintenance of robotic system.

Results

Table 41 presents the projected total costs of robot-assisted and open radical prostatectomy at the current adoption and the increased adoption of robot-assisted radical prostatectomy. It also shows the expected net budget impact in the next 5 years.

In the base case analysis, an increasing adoption would lead to a budget increase of about $0.8 million in the first year. With a continued trend of increasing adoption, the net budget increase would reach about $3.4 million by year 5. When we excluded the cost of the robotic surgical system and its maintenance costs, the net budget impact decreased substantially to $0.14 million in year 1 and $0.6 million in year 5.

Table 41: Total Costs and Net Budget Impact for an Increasing Adoption for RARP Versus Continued Current Adoption

Scenario	Adoption of RARP	Results, $ Million[a]				
		Year 1	Year 2	Year 3	Year 4	Year 5
Base case						
Total cost of RARP and ORP	Current: 34%	38,243,500	38,243,500	38,243,500	38,243,500	38,243,500
	Increasing	39,028,216	39,682,146	40,336,075	40,990,005	41,643,934
Net budget impact		784,716	1,438,645	2,092,575	2,746,505	3,400,434
Scenario analysis 1: using Ontario data for length of stay and operating room time						
Total cost of RARP and ORP	Current: 34%	31,675,109	31,675,109	31,675,109	31,675,109	31,675,109
	Increasing	32,776,312	33,693,982	34,611,651	35,529,320	36,446,990
Net budget impact		1,101,203	2,018,873	2,936,542	3,854,211	4,771,881
Scenario analysis 2: excluding the capital cost of the robotic surgical system						
Total cost of RARP and ORP	Current: 34%	36,289,180	36,289,180	36,289,180	36,289,180	36,289,180
	Increasing	36,729,016	37,095,546	37,462,075	37,828,605	38,195,134
Net budget impact		439,836	806,365	1,172,895	1,539,425	1,905,954
Scenario analysis 3: excluding the costs related to using the robotic surgical system and maintenance						
Total cost of RARP and ORP	Current: 34%	34,587,820	34,587,820	34,587,820	34,587,820	34,587,820
	Increasing	34,727,416	34,843,746	34,960,075	35,076,405	35,192,734
Net budget impact		139,596	255,925	372,255	488,585	604,914

Abbreviations: ORP, open radical prostatectomy; RARP, robot-assisted radical prostatectomy.
[a]Some numbers may appear inexact because of rounding. All costs are in 2016 Canadian dollars.

Discussion

There is some debate whether the capital cost for the robotic surgical system should be included in the cost analysis.[102] Some published economic analyses excluded the capital cost of the robotic system for a couple of reasons. In the United States, the payer (the insurance company) does not pay the cost of robotic equipment.[106] In Ontario, some robotic surgical systems were purchased through charitable donations from hospital foundations.

We considered the following when including the capital cost in the base case analysis:

- The donation is often from hospital foundations, not the manufacturer. If not used to purchase a robotic system, hospital foundation donation funds could be used for other goods or health care services
- Not every hospital offering radical prostatectomy surgery will receive a donated robotic surgical system. Even if a hospital receives donated robotic equipment, it may not receive another donated system or an upgraded system when the equipment needs to be replaced. In the long-term, the capital costs of robotic systems have to be covered by sources such as the hospital's global budget

Nevertheless, our sensitivity analyses did address a scenario without the capital cost of purchasing the robotic equipment.

Also, the capital cost of the robotic system (da Vinci Si) has increased substantially, from $2.8 million to $4.3 million, compared with that reported in a 2011 report published by the Canadian Agency for Drugs and Technologies in Health.[111] The changes in exchange rate largely contributed to the increased purchasing cost ($1 USD = $1.02 CAD in the 2011 report[111] vs. $1 USD = $1.32 CAD in January–August 2016).

A similar increase was identified for the costs of disposables, from $2,542 per procedure in the 2011 report[111] to $3,476 in our present analysis. Aside from the uncertainty of the exchange rate, generally the costs for robotic systems and disposables increase a few percent yearly.

Operating rooms used for robotic surgery need to be bigger than regular operating rooms. It was suggested that the operating room should be at least 52 m^2 and optimally 65 to 67 m^2.[27,113] Also, it is preferable to use a dedicated operating room so that the robotic system does not get damaged in transit from one room to another.[27,113] However, it is difficult to accurately estimate the cost to upgrade an operating room to use the robotic surgical system, and the opportunity cost of the dedicated operating room for the robotic system. According to consulted experts, the overhead cost for the hospital of using robotics was estimated to be about 30% of the capital cost. Thus, we estimated that in addition to the cost of purchasing the robotic surgical system, it costs about $1 million for the hospital to use it.

Also, a dedicated robotic surgery team would be required to perform the surgeries.[111] Thus, the true budget impact of robot-assisted surgeries may be even higher than our current estimate.

Finally, we did not include the assumption of a reduced adoption of robot-assisted radical prostatectomy. However, these results would be straightforward to calculate.

Conclusion

The current adoption of robot-assisted radical prostatectomy in Ontario is 34%. If the adoption continues to increase, this may lead to a considerable budget increase.

PUBLIC AND PATIENT ENGAGEMENT

Background

Public and patient engagement explores the lived experience of a person with a health condition, including how the condition and its treatment affect the patient, the patient's family or other caregivers, and the patient's personal environment. Public and patient engagement is intended to increase awareness and build appreciation for the needs, priorities, and preferences of the person at the centre of a treatment program. Insights gained through public and patient engagement provide an in-depth picture of lived experience, through an intimate look at the values that underpin the experience.

Lived experience is a unique source of evidence about the personal impact of a health condition and how that condition is managed, including what it is like to navigate the health care system with that condition, and how technologies might or might not make a difference in people's lives. Information shared from lived experience can both identify and supplement gaps or limitations in published research (e.g., outcome measures that do not reflect what is important to those with lived experience).[141-143] Additionally, lived experience can provide information or perspectives on the ethical and social values implications of technologies and treatments. Because the needs, priorities, preferences, and values of those with lived experience in Ontario are not often adequately explored by published literature, Health Quality Ontario makes an effort to reach out to, and directly speak with, people who live with the health condition, including those who have experience with the intervention in question.

Needs Assessment

For robot-assisted radical prostatectomy, the scope and direction of patient and public engagement were determined through a formal needs assessment by the Public, Patient, and Caregiver Engagement team at Health Quality Ontario. The purpose of this needs assessment was threefold:

- To determine if developing an evidence stream of lived experience would add value to the evidence-based analysis phase of the health technology assessment
- To define the goals and objectives of engagement, as needed
- To scope out the type of engagement activity that might be best for this project, as needed

To complete the needs assessment, we read background information on robot-assisted radical prostatectomy. This included reviewing the clinical review plan and consulting with clinical experts in the field. We also performed a qualitative literature search on patient-centred outcomes related to surgical procedures.

The needs assessment considered whether patient engagement would yield additional and relevant evidence on three dimensions: patient preferences and values in decision-making, patient preferences and values around outcomes, and health equity.

Patient Preferences and Values in Decision-Making

When we're assessing a health technology, engaging patients can often help us learn about the preferences and values that could inform a patient's decision to use the technology.

For robot-assisted prostatectomy, we consulted clinical experts, who were uncertain how much patient preference impacts the type of surgery patients receive. The choice between robot-assisted radical prostatectomy versus open or laparoscopic radical prostatectomy is often not within a patient's control for a number of reasons:

- Availability of the robotic technology
- Availability of an experienced surgeon
- Surgeon preference
- Type of surgery preferred at a hospital that is close to where the patient lives

Surgeons often specialize in one kind of surgery or another, not both. A patient rarely has a choice over which surgeon or type of surgery they can access. While direct patient engagement could help us learn patients' overall impressions and preferences regarding both types of surgery, their preferences and values would likely have little impact on their access to the technology under review.

Patient Preferences and Values Around Outcomes

Patients can also provide insights about the outcomes that are most important to them. For this health technology, the clinical review also included literature on patient values and preferences related to surgical outcomes, such as blood loss, pain, and days lost to work. Because these outcomes were included in the clinical literature, the need for direct patient engagement or a qualitative literature review was low.

Health Equity

Patient engagement can often highlight health equity issues related to the technology being assessed that are not evident in the published literature. In the case of robot-assisted radical prostatectomy, we were able to identify a possible equity issue—geographic access—through the clinical and economic data we examined. However, improved clinical outcomes are not associated with the robot-assisted radical prostatectomy, lessening any inequity concerns for those patients who don't live near health centres offering the procedure.

Clinical and economic data include information about how access to the surgery is clustered around certain centres, rather than distributed equally across the province. There is a natural tendency of surgeons and surgery types to be drawn to the same centres, rather than distributed equally across the province. This can affect patient access to these surgeries, owing to their geographic location.

Conclusion

After careful consideration of these factors within the needs assessment, we concluded that direct patient engagement for this health technology assessment would provide only moderate value and impact to this project. Patient engagement was therefore not prioritized for this health technology assessment.

ABBREVIATIONS

CI	Confidence interval
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effective ratio
IIEF	International Index of Erectile Function Questionnaire
OR	Odds ratio
PDE5	Phosphodiesterase type 5
PSA	Prostate-specific antigen
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial

GLOSSARY

Base case	A projected or virtual scenario in which no changes are made to current practice. The base case is used for comparison with an alternative scenario in which the technology under review is used.
Cohort	A group of individuals who share a common characteristic and who are part of a clinical trial or study.
Cost-effective	Good value for money. The overall benefit of the technique or intervention justifies the cost.
Cost-utility analysis	A type of analysis that estimates the value for money of an intervention by weighing the cost of the intervention against the improvements in length of life and quality of life. The result is expressed as a dollar amount per "quality-adjusted life-year" or QALY.
Decision-analytic model	A chosen method of decision-making to be used when evaluating the trade-offs between competing values, such as when weighing the costs and benefits or harms of a test or intervention.
Deterministic sensitivity analysis	A type of analysis that changes the variables to determine whether the final answer will change. The analysis is done by first setting values for each factor, and then substituting other possible values for one (in a one-way sensitivity analysis) or more (in a multi-way sensitivity analysis) factors to test how these changes affect the result.
Discounting	A method that considers that costs and health benefits are worth more today than in the future.
Dominance	A test or treatment is in a state of dominance over another when it is both more effective and less costly than the other treatment option.
Incremental cost	The extra cost associated with using one test or treatment instead of another.
Incremental cost-effectiveness ratio (ICER)	Determines "a unit of benefit" for an intervention by dividing the incremental cost by the effectiveness. The incremental cost is the difference between the cost of the treatment under study and an alternative treatment. The effectiveness is usually measured as additional years of life or as "quality-adjusted life-years."
Markov model	A type of modelling that measures the health state of a patient over the course of treatment. A patient may stay in one health state or move from one health state to another, depending on the effect of the treatment and the progression of the disease.
Monte Carlo simulation	Determines the uncertainty in an economic model by running many trials of the model. In each trial, random numbers are assigned wherever values are uncertain to see how the model result changes.
Prospective study	Sometimes called a prospective cohort study, a prospective study selects participants before they develop the outcome in question and observes them over time. A prospective study differs from a retrospective study, whose participants already have the outcome in question.

Quality-adjusted life-year (QALY)	A measurement that takes into account both the number of years gained by a patient from a procedure and the quality of those extra years (ability to function, freedom from pain, etc.). The QALY is commonly used as an outcome measure in cost-utility analyses.
Randomized controlled trial	A type of study in which subjects are assigned randomly into different groups, with one group receiving the treatment under study and the other group(s) receiving a different treatment or a placebo (no treatment) to determine the effectiveness of one approach compared with the other.
Retrospective study	Sometimes called a historic cohort study, a retrospective study selects participants after they develop the outcome in question and looks back at their past. A retrospective study differs from a prospective study, whose participants do not already have the outcome in question.
Sensitivity	The ability of a test to accurately identify persons with the condition tested for (that is, how well it returns positive results in persons who have the condition).
Sensitivity analysis	Every evaluation contains some degree of uncertainty. Study results can vary depending on the values taken by key parameters. Sensitivity analysis is a method that allows estimates for each parameter to be varied to show the impact on study results. There are various types of sensitivity analyses. Examples include deterministic, probabilistic, and scenario.
Statistical significance	The outcome of an analysis is statistically significant if the assumption that there is no effect (the “null hypothesis”) is sufficiently unlikely to be true. Typically, the outcome is considered statistically significant if there is less than a 5% chance that the outcome would have occurred if the null hypothesis were true.
Systematic review	A process to answer a research question by methodically identifying and assessing all available studies that evaluate the specified research question. The systematic review process is designed to be transparent and objective and is aimed at reducing bias in determining the answers to research questions.
Time horizon	Costs and outcomes are examined within a chosen time frame. In an economic evaluation, this time frame is referred to as the time horizon.
Utility	The perceived value placed on a person’s health status.

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Literature Search Strategy

Databases: EBM Reviews—Cochrane Central Register of Controlled Trials <February 2016>, EBM Reviews—Cochrane Database of Systematic Reviews <2005 to April 20, 2016>, EBM Reviews—Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews—Health Technology Assessment <1st Quarter 2016>, Embase <1980 to 2016 Week 16>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

---

1 exp Prostatic Neoplasms/ (285933)
2 Prostate/ (73484)
3 exp Neoplasms/ (6390985)
4 2 and 3 (37311)
5 (prostat* adj3 (cancer* or carcinoma* or neoplas* or tumo?r* or adenoma* or adenocarcinoma* or malignan*)).tw. (270937)
6 Prostatectomy/ (68799)
7 prostatectom*.tw. (62136)
8 or/1,4-7 (366595)
9 Robotic Surgical Procedures/ (1551)
10 Robotics/ (44514)
11 (robot* or RALRP or RALP or RARP or da vinci* or davinci*).tw. (63095)
12 or/9-11 (72656)
13 8 and 12 (9296)
14 Case Reports/ or Comment.pt. or Editorial.pt. or Letter.pt. or Congresses.pt. (4563899)
15 13 not 14 (8529)
16 exp Animals/ not (exp Animals/ and Humans/) (13432616)
17 15 not 16 (5450)
18 limit 17 to english language [Limit not valid in CDSR,DARE; records were retained] (5131)
19 limit 18 to yr="2006 -Current" [Limit not valid in DARE; records were retained] (4801)
20 19 use pmoz,cctr,coch,dare,clhta,cleed (2111)
21 exp prostate tumor/ (178504)
22 prostate/ (73484)
23 exp neoplasm/ (6385702)
24 22 and 23 (37293)
25 (prostat* adj3 (cancer* or carcinoma* or neoplas* or tumo?r* or adenoma* or adenocarcinoma* or malignan*)).tw. (270937)
26 prostatectomy/ (68799)
27 prostatectom*.tw. (62136)
28 or/21,24-27 (352528)
29 robot assisted surgery/ (1552)
30 robotics/ (44514)
31 (robot* or RALRP or RALP or RARP or da vinci* or davinci*).tw. (63095)
32 or/29-31 (72727)
33 28 and 32 (9233)
34 (exp animal/ or nonhuman/) not exp human/ (9718093)
35 33 not 34 (9194)

36 Case Report/ or Comment/ or Editorial/ or Letter/ or conference abstract.pt. (8496106)
37 35 not 36 (5204)
38 limit 37 to english language [Limit not valid in CDSR,DARE; records were retained] (4798)
39 limit 38 to yr="2006 -Current" [Limit not valid in DARE; records were retained] (4496)
40 39 use emez (2442)
41 20 or 40 (4553)
42 remove duplicates from 41 (2777)
43 41 use emez (2442)
44 41 use pmoz (1940)
45 41 use cctr (122)
46 41 use coch (7)
47 41 use dare (12)
48 41 use clhta (18)
49 41 use cleed (12)

Economic Literature Search Strategy

Databases: EBM Reviews—Cochrane Central Register of Controlled Trials <March 2016>, EBM Reviews—Cochrane Database of Systematic Reviews <2005 to April 20, 2016>, EBM Reviews—Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews—Health Technology Assessment <1st Quarter 2016>, EBM Reviews—NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2016 Week 16>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy:
---
1 exp Prostatic Neoplasms/ (285942)
2 Prostate/ (73489)
3 exp Neoplasms/ (6391232)
4 2 and 3 (37312)
5 (prostat* adj3 (cancer* or carcinoma* or neoplas* or tumo?r* or adenoma* or adenocarcinoma* or malignan*)).tw. (270988)
6 Prostatectomy/ (68800)
7 prostatectom*.tw. (62143)
8 or/1,4-7 (366647)
9 Robotic Surgical Procedures/ (1551)
10 Robotics/ (44516)
11 (robot* or RALRP or RALP or RARP or da vinci* or davinci*).tw. (63126)
12 or/9-11 (72687)
13 8 and 12 (9298)
14 economics/ (249292)
15 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (724001)
16 economics.fs. (375375)
17 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (670652)
18 exp "costs and cost analysis"/ (502959)
19 cost*.ti. (229501)
20 cost effective*.tw. (243277)
21 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (152210)

22 models, economic/ (131795)
23 markov chains/ or monte carlo method/ (117503)
24 (decision adj1 (tree* or analy* or model*)).tw. (32886)
25 (markov or markow or monte carlo).tw. (97100)
26 quality-adjusted life years/ (25825)
27 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (49079)
28 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (95126)
29 or/14-28 (2235309)
30 13 and 29 (929)
31 Case Reports/ or Comment.pt. or Editorial.pt. or Letter.pt. or Congresses.pt. (4564377)
32 30 not 31 (849)
33 32 use pmoz,cctr,coch,dare,clhta (230)
34 13 use cleed (13)
35 33 or 34 (243)
36 limit 35 to english language [Limit not valid in CDSR,DARE; records were retained] (214)
37 limit 36 to yr="2006 -Current" [Limit not valid in DARE; records were retained] (205)
38 exp prostate tumor/ (178504)
39 prostate/ (73489)
40 exp neoplasm/ (6385949)
41 39 and 40 (37294)
42 (prostat* adj3 (cancer* or carcinoma* or neoplas* or tumo?r* or adenoma* or adenocarcinoma* or malignan*)).tw. (270988)
43 prostatectomy/ (68800)
44 prostatectom*.tw. (62143)
45 or/38,41-44 (352580)
46 robot assisted surgery/ (1552)
47 robotics/ (44516)
48 (robot* or RALRP or RALP or RARP or da vinci* or davinci*).tw. (63126)
49 or/46-48 (72758)
50 45 and 49 (9235)
51 Economics/ (249292)
52 Health Economics/ or exp Pharmacoeconomics/ (212687)
53 Economic Aspect/ or exp Economic Evaluation/ (388945)
54 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (670652)
55 exp "Cost"/ (502959)
56 cost*.ti. (229501)
57 cost effective*.tw. (243277)
58 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (152210)
59 Monte Carlo Method/ (49678)
60 (decision adj1 (tree* or analy* or model*)).tw. (32886)
61 (markov or markow or monte carlo).tw. (97100)
62 Quality-Adjusted Life Years/ (25825)
63 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (49079)
64 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (95126)
65 or/51-64 (1834609)
66 50 and 65 (781)
67 Case Report/ or Comment/ or Editorial/ or Letter/ or conference abstract.pt. (8496580)

68 66 not 67 (585)
69 68 use emez (372)
70 limit 69 to english language [Limit not valid in CDSR,DARE; records were retained] (336)
71 limit 70 to yr="2006 -Current" [Limit not valid in DARE; records were retained] (310)
72 37 or 71 (515)
73 72 use emez (310)
74 72 use pmoz (164)
75 72 use cctr (7)
76 72 use coch (7)
77 72 use dare (3)
78 72 use clhta (12)
79 72 use cleed (12)
80 remove duplicates from 72 (369)

Appendix 2: Evidence Quality Assessment

Table A1: Risk of Bias[a] Among Randomized Controlled Trials (Cochrane Risk of Bias Tool)

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Incomplete Outcome Data	Selective Reporting	Other Bias
Robot-assisted vs. open radical prostatectomy						
Yaxley et al, 2016[27]	Low	Low	Low[b]	Low	Low	High[c,d]
Robot-assisted radical vs. laparoscopic radical prostatectomy						
Asimakopoulos et al, 2011[31]	Low	Unclear	Low[b]	Low	Low	High[d]
Porpiglia et al, 2013[30]	Low	Unclear	Low[b]	Low	Low	High[d]

[a]Possible risk of bias levels: low, high, and unclear.
[b]Not possible to blind patients and surgeons because of the nature of the surgical intervention.
[c]Only interim 12-week results, from an anticipated 2-year study. However, interim 3-month results were preplanned. Ended recruitment after nonsignificant differences between groups at 3 months.
[d]No intention-to-treat analysis; per-protocol analysis.

Table A2: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool)

Author, Year	Pre-intervention		At Intervention	Postintervention			
	Confounding	Study Participant Selection	Classification of Interventions	Deviations From Intended Intervention	Missing Data	Measurement of Outcomes	Selection of Reported Results
Robot-assisted vs. open radical prostatectomy							
Ball et al, 2006[34]	Serious[b,c]	Low	Low	Low	Low	Moderate[g,h,i]	Low
Bier et al, 2016[35]	Serious[b,c]	Low	Low	Low	Low	Moderate[g,h,i]	Low
Breyer et al, 2010[36]	Serious[c]	Moderate[d]	Low	Low	Low	Moderate[g,h,i]	Low
Carlsson et al, 2010[37]	Serious[b,c]	Moderate[d]	Low	Low	Low	Low	Low
Davison et al, 2014[21]	Serious[c]	Moderate[d]	Low	Low	Low	Low	Low
Di Pierro et al, 2011[38]	Serious[c]	Low	Low	Low	Low	Low	Low
Doumerc et al, 2010[39]	Serious[b,c]	Moderate[d]	Low	Low	Low	Moderate[g,h,i]	Low
Farnham et al, 2006[40]	Serious[b,c]	Moderate[d]	Low	Low	Low	Serious	Low
Ficarra et al, 2009[41]	Serious[c]	Low	Low	Low	Low	Moderate[g,h,i]	Low
Fode et al, 2014[42]	Serious[c]	Low	Low	Low	Moderate[e]	Low	Moderate[j]
Fracalanza et al, 2008[43]	Serious[b,c]	Moderate[d]	Low	Low	Low	Moderate[g,h,i]	Low
Geraerts et al, 2013[32]	Serious[c]	Moderate[d]	Low	Low	Moderate[e]	Low	Low
Haglind et al, 2015[44]	Serious[c]	Moderate[d]	Low	Low	Moderate[e]	Moderate[f,g,h,i]	Low
Ham et al, 2008[45]	Serious[b,c]	Moderate[d]	Low	Low	Low	Moderate[g,h,i]	Low
Hong et al, 2010[46]	Serious[b,c]	Moderate[d]	Low	Low	Low	Low	Low
Kim et al, 2011[47]	Serious[c]	Moderate[d]	Low	Low	Low	Low	Low
Kordan et al, 2010[48]	Serious[b,c]	Moderate[d]	Low	Low	Low	Moderate[f,g,h,i]	Low
Lott et al, 2015[50]	Serious[b,c]	Low	Low	Low	Moderate[e]	Low	Low
Ludovico et al, 2013[51]	Serious[b,c]	Moderate[d]	Low	Low	Moderate[e]	Moderate[g,h,i]	Moderate[j]
Miller et al, 2007[52]	Serious[b,c]	Low	Low	Low	Low	Moderate[g,h]	Low
Nelson et al, 2007[53]	Serious[b,c]	Moderate[d]	Low	Low	Low	Serious	Low
O'Malley et al, 2006[54]	Serious[b,c]	Moderate[d]	Low	Low	Low	Moderate[g,h]	Low

Author, Year	Pre-intervention		At Intervention	Postintervention			
	Confounding	Study Participant Selection	Classification of Interventions	Deviations From Intended Intervention	Missing Data	Measurement of Outcomes	Selection of Reported Results
Philippou et al, 2012[55]	Serious[b,c]	Low	Low	Low	Moderate[e]	Moderate[g,h,i]	Low
Thompson et al, 2013[56]	Serious[c]	Low	Low	Low	Low	Low	Low
Wallerstedt et al, 2015[33]	Serious[c]	Low	Low	Low	Moderate[e]	Moderate[g,h,i]	Low
Wood et al, 2007[57]	Serious[b,c]	Moderate[d]	Low	Low	Low	Moderate[g,h,i]	Low
Robot-assisted vs. laparoscopic radical prostatectomy							
Asimakopoulos et al, 2013[58]	Serious[b,c]	Low	Low	Low	Moderate[e]	Moderate[g,h,i]	Low
Berge et al, 2013[59]	Serious[c]	Low	Low	Low	Low	Moderate[g,h,i]	Low
Ploussard et al, 2009[60]	Serious[b,c]	Low	Low	Low	Low	Moderate[g,h,i]	Low
Ploussard et al, 2014[61]	Serious[b,c]	Low	Low	Low	Moderate[e]	Moderate[g,h,i]	Low
Willis et al, 2012[62]	Serious[c]	Low	Low	Low	Moderate[e]	Moderate[g,h,i]	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.
[a]Possible risk of bias levels: low, moderate, serious, critical, and no information.
[b]Lack of adjustment for differences in baseline patient or tumour characteristics between groups.
[c]No specific patient inclusion and exclusion criteria; unclear patient selection process (e.g., not stated whether patients were consecutive).
[d]Unclear role of physician or patient in deciding treatment group allocation.
[e]Potential differences in dropout rates or characteristics between groups.
[f]Differences in surgeon experiences owing to multiple surgeons performing a type of radical prostatectomy.
[g]Lack of validated measurements for sexual outcomes.
[h]Lack of validated measurements for continence outcomes.
[i]Biochemical recurrence or positive surgical margin as surrogate outcome for more patient-important outcome of cancer survival or mortality.
[j]Some outcomes specified in the analysis were not reported.

Our first consideration was study design; we started with the assumption that randomized controlled trials (RCTs) are high quality whereas observational studies are low quality. We then took into account five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias. Limitations in these areas resulted in downgrading the quality of evidence. Finally, we considered three main factors that may raise the quality of evidence: the large magnitude of effect, the dose-response gradient, and any residual confounding factors.[26] For more detailed information, please refer to the latest series of GRADE articles.[26]

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	We are very confident that the true prognosis (probability of future events) lies close to that of the estimate
Moderate	We are moderately confident that the true prognosis (probability of future events) is likely to be close to the estimate, but there is a possibility that it is substantially different
Low	Our confidence in the estimate is limited: the true prognosis (probability of future events) may be substantially different from the estimate
Very Low	We have very little confidence in the estimate: the true prognosis (probability of future events) is likely to be substantially different from the estimate

Table A3: GRADE Evidence Profile for Comparison of Robot-Assisted Versus Open Radical Prostatectomy

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Operative time							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
12 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Length of hospital stay							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
11 non-RCTs	Serious limitations (−1)[a]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Estimated blood loss							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	Large magnitude of effect (+1)	⊕⊕⊕ Moderate
16 non-RCTs	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	Large magnitude of effect (+1)	⊕ Low
Transfusion rates							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
11 non-RCTs	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Indwelling catheterization duration							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
7 non-RCTs	Serious limitations (−1)[a]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Hospital readmission rates							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
2 non-RCTs	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Complication rates							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
14 non-RCTs	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Urinary function							
1 RCT	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
12 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Erectile function							
1 RCT	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
11 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[e]	Undetected	None	⊕ Very low
Health-related quality of life							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
1 non-RCT	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Pain							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
2 non-RCTs	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Time to mobilization or return to work or activity							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
3 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Positive surgical margin rates							
1 RCT	No serious limitations	No serious limitations	Serious limitations (−1)[f]	Serious limitations (−1)[d]	Undetected	None	⊕⊕ Low
15 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Serious limitations (−1)[f]	Serious limitations (−1)[d]	Undetected	None	⊕ Very Low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Biochemical recurrence-free rates							
3 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Serious limitations (−1)[f]	Serious limitations (−1)[d]	Undetected	None	⨁ Very Low

Abbreviations: RCT, randomized controlled trial.

[a]Other than 1 RCT (where interim 3-month data are available), the rest of the evidence is limited to prospective comparative nonrandomized studies with methodological limitations. Follow-up period was limited in most studies. Observational studies start at low quality according to GRADE. Differences in baseline patient characteristics may impact results.

[b]Inconsistencies within results.

[c]Outcomes are related to hospital procedures and follow-up care.

[d]Not powered to detect differences between groups.

[e]Use of subjective, nonvalidated, or nonstandardized measurements for some outcomes.

[f]Surrogate outcomes for cancer control. Other factors such as patient characteristics and risk stratification may also impact cancer control.

Table A4: GRADE Evidence Profile for Comparison of Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Operative time							
2 RCTs	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
4 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Length of hospital stay							
2 RCTs	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
2 non-RCTs	Serious limitations (−1)[a]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Estimated blood loss							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
3 non-RCTs	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Transfusion rates							
1 RCT	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
3 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Indwelling catheterization duration							
2 RCTs	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
1 non-RCT	Serious limitations (−1)[a]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Complication rates							
2 RCTs	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕⊕⊕ Moderate
3 non-RCTs	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Urinary function							
2 RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
4 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[e]	Undetected	None	⊕ Very low
Erectile function							
2 RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
4 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[e]	Undetected	None	⊕ Very low
Health-related quality of life							
1 non-RCT	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Positive surgical margin rates							
2 RCTs	No serious limitations	No serious limitations	Serious limitations (−1)[f]	Serious limitations (−1)[d]	Undetected	None	⊕⊕ Low
4 non-RCTs	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Serious limitations (−1)[f]	Serious limitations (−1)[d]	Undetected	None	⊕ Very low
Biochemical recurrence-free rates							
2 RCTs	No serious limitations	No serious limitations	Serious limitations (−1)[f]	Serious limitations (−1)[d]	Undetected	None	⊕⊕ Low
2 non-RCTs	Serious limitations (−1)[a]	No serious limitations	Serious limitations (−1)[f]	Serious limitations (−1)[d]	Undetected	None	⊕ Very low

Abbreviations: RCT, randomized controlled trial.

[a]Prospective comparative nonrandomized (observational) studies with methodological limitations. Observational studies start at low quality according to GRADE. Differences in baseline patient characteristics may impact results. Follow-up period was limited in most studies.

[b]Inconsistencies within results.

[c]Outcomes are related to hospital procedures and follow-up care.

[d]Not powered to detect differences between groups.

[e]Use of subjective, nonvalidated, or nonstandardized measurements for some outcomes.

[f]Surrogate outcomes for cancer control. Other factors such as patient characteristics and risk stratification may also impact cancer control.

Appendix 3: Results of Clinical Evidence Review: Robot-Assisted Versus Open Radical Prostatectomy

Table A5: Operative Time Outcomes for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Measure	Time, Minutes ± SD[a]		*P* Value
		Robot-Assisted Surgery	Open Surgery	
Randomized controlled trial				
Yaxley et al, 2016[27]	Mean	246 ± 55	280 ± 36	< .001
Nonrandomized studies				
Wood et al, 2007[57]	Mean	210 ± 41	163 ± 29	< .001
Fracalanza et al, 2008[43]	Mean	196 ± 45	127 ± 32	< .001
Doumerc et al, 2010[39]	Mean	192 ± 52	148 ± 39	< .001
Hong et al, 2010[46]	Mean	167 ± 5	169 ± 7	Not significant
Di Pierro et al, 2011[38]	Mean	330 ± 54	253 ± 41	.020
Philippou et al, 2012[55]	Mean	125 ± 30	212 ± 71	< .001
Ficarra et al, 2009[41]	Median	185	135	< .001
Lott et al, 2015[50]	Median	272 (IQR 140–570)	153 (IQR 110–260)	.01
Ludovico et al, 2013[51]	Median	221	103	< .001
Haglind et al, 2015[44]	Median	236 (IQR 210–270)	126 (IQR 102–186)	< .001
Bier et al, 2016[35]	Median	252 (range 131–428)	186 (range 104–294)	< .001
Wallerstedt et al, 2015[33]	Mean	175 (range 45–575)	103 (range 40–428)	< .001

Abbreviation: IQR, interquartile range; SD, standard deviation.
[a]Where provided.

Table A6: Length of Hospital Stay Outcomes for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Measure	Length of Stay, Days ± SD[a]		*P* Value
		Robot-Assisted Surgery	Open Surgery	
Randomized controlled trial				
Yaxley et al, 2016[27]	Mean	1.6 ± 2.6	3.3 ± 1.5	< . 001
Nonrandomized studies				
Wood et al, 2007[57]	Mean	1.2 ± 0.8	1.3 ± 1.0	.048
Ham et al, 2008[45]	Mean	3.9 ± 0.7	7.6 ± 1.3	< .001
Doumerc et al, 2010[39]	Mean	2.8 ± 2.4	5.5 ± 2.7	< .001
Philippou et al, 2012[55]	Mean	1.3 (range 1–3)	3.8 (range 2–7)	< .001
Wallerstedt et al, 2015[33]	Mean	3.3 (range 2–53)	4.1 (range 1–17)	< .001
Nelson et al, 2007[53]	Median	1.0	1.1	.27
Fracalanza et al, 2008[43]	Median	5 (range 5–6)	8 (range 5–9)	.002
Ficarra et al, 2009[41]	Median	6 (range 5–8)	7 (range 6–9)	.01
Ludovico et al, 2013[51]	Median	4	8	< .001
Lott et al, 2015[50]	Median	2.6 (range 1–21)	2.6 (range 1–21)	.01
Haglind et al, 2015[44]	Median	3 (2–4)	4 (3–5)	< .001

Abbreviation: SD, standard deviation.
[a]Where provided.

Table A7: Estimated Blood Loss Outcomes for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Measure	Estimated Blood Loss, mL ± SD[a]		*P* Value
		Robot-Assisted Surgery	Open Surgery	
Randomized controlled trial				
Yaxley et al, 2016[27]	Mean	444 ± 294	1,338 ± 591	< .001
Nonrandomized studies				
Farnham et al, 2006[40]	Mean	191 ± 149	664 ± 418	< .001
Wood et al, 2007[57]	Mean	151 ± 97	707 ± 445	< .001
Ham et al, 2008[45]	Mean	382 ± 213	897 ± 270	< .001
Ficarra et al, 2009[41]	Mean	300 ± 234	500 ± 315	< .001
Hong et al, 2010[46]	Mean	457 ± 281	1410 ± 901	< .05
Philippou et al, 2012[55]	Mean	132 ± 151	513 ± 343	< .001
Bier et al, 2016[35]	Median	400 (range 100–1,300)	700 (range 234–1,600)	< .001
Doumerc et al, 2010[39]	—	Blood loss < 499: 349/502 (69.7%) Blood loss 500–999: 147/502 (29.1%) Blood loss > 1,000: 6/502 (1.2%)	Blood loss < 499: 208/212 (98.4%) Blood loss 500–999: 4/212 (1.6%) Blood loss > 1,000: 0/212 (0%)	< .001 < .001 .25
Fode et al, 2014[42]	Median	150 (range 5–1,500)	600 (range 50–4,320)	< .001
Fracalanza et al, 2008[43]	Median	300 (range 200–400)	500 (range 250–650)	< .02
Kordan et al, 2010[48]	Median	100 (range 50–200)	450 (range 300–600)	< .001
Lott et al, 2015[50]	Median	212 (range 50–1,200)	487 (range 150–1,250)	.01
Ludovico et al, 2013[51]	Not specified	280	565	< .001
Miller et al, 2007[52]	—	Blood loss > 500: not reported	Blood loss > 500: not reported	< .001
Haglind et al, 2015[44]	Mean	100 (range 50–200)	550 (range 350–800)	< .001
Wallerstedt et al, 2015[33]	Mean	185 (range 0–5,200)	683 (range 50–8,000)	< .001

Abbreviation: SD, standard deviation.
[a]Where provided.

Table A8: Indwelling Catheterization Duration for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Outcome	Robot-Assisted Surgery	Open Surgery	*P* Value
Randomized controlled trials				
Yaxley et al, 2016[27]	Mean duration, days ± SDs	8.2 ± 3.6	8.4 ± 3.3	.59
Nonrandomized studies				
Ham et al, 2008[45]	Mean duration, days ± SDs	7.3 ± 0.6	7.7 ± 0.7	< .001
Wood et al, 2007[57]	Median duration, days	10	10	Not reported
Ludovico et al, 2013[51]	Median duration, days	3	7	< .001
Doumerc et al, 2010[39]	Median duration, days	6.3 (range 6–21)	7.9 (range 6–20)	< .001
	Prolonged catheterization	4%	12%	Not reported
Ficarra et al, 2009[41]	Median duration, days	5 (range 4–7)	6 (range 5–12)	< .001
Geraerts et al, 2013[32]	Median duration, days	11	12	Not reported
Di Pierro et al, 2011[38]	Catheter-free rate at postoperative day 10	71/75 patients (95%)	66/75 patients (88%)	Not reported
	Catheter-free rate at postoperative day 15	71/75 patients (95%)	75/75 patients (100%)	Not reported
	Prolonged catheterization (> 10 days after surgery)	4/75 patients (5%)	9/75 patients (12%)	.056

Abbreviation: SD, standard deviation.

Table A9: Rates of Hospital Readmission for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Outcome	Robot-Assisted Surgery, n (%)	Open Surgery, n (%)	*P* Value
Randomized controlled trial				
Yaxley et al, 2016[27]	Readmission at 3 months	8 (5)	12 (8)	.32
Nonrandomized studies				
Nelson et al, 2007[53]	Readmission	45/629 (7)	18/374 (5)	.12
	Unscheduled clinical and emergency room visits	63/629 (10)	37/374 (10)	.95
Wallerstedt et al, 2015[33]	Readmission at 3 months	163 (9.3)	57 (7.7)	Not significant
	Readmission leading to reoperation	29 (1.6)	13 (1.7)	Not significant
	Readmission not leading to reoperation	116 (6.3)	36 (4.6)	Not significant

Table A10: Complication Rates for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Adverse Event/ Complication	Rates of Complications, n (%)[a]		*P* Value
		Robot-Assisted Surgery	Open Surgery	
Randomized controlled trial				
Yaxley et al, 2016[27]	**Total complications**	**4/157 (2.5)**	**6/157 (3.8)**	**.052**
Nonrandomized studies				
Carlsson et al, 2010[37]	Bladder neck contracture	3/1,253 (0.2)	22/485 (4.5)	< .001
	Surgery for urinary incontinence	7/1,253 (0.5)	11/485 (2.2)	< .001
	Death	0	1/485 (0.2)	NS
	Rectal injury—perioperative	1/1,253 (0.1)	7/485 (1.4)	< .05
	Rectal injury—postoperative	1/1,253 (0.1)	1/485 (0.2)	NS
	Small bowel injury	1/1,253 (0.1)	0	NS
	Ureteral injury	1/1,253 (0.08)	0	NS
	Femoral nerve injury	2/1,253 (0.1)	0	NS
	Obturator nerve injury	0	2/485 (0.4)	NS
	Pulmonary embolism	2/1,253 (0.1)	5/485 (1.0)	< .001
	Myocardial infarction	1/1,253 (0.07)	2/485 (0.4)	NS
	Pneumonia	0	4/485 (0.8)	< .001
	Infected lymphocele	1/1,253 (0.08)	3/485 (0.6)	NS
	Wound infection	6/1,253 (0.4)	29/485 (5.9)	< .05
	Anastomotic leakage (grade IIIa)	8/1,253 (0.6)	3/485 (0.6)	NS
	Anastomotic leakage (grade IIIb)	5/1,253 (0.3)	5/485 (1.0)	NS
	Surgical reintervention	24/1,253 (1.9)	14/485 (2.8)	NS
	Total complications	**197/1,253 (15.7)**	**159/485 (32.8)**	**NR**
Ficarra et al, 2009[41]	Colon lesion	1/103 (1.0)	0	NR
	Rectal lesion	1/103 (1.0)	0	NR
	Paralytic ileus	1/103 (1.0)	1/105 (1.0)	NR
	Cardiovascular complications	0	2/105 (2.0)	NR
	Wound dehiscence	0	1/105 (1.0)	NR
	Urethrovesical anastomotic stenosis	3/103 (2.9)	6/105 (5.7)	.32
	Total complications	**10/103 (9.7)**	**11/105 (10.5)**	**.85**

Author, Year	Adverse Event/ Complication	Rates of Complications, n (%)[a]		*P* Value
		Robot-Assisted Surgery	Open Surgery	
Di Pierro et al, 2011[38]	Clavien grade—minor	26/31 (83.9)	18/39 (46.1)	.005
	Clavien grade—1	20/31 (64.5)	13/39 (33.3)	NR
	Clavien grade—2	6/31 (19.4)	5/39 (12.8)	NR
	Clavien grade—major	5/31 (16.1)	21/39 (53.8)	.02
	Clavien grade—3a	3/31 (9.7)	15/39 (38.5)	NR
	Clavien grade—3b	2/31 (6.5)	6/39 (15.4)	NR
	Clavien grade—4a, 4b, 5	0	0	NR
	Total complications	**28/75 (37.3)**	**30/75 (40.0)**	
Doumerc et al, 2010[39]	Dindo—major (IIIa–V)	4/212 (1.9)	4/502 (0.8)	.38
Geraerts et al, 2013[32]	Additional radiotherapy	8/64 (12.5)	15/116 (12.9)	NR
	Conversion to open	5/64 (7.8)	—	—
Ham et al, 2008[45]	Conversion to open	1/188 (0.5) (because of system malfunction)	—	—
	Major—rectal injury	1/188 (0.5)	1/110 (1.0)	NR
	Major—infected hematoma	0	0	NR
	Minor—retention	0	0	NR
	Minor—anastomotic leakage	0	2/110 (1.8)	NR
	Minor—lymphocele	3/188 (1.6)	3/110 (2.7)	NR
	Minor—ileus	0	2/110 (1.8)	NR
	Total complications	**4/188 (2.1)**	**8/110 (7.3)**	**< .001**
Lott et al, 2015[50]	Clavien (grades I–IV)	9/50 (18.0)	8/34 (23.5)	< .001
Nelson et al, 2007[53]	Caused unscheduled visit or hospital readmission:			
	Post-catheter retention	2/629 (0.3)	4/374 (1.1)	NR
	Lymphocele	2/629 (0.3)	1/374 (0.3)	NR
	Wound infection	2/629 (0.3)	5/374 (1.4)	NR
	DVT/pulmonary embolism	3/629 (0.5)	0	NR
	DVT	0	4/374 (1.1)	NR
	Urinary tract infection	5/629 (0.8)	4/374 (1.1)	NR
	Ileus	6/629 (1.0)	6/374 (1.6)	NR
	Epididymitis	6/629 (1.0)	0	NR
	Clot retention	9/629 (1.5)	4/374 (1.1)	NR
	Urinary leakage/urinoma	15/629 (2.4)	4/374 (1.1)	NR
	Caused hospital readmission:			
	Port hernia	1/629 (0.15)	0	NR
	Pulmonary embolism	1/629 (0.15)	0	NR
	Rectal injury	1/629 (0.15)	0	NR
	Postoperative hemorrhage	1/629 (0.15)	0	NR
	Clot retention	2/629 (0.3)	0	NR
	Urinary tract infection	3/629 (0.5)	0	NR
	Ileus	20/629 (3.2)	0	NR

Author, Year	Adverse Event/ Complication	Rates of Complications, n (%)[a]		*P* Value
		Robot-Assisted Surgery	Open Surgery	
	DVT	0	9/374 (2.5)	NR
	Lymphocele	0	4/374 (1.1)	NR
	Fever	0	1/374 (0.3)	NR
Philippou et al, 2012[55]	Conversion to ORP	0	—	—
	Clavien grades—minor (I + II)	5/50 (10.0)	9/50 (18.0)	.25
	Clavien grades—major (III + IV)	1/50 (2.0)	2/50 (4.0)	.88
	Total complications	**6/50 (12.0)**	**11/50 (22.0)**	**.18**
	Anastomotic strictures	2/50 (4.0)	4/50 (8.0)	.68
Fracalanza et al, 2008[43]	Fever > 38°C	2/37 (5.4)	4/26 (15.4)	.22
Hong et al, 2010[46]	**Total complications**	**3/37 (8.1)**	**7/26 (26.9)**	**NR**
	Intraoperative venous gas embolism	10/26 (38.5)	20/25 (80.0)	< .05
Ludovico et al, 2013[51]	Clavien grades—minor (I + II)	7/82 (8.5)	4/48 (8.3)	NR
	Clavien grades—major (III)	1/82 (1.2)	1/48 (2.1)	NR
	Total complications	**8/82 (9.8)**	**5/48 (10.4)**	**.01**
Wood et al, 2007[57]	**Total complications**	**25/117 (21.4)**	**37/89 (41.6)**	**.002**
Breyer et al, 2010[36]	Bladder neck contracture	4/293 (1.4)	18/695 (2.6)	.12

Abbreviations: DVT, deep vein thrombosis; NR, not reported; NS, not significant; ORP, open radical prostatectomy.
[a]Unless otherwise indicated.

Table A11: Urinary Function Outcomes for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Outcome Definition	Time	Robot-Assisted Surgery	Open Surgery	*P* Value
Randomized controlled trial					
Yaxley et al, 2016[27]	EPIC urinary domain score	3 months	83.8 (95% CI 81.3–86.2)	82.5 (95% CI 80–85)	.48
Nonrandomized studies					
Ball et al, 2006[34]	% baseline urinary function (UCLA-PCI)	3 months	58%	62%	NS
		6 months	69%	75%	NS
Ficarra et al, 2009[41]	Mean time to continence	—	25 ± 39 days	75 ± 116 days	< .001
Geraerts et al, 2013[32]	Mean time to continence	—	16 days	46 days	.026
Kim et al, 2011[47]	Median time to continence	—	3.7 months	4.3 months	.161
Ludovico et al, 2013[51]	Mean time to continence	—	4.1 ± 0.8 months	6.9 ± 1.4 months	< .001

Abbreviations: CI, confidence interval; EPIC, Expanded Prostate Cancer Index Composite; NS, not significant; UCLA-PCI, University of California–Los Angeles Prostate Cancer Index.

Table A12: Erectile Function Outcomes for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Outcome Definition	Time	Robot-Assisted Surgery	Open Surgery	*P* Value
Randomized controlled trial					
Yaxley et al, 2016[27]	EPIC sexual domain score	3 months	38.9 (95% CI 34.8–43.0)	35.0 (95% CI 30.9–39.1)	.18
	IIEF total score	3 months	30.1 (95% CI 26.5–30.8)	27.6 (95% CI 24.3–30.8)	.31
Nonrandomized studies					
Davison et al, 2014[21]	Adjusted EPIC sexual summary score (SD)	6 months	27.2 (17.2)	20.7 (17.3)	NS when adjusted
		12 months	32.6 (20.8)	25.4 (19.9)	
Ball et al, 2006[34]	Baseline sexual function (UCLA-PCI)	3 months	35%	24%	< .05
		6 months	43%	33%	NS
Lott et al, 2015[50]	IIEF-5	6 months	Median 13.1 (IQR 5–24)	Median 7.2 (IQR 5–21)	.01
		12 months	Median 15.0 (IQR 5–24)	Median 8.6 (IQR 5–19)	.01
Kim et al, 2011[47]	Erection sufficient for intercourse with or without PDE5 inhibitor	6 months	33.0%	6.7%	Significant when adjusted (OR 0.81, 95% CI 0.66–0.98)
		12 months	57.1%	28.1%	
		24 months	83.8%	47.5%	
	Median time to potency (months)	—	9.8	24.7	< .001
Ludovico et al 2013[51]	Mean IIEF score	12 months	17.0	17.2	.16
	Return to baseline IIEF with drugs (%)	12 months	19/82 (23.2)	9/48 (18.7)	NS
	Return to baseline IIEF without drugs (%)	12 months	3/82 (3.7)	3/48 (6.3)	NS

Abbreviations: CI, confidence interval; IIEF, International Index of Erectile Function Questionnaire; IQR, interquartile range; OR, odds ratio; NS, not significant; PDE5, phosphodiesterase-5; SD, standard deviation; UCLA-PCI, University of California–Los Angeles Prostate Cancer Index.

Table A13: Outcomes for Health-Related Quality of Life for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Assessment Method	Time	Robot-Assisted Surgery	Open Surgery	*P* Value
Randomized controlled trial					
Yaxley et al, 2016[27]	SF-36 Physical Function score (95% CI)	Baseline	59.77 (58.79–60.75)	59.29 (58.17–60.41)	.52
		6 weeks	53.70 (52.70–54.70)	51.96 (50.71–53.20)	.03
		12 weeks	59.57 (58.51–60.63)	59.39 (58.39–60.39)	.81
	SF-36 Mental Function score (95% CI)	Baseline	47.34 (45.61–49.07)	45.57 (43.71–47.43)	.17
		6 weeks	47.99 (46.19–49.79)	45.83 (43.72–47.94)	.13
		12 weeks	49.52 (47.82–51.21)	47.45 (45.49–49.41)	.97
	EPIC bowel domain score (95% CI)	Baseline	94.10 (92.74–95.41)	93.70 (92.23–95.21)	.72
		6 weeks	91.40 (89.66–93.14)	92.30 (90.82–93.82)	.43
		12 weeks	94.50 (93.32–95.64)	93.70 (91.80–95.54)	.46
	Revised Impact of Events Scale (RIES) score (95% CI)	Baseline	12.65 (10.52–14.79)	14.92 (12.52–17.33)	.16
		6 weeks	6.71 (5.19–8.23)	8.65 (6.52–10.79)	.15
		12 weeks	4.30 (2.91–5.69)	6.47 (4.65–8.29)	.06
	Hospital Anxiety and Depression Scale (HADS) score (95% CI)	Baseline	7.82 (6.76–8.87)	8.35 (7.25–9.46)	.49
		6 weeks	6. 16 (5.10–7.22)	6.85 (5.66–8.04)	.39
		12 weeks	5.26 (4.16–6.36)	7.03 (5.78–8.28)	.04
Nonrandomized study					
Miller et al, 2007[52]	SF-12 Physical Component Score ± SDs	Baseline	57.6 ± 2.4	56.9 ± 6.0	.67
		Week 1	34.7 ± 7.6	31.7 ± 6.6	.42
		Week 3	48.6 ± 3.9	42.1 ± 7.0	< .001
		Week 6	56.4 ± 1.7	52.8 ± 4.7	.003
	SF-12 Mental Component Score ± SDs	Baseline	49.8 ± 6.2	45.7 ± 9.8	.03
		Week 1	52.7 ± 8.5	54.6 ± 7.6	.03
		Week 3	55.5 ± 7.3	56.1 ± 5.8	.25
		Week 6	57.4 ± 4.3	58.0 ± 4.7	.30

Abbreviations: CI, confidence interval; SD, standard deviation; SF-12, 12-Item Short-Form Health Survey; SF-36, 36-Item Short-Form Health Survey.

Table A14: Pain Outcomes for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Assessment Method	Pain Outcome	Robot-Assisted Surgery	Open Surgery	*P* Value
Randomized controlled trial					
Yaxley et al, 2016[27]	Surgical Pain Scale (0–10) score (95% CI)	Pain at rest at 3 months	0.39 (0.21–0.58)	0.48 (0.29–0.66)	.54
		Pain during activities at 3 months	0.55 (0.33–0.77)	0.61 (0.38–0.83)	.70
		Worst pain at 3 months	0.49 (0.26–0.72)	0.48 (0.25–0.72)	.96
Nonrandomized controlled trial					
Wallerstedt et al, 2015[33]	Patients using analgesics (%)	Pain in the operation wound at 3 months	42 (2.4)	49 (6.6)	Not significant
		Pain in lower abdomen at 3 months	149 (8.4)	58 (7.8)	Not significant
		Pain in upper abdomen at 3 months	57 (3.2)	20 (2.7)	Not significant
Wood et al, 2007[57]	Michigan Urological Survey pain scale (0–10) score ± SDs	Overall mean discomfort at 2 weeks	2.8 ± 1.9	2.7 ± 1.9	.76
		Overall mean discomfort at 6 weeks	1.8 ± 1.8	1.4 ± 1.5	.15

Abbreviation: SD, standard deviation.

Table A15: Biochemical Recurrence-Free Rates for Robot-Assisted Versus Open Radical Prostatectomy

Author, Year	Definition	Time	Biochemical Recurrence-Free Rates		*P* Value
			Robot-Assisted Surgery	Open Surgery	
Di Pierro et al, 2011[38]	2 consecutive PSA ≥ 0.2 ng/mL	3 months	66/75 (88%)	68/75 (91%)	.71
		12 months	40/45 (89%)	65/75 (87%)	.36
Philippou et al, 2012[55]	2 consecutive PSA ≥ 0.2 ng/mL	12 months	92%	88%	.51
Breyer et al, 2010[36]	2 consecutive PSA ≥ 0.2 ng/mL	3 years	81%	87%	.02

Abbreviations: PSA, prostate-specific antigen.

Appendix 4: Results of Clinical Evidence Review: Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Table A16: Estimated Blood Loss for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Author, Year	Estimated Blood Loss, mL ± SD		*P* Value
	Robot-Assisted Surgery	Laparoscopic Surgery	
Randomized controlled trial			
Porpiglia et al, 2013[30]	202 ± 124	234 ± 150	.20
Nonrandomized studies			
Ploussard et al, 2009[60]	469 ± 380	889 ± 531	< .01
Willis et al, 2012[62]	148 ± 87	173 ± 95	.01
Berge et al, 2013[59]	190 ± 187	203 ± 226	.05

Abbreviation: SD, standard deviation.

Table A17: Complication Rates for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Author, Year	Complication	Complication Rates		*P* Value
		Robot-Assisted	Laparoscopic	
Randomized controlled trials				
Asimakopoulos et al, 2011[31]	Conversion to open	0	0	—
	Deaths	0	0	—
	Cardiac complications	0	0	—
	"Paravesical" hematoma	5/52 (10%)	5/60 (8%)	—
	Venous thromboembolism	1/52 (2%)	0	—
	Bronchitis	1/52 (2%)	0	—
	Epididymitis	1/52 (2%)	0	—
	Overall complication rate	**8/52 (15%)**	**5/60 (8%)**	**.24**
Porpiglia et al, 2013[30]	< 30-day Clavien 1–2 minor complications	9/60 (15%)	5/60 (8%)	—
	< 30-day Clavien 3–4 major complications	0	0	—
	31- to 90-day Clavien 1–2 minor complications	1/60 (2%)	2/60 (3%)	—
	31- to 90-day Clavien 1–2 major complications	0	0	—
	Overall complication rate	**10/60 (17%)**	**7/60 (12%)**	**.43**
Nonrandomized studies				
Asimakopoulos et al, 2013[58]	**Overall complication rate**	**15%**	**12%**	**.06**
Ploussard et al, 2009[60]	Urinary infection	2%	2%	—
	Urinary sepsis	0	1%	—
	Retention	0	2%	—
	Renal insufficiency	0	1%	—
	Pelvic hematoma	1%	2%	—
	Minor complications	4%	6%	—
	Postoperative bleeding	0	1%	—
	Anastomotic leakage	0	2%	—
	Rectal injury	0	1%	—
	Overall complication rate	**4%**	**8%**	**.16**
Ploussard et al, 2014[61]	Anastomotic leakage	2%	10%	< .001
	Anastomotic stenosis	1%	2%	.08
	Overall complication rate	**5%**	**4%**	**.80**

Table A18: Urinary Function Outcomes for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Author, Year	Assessment Method	Outcome Definition	Time	Robot-Assisted Surgery	Laparoscopic Surgery	*P* Value
Randomized controlled trials						
Asimakopoulos et al, 2011[31]	Telephone interview	No leakage/need of any protective pad	3 months	69%	63%	.51
			6 months	88%	75%	.06
			12 months	94%	83%	.07
	—	Time to continence	—	2.6 ± 4.2 months	3.0 ± 2.9 months	.27
Porpiglia et al, 2013[30]	Telephone interview	0 or 1 pad/day	3 months	48/60 (80%)	37/60 (62%)	.03
			6 months	53/60 (88%)	44/60 (73%)	.04
Nonrandomized studies						
Berge et al, 2013[59]	Mailed questionnaire	UCLA-PCI urinary function score	Baseline	94.1 ± 11.0	92.4 ± 13.4	—
			3 months	62.1 ± 26.2	60.2 ± 27.2	.9
			12 months	77.4 ± 22.4	78.5 ± 23.4	.2
			36 months	77.0 ± 23.2	80.4 ± 22.7	.06
Asimakopoulos et al, 2013[58]	Telephone interview	No leakage/need for any protective pad	12 months	123 (90%)	74 (81%)	.05
Ploussard et al, 2014[61]	Mailed questionnaire	No pad usage	3 months	50%	39%	.02
			12 months	75%	69%	.18
			24 months	84%	79%	.02
Willis et al, 2012[62]	Questionnaire	0 or 1 pad/day	Baseline	100%	100%	—
			3 months	76%	72%	.46
			6 months	87%	89%	.67
			12 months	93%	93%	.99
	Questionnaire	EPIC urinary summary score	Baseline	90.3 ± 1.4	89.8 ± 11.7	—
			3 months	76.6 ± 15.3	76.5 ± 14.4	.96
			6 months	82.7 ± 14.9	83.4 ± 13.3	.70
			12 months	83.5 ± 16.1	85.6 ± 13.4	.25

Abbreviations: EPIC, Expanded Prostate Cancer Index Composite; UCLA-PCI, University of California–Los Angeles Prostate Cancer Index.

Table A19: Erectile Function Outcomes for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Author, Year	Assessment Method	Outcome Definition	Time	Robot-Assisted Surgery	Laparoscopic Surgery	*P* Value
Randomized controlled trials						
Porpiglia et al, 2013[30]	Questionnaire	IIEF-5 score > 17	3 months	60%	40%	.09
			6 months	66%	49%	.14
			12 months	80%	54%	.02
Asimakopoulos et al, 2011[31]	Telephone interview	Erection firm enough for intercourse	3 months	63%	13%	< .001
			6 months	75%	22%	< .001
			12 months	77%	32%	< .001
	—	Time to potency	—	2.4 ± 2.3 days	6.3 ± 5.2 days	< .001
Nonrandomized studies						
Asimakopoulos et al, 2013[58]	Telephone interview	Erection firm enough for intercourse	12 months	66%	40%	< .001
Berge et al, 2013[59]	Mailed questionnaire	UCLA-PCI sexual function score	Baseline[a]	76.0 ± 15.7	75.3 ± 13.0	—
			3 months[a]	27.7 ± 16.8	24.8 ± 19.1	.3
			12 months[a]	34.1 ± 21.9	35.2 ± 23.2	.4
			36 months[a]	46.6 ± 28.6	43.2 ± 25.8	.5
Ploussard et al, 2014[61]	Questionnaire	Erection firm enough for intercourse	3 months	35%	16%	.001
			6 months	42%	20%	< .001
			12 months	58%	32%	< .001
			24 months	69%	55%	< .001
	Questionnaire	IIEF-5 score	Baseline	17.7	17.6	.85
			3 months	8.8	6.1	< .001
			6 months	10.6	7.0	< .001
			12 months	11.5	8.2	< .001
			24 months	13.5	8.1	< .001
Willis et al, 2012[62]	Mailed questionnaire	Erection firm enough for intercourse	3 months	105/121 (87%)	142/161 (88%)	.72
			6 months	77/110 (70%)	122/161 (76%)	.29
			12 months	44/74 (60%)	120/161 (75%)	.02
	Mailed questionnaire	EPIC sexual summary score	Baseline	77.1 ± 14.7	76.6 ± 15.5	—
			3 months	47.2 ± 23.9	31.6 ± 23.8	< .001
			6 months	54.9 ± 22.1	38.6 ± 24.3	< .001
			12 months	54.5 ± 17.9	50.4 ± 23.5	.33

Abbreviations: EPIC, Expanded Prostate Cancer Index Composite; IIEF, International Index of Erectile Function Questionnaire; UCLA-PCI, University of California–Los Angeles Prostate Cancer Index.
[a]In patients with preoperative erectile function sufficient for intercourse and who received nerve-sparing surgery.

Table A20: Biochemical Recurrence-Free Rates for Robot-Assisted Versus Laparoscopic Radical Prostatectomy

Author, Year	Outcome Definition	Time	Robot-Assisted Surgery (%)	Laparoscopic Surgery (%)	*P* Value
Randomized controlled trials					
Asimakopoulos et al, 2011[31]	PSA level > 0.2 ng/mL on 2 consecutive measurements	12 months	92	97	.3
Porpiglia et al, 2013[30]	PSA level > 0.2 ng/mL	12 months	98	93	.19
Nonrandomized studies					
Asimakopoulos et al, 2013[58]	PSA level > 0.2 ng/mL on 2 consecutive measurements	Variable	96	100	.08
Ploussard et al, 2009[60]	PSA level > 0.2 ng/mL	Variable	90	82	.82

Abbreviation: PSA, prostate-specific antigen.

Appendix 5: Health Technology Assessments and Systematic Reviews on Robot-Assisted Versus Open or Laparoscopic Radical Prostatectomy from 2011 to 2016

Table A21: Summary of Recent Health Technology Assessments and Systematic Reviews on Robot-Assisted Versus Open or Laparoscopic Radical Prostatectomy

Author, Year	Search Period and Databases	Included Studies	Comparison	Primary Conclusions
Duffey et al, 2011[144]	?–Nov 2010 (Medline)	21 non-RCTs	Open	Robot-assisted: lower blood loss, transfusion rate, length of stay; no definitive conclusions for functional and oncological outcomes
Ferronha et al, 2011[145]	2000–Oct 2009 (PubMed, Medline)	37 studies	Open, laparoscopic	Robot-assisted and laparoscopic: lower blood loss, transfusion rate No difference in PSM rate, continence, and potency between 3 groups
Health Information and Quality Authority, 2011[146]	1950–Mar 2011 (Medline, Embase, EBSCO, CINAHL, Cochrane, DARE, HTA database, Journal of Robotic Surgery)	50 studies (1 RCT, 49 non-RCTs)	Open, laparoscopic	Robot-assisted vs. open: decreased PSM rate for pT2 cancer, improved functional outcomes (urinary continence and sexual function), reduced transfusion rate and length of stay; increased operative time Robot-assisted vs. laparoscopic: no significant differences for operative time, transfusion rate, conversion to open, sexual function, oncologic outcomes; marginal improvements in urinary continence, small reductions in length of stay
Ho et al, 2011[111]	1950–Oct 2009 (Medline, BIOSIS Previews, Embase, CINAHL)	51 non-RCTs	Open, laparoscopic	Robot-assisted vs. open: longer operative time; shorter length of stay; reduced PSM rate in pT2 (inconclusive for pT3), complication rate, blood loss, and transfusion rate; improved continence at 3 and 12 months, improved sexual function at 12 months Robot-assisted vs. laparoscopic: reduced operative time, length of stay, blood loss, and transfusion rate; inconclusive for PSM rate, complication rate, and urinary continence
Ficarra et al, 2012[147]	Jan 2008–Aug 2011 (Medline, Embase, Web of Science)	44 studies	Open, laparoscopic	12- and 24-month potency rates ranged from 54% to 90% and from 63% to 94%, respectively Robot-assisted radical prostatectomy vs. open: better potency rates at 12 months (OR 2.84, 95% CI 1.46–5.43, *P* = .002) Robot-assisted vs. laparoscopic for potency: nonsignificant improvement (OR 1.89, *P* = .21) Age, baseline potency status, comorbidities index, and extension of the nerve-sparing procedure were the most relevant preoperative and intraoperative predictors of potency recovery after robot-assisted radical prostatectomy

Author, Year	Search Period and Databases	Included Studies	Comparison	Primary Conclusions
				Available data seemed to support the use of cautery-free dissection or pinpointed low-energy cauterization for robot-assisted radical prostatectomy
Ficarra et al, 2012[148]	Jan 2008–Aug 2011 (Medline, Embase, Web of Science)	51 studies	Open, laparoscopic	Robot-assisted vs. open: better 12-month urinary continence recovery (OR 1.53, *P* = .03) Robot-assisted vs. laparoscopic: better 12-month urinary continence recovery (OR 2.39, *P* = .006) 12-month urinary incontinence rates ranged from 4% to 31%, with a mean value of 16% using a no-pad definition; considering a no-pad or safety-pad definition, incidence ranged from 8% to 11%, with a mean value of 9% Age, body mass index, comorbidity index, lower urinary tract symptoms, and prostate volume were the most relevant preoperative predictors of urinary incontinence after robot-assisted radical prostatectomy Posterior musculofascial reconstruction with or without anterior reconstruction was associated with a small advantage in urinary continence recovery 1 month after robot-assisted radical prostatectomy Only complete reconstruction was associated with a significant advantage in urinary continence 3 months after robot-assisted radical prostatectomy (OR 0.76, *P* = .04)
Gleitsmann et al, 2012[149]	Jan 2002–Jan 2012 (Medline)	55 studies	Open, laparoscopic	Robot-assisted vs. open and laparoscopic: moderate evidence for reduced length of hospital stay, blood loss, and transfusion rates; moderate evidence for no difference in complication rates Robot-assisted vs. open: moderate evidence for increased operative time, reduced PSM rate, increased urinary continence and sexual function; low evidence of no difference in biochemical recurrence Robot-assisted vs. laparoscopic: moderate evidence for reduced operative time; no difference in PSM rate Moderate evidence that surgeons experienced in robot-assisted had improvements in most clinical outcomes (except blood loss) compared with less experienced surgeons
Moran et al, 2013[150]	Jan 2000–Mar 2011 (Medline, Embase)	51 studies (1 RCT, 50 non-RCT)	Open, laparoscopic	Robot-assisted vs. open: reduced PSM rates for pT2 (RR 0.63, 95% CI 0.49–0.81, *P* < .001), improved sexual function at 12 months (RR 1.60, 95% CI 1.33–1.93, *P* < .001), improved urinary function at 12 months (RR 1.06, 95% CI 1.02–1.11, *P* < .01) Robot-assisted vs. laparoscopic: slightly improved urinary function at 12 months (RR 1.09, 95% CI 1.02–1.17, *P* = .013)
Novara et al, 2012[151]	Jan 2008–Aug 2011	79 studies	Open, laparoscopic	Mean PSM rate was 15% in all cancers and 9% in pathologically localized cancers, with some tumour characteristics being the most relevant predictors of PSMs Robot-assisted vs. open: similar overall PSM rate (OR 1.21, *P* = .19) and pT2 PSM rate (OR 1.25, *P* = .31); similar biochemical recurrence-free survival (HR 0.9, *P* = .53)

Author, Year	Search Period and Databases	Included Studies	Comparison	Primary Conclusions
	(Medline, Embase, Web of Science)			Robot-assisted vs. laparoscopic: similar overall PSM rate (OR 1.12, *P* = .47) and pT2 PSM rate (OR 0.99; *P* = .97); similar biochemical recurrence-free survival (HR 0.5, *P* = .14) Several surgeon-related characteristics or procedure-related issues may play a major role in PSM rates 7-year biochemical recurrence-free survival estimates of about 80%
Novara et al, 2012[152]	Jan 2008–Aug 2011 (Medline, Embase, Web of Science)	110 studies	Open, laparoscopic	Robot-assisted: overall mean operative time 152 minutes; mean blood loss 166 mL; mean transfusion rate 2%; mean catheterization time 6.3 days; mean length of hospital stay 1.9 days; mean complication rate 9%, with most of the complications being of low grade—lymphocele/lymphorrhea (3.1%), urine leak (1.8%), and reoperation (1.6%) were the most prevalent surgical complications Robot-assisted vs. open: lower blood loss (weighted mean difference 582.77, *P* < .001) and transfusion rate (OR 7.55, *P* < .001); no difference in operative time or complication rate Robot-assisted vs. laparoscopic: reduced transfusion rate (OR 2.56, *P* = .005); no difference in operative time, blood loss, or complication rate
Ramsay et al, 2012[153]	1995–Oct 2010 (Medline, Embase, BIOSIS, Science Citation Index, CENTRAL, conference abstracts)	58 studies (1 RCT, 57 non-RCTs)	Laparoscopic	Robot-assisted vs. laparoscopic: reduced complications (0.4% vs. 2.9%, OR 0.03, 95% credible interval 0.03–0.76), lower PSM rate (17.6% vs. 23.6%, OR 0.69, 95% credible interval 0.51–0.96); no difference in urinary continence at 12 months (OR 0.55, 95% credible interval 0.09–2.84); insufficient data for sexual function outcomes; no difference in surgeon learning rates
Tewari et al, 2012[154]	Jan 2012–Dec 2010 (PubMed, Scopus)	400 studies (187 robot-assisted, 96 open, 117 laparoscopic)	Open, laparoscopic	Robot-assisted and laparoscopic vs. open: lower blood loss, transfusion rate, and length of stay Robot-assisted vs. open and laparoscopic: lower complication rates After propensity adjustment, PSM rates for laparoscopic were higher than robot-assisted but were similar to open Complication rates low for all groups, but lowest for robot-assisted Rates for the following showed significant differences between groups, generally favouring robot-assisted: readmission; reoperation; nerve, ureteral, or rectal injury; deep vein thrombosis; pneumonia; hematoma; lymphocele; anastomotic leak; fistula; and wound infection

Author, Year	Search Period and Databases	Included Studies	Comparison	Primary Conclusions
Sandoval Salinas et al, 2013[155]	1950–Oct 2012 (Medline, Embase, LILACS, CENTRAL)	2 RCTs	Laparoscopic	Robot-assisted vs. laparoscopic: improved sexual function and urinary continence; no differences in perioperative outcomes
De Carlo et al, 2014[156]	?–Dec 2013 (PubMed, Embase)	25 studies	Open, laparoscopic	Robot-assisted and laparoscopic: operative time, blood loss, transfusion rates, catheterization duration, length of hospital stay, complication rate were most optimal in robot-assisted group Data insufficient to prove superiority of any surgical approach for functional and oncological outcomes
Agarwal et al, 2015[157]	Search period unspecified (PubMed, Cochrane)	19 non-RCTs	Open	Robot-assisted: not unequivocally shown to be superior to open for functional and oncological outcomes
Pan et al, 2015[158]	Jan 2009–Oct 2013 (PubMed, Google Scholar, Embase, Web of Science)	6 studies	Open	Robot-assisted vs. open: longer operative time (weighted mean difference 64.84, 95% CI 44.12–85.55, $P < .001$); no difference in transfusion rate, PSM rate, or 3- and 12-month urinary continence; improved potency at 3 months (OR 2.80, 95% CI 1.83–4.27, $P < .001$) and 12 months (OR 1.70, 95% CI 1.30–2.23, $P < .001$)
Allan et al, 2016[159]	1950–Dec 2014 (Medline, Scopus, CDSR, Central)	2 RCTs	Laparoscopic	Robot-assisted: significantly higher rate of return to erectile function (RR 1.51, 95% CI 1.19–1.92) and continence (RR 1.14, 95% CI 1.04–1.24); no significant differences in operative time, blood loss, transfusion rate, or biochemical recurrence (RR 1.01, 95% CI 0.91–1.12)
Seo et al, 2016[131]	Jan 1980–Aug 2013 (Medline, Embase, Cochrane, KoreaMed, KMbase, RISS4U, KISS, KISTI, NDSL)	61 non-RCTs (38 from previous systematic reviews)	Open	Robot-assisted: improved perioperative and functional outcomes, lower complication rate; no difference for positive surgical margin or biochemical recurrence

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CI, confidence interval; CINAHL, Cumulative Index of Nursing and Allied Health Literature; DARE, Database of Abstracts and Reviews of Effects; HR, hazard ratio; HTA, health technology assessment; KISS, Korean Studies Information Service System; KISTI, Korean Institute of Science and Technology Information; LILACS, Latin American and Caribbean Literature on the Health Sciences; NDSL, National Digital Science Library; OR, odds ratio; PSM, positive surgical margin; RCT, randomized controlled trial; RISS4U, Research Information Service System for You; RR, relative risk.

Appendix 6: Guideline Recommendations on Robot-Assisted Radical Prostatectomy

Table A22: Summary of Guideline Recommendations on Robot-Assisted Radical Prostatectomy

Author, Year Title	Recommendation Excerpts	Level of Evidence
Montorsi et al, 2012[67] Best Practices in Robot-Assisted Radical Prostatectomy: Recommendations of the Pasadena Consensus Panel	The following recommendations are made with regard to patient selection and surgical technique: • There are no absolute contraindications to RARP. • Obesity, previous abdominal surgery, larger prostate size, and previous radiation are not absolute contraindications for RARP, although such patients may be best operated on by only experienced clinicians. • A transperitoneal antegrade surgical approach is the most commonly used. • Robotic techniques have changed the understanding of prostate anatomy, thus making obsolete some commonly used terms use as interfascial or intrafascial dissections. The newer concept of incremental nerve-sparing procedures (full, partial, and minimal) should be adopted. • Thermal energy should be used judiciously and with low cautery levels. Traction of tissues should also be minimized. • Seminal vesicles can be removed either partially or completely during RARP according to the patient's oncologic status. • RARP and RRP have equivalent efficacy for performing prostatectomy-related extended PLND. • Single running suture is the most frequently used technique to perform the urethrovesical anastomosis. Monofilament is the standard suture. Barbed suture is an acceptable option. • The use of medical DVT prophylaxis is optional. If used, clinicians should follow NICE or other national guidelines. The following recommendations are made with regard to cancer control: • Available data suggest that RARP may also be used in patients with D'Amico high-risk cancers, provided that standard criteria for patient selection, lymph node dissection, and nerve preservation are fulfilled. • Positive surgical margin rates after RARP are equivalent to those reported after RRP and LRP. • When appropriately performed, RARP is not associated with an increased risk of patients needing adjuvant therapies. • Biochemical disease-free survival after RARP seems to be equivalent to other approaches, although existing data are limited.	Not reported

Author, Year Title	Recommendation Excerpts	Level of Evidence
	• RARP is appropriate for those with high-risk disease; the surgical approach should be determined by the surgeon's experience and expertise. The following recommendations are made with regard to functional outcomes and complications of RARP: • The definition of surgical complications should be standardized, complications should be assessed in detail from the intraoperative period until at least 3 months postoperatively, and results should be available in most patients. • Systematic reviews indicate the potential superiority of RARP for preservation of continence and potency following RP surgery; however, methodological limitations in most studies and the lack of prospective randomized trials need to be considered. Other factors, such as the level of surgeon experience, means of outcome assessment, premorbid function, and postsurgical rehabilitation of the patient, can have a significant impact on functional outcomes. • Comparative studies of functional outcomes following RP surgery performed according to best practice guidelines are needed. • Postoperative anejaculation and fertility preservation strategies should be discussed with patients, and realistic expectations should be set regarding a return to continence and baseline potency. • Although the most appropriate way to report composite outcomes following RP has yet to be standardized, such reporting should take into account baseline patient characteristics, type of surgery, use of adjuvant therapies, and peri- and postoperative complications and sequelae.	
National Institute for Health and Care Excellence (NICE), 2014[66] Prostate Cancer: Diagnosis and Treatment	Commissioners of urology services should consider providing robotic surgery to treat localised prostate cancer. Commissioners should ensure that robotic systems for the surgical treatment of localised prostate cancer are cost effective by basing them in centres that are expected to perform at least 150 robot-assisted laparoscopic radical prostatectomies per year.	Not reported

Author, Year Title	Recommendation Excerpts	Level of Evidence
Merseburger et al (European Association of Urology), 2014[65] Guidelines on Robotic- and Single-Site Surgery in Urology[a]	Surgical and oncological outcomes: • Robotic surgery does not improve oncological outcomes in comparison to ORP and LRP; surgical expertise is the crucial factor. Use of the robot is not recommended to improve surgical outcomes. (Grade A recommendation: based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomized controlled trial)	• RARP for localised prostate cancer is now a well-established surgical approach offering similar positive surgical margin rates with ORP and LRP. (Level of evidence 2a: from one well-designed controlled study without randomisation) • Long-term PSA-free survival of patients treated with RARP as documented for up to 5 years is comparable with other radical prostatectomy approaches. (Level of evidence 3: from well-designed nonexperimental studies, such as comparative studies, correlation studies and case reports) • In the absence of level 1a data and very limited long-term data, a firm conclusion regarding the oncological superiority of the technique over other techniques cannot be drawn. (Level of evidence 2a: from one well-designed controlled study without randomisation)
	Incontinence: • To achieve better early continence results, the use of robotic technique is recommended.* (Grade C recommendation: made despite the absence of directly applicable clinical studies of good quality) *The expert panel would like to stress that a well-done laparoscopy or open procedure would produce similar results.	• RARP for localised prostate cancer is a surgical approach offering high continence rates, at least comparable with ORP and LRP. (Level of evidence 2a: from one well-designed controlled study without randomisation) • Experienced robotic surgeons achieve good early continence results. (Level of evidence 3: from well-designed nonexperimental studies, such as comparative studies, correlation studies and case reports) • There is a trend towards faster recovery of continence after RARP in comparison to ORP and LRP. (Level of evidence 3: from well-designed nonexperimental studies, such as comparative studies, correlation studies and case reports)

Author, Year Title	Recommendation Excerpts	Level of Evidence
	Potency: • To achieve better early potency results, the use of laparoscopy or robotic techniques are *[sic]* recommended.* (Grade C recommendation: made despite the absence of directly applicable clinical studies of good quality) • To achieve better early potency results, a cautery-free (i.e. athermal) technique during neurovascular bundle dissection is recommended. (Grade A recommendation: based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised controlled trial) *The expert panel would like to stress that a well-done laparoscopy or open procedure would produce similar results.	• Potency assessment after radical prostatectomy has many limitations, which partly explains the wide variation in potency outcomes among different studies. (Level of evidence 2a: from one well-designed controlled study without randomisation) • RARP is not inferior to ORP and LRP for potency rates. (Level of evidence 2a: from one well-designed controlled study without randomisation) • There is a trend towards faster recovery of potency after robotic assisted laparoscopic radical prostatectomy (RALP) in comparison to ORP and LRP. (Level of evidence 2a-3: from one well-designed controlled study without randomisation; and well-designed nonexperimental studies, such as comparative studies, correlation studies, and case reports)
Mottet et al (European Association of Urology), 2015[68] Guidelines on Prostate Cancer	In patients who are surgical candidates for radical prostatectomy, all approaches (i.e. open, laparoscopic or robotic) are acceptable as no single approach has shown clear superiority in terms of functional or oncological results. (Grade A recommendation: based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised controlled trial)	• Level of evidence 1a: from meta-analysis of randomised trials

Abbreviations: DVT, deep vein thrombosis; LRP, laparoscopic radical prostatectomy; NICE, National Institute for Health and Care Excellence; PLND, pelvic lymph node dissection; RARP, robot-assisted radical prostatectomy; RP, radical prostatectomy; RRP, retropubic radical prostatectomy.

[a]Now a discontinued European Association of Urology (EAU) guideline topic.

Appendix 7: Ongoing Studies Related to Robot-Assisted Radical Prostatectomy

Table A23: Ongoing Comparative Studies on Robot-Assisted Radical Prostatectomy

ID	Registry	Country	Design	Scientific Title	Comparator
ACTRN12611000593932	Australian New Zealand Clinical Trials Registry	Australia	Prospective Nonrandomized	Patient outcomes after open and minimally invasive surgery for prostate cancer	Open and laparoscopic radical prostatectomy
ACTRN12612001219875	Australian New Zealand Clinical Trials Registry	China	Randomized controlled trial	Effectiveness and safety of robot-assisted laparoscopic radical prostatectomy versus laparoscopic radical prostatectomy in patients with prostate cancer by one experienced laparoscopic surgeon: a prospective controlled trial from China	Laparoscopic radical prostatectomy
DRKS00007138	German Clinical Trials Register	Germany	Randomized controlled trial	Randomized, multicenter study comparing robot-assisted and conventional laparoscopic radical prostatectomy	Laparoscopic radical prostatectomy
NCT00578123	clinicaltrials.gov	United States	Prospective Nonrandomized	Prospective assessment of clinical and quality of life outcomes after open or robotic-assisted laparoscopic radical prostatectomy	Open radical prostatectomy
NCT01325506	clinicaltrials.gov	United States	Prospective Nonrandomized	Effectiveness of open and robotic prostatectomy: the PROSTQA-RP2 study	Open radical prostatectomy
NCT01577836	clinicaltrials.gov	France	Prospective Nonrandomized	Medico-economic comparison of robot-assisted radical prostatectomy using the da Vinci System versus radical prostatectomy via laparotomy	Laparoscopic radical prostatectomy
NCT01578356	clinicaltrials.gov	Belgium	Prospective Nonrandomized	Oncological and functional outcomes after radical prostatectomy for prostate cancer: comparing open with robot-assisted surgery	Open radical prostatectomy
NCT02292914	clinicaltrials.gov	Brazil	Randomized controlled trial	Prospective analysis of robot-assisted surgery (includes robot-assisted radical prostatectomy)	Conventional surgery (includes open radical prostatectomy)
NCT02784314	clinicaltrials.gov	France	Prospective Nonrandomized	Medico-economic evaluation of robotic-assisted radical prostatectomy versus laparoscopic radical prostatectomy	Laparoscopic radical prostatectomy

Table A24: Ongoing Systematic Reviews Related to Robot-Assisted Radical Prostatectomy

ID	Registry	Title	Review Question	Intervention and Comparator
CRD42016035336	PROSPERO	Robotic surgery in urology: a systematic review of randomised controlled trials	To assess the effectiveness and safety of robotic surgery in the treatment of people with uro-oncological disease	Robot-assisted surgery compared with open or laparoscopic surgery
CRD42016043331	PROSPERO	Positive surgical margins in robot-assisted radical prostatectomy versus open radical prostatectomy: a meta-analysis of comparative studies	How surgical approach (robotic-assisted radical prostatectomy or open radical prostatectomy) impacts positive surgical margin	Open radical prostatectomy
CD009625	Cochrane (Protocol)	Laparoscopic versus open prostatectomy for the treatment of localised prostate cancer	To determine whether laparoscopic radical prostatectomy, specifically robot-assisted radical prostatectomy, is more effective than open radical prostatectomy in reducing prostate cancer-specific mortality and increasing biochemical recurrence-free survival	Open radical prostatectomy

Appendix 8: Results of Applicability Checklist for Studies Included in the Economic Literature Review

Table A25: Applicability of Included Studies to the Ontario Context

Objective: To Assess the Cost-Effectiveness of Robot-Assisted Versus Open Radical Prostatectomy					
Author, Year	**Is the Study Population Similar to the Question?**	**Are the Interventions Similar to the Question?**	**Is the Health Care System in Which the Study Was Conducted Sufficiently Similar to the Current Ontario Context?**	**Was the Perspective Clearly Stated and What Was It?**	**Are Estimates of Relative Treatment Effect From the Best Available Source?**
Cooperberg et al, 2013[106]	Yes	Yes	No (United States)	Yes; payer	Partially
Hohwu et al, 2011[107]	Yes	Yes	Yes (Denmark)	Yes; societal	No
Medical Services Advisory Committee, 2006[160]	Yes	Yes	Yes (Australia)	Yes; payer	No
Author, Year	**Are All Future Costs and Outcomes Discounted? (If Yes, at What Rate?)**	**Is the Value Of Health Effects Expressed in Terms of Quality-Adjusted Life-Years?**	**Are Costs and Outcomes From Other Sectors Fully and Appropriately Measured and Valued?**	**Overall Judgment (Directly Applicable/Partially Applicable/ Not Applicable)**	
Cooperberg et al, 2013[106]	Yes; 3%	Yes	No	Not applicable	
Hohwu et al, 2011[107]	No (time horizon: 1 year)	Yes	Yes	Not applicable	
Medical Services Advisory Committee, 2006[160]	Yes; 5%	Yes	No	Not applicable	

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

About the Ontario Health Technology Advisory Committee (OHTAC)

About OHTAS

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