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ROBOTIC vs. OPEN UROLOGIC ONCOLOGIC SURGERY: STUDY PROTOCOL OF A SYSTEMATIC REVIEW AND META-ANALYSIS

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Keywords

Robotic Surgery, Oncology, Urology, Robotic Radical Prostatectomy, RRP, Robotic Radical cystectomy, RRC, Robotic Partial Nephrectomy, RPN, Robotic Radical Nephrectomy, RRN, retroperitoneal lymphadenectomy

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ABSTRACT

Introduction

Minimally invasive surgery (MIS) in urology has grown considerably in application since its initial description in the early 1990s. Herein, we present the protocol for a systematic review and meta-analysis comparing open versus robotic urologic oncologic surgery for various clinically-relevant outcomes, as well as to assess their comparative penetrance over the past 20 years (2000-2020).

Methods and analysis

We will document the penetrance of robotic versus open surgery in the urologic-oncologic field using a national database.

Secondly, we will perform a systematic review and meta-analysis of all published full-text English and non-English language articles from Pubmed ®, Scopus® and Web of Science® search engines on surgical treatment of localized prostate, bladder, kidney and testis cancer published between 01/01/2000 and 01/10/2020. We will focus on the highest-volume urologic oncologic surgeries, namely, radical prostatectomy (RP), radical cystectomy (RC) partial nephrectomy (PN), radical nephrectomy (RN) and retroperitoneal lymph node dissection (RPLND). Study inclusion criteria will comprise clinical trials and prospective and retrospective studies (cohort or case-control series) comparing robotic versus open surgery. Exclusion criteria will comprise meta-analyses, multi-institutional studies, multiple papers from single institutions with overlapping periods, studies analyzing national databases and case series describing only one approach (robotic or open). Risk-of-bias for included studies will be assessed by the appropriate Cochrane risk of bias tool. Principal outcomes assessed will include peri-operative, functional, oncologic, survival and financial outcomes of open versus robotic uro-oncologic surgery. Sensitivity-analyses will be performed to correlate outcomes of interest with key baseline characteristics and surrogates of surgical expertise.

Ethics and dissemination

This comprehensive systematic review and meta-analysis will provide rigorous, consolidated information on contemporary outcomes and trends of open versus robotic urologic oncologic surgery based on all the available literature. These aggregate data will help physicians better advise patients seeking surgical care for urologic cancers. (PROSPERO registration number: CRD42017064958).

STRENGTHS AND LIMITATIONS

- Strengths of this protocol includes standardized and transparent methods and processes that minimize possible biases.
- The present study will be the first to evaluate the 5 highest-volume open versus robotic urologic oncologic surgeries over 20 years (2000-2020) as regards outcomes, costs and comparative penetrance.
- This protocol is the first to correlate outcomes of interest with baseline characteristics and surrogates of surgical expertise (i.e., surgical case-volumes and year-of-publication).
- The quality of evidence will be assessed to provide confidence in the effect estimates, thereby reporting the strength of recommendations and deriving clinical meaning from the statistical findings.
- Limitations of the study will be the paucity of randomized controlled trials and the heterogeneity amongst available publications.

INTRODUCTION

Minimally invasive surgery (MIS) in urology has grown considerably in application since its initial description over three decades ago. Initially, throughout the 1990s, urologic MIS consisted mostly of laparoscopic surgery, which, due to its skill-intensive nature, was slow to be adopted by practitioners in the field. Robotic surgery, initially applied to urology in the early 2000s, has gradually, and now virtually completely, replaced laparoscopy in uro-oncologic surgery in the United States. Specifically, robotics has now also emerged as a viable alternative to open surgery in many uro-oncologic applications. This shift away from open surgery and towards robotic surgery is relatively recent and significant.

Robotic surgery is increasing in application and scope. By the end of 2017, a total of 4409 robotic platforms had been installed globally, 43 000 robotic surgeons trained, over 5 million robotic surgeries performed across various disciplines worldwide, with over 15 000 publications [1]. In 2017, total revenue for Intuitive Surgical, the sole manufacturer of the da Vinci robot was reportedly $3.1 billion. Globally, estimated annual case volumes increased from 136 000 in 2008 to 877 000 in 2017; in urology, robotic procedures increased from 85 000 to 118 000 annually (2010-2017) [2]. Given the significant increase in the number of robotic surgeries for prostate, bladder and kidney cancer, robotic surgery is now a major domain in urologic oncologic surgery.

We seek to examine the state-of-the-field of open versus robotic urologic oncologic surgery over the past 20 years (2000-2020) by assessing the highest-volume oncologic surgeries: radical prostatectomy (RP) for prostate cancer, radical cystectomy (RC) for bladder cancer, partial nephrectomy (PN) and radical nephrectomy (RN) for kidney cancer and retroperitoneal lymph node dissection (RPLND) for testis cancer. For each of these procedures that have the requisite published comparative data, we will compare the two surgical approaches, open versus robotic, as follows: for prostate cancer - open radical prostatectomy (ORP) vs robotic radical prostatectomy (RRP); for bladder cancer - open radical cystectomy

(ORC) vs robotic radical cystectomy (RRC); for kidney cancer - open partial nephrectomy (OPN) vs robotic partial nephrectomy (RPN) and open radical nephrectomy (ORN) vs robotic radical nephrectomy (RRN); and, for testis cancer - open retroperitoneal lymph node dissection (ORPLND) vs. robotic retroperitoneal lymph node dissection (RRPLND). For each procedure type, we will also interrogate a national data base (the Premiere database) to assess comparative penetrance in the field, Suddenly, we will compare open versus robotic surgery as regards peri-operative data, procedural morbidity, oncologic outcomes, functional outcomes and financial costs. This penetrance analysis, systematic review and meta-analysis will help inform physicians and patients about contemporary trends in oncologic surgery for urologic cancers.

OBJECTIVES

The aim of this study is to present a protocol paper for a rigorous systematic review and meta-analysis of all published comparative studies of robotic versus open urologic oncologic surgery from 2000-2020, as well as an evaluation of the Premiere database, to answer the following Key Questions (KQs).

Key Questions

KQ 1: What is the annual comparative penetrance of open vs robotic urologic oncologic surgery?

KQ2: What are the peri-operative outcomes and complications of open vs robotic urologic oncologic surgery?

KQ3: What are the oncologic outcomes and short-term survival data of open vs robotic urologic oncologic surgery?

KQ4: What are the functional outcomes and health-related quality-of-life outcomes of open vs robotic urologic oncologic surgery?

KQ5: What is the financial cost comparison of open vs robotic urologic oncologic surgery?

For each procedure type, we will methodically and separately compare open versus robotic surgery as regards five key questions: penetrance in the field, peri-operative data, procedural morbidity, oncologic outcomes, functional outcomes and financial cost

METHODS

a) Trends analysis - Penetrance-in-the-field

We will analyze data from the Premier Hospital Database (Premier Inc., Charlotte, NC, USA), a nationally representative all-payer database capturing more than 152 million hospital inpatient discharges in 700 hospitals, representative of about 20% of all in-patient admissions in the United States. The Premier database has been validated and used in previous studies [3-7]. Using the International Classification of Diseases, 9th Revision (ICD-9) codes, we will identify patients diagnosed with prostate cancer (code 185), bladder cancer (codes 188.x,233.7, 236.7) and renal cancer (code 189) and testicular cancer (code 186.9) who have undergone radical prostatectomy (code 60.5), radical cystectomy (code 57.71), partial nephrectomy (code 55.4), radical nephrectomy 55.5 and retroperitoneal lymphadenectomy (codes 40.2 and 40.5) between 2000 and 2020. Codes 17.42, 17.44 or 17.49 will be used to classify robotic procedures. We will examine yearly trends in the adoption rates of robotic procedures over time, defined as the percentage of procedures performed robotically.

b) Systematic review and meta-analysis of the literature

Patient and public involvement statement

Patients and the public were not involved in the development of the research questions, outcome measures and study design.

Study design

This study will be performed according to The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 guidelines [8].

Eligibility Criteria

A summary of the participants, interventions, comparators, outcomes and time and settings considered is provided, alongwith the type of studies included according to PICOTS strategy (Population, Intervention, Comparators, Outcomes, Timing and Setting; **Table 1).** Following is the detailed description.

1. Types of studies to be included

All available clinical prospective randomized and non-randomized trials and retrospective comparative studies (cohort or case-control series) comparing ORP vs. RRP, ORC vs. RRC, OPN vs. RPN, ORN vs. RRN and ORPLND vs. RRPLND and published between 2000 and 2020 will be included. No language restrictions will be applied. Native speaking urologists will be involved in the translation of non-English publications.

2. Condition being studied

We will examine the literature of open versus robotic urologic oncologic surgery by assessing the commonest oncologic surgeries: RP for localized prostate cancer, RC for invasive bladder cancer, PN and RN for renal mass and RPLND for testis cancer.

3. Type of Participants/population

We will include adult participants (age ≥18 yrs), with diagnoses of urologic neoplasia (localized prostate cancer, invasive bladder cancer, renal mass, testis cancer).

4. Type of Intervention and Comparators

We will evaluate the comparator intervention (open approach) vs. the experimental intervention (robotic approach) separately, for each surgical procedure: RP, RC, PN, RN and RPLND.

5. Type of outcomes measures

We will compare the following outcomes between open and robotic uro-oncologic surgery: .

a) Penetrance: U.S. data for the number of surgeries performed annually for each procedure type (Premiere Database).

b) Peri-operative outcomes: Operative time (min); estimated blood loss (ml); length of hospital stay (days); blood transfusion rate (%); complication rate (%) – overall, minor (Clavien-Dindo ≤ 3), major (Clavien-Dindo ≥ 3), early (within 30 days), late (31-90 days); rate of specific complications (wound, anastmotic, cardio-vascular, gastro-intestinal, thrombo-embolic, infectious); and, re-admission rate (%).

c) Functional outcomes: At four time-points after surgery - *early* (at 3 months), *intermediate* (at 6 months), *late* (at 12 months) and *overall* (latest month) - assess erectile dysfunction rate (%) and incontinence rate (%) after RP; and decline in estimated glomerular rate (eGFR) after PN and RN.

d) Oncologic and Survival outcomes: Rate of positive surgical margins (%); lymph node yield; recurrence rate (%); cancer-specific survival rate (%); and overall survival rate (%).

e) Hospital Costs: operative costs and non-operative costs.

Search Strategy for Relevant Studies

The systematic review will be performed in accordance with the Cochrane Guidelines [9], the Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) [10] and graded strength of evidence using the scheme recommended by Methods and Guide for effectiveness and comparative Effectiveness Review of the Agency for Healthcare Research and Quality (AHRQ) [11]. The present study is registered with PROSPERO, number CRD42017064958 (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017064958).

We will search Pubmed ®, Scopus® and Web of Science® databases for all published full text English and non-English language articles on the treatment of localized prostate, bladder, kidney and testis cancer, using the keywords *"radical prostatectomy"* OR *"radical cystectomy" OR "partial nephrectomy"* OR *"radical nephrectomy" OR "retroperitoneal lymph node dissection"* published between January 1, 2000 and January 10, 2020. No language restriction will be applied. References will be manually reviewed to identify supplementary studies of interest.

We will exclude case-series describing only one approach (robotic or open), studies not comparing open versus robotic approach, non-comparative series, multi-institutional studies reporting overlapping data with series previously published, studies from the same institution with overlapping data, reviews, meta-analyses, surgical technique description papers, replies, commentaries and editorial comments, single case reports, papers about paediatric surgery, non-matching articles and studies not providing outcomes of interest,.

Multi-institutional studies which report data never published by participating single-center studies will be considered. When an institution has published multiple papers with overlapping surgical periods, we will consider only the latest published paper. We will exclude studies

analyzing national databases because of the high risk of overlapping data. The words “robot(ic)-assisted” and “robotic” will be used interchangeably.

Screening and Data Extraction

Two paired investigators (G.E.C and I.S.G) will independently screen all articles focusing the research on open versus robotic surgery. All available clinical trials, prospective and retrospective studies (cohort or case control series) comparing open vs. robotic surgery will be included. Any disagreements about eligibility will be resolved by discussion between the paired investigators until consensus is reached.

Quality Assessment

All papers will be categorized according to the Oxford Level of Evidence Working Group 2011 levels of evidence (LOEs) for therapy studies [12]. Two paired investigators (G.E.C and I.S.G) will independently weigh the risk of bias for all the studies according to the Cochrane Handbook for Systematic Reviews of Interventions for including nonrandomized studies [15]. In consideration of the design of studies, we will likewise examine the risk of preassigned confounders identified as the possible predictors at the time of surgery. We will examine articles for specific data on baseline characteristics that may have impact on outcomes of interest within their univariate analysis models.

Statistical Analysis

Figure 1 summarizes the steps of the present systematic review. A cumulative meta-analysis will be conducted using Review Manager®5.3 (Cochrane Collaboration, Oxford, UK). Weighted mean difference (WMD) will be used to compare continuous variables and odds ratio (OR), and Risk Ratio (RR) and Hazard Ratios (HR) will be used to compare dichotomous variables, respectively. Baseline characteristics will be analyzed in the same fashion.

All results will be reported with 95% confidential intervals (CI). Statistical heterogeneity between studies will be tested using the I^2 statistic [9]. Heterogeneity will be considered low, moderate and high when the values are below 25%, between 25% and 75%, and above 75%, respectively [9, 16].

Random and fixed effects will be used in case of the presence or absence of heterogeneity, respectively [9]. A two-sided p-value < 0.05 will be considered statistically significant. Pooled analysis of continuous variables is possible only when data are presented as mean and standard deviation (SD). Since some studies may report continuous variables in "median" and "interquartile range" or "min/max" range, we will use a validated mathematical method to estimate "mean" and "SD" [17]. When available, we will use data reported in a matched-pair comparison manner.

The use of pooled graphical effect of a meta-analysis that includes RCTs and non-RCTs allows assessment of the similarity between the studies. Forest plots allow the presentation of estimates and standard errors for each study. Graphical representation of pooled findings will be made according to the heterogeneity [9].

Assessment of publication bias

Funnel plots will be visually inspected to assess both the degree of publication bias and its effect on the study findings. Egger's weighted regression will be used to test for publication bias, with p<0.1 considered indicative of statistically significant publication bias. When asymmetry is found, extreme outliers (i.e. small studies) will be removed from the funnel plot, Duval and Tweedie non-parametric 'trim and fill' analysis to formalize the use of funnel plot and and re-computing the effect size to correct for publication bias [15]. When necessary, to assess the risk of bias in the non-RCTs included in our meta-analysis, we will independently weigh the risk-of-bias for all studies according to the Cochrane Handbook for Systematic Reviews of Interventions for including non-randomized studies [9]. In considering the design of studies, we

will likewise examine the risk of pre-assigned confounders identified as possible predictors at the time of surgery. We will examine all publications for specific data on baseline characteristics that may impact outcomes of interest within their univariate analysis models.

Sensitivity Analyses

a) Temporal Meta-Analysis

The chronologic time of publication may impact the reported outcomes of urologic oncologic surgery; in other words, earlier publications which reflect the 'discovery' era of a novel technology may demonstrate different/inferior outcomes than later publications, when the initial learning curve has been surmounted. As such, we will perform a temporal meta-analysis to evaluate the evolving impact of time-of-publication on reported outcomes of open and robotic uro-oncologic surgery. First, a meta-regression model will be performed to assess the association between the year-of-publication and the outcomes of interest. Then, we will divide all available comparative studies into two equivalent temporal cohorts. Various outcomes of ORP vs. RRP, ORC vs. RRC , OPN vs. RPN, ORN vs. RRN and ORLND vs. RRLND will be compared between these two cohorts to assess the temporal impact of the robotic learning curve.

b) Proficiency Meta-Analysis

Similarly, surgical case volumes can impact the outcomes of urologic oncologic surgery; in other words, because of presumed differences in surgical 'proficiency', low-volume centers may deliver inferior outcomes compared to high-volume centers [18]. However, a clear definition of low- and high-volume centres is still lacking. To evaluate the impact of surgical volumes on the outcomes of interest, we will perform a "proficiency" meta- analysis. We will exclude all multi-centre studies, propensity score-matched studies and studies that do not report the surgical period. The mean number of robotic procedures performed per month will be calculated by dividing the total number of robotic procedures reported by the number of months in the study

period. First, a meta-regression model will be performed to assess the association between the number of robotic procedures/month and the outcomes of interest. Next, we will calculate the mean number of procedures/month to determine the cut-off to distinguish between low-volume (number of robotic procedures/month below the cut-off value) vs. high volume (number of robotic procedures/month above the cut-off value) centres. Various outcomes of ORP vs. RRP, ORC vs. RRC OPN vs. RPN, ORN vs. RRN and ORLND vs. RRLND will be compared between low- and high-volume centers. Since data on single-surgeon experience in studies comparing open vs. robotic uro-oncology surgery are sparse, those cut-offs will be considered as a surrogate to evaluate the impact of surgical skill proficiency on perioperative, functional and oncological outcomes.

c) Assessment of Baseline Characteristics

Differences in baseline characteristics between cohorts may be present in the studies included in a meta-analysis. Ignoring such substantial variability in one or more baseline characteristics may lead to misleading conclusions, which can jeopardize the overall applicability of the pooled estimates [19]. Therefore, comparability of baseline patient characteristics between the 2 cohorts is crucial for minimizing the impact of heterogeneity on study outcomes.

To account for the impact of baseline characteristics on a given outcome and explore the possible relationship between baseline characteristics and outcomes-of-interest, we will perform a pooled analysis of the baseline characteristics (***Table 2).*** Then, we will perform a sensitivity analysis of the pooled estimate of the baseline characteristics reported by the studies reporting a given outcome to assess differences between the two cohorts. Sensitivity analyses will be performed plotting only papers reporting comparable baseline characteristics estimates (mean for continues variable and OR for dichotomous variable) defined as estimates with 95%

confidence interval for an effect including the null value (such as an odds ratio of 1.0 or a risk difference of 0) [15] .

d) Risk of Incontinence and Erectile dysfunction after Radical Prostatectomy

For the analysis of continence and potency recovery rates following radical prostatectomy (open versus robotic), we will assess the relative risk of incontinence and erectile dysfunction, respectively. We will consider as "total" the number of men reporting to be continent or potent before surgery or, if not specified, the total number of men evaluated at last follow up. We will consider as "events" the total number of men who report to have incontinence or erectile dysfunction after surgery. This number will be calculated by the difference (Δ) between the total of the *"continent or potent patients following surgery"* and the *"total"* (the number of patients that are continent or potent *before* surgery or, if not specified, the total of patients evaluated at last follow up). Inconsistency in the definition will be reported..

e) Cost analyses

We will evaluate costs of open versus robotic uro-oncologic surgery. We will select only comparative studies (open vs. robotic) reporting operative and non-operative costs; studies reporting charges, modelling and analyses of national databases will be excluded. We will include the following items in operative costs: 1) labor (professional fees); 2) surgical equipment; 3) robot-related costs (capital, maintenance); and 4) anesthesia supply/technician labor cost. We will include the following items in non-operative costs: 1) post-anesthesia care; 2) professional fees; 3) hospital stay costs (room/day, nursing costs); 4) drugs and supplies; 4) blood transfusion costs; and 5) technical services (laboratory, radiology). Difference (Δ) in overall operative cost will be calculated as overall robotic operative cost minus overall open operative cost. Difference (Δ) in overall non-operative cost will be calculated as overall robotic non-operative cost minus overall open non-operative cost. Percentages indicating the overall

total cost differential of robotic vis-a-vis open surgery will be considered. We will convert all currencies to the 2020 exchange rate using the Consumer Price Index (CPI) inflation calculator (https://www.bls.gov/data/inflation_calculator.htm). Foreign currency will first be converted to dollars using historical exchange rates at the year of publication and then adjusted to the 2020 exchange rate using the CPI inflation calculator.

Grade Of The Evidence

The quality of scientific evidence and outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE offers a specific definition of the quality of evidence that is different in the context of making recommendations and in the context of summarizing the findings of a systematic review [13, 14] The GRADE methodology involves rating evidence for a given outcome by upgrading or downgrading the evidence. Indications for upgrading the quality of evidence include having a large effect size and dose-response gradient. Indications for downgrading the quality of evidence include serious risk of bias, serious inconsistency between studies, serious indirectness, serious imprecision and likely publication bias [20]. Summary of Findings (SoF) tables will provide a summary of findings for each of the included outcomes and the quality of evidence rating for each outcome [20]. The format of the Sof will include:

1. A list of the outcomes of interest
2. The assumed risk; a measure of the typical burden of the outcomes, i.e. illustrative risk or also called baseline risk, baseline score, or control group risk
3. The corresponding risk; a measure of the burden of the outcomes after the intervention is applied, i.e. the risk of an outcome in treated/exposed people based on the relative magnitude of an effect and assumed (baseline) risk

4. The relative effect; for dichotomous outcomes the table will provide risk ratio, odds ratio, or hazard ratio
5. The number of participants, the number of studies and their designs
6. Rating of the overall quality of evidence for each outcome

Presentation of results and reporting

The PRISMA guidelines [10] will be used and the checklist will accompany the publication. Quantitative data will be summarized and presented in tables and as forst plots where necessary [9].

Potential amendments

We do not anticipate any amendments to the current protocol. However, should an amendment be necessary, it will be notified, registered and reported.

Ethics and Dissemnination

No ethics clearance is necessary as no primary data will be collected. Results will be published in a peer-reviewed journal. These results will likely help inform directions and design of future studies.

IMPLICATIONS OF THE REVIEW

We believe this aggregate information will be of interest and practical use to the general medical community at large, who need to be aware of contemporary trends in urologic oncologic surgery, thereby to better advice patients seeking care for urologic cancers.

CONCLUSION

This systematic review and meta-analysis will compare multiple outcomes of open versus robotic urologic oncologic surgery over two decades, from 2000-2020. A synthesis of all available studies will identify the quality of data. This meta-analysis will be used to inform future studies to fulfill gaps in knowledge in comparative outcomes of open and robotic urologic oncologic surgery.

FOOTNOTES

Contributorship statement : I.S.G and G.E.C conceptualised and designed the protocol, drafted the initial manuscript and reviewed the manuscript. I.S.G and G.E.C defined the concepts and search items, data extraction process as well as methodological appraisal of the studies. G.E.C, K.S.G and I.S.G planned the data extraction and statistical analysis. I.S.G and G.E.C, provided critical insights. All authors have approved and contributed to the final written manuscrip

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Data sharing statement: There are no data in this work

REFERENCES

1. Data, I.s., *https://www.youtube.com/watch?v=1CHUlrfM9C4*. 2017.
2. Childers, C.P. and M. Maggard-Gibbons, *Estimation of the acquisition and operating costs for robotic surgery.* Jama, 2018. **320**(8): p. 835-836.
3. Leow, J.J., et al., *Variations in the costs of radical cystectomy for bladder cancer in the USA.* European urology, 2018. **73**(3): p. 374-382.

4. Leow, J.J., et al., *Robot-assisted versus open radical prostatectomy: a contemporary analysis of an all-payer discharge database.* European urology, 2016. **70**(5): p. 837-845.
5. Cheung, H., et al., *Adoption of Robot-Assisted Partial Nephrectomies: A Population-Based Analysis of U.S. Surgeons from 2004 to 2013.* J Endourol, 2017. **31**(9): p. 886-892.
6. Lindenauer, P.K., et al., *Perioperative beta-blocker therapy and mortality after major noncardiac surgery.* New England Journal of Medicine, 2005. **353**(4): p. 349-361.
7. Wright, J.D., et al., *Robotically assisted vs laparoscopic hysterectomy among women with benign gynecologic disease.* Jama, 2013. **309**(7): p. 689-698.
8. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Systematic reviews, 2015. **4**(1): p. 1.
9. Higgins J, G.S., *Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 [Accessed September 2019].* 2019.
10. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* Int J Surg, 2010. **8**(5): p. 336-41.
11. Quality, A.A.f.H.R.a., *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.* Available at http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318, 2015.
12. Jeremy Howick, I.C.J.L.L., Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson, OCEBM Levels of Evidence Working Group, *The Oxford 2011 Levels of Evidence, Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653.*
13. Group, G.W., *Grading quality of evidence and strength of recommendations.* BMJ: British Medical Journal, 2004. **328**(7454): p. 1490.
14. Guyatt, G.H., et al., *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* Bmj, 2008. **336**(7650): p. 924-6.
15. Higgins JPT, G.S.e., *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.*
16. Higgins, J.P. and S.G. Thompson, *Quantifying heterogeneity in a meta-analysis.* Stat Med, 2002. **21**(11): p. 1539-58.
17. Wan, X., et al., *Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range.* BMC Med Res Methodol, 2014. **14**: p. 135.
18. Bach, P.B., et al., *The influence of hospital volume on survival after resection for lung cancer.* N Engl J Med, 2001. **345**(3): p. 181-8.
19. Chaimani, A., *Accounting for baseline differences in meta-analysis.* Evidence Based Mental Health, 2015. **18**(1): p. 23-26.
20. GRADEPro, *https://gdt.gradepro.org/app/handbook/handbook.html#h.wlsfq2lmj0gb.* GRADEpro.

FIGURE CAPTATION

Figure 1. study design flow chart

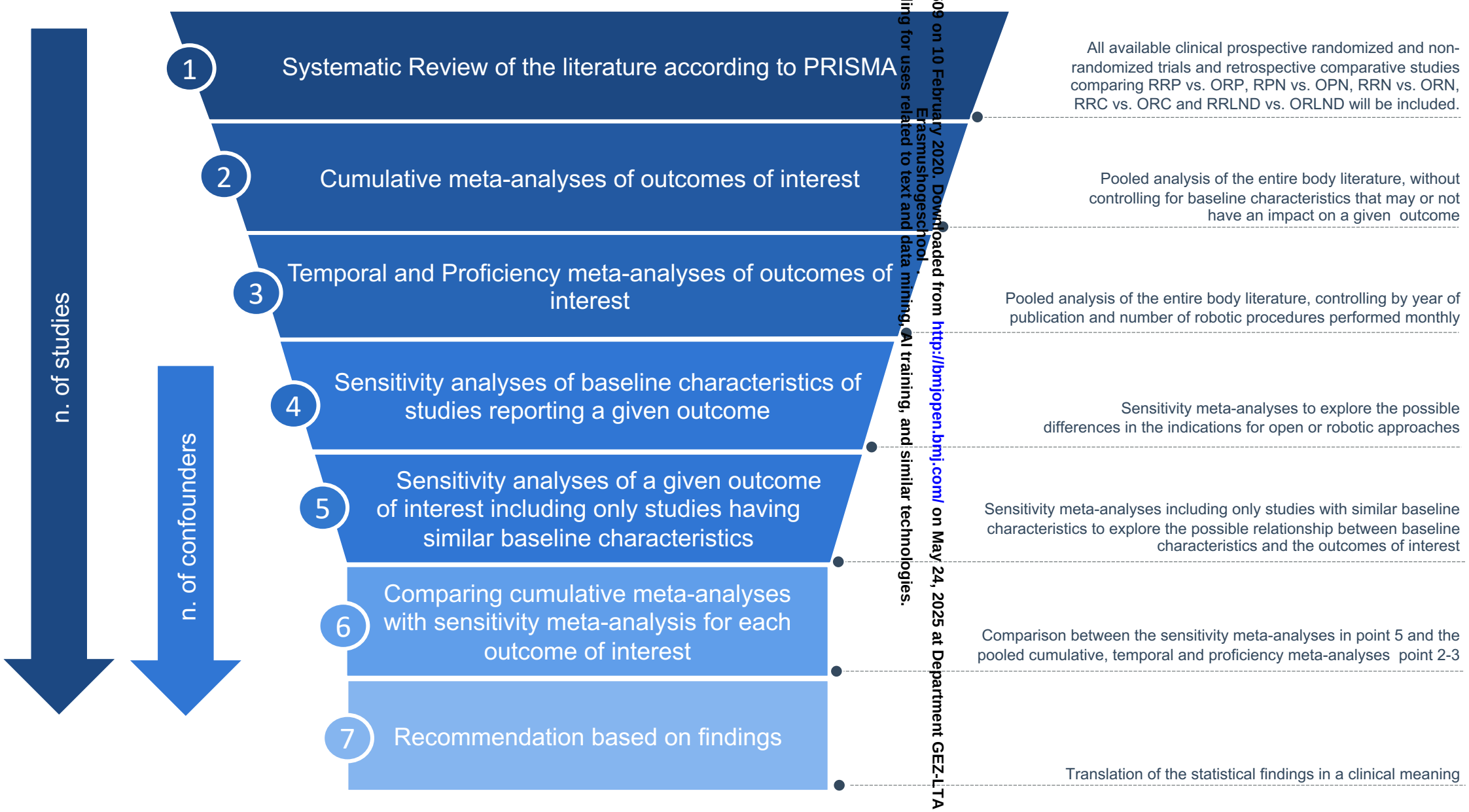
TABLES

Table 1. Description of the PICOTS strategy as applied to this study

	INCLUSION
POPULATION	**Age ≥ 18 yrs** **Diagnoses:** urologic neoplasia in adults: •Localized prostate cancer •Renal mass •Invasive bladder cancer •Testicular Cancer
INTERVENTIONS	•Radical Prostatectomy (open vs robotic approach) •Radical Cystectomy (open vs robotic approach) •Partial Nephrectomy (open vs robotic approach) •Radical Nephrectomy (open vs robotic approach) • Retroperitoneal Lymphnode dissection (open vs robotic approach)
COMPARATORS	Comparison between open and robotic approaches in the treatment of urologic cancers included in the list above
OUTCOMES	**Peri-operative outcomes:** •Operative time (min) •Estimated blood loss (ml) •Length of hospital stay (days) •Blood transfusion rate (%) •Overall complication rate (%) •Major and Minor postoperative complication rate (%) •Early and Late complication rate (%) •Readmission rate (%) **Oncologic outcomes:** •Positive margins •Lymph node counts •Cancer specific survival •Overall survival •Recurrence free survival **Functional outcomes:** •Potency recovery rate (n) •Continence recovery rate (n) •Health related quality of life •Renal Function (eGFR change) **Hospital Costs:** •Operative costs •Non-operative costs
TYPE OF STUDIES	All available clinical, prospective randomized and non-randomized trials and retrospective comparative studies (cohort or case control series) comparing RRP vs ORP, RRC vs ORC, RPN vs OPN, RRN vs ORN and RRLND vs ORLND were included. Published between 2000 and 2020.
TIMING AND SETTING	Any time point and setting

Table 2. Baseline characteristics evaluated for each comparison

Surgical Procedure	Baseline characteristics
Radical Prostatectomy (ORP vs. RRP)	Age, years
	BMI, Kg/m²
	ASA score
	PSA ng/Ml
	Clinical GS ≤ 6, %
	Clinical GS = 7, %
	Clinical GS ≥ 8, %
	Pathological GS ≤ 6, %
	Pathological GS = 7, %
	Pathological GS ≥ 8, %
	pT ≥ 3, %
	pN ≥ 1, %
Radical Cystectomy (ORC vs. RRC)	Age, years
	BMI, Kg/m²
	ASA score
	Male, %
	Female, %
	NACH, %
	pT ≥ 3, %
	pN ≥ 1, %
	n of node removed, mean
Partial nephrectomy (OPN vs. RPN) and Radical Nephrectomy (ORN vs. RRN)	Age, years
	BMI, Kg/m²
	ASA score, %
	Male, %
	Preoperative eGFR
	Left/right side, %
	Tumor size, cm
	RENAL score
	Renal Score ≤ 6 , %
	Renal score 7-10, %
	Renal Score 11-12, %
	pT ≥ 1b, %
Retroperitoneal Lymphnode Dissection (ORLND vs. RRLND)	Age, years
	BMI, Kg/m²
	ASA score
	Primary lateraly Left/right side, %
	Preoperative AFP (ng/mL)
	Preoperative hCG (mIU/mL)
	Lympho vascular invasion, %
	pT ≥ 2, %
	pN ≥ 1, %
	n of node removed, mean



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ROBOTIC vs. OPEN UROLOGIC ONCOLOGIC SURGERY: STUDY PROTOCOL OF A SYSTEMATIC REVIEW AND META-ANALYSIS

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Keywords

Robotic Surgery, Oncology, Urology, Robotic Radical Prostatectomy, RRP, Robotic Radical cystectomy, RRC, Robotic Partial Nephrectomy, RPN, Robotic Radical Nephrectomy, RRN, retroperitoneal lymphadenectomy

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ABSTRACT

Introduction

Minimally invasive surgery (MIS) in urology has grown considerably in application since its initial description in the early 1990s. Herein, we present the protocol for a systematic review and meta-analysis comparing open versus robotic urologic oncologic surgery for various clinically-relevant outcomes, as well as to assess their comparative penetrance over the past 20 years (2000-2020).

Methods and analysis

We will document the penetrance of robotic versus open surgery in the urologic-oncologic field using a national database.

Secondly, we will perform a systematic review and meta-analysis of all published full-text English and non-English language articles from Pubmed ®, Scopus® and Web of Science® search engines on surgical treatment of localized prostate, bladder, kidney and testis cancer published between 01/01/2000 and 01/10/2020. We will focus on the highest-volume urologic oncologic surgeries, namely, radical prostatectomy (RP), radical cystectomy (RC) partial nephrectomy (PN), radical nephrectomy (RN) and retroperitoneal lymph node dissection (RPLND). Study inclusion criteria will comprise clinical trials and prospective and retrospective studies (cohort or case-control series) comparing robotic versus open surgery. Exclusion criteria will comprise meta-analyses, multi-institutional studies, multiple papers from single institutions with overlapping periods, studies analyzing national databases and case series describing only one approach (robotic or open). Risk-of-bias for included studies will be assessed by the appropriate Cochrane risk of bias tool. Principal outcomes assessed will include perioperative, functional, oncologic, survival and financial outcomes of open versus robotic uro-oncologic surgery. Sensitivity-analyses will be performed to correlate outcomes of interest with key baseline characteristics and surrogates of surgical expertise.

Ethics and dissemination

This comprehensive systematic review and meta-analysis will provide rigorous, consolidated information on contemporary outcomes and trends of open versus robotic urologic oncologic surgery based on all the available literature. These aggregate data will help physicians better advise patients seeking surgical care for urologic cancers. (PROSPERO registration number: CRD42017064958).

STRENGTHS AND LIMITATIONS

- The strengths of this protocol include standardized and transparent methods and processes that minimize possible biases. The quality of evidence will be assessed to provide confidence in the effect estimates, thereby reporting the strength of recommendations and deriving clinical meaning from the statistical findings.
- The present study will be the first to evaluate the five highest-volume open versus robotic urologic oncologic surgeries over 20 years (2000-2020) as regards outcomes, costs and comparative penetrance.
- This meta-analysis will be used to inform future studies to fulfill gaps in knowledge in comparative outcomes of open and robotic urologic oncologic surgery.
- This protocol is the first to correlate outcomes of interest with baseline characteristics and surrogates of surgical expertise (i.e., surgical case-volumes and year-of-publication).
- Limitations of the study will be the paucity of randomized controlled trials and the heterogeneity amongst available publications.

INTRODUCTION

Minimally invasive surgery (MIS) in urology has grown considerably in application since its initial description over three decades ago. Initially, throughout the 1990s, urologic MIS consisted mostly of laparoscopic surgery, which, due to its skill-intensive nature, was slow to be adopted by practitioners in the field. Robotic surgery, initially applied to urology in the early 2000s, has gradually, and now virtually completely, replaced laparoscopy in uro-oncologic surgery in the United States. Specifically, robotics has now also emerged as a viable alternative to open surgery in many uro-oncologic applications. This shift away from open surgery and towards robotic surgery is relatively recent and significant.

Robotic surgery is increasing in application and scope. By the end of 2017, a total of 4409 robotic platforms had been installed globally, 43 000 robotic surgeons trained, over 5 million robotic surgeries performed across various disciplines worldwide, with over 15 000 publications [1]. In 2017, total revenue for Intuitive Surgical, the sole manufacturer of the da Vinci robot was reported $3.1 billion. Globally, estimated annual case volumes increased from 136 000 in 2008 to 877 000 in 2017; in urology, robotic procedures increased from 85 000 to 118 000 annually (2010-2017) [2]. Given the significant increase in the number of robotic surgeries for prostate, bladder and kidney cancer, robotic surgery is now a major domain in urologic oncologic surgery.

We seek to examine the state-of-the-field of open versus robotic urologic oncologic surgery over the past 20 years (2000-2020) by assessing the highest-volume oncologic surgeries: radical prostatectomy (RP) for prostate cancer, radical cystectomy (RC) for bladder cancer, partial nephrectomy (PN) and radical nephrectomy (RN) for kidney cancer and retroperitoneal lymph node dissection (RPLND) for testis cancer. For each of these procedures that have the requisite published comparative data, we will compare the two surgical approaches, open versus robotic, as follows: for prostate cancer - open radical prostatectomy (ORP) vs. robotic radical prostatectomy (RRP); for bladder cancer - open radical cystectomy

(ORC) vs. robotic radical cystectomy (RRC); for kidney cancer - open partial nephrectomy (OPN) vs. robotic partial nephrectomy (RPN) and open radical nephrectomy (ORN) vs. robotic radical nephrectomy (RRN); and, for testis cancer - open retroperitoneal lymph node dissection (ORPLND) vs. robotic retroperitoneal lymph node dissection (RRPLND). For each procedure type, we will also interrogate a national database (the Premiere database) to assess comparative penetrance in the field. Suddenly, we will compare open versus robotic surgery as regards perioperative data, procedural morbidity, oncologic outcomes, functional outcomes and financial costs. This penetrance analysis, systematic review and meta-analysis will help inform physicians and patients about contemporary trends in oncologic surgery for urologic cancers.

OBJECTIVES

The aim of this study is to present a protocol paper for a rigorous systematic review and meta-analysis of all published comparative studies of robotic versus open urologic oncologic surgery from 2000-2020, as well as an evaluation of the Premiere database, to answer the following Key Questions (KQs).

Key Questions

KQ 1: What is the annual comparative penetrance of open vs robotic urologic oncologic surgery?

KQ2: What are the perioperative outcomes and complications of open vs. robotic urologic oncologic surgery?

KQ3: What are the oncologic outcomes and short-term survival data of open vs. robotic urologic oncologic surgery?

KQ4: What are the functional outcomes and health-related quality-of-life outcomes of open vs. robotic urologic oncologic surgery?

KQ5: What is the financial cost comparison of open vs. robotic urologic oncologic surgery?

For each procedure type, we will methodically and separately compare open versus robotic surgery as regards five key questions: penetrance in the field, perioperative data, procedural morbidity, oncologic outcomes, functional outcomes and financial cost

METHODS

a) Trends analysis - Penetrance-in-the-field

We will analyze data from the Premier Hospital Database (Premier Inc., Charlotte, NC, USA), a nationally representative all-payer database capturing more than 152 million hospital inpatient discharges in 700 hospitals, representative of about 20% of all in-patient admissions in the United States. The Premier database has been validated and used in previous studies [3-7]. Using the International Classification of Diseases, 9th Revision (ICD-9) codes, we will identify patients diagnosed with prostate cancer (code 185), bladder cancer (codes 188.x,233.7, 236.7) and renal cancer (code 189) and testicular cancer (code 186.9) who have undergone radical prostatectomy (code 60.5), radical cystectomy (code 57.71), partial nephrectomy (code 55.4), radical nephrectomy 55.5 and retroperitoneal lymphadenectomy (codes 40.2 and 40.5) between 2000 and 2020. Codes 17.42, 17.44, or 17.49 will be used to classify robotic procedures. We will examine yearly trends in the adoption rates of robotic procedures over time, defined as the percentage of procedures performed robotically.

b) Systematic review and meta-analysis of the literature

Patient and public involvement statement

Patients and the public were not involved in the development of the research questions, outcome measures and study design.

Study design

This study will be performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 guidelines [8] (Appendix A).

Eligibility Criteria

A summary of the participants, interventions, comparators, outcomes and time and settings considered is provided, alongwith the type of studies included according to PICOTS strategy (Population, Intervention, Comparators, Outcomes, Timing and Setting; **Table 1).** Following is the detailed description.

1. Types of studies to be included

All available clinical prospective randomized and non-randomized trials and retrospective comparative studies (cohort or case-control series) comparing ORP vs. RRP, ORC vs. RRC, OPN vs. RPN, ORN vs. RRN and ORPLND vs. RRPLND and published between 2000 and 2020 will be included. No language restrictions will be applied. Native speaking urologists will be involved in the translation of non-English publications.

2. Condition being studied

We will examine the literature of open versus robotic urologic oncologic surgery by assessing the commonest oncologic surgeries: RP for localized prostate cancer, RC for invasive bladder cancer, PN and RN for renal mass and RPLND for testis cancer.

3. Type of Participants/population

We will include adult participants (age ≥18 yrs), with diagnoses of urologic neoplasia (localized prostate cancer, invasive bladder cancer, renal mass, testis cancer).

4. Type of Intervention and Comparators

We will evaluate the comparator intervention (open approach) vs. the experimental intervention (robotic approach) separately for each surgical procedure: RP, RC, PN, RN and RPLND.

5. Type of outcomes measures

We will compare the following outcomes between open and robotic uro-oncologic surgery:

a) Penetrance: U.S. data for the number of surgeries performed annually for each procedure type (Premiere Database).

b) Peri-operative outcomes: Operative time (min); estimated blood loss (ml); length of hospital stay (days); blood transfusion rate (%); complication rate (%) – overall, minor (Clavien-Dindo ≤ 3), major (Clavien-Dindo ≥ 3), early (within 30 days), late (31-90 days); rate of specific complications (wound, anastmotic, cardio-vascular, gastro-intestinal, thrombo-embolic, infectious); and, re-admission rate (%).

c) Functional outcomes: At four time-points after surgery - *early* (at 3 months), *intermediate* (at 6 months), *late* (at 12 months) and *overall* (latest month) - assess erectile dysfunction rate (%) and incontinence rate (%) after RP; and decline in estimated glomerular rate (eGFR) after PN and RN.

d) Oncologic and Survival outcomes: Rate of positive surgical margins (%); lymph node yield; recurrence rate (%); cancer-specific survival rate (%); and overall survival rate (%).

e) Hospital Costs: operative costs and non-operative costs.

Search Strategy for Relevant Studies

The systematic review will be performed in accordance with the Cochrane Guidelines [9], the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] and graded strength of evidence using the scheme recommended by Methods and Guide for effectiveness and Comparative Effectiveness Review of the Agency for Healthcare Research and Quality (AHRQ) [11]. The present study is registered with PROSPERO, number CRD42017064958 (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017064958).

We will search Pubmed ®, Scopus® and Web of Science® databases for all published full-text English and non-English language articles on the treatment of localized prostate, bladder, kidney and testis cancer, using the keywords *"radical prostatectomy"* OR *"radical cystectomy" OR "partial nephrectomy"* OR *"radical nephrectomy" OR "retroperitoneal lymph node dissection"* published between January 1, 2000, and January 10, 2020. No language restriction will be applied (Appendix B). References will be manually reviewed to identify supplementary studies of interest.

We will exclude case-series describing only one approach (robotic or open), studies not comparing open versus robotic approach, non-comparative series, multi-institutional studies reporting overlapping data with series previously published, studies from the same institution with overlapping data, reviews, meta-analyses, surgical technique description papers, replies, commentaries and editorial comments, single case reports, papers about pediatric surgery, non-matching articles and studies not providing outcomes of interest,.

Multi-institutional studies that report data never published by participating single-center studies will be considered. When an institution has published multiple papers with overlapping surgical periods, we will consider only the latest published paper. We will exclude studies

analyzing national databases because of the high risk of overlapping data. The words “robot(ic)-assisted” and “robotic” will be used interchangeably.

Screening and Data Extraction

Two paired investigators (G.E.C and I.S.G) will independently screen all articles focusing the research on open versus robotic surgery. All available clinical trials, prospective and retrospective studies (cohort or case-control series) comparing open vs. robotic surgery will be included. Any disagreements about eligibility will be resolved by discussion between the paired investigators until a consensus is reached.

Quality Assessment

All papers will be categorized according to the Oxford Level of Evidence Working Group 2011 levels of evidence (LOEs) for therapy studies [12]. Two paired investigators (G.E.C and I.S.G) will independently weigh the risk of bias for all the studies according to the Cochrane Handbook for Systematic Reviews of Interventions for including non-randomized studies [13]. In consideration of the design of studies, we will likewise examine the risk of preassigned confounders identified as the possible predictors at the time of surgery. We will examine articles for specific data on baseline characteristics that may have an impact on outcomes of interest within their univariate analysis models.

Statistical Analysis

Figure 1 summarizes the steps of the present systematic review. A cumulative meta-analysis will be conducted using Review Manager®5.3 (Cochrane Collaboration, Oxford, UK). Weighted mean difference (WMD) will be used to compare continuous variables and odds ratio (OR), and Risk Ratio (RR) and Hazard Ratios (HR) will be used to compare dichotomous variables, respectively. Baseline characteristics will be analyzed in the same fashion.

All results will be reported with 95% confidential intervals (CI). Statistical heterogeneity between studies will be tested using the I^2 statistic [9]. Heterogeneity will be considered low, moderate and high when the values are below 25%, between 25% and 75%, and above 75%, respectively [9, 14].

Random and fixed effects will be used in case of the presence or absence of heterogeneity, respectively [9]. A two-sided p-value < 0.05 will be considered statistically significant. Pooled analysis of continuous variables is possible only when data are presented as mean and standard deviation (SD). Since some studies may report continuous variables in "median" and "interquartile range" or "min/max" range, we will use a validated mathematical method to estimate "mean" and "SD" [15]. When available, we will use data reported in a matched-pair comparison manner.

The use of the pooled graphical effect of a meta-analysis that includes RCTs and non-RCTs allows assessment of the similarity between the studies. Forest plots allow the presentation of estimates and standard errors for each study. Graphical representation of pooled findings will be made according to the heterogeneity [9].

Assessment of publication bias

Funnel plots will be visually inspected to assess both the degree of publication bias and its effect on the study findings. Egger's weighted regression will be used to test for publication bias, with p<0.1 considered indicative of statistically significant publication bias. When asymmetry is found, extreme outliers (i.e. small studies) will be removed from the funnel plot, Duval and Tweedie non-parametric 'trim and fill' analysis to formalize the use of funnel plot and re-computing the effect size to correct for publication bias [13]. When necessary, to assess the risk of bias in the non-RCTs included in our meta-analysis, we will independently weigh the risk-of-bias for all studies according to the Cochrane Handbook for Systematic Reviews of Interventions for including non-randomized studies [9]. In considering the design of studies, we

will likewise examine the risk of preassigned confounders identified as possible predictors at the time of surgery. We will examine all publications for specific data on baseline characteristics that may impact outcomes of interest within their univariate analysis models.

Sensitivity Analyses

a) Temporal Meta-Analysis

The chronologic time of publication may impact the reported outcomes of urologic oncologic surgery; in other words, earlier publications that reflect the 'discovery' era of a novel technology may demonstrate different/inferior outcomes than later publications, when the initial learning curve has been surmounted. As such, we will perform a temporal meta-analysis to evaluate the evolving impact of time-of-publication on reported outcomes of open and robotic uro-oncologic surgery. First, a meta-regression model will be performed to assess the association between the year-of-publication and the outcomes of interest. Then, we will divide all available comparative studies into two equivalent temporal cohorts. Various outcomes of ORP vs. RRP, ORC vs. RRC , OPN vs. RPN, ORN vs. RRN and ORLND vs. RRLND will be compared between these two cohorts to assess the temporal impact of the robotic learning curve.

b) Proficiency Meta-Analysis

Similarly, surgical case volumes can impact the outcomes of urologic oncologic surgery; in other words, because of presumed differences in surgical 'proficiency', low-volume centers may deliver inferior outcomes compared to high-volume centers [16]. However, a clear definition of low- and high-volume centres is still lacking. To evaluate the impact of surgical volumes on the outcomes of interest, we will perform a "proficiency" meta-analysiss. We will exclude all multi-centre studies, propensity score-matched studies and studies that do not report the surgical period. The mean number of robotic procedures performed per month will be calculated by dividing the total number of robotic procedures reported by the number of months in the study period. First, a meta-regression model will be performed to assess the association between the

number of robotic procedures/month and the outcomes of interest. Next, we will calculate the mean number of procedures/month to determine the cut-off to distinguish between low-volume (number of robotic procedures/month below the cut-off value) vs. high volume (number of robotic procedures/month above the cut-off value) centres. Various outcomes of ORP vs. RRP, ORC vs. RRC OPN vs. RPN, ORN vs. RRN and ORLND vs. RRLND will be compared between low- and high-volume centers. Since data on single-surgeon experience in studies comparing open vs. robotic uro-oncology surgery are sparse, those cut-offs will be considered as a surrogate to evaluate the impact of surgical skill proficiency on perioperative, functional and oncological outcomes.

c) Assessment of Baseline Characteristics

Differences in baseline characteristics between cohorts may be present in the studies included in a meta-analysis. Ignoring such substantial variability in one or more baseline characteristics may lead to misleading conclusions, which can jeopardize the overall applicability of the pooled estimates [17]. Therefore, comparability of baseline patient characteristics between the two cohorts is crucial for minimizing the impact of heterogeneity on study outcomes.

To account for the impact of baseline characteristics on a given outcome and explore the possible relationship between baseline characteristics and outcomes-of-interest, we will perform a pooled analysis of the baseline characteristics (***Table 2).*** Then, we will perform a sensitivity analysis of the pooled estimate of the baseline characteristics reported by the studies reporting a given outcome to assess differences between the two cohorts. Sensitivity analyses will be performed plotting only papers reporting comparable baseline characteristics estimates (mean for continues variable and OR for dichotomous variable) defined as estimates with 95% confidence interval for effect including the null value (such as an odds ratio of 1.0 or a risk difference of 0) [13].

d) Risk of Incontinence and Erectile dysfunction after Radical Prostatectomy

For the analysis of continence and potency recovery rates following radical prostatectomy (open versus robotic), we will assess the relative risk of incontinence and erectile dysfunction, respectively. We will consider as "total" the number of men reporting to be continent or potent before surgery or, if not specified, the total number of men evaluated at last follow up. We will consider as "events" the total number of men who report having incontinence or erectile dysfunction after surgery. This number will be calculated by the difference (Δ) between the total of the *"continent or potent patients following surgery"* and the *"total"* (the number of patients that are continent or potent *before* surgery or, if not specified, the total of patients evaluated at last follow up). Inconsistency in the definition will be reported.

e) Cost analyses

We will evaluate the costs of open versus robotic uro-oncologic surgery. We will select only comparative studies (open vs. robotic) reporting operative and non-operative costs; studies reporting charges, modeling and analyses of national databases will be excluded. We will include the following items in operative costs: 1) labor (professional fees); 2) surgical equipment; 3) robot-related costs (capital, maintenance); and 4) anesthesia supply/technician labor cost. We will include the following items in non-operative costs: 1) post-anesthesia care; 2) professional fees; 3) hospital stay costs (room/day, nursing costs); 4) drugs and supplies; 4) blood transfusion costs; and 5) technical services (laboratory, radiology). Difference (Δ) in overall operative cost will be calculated as overall robotic operative cost minus overall open operative cost. Difference (Δ) in overall non-operative cost will be calculated as overall robotic non-operative cost minus overall open non-operative cost. Percentages indicating the overall total cost differential of robotic vis-a-vis open surgery will be considered. We will convert all currencies to the 2020 exchange rate using the Consumer Price Index (CPI) inflation calculator

(https://www.bls.gov/data/inflation_calculator.htm). Foreign currency will first be converted to dollars using historical exchange rates at the year of publication and then adjusted to the 2020 exchange rate using the CPI inflation calculator.

Grade Of The Evidence

The quality of scientific evidence and outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE offers a specific definition of the quality of evidence that is different in the context of making recommendations and in the context of summarizing the findings of a systematic review [18, 19]. The GRADE methodology involves rating evidence for a given outcome by upgrading or downgrading the evidence. Indications for upgrading the quality of evidence include having a large effect size and dose-response gradient. Indications for downgrading the quality of evidence include serious risk of bias, serious inconsistency between studies, serious indirectness, serious imprecision and likely publication bias [18]. Summary of Findings (SoF) tables will provide a summary of findings for each of the included outcomes and the quality of evidence rating for each outcome [18]. The format of the Sof will include:

1. A list of the outcomes of interest
2. The assumed risk; a measure of the typical burden of the outcomes, i.e. illustrative risk or also called baseline risk, baseline score, or control group risk
3. The corresponding risk; a measure of the burden of the outcomes after the intervention is applied, i.e. the risk of an outcome in treated/exposed people based on the relative magnitude of an effect and assumed (baseline) risk
4. The relative effect; for dichotomous outcomes, the table will provide risk ratio, odds ratio, or hazard ratio
5. The number of participants, the number of studies and their designs

6. Rating of the overall quality of evidence for each outcome

Presentation of results and reporting

The PRISMA guidelines [10] will be used and the checklist will accompany the publication. Quantitative data will be summarized and presented in tables and as forest plots where necessary [9].

Potential amendments

We do not anticipate any amendments to the current protocol. However, should an amendment be necessary, it will be notified, registered and reported.

Ethics and Dissemnination

No ethics clearance is necessary, as no primary data will be collected. Results will be published in a peer-reviewed journal. These results will likely help inform directions and design of future studies.

IMPLICATIONS OF THE REVIEW

We believe this aggregate information will be of interest and practical use to the general medical community at large, who need to be aware of contemporary trends in urologic oncologic surgery, thereby to better advise patients seeking care for urologic cancers.

FOOTNOTES

Contributorship statement : I.S.G and G.E.C conceptualised and designed the protocol, drafted the initial manuscript and reviewed the manuscript. I.S.G and G.E.C defined the concepts and search items, data extraction process as well as methodological appraisal of the studies. G.E.C, K.S.G and I.S.G planned the data extraction and statistical analysis. I.S.G and G.E.C, provided critical insights. All authors have approved and contributed to the final written manuscript

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REFERENCES

1. Data, I.s., https://www.youtube.com/watch?v=1CHUlrfM9C4. 2017.
2. Childers, C.P. and M. Maggard-Gibbons, *Estimation of the acquisition and operating costs for robotic surgery.* Jama, 2018. **320**(8): p. 835-836.
3. Leow, J.J., et al., *Variations in the costs of radical cystectomy for bladder cancer in the USA.* European urology, 2018. **73**(3): p. 374-382.
4. Leow, J.J., et al., *Robot-assisted versus open radical prostatectomy: a contemporary analysis of an all-payer discharge database.* European urology, 2016. **70**(5): p. 837-845.
5. Cheung, H., et al., *Adoption of Robot-Assisted Partial Nephrectomies: A Population-Based Analysis of U.S. Surgeons from 2004 to 2013.* J Endourol, 2017. **31**(9): p. 886-892.
6. Lindenauer, P.K., et al., *Perioperative beta-blocker therapy and mortality after major noncardiac surgery.* New England Journal of Medicine, 2005. **353**(4): p. 349-361.
7. Wright, J.D., et al., *Robotically assisted vs laparoscopic hysterectomy among women with benign gynecologic disease.* Jama, 2013. **309**(7): p. 689-698.

8. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Systematic reviews, 2015. **4**(1): p. 1.
9. Higgins J, G.S., *Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 [Accessed September 2019].* 2019.
10. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* Int J Surg, 2010. **8**(5): p. 336-41.
11. Quality, A.A.f.H.R.a., *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.* Available at http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318, 2015.
12. Jeremy Howick, I.C.J.L.L., Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson, OCEBM Levels of Evidence Working Group, *The Oxford 2011 Levels of Evidence, Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653.*
13. Higgins JPT, G.S.e., *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.*
14. Higgins, J.P. and S.G. Thompson, *Quantifying heterogeneity in a meta-analysis.* Stat Med, 2002. **21**(11): p. 1539-58.
15. Wan, X., et al., *Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range.* BMC Med Res Methodol, 2014. **14**: p. 135.
16. Bach, P.B., et al., *The influence of hospital volume on survival after resection for lung cancer.* N Engl J Med, 2001. **345**(3): p. 181-8.
17. Chaimani, A., *Accounting for baseline differences in meta-analysis.* Evidence Based Mental Health, 2015. **18**(1): p. 23-26.
18. GRADEPro, *https://gdt.gradepro.org/app/handbook/handbook.html#h.wlsfq2lmj0gb.* GRADEpro.
19. Guyatt, G.H., et al., *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* Bmj, 2008. **336**(7650): p. 924-6.

FIGURE CAPTATION

Figure 1. study design flow chart

TABLES

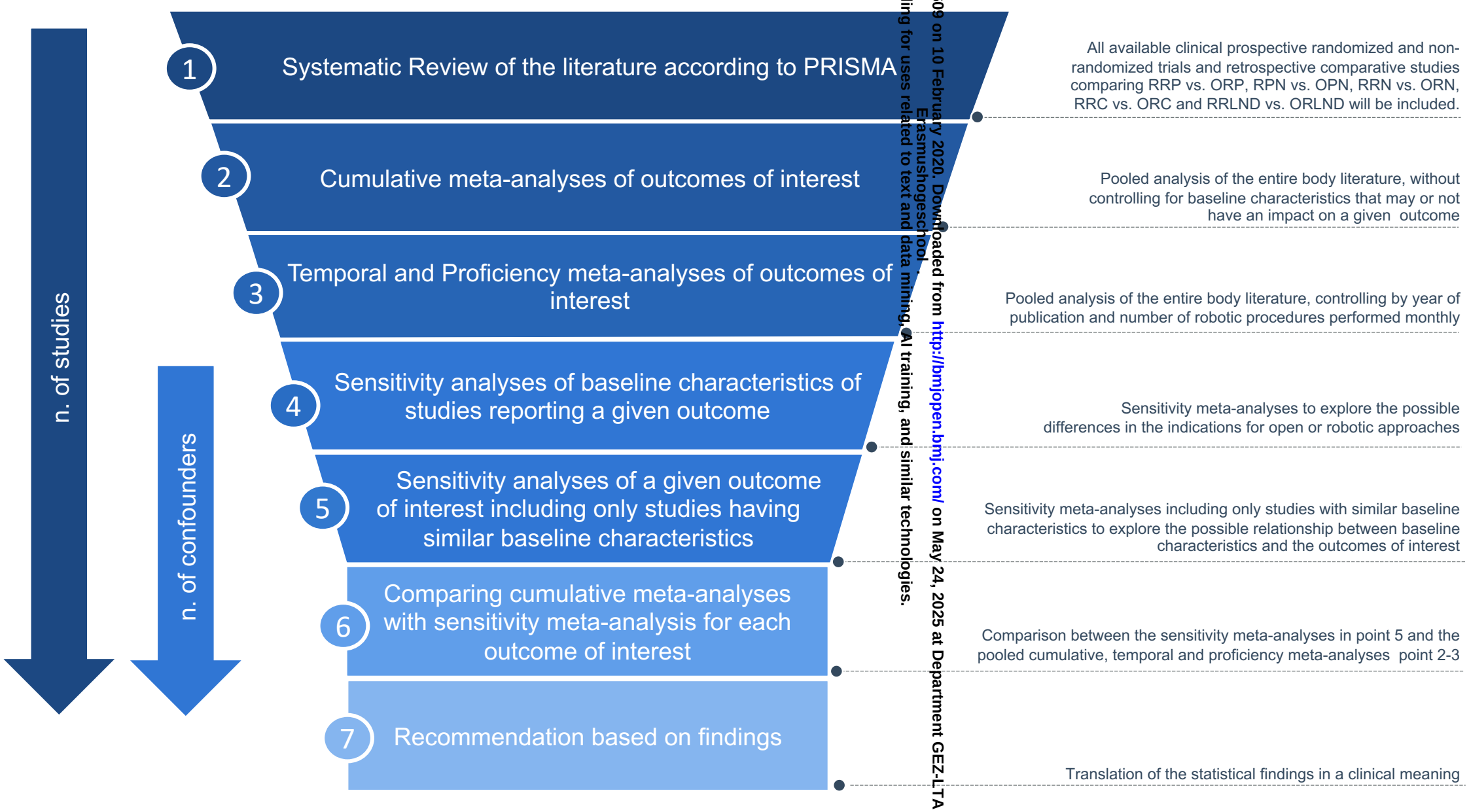
Table 1. Description of the PICOTS strategy as applied to this study

	INCLUSION
POPULATION	**Age ≥ 18 yrs** **Diagnoses:** urologic neoplasia in adults: •Localized prostate cancer •Renal mass •Invasive bladder cancer •Testicular Cancer
INTERVENTIONS	•Radical prostatectomy (open vs. robotic approach) •Radical cystectomy (open vs. robotic approach) •Partial nephrectomy (open vs. robotic approach) •Radical nephrectomy (open vs. robotic approach) • Retroperitoneal Lymph node dissection (open vs robotic approach)
COMPARATORS	Comparison between open and robotic approaches in the treatment of urologic cancers included in the list above
OUTCOMES	**Perioperative outcomes:** •Operative time (min) •Estimated blood loss (ml) •Length of hospital stay (days) •Blood transfusion rate (%) •Overall complication rate (%) •Major and Minor postoperative complication rate (%) •Early and Late complication rate (%) •Readmission rate (%) **Oncologic outcomes:** •Positive margins •Lymph node counts •Cancer-specific survival •Overall survival •Recurrence-free survival **Functional outcomes:** •Potency recovery rate (n) •Continence recovery rate (n) •Health-related quality of life •Renal Function (eGFR change) **Hospital Costs:** •Operative costs •Non-operative costs
TYPE OF STUDIES	All available clinical, prospective randomized and non-randomized trials and retrospective comparative studies (cohort or case control series) comparing RRP vs. ORP, RRC vs. ORC, RPN vs. OPN, RRN vs. ORN and RRLND vs. ORLND were included. Published between 2000 and 2020.
TIMING AND SETTING	Any time point and setting

529 **Table 2**. Baseline characteristics evaluated for each comparison

Surgical Procedure	Baseline characteristics
Radical Prostatectomy (ORP vs. RRP)	Age, years
	BMI, Kg/m²
	ASA score
	PSA ng/ml
	Clinical GS ≤ 6, %
	Clinical GS = 7, %
	Clinical GS ≥ 8, %
	Pathological GS ≤ 6, %
	Pathological GS = 7, %
	Pathological GS ≥ 8, %
	pT ≥ 3, %
	pN ≥ 1, %
Radical Cystectomy (ORC vs. RRC)	Age, years
	BMI, Kg/m²
	ASA score
	Male, %
	Female, %
	NACH, %
	pT ≥ 3, %
	pN ≥ 1, %
	n of node removed, mean
Partial nephrectomy (OPN vs. RPN) and Radical Nephrectomy (ORN vs. RRN)	Age, years
	BMI, Kg/m²
	ASA score, %
	Male, %
	Preoperative eGFR
	Left/right side, %
	Tumor size, cm
	RENAL score
	Renal Score ≤ 6 , %
	Renal score 7-10, %
	Renal Score 11-12, %
	pT ≥ 1b, %
Retroperitoneal Lymph node Dissection (ORLND vs. RRLND)	Age, years
	BMI, Kg/m²
	ASA score
	Primary laterality Left/right side, %
	Preoperative AFP (ng/mL)
	Preoperative hCG (mIU/mL)
	Lympho vascular invasion, %
	pT ≥ 2, %
	pN ≥ 1, %
	n of node removed, mean

530



PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	10
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	17
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	18
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-11

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10 and supplementary appendix B
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11 and table 1
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 9 and Table 1-2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11-12
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	4

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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APPENDIX 1: Search details PUBMED, Scopus and Web of science.

((((radical[All Fields] AND ("prostatectomy"[MeSH Terms] OR "prostatectomy"[All Fields])) OR (radical[All Fields] AND ("cystectomy"[MeSH Terms] OR "cystectomy"[All Fields]))) OR (partial[All Fields] AND ("nephrectomy"[MeSH Terms] OR "nephrectomy"[All Fields]))) OR (radical[All Fields] AND ("nephrectomy"[MeSH Terms] OR "nephrectomy"[All Fields]))) OR (("retroperitoneal space"[MeSH Terms] OR ("retroperitoneal"[All Fields] AND "space"[All Fields]) OR "retroperitoneal space"[All Fields] OR "retroperitoneal"[All Fields]) AND ("lymph node excision"[MeSH Terms] OR ("lymph"[All Fields] AND "node"[All Fields] AND "excision"[All Fields]) OR "lymph node excision"[All Fields] OR ("lymph"[All Fields] AND "node"[All Fields] AND "dissection"[All Fields]) OR "lymph node dissection"[All Fields])) AND ("2000/01/01"[PDAT] : "2020/01/01"[PDAT])