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BMJ Open

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

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5	2	SYSTEMATIC REVIEW AND META-ANALYSIS
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, 8	2	Giovanni E. Cacciamani MD. Karanvir Gill MS and Inderhir S. Gill. MD*
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25	12	cystectomy, RRC, Robotic Partial Nephrectomy, RPN, Robotic Radical Nephrectomy, RRN,
26	13	retroperitoneal lymphadenectomy
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1 2		
3	41	ABSTRACT
4 5	42	
6	43	Introduction
7 8 0	44	Minimally invasive surgery (MIS) in urology has grown considerably in application since
) 10 11	45	its initial description in the early 1990s. Herein, we present the protocol for a systematic review
12 13	46	and meta-analysis comparing open versus robotic urologic oncologic surgery for various
14 15	47	clinically-relevant outcomes, as well as to assess their comparative penetrance over the past 20
16 17	48	years (2000-2020).
18 19	49	Methods and analysis
20 21	50	We will document the penetrance of robotic versus open surgery in the urologic-
22 23	51	oncologic field using a national database.
24 25	52	Secondly, we will perform a systematic review and meta-analysis of all published full-text
26 27 28	53	English and non-English language articles from Pubmed $\ensuremath{\mathbb{R}}$, Scopus $\ensuremath{\mathbb{R}}$ and Web of Science $\ensuremath{\mathbb{R}}$
28 29 30	54	search engines on surgical treatment of localized prostate, bladder, kidney and testis cancer
30 31 32	55	published between 01/01/2000 and 01/10/2020. We will focus on the highest-volume urologic
33 34	56	oncologic surgeries, namely, radical prostatectomy (RP), radical cystectomy (RC) partial
35 36	57	nephrectomy (PN), radical nephrectomy (RN) and retroperitoneal lymph node dissection
37 38	58	(RPLND). Study inclusion criteria will comprise clinical trials and prospective and retrospective
39 40	59	studies (cohort or case-control series) comparing robotic versus open surgery. Exclusion criteria
41 42	60	will comprise meta-analyses, multi-institutional studies, multiple papers from single institutions
43 44	61	with overlapping periods, studies analyzing national databases and case series describing only
45 46	62	one approach (robotic or open). Risk-of-bias for included studies will be assessed by the
47 48 40	63	appropriate Cochrane risk of bias tool. Principal outcomes assessed will include peri-operative,
49 50 51	64	functional, oncologic, survival and financial outcomes of open versus robotic uro-oncologic
52 53	65	surgery. Sensitivity-analyses will be performed to correlate outcomes of interest with key
54 55 56	66	baseline characteristics and surrogates of surgical expertise.
57 58 59		2

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3 4	67	
5 6	68	Ethics and dissemination
7 8	69	This comprehensive systematic review and meta-analysis will provide rigorous,
9 10	70	consolidated information on contemporary outcomes and trends of open versus robotic urologic
11 12	71	oncologic surgery based on all the available literature. These aggregate data will help
13 14 15	72	physicians better advise patients seeking surgical care for urologic cancers. (PROSPERO
15 16 17	73	registration number: CRD42017064958).
17 18 19	74	
20 21	75	
22 23	76	
24 25 26 27	77	
27 28 29 30	78	
31 32 33	79	
34 35	80	
36 37 38	81	
39 40 41	82	
42 43 44	83	
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1 2 3 4	89	STRENGTHS AND LIMITATIONS
5 6 7	90	Strengths of this protocol includes standardized and transparent methods and processes that
/ 8 0	91	minimize possible biases.
9 10 11	92	• The present study will be the first to evaluate the 5 highest-volume open versus robotic urologic
12 13	93	oncologic surgeries over 20 years (2000-2020) as regards outcomes, costs and comparative
14 15	94	penetrance.
16 17	95	This protocol is the first to correlate outcomes of interest with baseline characteristics and surrogates
18 19	96	of surgical expertise (i.e., surgical case-volumes and year-of-publication).
20 21	97	The quality of evidence will be assessed to provide confidence in the effect estimates, thereby
22 23 24	98	reporting the strength of recommendations and deriving clinical meaning from the statistical findings.
25 25 26	99	Limitations of the study will be the paucity of randomized controlled trials and the heterogeneity
27 28	100	amongst available publications.
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 9 50 51 52 53 54 55 56 57	101	
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2		
3 4	103	INTRODUCTION
5	104	Minimally invasive surgery (MIS) in urology has grown considerably in application since
0 7 8	105	its initial description over three decades ago. Initially, throughout the 1990s, urologic MIS
9 10	106	consisted mostly of laparoscopic surgery, which, due to its skill-intensive nature, was slow to be
10 11 12	107	adopted by practitioners in the field. Robotic surgery, initially applied to urology in the early
13 14	108	2000s, has gradually, and now virtually completely, replaced laparoscopy in uro-oncologic
15 16	109	surgery in the United States. Specifically, robotics has now also emerged as a viable alternative
17 18	110	to open surgery in many uro-oncologic applications. This shift away from open surgery and
19 20	111	towards robotic surgery is relatively recent and significant.
21 22	112	Robotic surgery is increasing in application and scope. By the end of 2017, a total of
23 24 25	113	4409 robotic platforms had been installed globally, 43 000 robotic surgeons trained, over 5
25 26 27	114	million robotic surgeries performed across various disciplines worldwide, with over 15 000
27 28 29	115	publications [1]. In 2017, total revenue for Intuitive Surgical, the sole manufacturer of the da
30 31	116	Vinci robot was reportedly \$3.1 billion. Globally, estimated annual case volumes increased from
32 33	117	136 000 in 2008 to 877 000 in 2017; in urology, robotic procedures increased from 85 000 to
34 35	118	118 000 annually (2010-2017) [2]. Given the significant increase in the number of robotic
36 37	119	surgeries for prostate, bladder and kidney cancer, robotic surgery is now a major domain in
38 39	120	urologic oncologic surgery.
40 41 42	121	We seek to examine the state-of-the-field of open versus robotic urologic oncologic
42 43	122	surgery over the past 20 years (2000-2020) by assessing the highest-volume oncologic
44 45 46	123	surgeries: radical prostatectomy (RP) for prostate cancer, radical cystectomy (RC) for bladder
47 48	124	cancer, partial nephrectomy (PN) and radical nephrectomy (RN) for kidney cancer and
49 50	125	retroperitoneal lymph node dissection (RPLND) for testis cancer. For each of these procedures
51 52	126	that have the requisite published comparative data, we will compare the two surgical
53 54	127	approaches, open versus robotic, as follows: for prostate cancer - open radical prostatectomy
55 56	128	(ORP) vs robotic radical prostatectomy (RRP); for bladder cancer - open radical cystectomy
57 58		5

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3 4	129	(ORC) vs robotic radical cystectomy (RRC); for kidney cancer - open partial nephrectomy (OPN)
5 6	130	vs robotic partial nephrectomy (RPN) and open radical nephrectomy (ORN) vs robotic radical
7 8	131	nephrectomy (RRN); and, for testis cancer - open retroperitoneal lymph node dissection
9 10	132	(ORPLND) vs. robotic retroperitoneal lymph node dissection (RRPLND). For each procedure
11 12	133	type, we will also interrogate a national data base (the Premiere database) to assess
13 14	134	comparative penetrance in the field, Suddenly, we will compare open versus robotic surgery as
15 16 17	135	regards peri-operative data, procedural morbidity, oncologic outcomes, functional outcomes and
17 18 10	136	financial costs. This penetrance analysis, systematic review and meta-analysis will help inform
20 21	137	physicians and patients about contemporary trends in oncologic surgery for urologic cancers.
22 23	138	
24		
25	139	OBJECTIVES
26		
27 28	140	The aim of this study is to present a protocol paper for a rigorous systematic review and
29 30 31	141	meta-analysis of all published comparative studies of robotic versus open urologic oncologic
32 33	142	surgery from 2000-2020, as well as an evaluation of the Premiere database, to answer the
34 35	143	following Key Questions (KQs).
36 37 38	144	Key Questions
39 40	145	KQ 1: What is the annual comparative penetrance of open vs robotic urologic oncologic
41 42 42	146	surgery?
45 44 45	147	KQ2: What are the peri-operative outcomes and complications of open vs robotic urologic
46 47	148	oncologic surgery?
48 49 50	149	KQ3: What are the oncologic outcomes and short-term survival data of open vs robotic urologic
50 51 52	150	oncologic surgery?
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Page 8 of 23

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> 151 KQ4: What are the functional outcomes and health-related quality-of-life outcomes of open vs 152 robotic urologic oncologic surgery?

KQ5: What is the financial cost comparison of open vs robotic urologic oncologic surgery? 153

154 For each procedure type, we will methodically and separately compare open versus 155 robotic surgery as regards five key questions: penetrance in the field, peri-operative data, 156 procedural morbidity, oncologic outcomes, functional outcomes and financial cost

METHODS 157

a) Trends analysis - Penetrance-in-the-field 158

159 We will analyze data from the Premier Hospital Database (Premier Inc., Charlotte, NC, 160 USA), a nationally representative all-payer database capturing more than 152 million hospital 161 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]. 162 Using the International Classification of Diseases, 9th Revision (ICD-9) codes, we will identify 163 patients diagnosed with prostate cancer (code 185), bladder cancer (codes 188.x,233.7, 236.7) 164 165 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), 166 167 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 168 169 procedures. We will examine yearly trends in the adoption rates of robotic procedures over time. 170 defined as the percentage of procedures performed robotically. 171 b) Systematic review and meta-analysis of the literature 172 Patient and public involvement statement 173 7

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1 2		
2 3 4	174	Patients and the public were not involved in the development of the research questions,
5 6 7	175	outcome measures and study design.
8 9	176	Study design
10 11 12	177	This study will be performed according to The Preferred Reporting Items for Systematic
12 13 14	178	Review and Meta-Analysis Protocols (PRISMA-P) 2015 guidelines [8].
15 16 17	179	Eligibility Criteria
18 19	180	A summary of the participants, interventions, comparators, outcomes and time and settings
20 21	181	considered is provided, alongwith the type of studies included according to PICOTS strategy
22 23 24	182	(Population, Intervention, Comparators, Outcomes, Timing and Setting; Table 1). Following is
25 26	183	the detailed description.
27 28 29	184	1. Types of studies to be included
30 31	185	All available clinical prospective randomized and non-randomized trials and retrospective
32 33	186	comparative studies (cohort or case-control series) comparing ORP vs. RRP, ORC vs. RRC,
34 35	187	OPN vs. RPN, ORN vs. RRN and ORPLND vs. RRPLND and published between 2000 and
36 37	188	2020 will be included. No language restrictions will be applied. Native speaking urologists will be
38 39 40	189	involved in the translation of non-English publications.
41 42 43	190	2. Condition being studied
44 45	191	We will examine the literature of open versus robotic urologic oncologic surgery by
46 47	192	assessing the commonest oncologic surgeries: RP for localized prostate cancer, RC for
48 49	193	invasive bladder cancer, PN and RN for renal mass and RPLND for testis cancer.
50 51	194	
52 53 54 55	195	3. Type of Participants/population
56 57		
58 59		8

Page 10 of 23

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2 3	196	We will include adult participants (age ≥18 vrs), with diagnoses of urologic neoplasia
4 5	150	
6 7	197	(localized prostate cancer, invasive bladder cancer, renal mass, testis cancer).
8	198	
9 10 11	199	4. Type of Intervention and Comparators
12 13	200	We will evaluate the comparator intervention (open approach) vs. the experimental
14 15	201	intervention (robotic approach) separately, for each surgical procedure: RP, RC, PN, RN and
16 17	202	RPLND.
18 19	203	
20 21 22	204	5. Type of outcomes measures
22 23 24	205	We will compare the following outcomes between open and robotic uro-oncologic surgery: .
25 26	206	a) Penetrance: U.S. data for the number of surgeries performed annually for each
27	207	procedure type (Premiere Database).
29 30 31	208	b) Peri-operative outcomes: Operative time (min); estimated blood loss (ml); length of
32	209	hospital stay (days); blood transfusion rate (%); complication rate (%) – overall, minor
34 35	210	(Clavien-Dindo \leq 3), major (Clavien-Dindo \geq 3), early (within 30 days), late (31-90 days);
36 37	211	rate of specific complications (wound, anastmotic, cardio-vascular, gastro-intestinal,
38 39	212	thrombo-embolic, infectious); and, re-admission rate (%).
40 41	213	c) Functional outcomes: At four time-points after surgery - early (at 3 months), intermediate
42 43	214	(at 6 months), late (at 12 months) and overall (latest month) - assess erectile dysfunction
44 45	215	rate (%) and incontinence rate (%) after RP; and decline in estimated glomerular rate
46 47 48	216	(eGFR) after PN and RN.
40 49	217	d) Oncologic and Survival outcomes: Rate of positive surgical margins (%); lymph node
50 51 52	218	yield; recurrence rate (%); cancer-specific survival rate (%); and overall survival rate
53 54	219	(%).
55 56	220	e) Hospital Costs: operative costs and non-operative costs.
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- 3 4	221	
5 6	222	Search Strategy for Relevant Studies
7 8	223	The systematic review will be performed in accordance with the Cochrane Guidelines
9 10	224	[9], the Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) [10]
11 12	225	and graded strength of evidence using the scheme recommended by Methods and Guide for
13 14	226	effectiveness and comparative Effectiveness Review of the Agency for Healthcare Research
15 16	227	and Quality (AHRQ) [11]. The present study is registered with PROSPERO, number
17 18 10	228	CRD42017064958
19 20 21	229	(https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017064958).
22 23	230	We will search Pubmed $^{\ensuremath{\mathbb{R}}}$, Scopus $^{\ensuremath{\mathbb{R}}}$ and Web of Science $^{\ensuremath{\mathbb{R}}}$ databases for all published
24 25	231	full text English and non-English language articles on the treatment of localized prostate,
26 27	232	bladder, kidney and testis cancer, using the keywords "radical prostatectomy" OR "radical
28 29	233	cystectomy" OR "partial nephrectomy" OR "radical nephrectomy" OR "retroperitoneal lymph
30 31	234	node dissection" published between January 1, 2000 and January 10, 2020. No language
32 33	235	restriction will be applied. References will be manually reviewed to identify supplementary
34 35 36	236	studies of interest.
30 37 38	237	We will exclude case-series describing only one approach (robotic or open), studies not
39 40	238	comparing open versus robotic approach, non-comparative series, multi-institutional studies
41 42	239	reporting overlapping data with series previously published, studies from the same institution
43 44	240	with overlapping data, reviews, meta-analyses, surgical technique description papers, replies,
45 46	241	commentaries and editorial comments, single case reports, papers about paediatric surgery,
47 48	242	non-matching articles and studies not providing outcomes of interest,.
49 50	243	Multi-institutional studies which report data never published by participating single-center
51 52	244	studies will be considered. When an institution has published multiple papers with overlapping
53 54 55 56	245	surgical periods, we will consider only the latest published paper. We will exclude studies
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3 4	246	analyzing national databases because of the high risk of overlapping data. The words "robot(ic)-
5 6	247	assisted" and "robotic" will be used interchangeably.
7 8	248	
9 10	249	Screening and Data Extraction
11 12	250	Two paired investigators (G.E.C and I.S.G) will independently screen all articles focusing
13 14 15	251	the research on open versus robotic surgery. All available clinical trials, prospective and
15 16 17	252	retrospective studies (cohort or case control series) comparing open vs. robotic surgery will be
18 19	253	included. Any disagreements about eligibility will be resolved by discussion between the paired
20 21	254	investigators until consensus is reached.
22 23	255	
24 25	256	Quality Assessment
26 27	257	All papers will be categorized according to the Oxford Level of Evidence Working Group
28 29	258	2011 levels of evidence (LOEs) for therapy studies [12]. Two paired investigators (G.E.C and
30 31 22	259	I.S.G) will independently weigh the risk of bias for all the studies according to the Cochrane
32 33 24	260	Handbook for Systematic Reviews of Interventions for including nonrandomized studies [15]. In
34 35 36	261	consideration of the design of studies, we will likewise examine the risk of preassigned
37 38	262	confounders identified as the possible predictors at the time of surgery. We will examine articles
39 40	263	for specific data on baseline characteristics that may have impact on outcomes of interest within
41 42	264	their univariate analysis models.
43 44	265	
45 46	266	Statistical Analysis
47 48	267	Figure 1 summarizes the steps of the present systematic review. A cumulative meta-
49 50	268	analysis will be conducted using Review Manager®5.3 (Cochrane Collaboration, Oxford, UK).
51 52	269	Weighted mean difference (WMD) will be used to compare continuous variables and odds ratio
53 54 55	270	(OR), and Risk Ratio (RR) and Hazard Ratios (HR) will be used to compare dichotomous
55 56 57	271	variables, respectively. Baseline characteristics will be analyzed in the same fashion.
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2 3 4	272	All results will be reported with 95% confidential intervals (CI). Statistical heterogeneity
5 6	273	between studies will be tested using the l^2 statistic [9]. Heterogeneity will be considered low,
7 8	274	moderate and high when the values are below 25%, between 25% and 75%, and above 75%,
9 10	275	respectively [9, 16].
11 12	276	Random and fixed effects will be used in case of the presence or absence of
13 14	277	heterogeneity, respectively [9]. A two-sided p-value < 0.05 will be considered statistically
15 16 17	278	significant. Pooled analysis of continuous variables is possible only when data are presented as
17 18 10	279	mean and standard deviation (SD). Since some studies may report continuous variables in
20 21	280	"median" and "interquartile range" or "min/max" range, we will use a validated mathematical
22 23	281	method to estimate "mean" and "SD" [17]. When available, we will use data reported in a
24 25	282	matched-pair comparison manner.
26 27	283	The use of pooled graphical effect of a meta-analysis that includes RCTs and non-RCTs
28 29	284	allows assessment of the similarity between the studies. Forest plots allow the presentation of
30 31	285	estimates and standard errors for each study. Graphical representation of pooled findings will be
32 33	286	made according to the heterogeneity [9].
34 35	287	
36 37 38	288	Assessment of publication bias
30 39 40	289	Funnel plots will be visually inspected to assess both the degree of publication bias and
41 42	290	its effect on the study findings. Egger's weighted regression will be used to test for publication
43 44	291	bias, with p<0.1 considered indicative of statistically significant publication bias. When
45 46	292	asymmetry is found, extreme outliers (i.e. small studies) will be removed from the funnel plot,
47 48	293	Duval and Tweedie non-parametric 'trim and fill' analysis to formalize the use of funnel plot and
49 50	294	and re-computing the effect size to correct for publication bias [15]. When necessary, to assess
51 52	295	the risk of bias in the non-RCTs included in our meta-analysis, we will independently weigh the
53 54 55	296	risk-of-bias for all studies according to the Cochrane Handbook for Systematic Reviews of
55 56 57	297	Interventions for including non-randomized studies [9]. In considering the design of studies, we
58		12
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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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.

302 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.

9 315 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 multicentre 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

Page 17 of 23

1 2		
2 3 4	375	total cost differential of robotic vis-a-vis open surgery will be considered. We will convert all
5 6	376	currencies to the 2020 exchange rate using the Consumer Price Index (CPI) inflation calculator
7 8	377	(https://www.bls.gov/data/inflation_calculator.htm). Foreign currency will first be converted to
9 10	378	dollars using historical exchange rates at the year of publication and then adjusted to the 2020
11 12	379	exchange rate using the CPI inflation calculator.
13 14	380	
15 16 17	381	Grade Of The Evidence
18 19	382	The quality of scientific evidence and outcomes will be assessed using the Grading of
20 21	383	Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE
22 23 24 25 26 27 28 29 30	384	offers a specific definition of the quality of evidence that is different in the context of making
	385	recommendations and in the context of summarizing the findings of a systematic review [13, 14]
	386	The GRADE methodology involves rating evidence for a given outcome by upgrading or
	387	downgrading the evidence. Indications for upgrading the quality of evidence include having a
31 32	388	large effect size and dose-response gradient. Indications for downgrading the quality of
 33 34 35 36 37 38 39 40 41 	389	evidence include serious risk of bias, serious inconsistency between studies, serious
	390	indirectness, serious imprecision and likely publication bias [20]. Summary of Findings (SoF)
	391	tables will provide a summary of findings for each of the included outcomes and the quality of
	392	evidence rating for each outcome [20]. The format of the Sof will include:
41 42 43	393	1. A list of the outcomes of interest
44 45	394	2. The assumed risk; a measure of the typical burden of the outcomes, i.e. illustrative risk or
46 47	395	also called baseline risk, baseline score, or control group risk
48 49	396	3. The corresponding risk; a measure of the burden of the outcomes after the intervention is
50 51	397	applied, i.e. the risk of an outcome in treated/exposed people based on the relative
52 53	398	magnitude of an effect and assumed (baseline) risk
54 55		
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58 59		16
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3 4	399	4. The relative effect; for dichotomous outcomes the table will provide risk ratio, odds ratio, or
5 6	400	hazard ratio
7 8	401	5. The number of participants, the number of studies and their designs
9 10	402	6. Rating of the overall quality of evidence for each outcome
11 12 13	403	Presentation of results and reporting
14 15 16	404	The PRISMA guidelines [10] will be used and the checklist will accompany the publication.
17 18	405	Quantitative data will be summarized and presented in tables and as forst plots where
19 20	406	necessary [9].
21 22 23	407	Potential amendments
24 25 26	408	We do not anticipate any amendments to the current protocol. However, should an amendment be
20 27 28	409	necessary, it will be notified, registered and reported.
29 30 31	410	Ethics and Dissemnination
32 33	411	No ethics clearance is necessary as no primary data will be collected. Results will be published in a peer-
34 35 36	412	reviewed journal. These results will likely help inform directions and design of future studies.
37 38	413	
39 40 41 42	414	IMPLICATIONS OF THE REVIEW
43 44	415	We believe this aggregate information will be of interest and practical use to the general medical
45 46	416	community at large, who need to be aware of contemporary trends in urologic oncologic
47 48	417	surgery, thereby to better advice patients seeking care for urologic cancers.
49 50	418	
51 52 53 54 55	419	CONCLUSION
56 57		
58 59		17

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2 3	420	This systematic review and meta-analysis will compare multiple outcomes of open versus robotic urologic
4 5 6	421	oncologic surgery over two decades, from 2000-2020. A synthesis of all available studies will identify the
0 7 8	422	quality of data. This meta-analysis will be used to inform future studies to fulfill gaps in knowledge in
9 10	423	comparative outcomes of open and robotic urologic oncologic surgery.
11 12 13	424	
14	425	FOOTNOTES
15	120	Contributorship statement : LSC and CEC concentualized and designed the protocol
16 17	426	Contributorship statement : 1.5.G and G.E.C conceptualised and designed the protocol,
18 19	427	drafted the initial manuscript and reviewed the manuscript. I.S.G and G.E.C defined the
20 21	428	concepts and search items, data extraction process as well as methodological appraisal of the
22 23	429	studies. G.E.C, K.S.G and I.S.G planned the data extraction and statistical analysis. I.S.G and
24 25	430	G.E.C, provided critical insights. All authors have approved and contributed to the final written
26 27 28	431	manuscrip
28 29 30 31	432	
32 33	433	Competing interests: None declared.
34 35 36	434	
37 38	435	Funding: The authors have not declared a specific grant for this research from any funding
39 40 41	436	agency in the public, commercial or not-for-profit sectors.
42 43 44	437	
45 46	438	Data sharing statement: There are no data in this work
47 48 40	439	
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1 2		
2 3 1	490	FIGURE CAPTATION
5	491	Figure 1. study design flow chart
7	492	
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TABLES

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

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 RR
	vs ORP, RRC vs ORC, RPN vs OPN, RRN vs ORN and RRLND vs ORLND were
	included. Published between 2000 and 2020.



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

Surgical Procedure	Baseline characteristics
Radical Prostatectomy	Age, years
(ORP vs. RRP)	BMI, Kg/m²
	ASA score
	PSA ng/MI
	Clinical GS \leq 6, %
	Clinical GS = 7, %
	Clinical GS ≥ 8, %
	Pathological GS ≤ 6, %
	Pathological GS = 7, %
	Pathological GS ≥ 8, %
	pT ≥ 3, %
	pN ≥ 1, %
Radical Cystectomy	Age, years
(ORC vs. RRC)	BMI, Kg/m²
	ASA score
	Male, %
	Female, %
	NACH, %
	pT ≥ 3, %
	pN ≥ 1, %
	n of node removed, mean
Partial nephrectomy (OPN vs. RPN) and Radical	Age, years
Nephrectomy (ORN vs. RRN)	BMI, Kg/m ²
	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	Age, vears
(ORIND vs. RRIND)	BMI. Kg/m ²
	ASA score
	Primary lateraly Left/right side, %
	Preoperative AFP (ng/mL)
	Preoperative hCG (mlU/ml)
	Lympho vascular invasion %
	nT > 2 %
	$p_{1} = 2, 70$ nN > 1 %
	PIN = 1, /0

Page 24 of 23



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

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Primary Subject Heading :	Urology
Secondary Subject Heading:	Oncology, Evidence based practice, Health economics, Surgery
Keywords:	Prostate disease < UROLOGY, Bladder disorders < UROLOGY, Kidney tumours < NEPHROLOGY, UROLOGY, Minimally invasive surgery < GYNAECOLOGY





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6	2	SYSTEMATIC REVIEW AND META-ANALYSIS
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14	5	USC Institute of Urology & the Catherine and Joseph Aresty Department of Urology, Keck
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21 22	10	Konworde
22	10	Reywords
24	11	Robotic Surgery, Oncology, Urology, Robotic Radical Prostatectomy, RRP, Robotic Radical
25	12	cystectomy, RRC, Robotic Partial Nephrectomy, RPN, Robotic Radical Nephrectomy, RRN,
26	13	retroperitoneal lymphadenectomy
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31 32	17	Total words: 3684 Abstract: 297: Text: 3398
33	18	References: 20
34	19	Tables: 2
35	20	Figures: 1
36	21	
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3	41	ABSTRACT
5	42	
6 7	43	Introduction
7 8 9	44	Minimally invasive surgery (MIS) in urology has grown considerably in application since
) 10 11	45	its initial description in the early 1990s. Herein, we present the protocol for a systematic review
12 13	46	and meta-analysis comparing open versus robotic urologic oncologic surgery for various
14 15	47	clinically-relevant outcomes, as well as to assess their comparative penetrance over the past 20
16 17	48	years (2000-2020).
18 19	49	Methods and analysis
20 21	50	We will document the penetrance of robotic versus open surgery in the urologic-
22 23	51	oncologic field using a national database.
24 25	52	Secondly, we will perform a systematic review and meta-analysis of all published full-text
26 27 28	53	English and non-English language articles from Pubmed $\ensuremath{\mathbb{R}}$, Scopus $\ensuremath{\mathbb{R}}$ and Web of Science $\ensuremath{\mathbb{R}}$
20 29 30	54	search engines on surgical treatment of localized prostate, bladder, kidney and testis cancer
30 31 32	55	published between 01/01/2000 and 01/10/2020. We will focus on the highest-volume urologic
33 34	56	oncologic surgeries, namely, radical prostatectomy (RP), radical cystectomy (RC) partial
35 36	57	nephrectomy (PN), radical nephrectomy (RN) and retroperitoneal lymph node dissection
37 38	58	(RPLND). Study inclusion criteria will comprise clinical trials and prospective and retrospective
39 40	59	studies (cohort or case-control series) comparing robotic versus open surgery. Exclusion criteria
41 42	60	will comprise meta-analyses, multi-institutional studies, multiple papers from single institutions
43 44	61	with overlapping periods, studies analyzing national databases and case series describing only
45 46 47	62	one approach (robotic or open). Risk-of-bias for included studies will be assessed by the
47 48 49	63	appropriate Cochrane risk of bias tool. Principal outcomes assessed will include perioperative,
49 50 51	64	functional, oncologic, survival and financial outcomes of open versus robotic uro-oncologic
52 53	65	surgery. Sensitivity-analyses will be performed to correlate outcomes of interest with key
54 55 56	66	baseline characteristics and surrogates of surgical expertise.
57 58 59		2

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1 2		
3	67	
5 6	68	Ethics and dissemination
7 8	69	This comprehensive systematic review and meta-analysis will provide rigorous,
9 10	70	consolidated information on contemporary outcomes and trends of open versus robotic urologic
11 12	71	oncologic surgery based on all the available literature. These aggregate data will help
13 14 15	72	physicians better advise patients seeking surgical care for urologic cancers. (PROSPERO
15 16 17	73	registration number: CRD42017064958).
17 18 19	74	
20 21	75	
22 23 24	76	
25 26 27	77	
28 29 30	78	
31 32 33	79	
34 35	80	
36 37 38	81	
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89	STRENGTHS AND LIMITATIONS
90	The strengths of this protocol include standardized and transparent methods and processes that
91	minimize possible biases. The quality of evidence will be assessed to provide confidence in the effect
92	estimates, thereby reporting the strength of recommendations and deriving clinical meaning from the
93	statistical findings.
94	The present study will be the first to evaluate the five highest-volume open versus robotic urologic
95	oncologic surgeries over 20 years (2000-2020) as regards outcomes, costs and comparative
96	penetrance.
97	This meta-analysis will be used to inform future studies to fulfill gaps in knowledge in comparative
98	outcomes of open and robotic urologic oncologic surgery.
99	This protocol is the first to correlate outcomes of interest with baseline characteristics and surrogates
100	of surgical expertise (i.e., surgical case-volumes and year-of-publication).
101	Limitations of the study will be the paucity of randomized controlled trials and the heterogeneity
102	amongst available publications.
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1 2		
3 4	105	INTRODUCTION
5 6	106	Minimally invasive surgery (MIS) in urology has grown considerably in application since
0 7 8	107	its initial description over three decades ago. Initially, throughout the 1990s, urologic MIS
9 10	108	consisted mostly of laparoscopic surgery, which, due to its skill-intensive nature, was slow to be
11 12	109	adopted by practitioners in the field. Robotic surgery, initially applied to urology in the early
13 14	110	2000s, has gradually, and now virtually completely, replaced laparoscopy in uro-oncologic
15 16	111	surgery in the United States. Specifically, robotics has now also emerged as a viable alternative
17 18 19 20 21	112	to open surgery in many uro-oncologic applications. This shift away from open surgery and
	113	towards robotic surgery is relatively recent and significant.
21 22 22	114	Robotic surgery is increasing in application and scope. By the end of 2017, a total of
23 24 25 26 27 28 29 30 31 32 33	115	4409 robotic platforms had been installed globally, 43 000 robotic surgeons trained, over 5
	116	million robotic surgeries performed across various disciplines worldwide, with over 15 000
	117	publications [1]. In 2017, total revenue for Intuitive Surgical, the sole manufacturer of the da
	118	Vinci robot was reported \$3.1 billion. Globally, estimated annual case volumes increased from
	119	136 000 in 2008 to 877 000 in 2017; in urology, robotic procedures increased from 85 000 to
34 35	120	118 000 annually (2010-2017) [2]. Given the significant increase in the number of robotic
36 37	121	surgeries for prostate, bladder and kidney cancer, robotic surgery is now a major domain in
38 39	122	urologic oncologic surgery.
40 41 42	123	We seek to examine the state-of-the-field of open versus robotic urologic oncologic
42 43 44	124	surgery over the past 20 years (2000-2020) by assessing the highest-volume oncologic
45 46	125	surgeries: radical prostatectomy (RP) for prostate cancer, radical cystectomy (RC) for bladder
47 48	126	cancer, partial nephrectomy (PN) and radical nephrectomy (RN) for kidney cancer and
49 50	127	retroperitoneal lymph node dissection (RPLND) for testis cancer. For each of these procedures
51 52	128	that have the requisite published comparative data, we will compare the two surgical
53 54	129	approaches, open versus robotic, as follows: for prostate cancer - open radical prostatectomy
55 56	130	(ORP) vs. robotic radical prostatectomy (RRP); for bladder cancer - open radical cystectomy
57 58		5

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2 3 4	131	(ORC) vs. robotic radical cystectomy (RRC); for kidney cancer - open partial nephrectomy
5 6	132	(OPN) vs. robotic partial nephrectomy (RPN) and open radical nephrectomy (ORN) vs. robotic
7 8	133	radical nephrectomy (RRN); and, for testis cancer - open retroperitoneal lymph node dissection
9 10	134	(ORPLND) vs. robotic retroperitoneal lymph node dissection (RRPLND). For each procedure
11 12	135	type, we will also interrogate a national database (the Premiere database) to assess
13 14	136	comparative penetrance in the field. Suddenly, we will compare open versus robotic surgery as
15 16	137	regards perioperative data, procedural morbidity, oncologic outcomes, functional outcomes and
17 18 10	138	financial costs. This penetrance analysis, systematic review and meta-analysis will help inform
19 20 21	139	physicians and patients about contemporary trends in oncologic surgery for urologic cancers.
21 22 23	140	
24		
25 26	141	OBJECTIVES
27 28	142	The aim of this study is to present a protocol paper for a rigorous systematic review and
29 30 31	143	meta-analysis of all published comparative studies of robotic versus open urologic oncologic
32 33	144	surgery from 2000-2020, as well as an evaluation of the Premiere database, to answer the
34 35	145	following Key Questions (KQs).
36 37	146	Key Questions
30 39 40	147	KQ 1: What is the annual comparative penetrance of open vs robotic urologic oncologic
41 42 43	148	surgery?
44 45	149	KQ2: What are the perioperative outcomes and complications of open vs. robotic urologic
46 47 48	150	oncologic surgery?
48 49 50	151	KQ3: What are the oncologic outcomes and short-term survival data of open vs. robotic urologic
51 52 53	152	oncologic surgery?
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Page 8 of 26

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> 153 KQ4: What are the functional outcomes and health-related quality-of-life outcomes of open vs. robotic urologic oncologic surgery? 154

KQ5: What is the financial cost comparison of open vs. robotic urologic oncologic surgery? 155

156 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, 157

158 procedural morbidity, oncologic outcomes, functional outcomes and financial cost

METHODS 159

a) Trends analysis - Penetrance-in-the-field 160

161 We will analyze data from the Premier Hospital Database (Premier Inc., Charlotte, NC, 162 USA), a nationally representative all-payer database capturing more than 152 million hospital 163 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]. 164 Using the International Classification of Diseases, 9th Revision (ICD-9) codes, we will identify 165 patients diagnosed with prostate cancer (code 185), bladder cancer (codes 188.x,233.7, 236.7) 166 167 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), 168 radical nephrectomy 55.5 and retroperitoneal lymphadenectomy (codes 40.2 and 40.5) 169 170 between 2000 and 2020. Codes 17.42, 17.44, or 17.49 will be used to classify robotic 171 procedures. We will examine yearly trends in the adoption rates of robotic procedures over time. 172 defined as the percentage of procedures performed robotically. 173 b) Systematic review and meta-analysis of the literature 174 Patient and public involvement statement 175 7

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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

Page 10 of 26

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2 3	198	We will include adult participants (age ≥18 yrs), with diagnoses of urologic neoplasia
4 5 6 7 8 9	199	(localized prostate cancer, invasive bladder cancer, renal mass, testis cancer).
	200	
	201	4 Type of Intervention and Comparators
10 11	201	4. Type of mervention and comparators
12 13	202	We will evaluate the comparator intervention (open approach) vs. the experimental
14 15	203	intervention (robotic approach) separately for each surgical procedure: RP, RC, PN, RN and
16 17	204	RPLND.
18 19	205	
20 21 22	206	5. Type of outcomes measures
22 23 24	207	We will compare the following outcomes between open and robotic uro-oncologic surgery:
25 26 27	208	a) Penetrance: U.S. data for the number of surgeries performed annually for each
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41	209	procedure type (Premiere Database).
	210	b) Peri-operative outcomes: Operative time (min); estimated blood loss (ml); length of
	211	hospital stay (days); blood transfusion rate (%); complication rate (%) – overall, minor
	212	(Clavien-Dindo \leq 3), major (Clavien-Dindo \geq 3), early (within 30 days), late (31-90 days);
	213	rate of specific complications (wound, anastmotic, cardio-vascular, gastro-intestinal,
	214	thrombo-embolic, infectious); and, re-admission rate (%).
	215	c) Functional outcomes: At four time-points after surgery - early (at 3 months), intermediate
42 43	216	(at 6 months), late (at 12 months) and overall (latest month) - assess erectile dysfunction
44 45	217	rate (%) and incontinence rate (%) after RP; and decline in estimated glomerular rate
46 47	218	(eGFR) after PN and RN.
48 49	219	d) Oncologic and Survival outcomes: Rate of positive surgical margins (%); lymph node
50 51	220	yield; recurrence rate (%); cancer-specific survival rate (%); and overall survival rate
52 53	221	(%).
55 56	222	e) Hospital Costs: operative costs and non-operative costs.
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2 3 4	223	
5 6	224	Search Strategy for Relevant Studies
7 8	225	The systematic review will be performed in accordance with the Cochrane Guidelines
9 10	226	[9], the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10]
11 12	227	and graded strength of evidence using the scheme recommended by Methods and Guide for
13 14	228	effectiveness and Comparative Effectiveness Review of the Agency for Healthcare Research
15 16	229	and Quality (AHRQ) [11]. The present study is registered with PROSPERO, number
17 18	230	CRD42017064958
19 20 21	231	(https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017064958).
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40	232	We will search Pubmed $^{\ensuremath{\mathbb R}}$, Scopus $^{\ensuremath{\mathbb R}}$ and Web of Science $^{\ensuremath{\mathbb R}}$ databases for all published
	233	full-text English and non-English language articles on the treatment of localized prostate,
	234	bladder, kidney and testis cancer, using the keywords "radical prostatectomy" OR "radical
	235	cystectomy" OR "partial nephrectomy" OR "radical nephrectomy" OR "retroperitoneal lymph
	236	node dissection" published between January 1, 2000, and January 10, 2020. No language
	237	restriction will be applied (Appendix B). References will be manually reviewed to identify
	238	supplementary studies of interest.
	239	We will exclude case-series describing only one approach (robotic or open), studies not
	240	comparing open versus robotic approach, non-comparative series, multi-institutional studies
40 41 42	241	reporting overlapping data with series previously published, studies from the same institution
43 44	242	with overlapping data, reviews, meta-analyses, surgical technique description papers, replies,
45 46	243	commentaries and editorial comments, single case reports, papers about pediatric surgery, non-
47 48	244	matching articles and studies not providing outcomes of interest,.
49 50	245	Multi-institutional studies that report data never published by participating single-center
51 52	246	studies will be considered. When an institution has published multiple papers with overlapping
53 54 55	247	surgical periods, we will consider only the latest published paper. We will exclude studies
50 57 58		10
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3 4	248	analyzing national databases because of the high risk of overlapping data. The words "robot(ic)-
5 6	249	assisted" and "robotic" will be used interchangeably.
7 8	250	
9 10	251	Screening and Data Extraction
11 12	252	Two paired investigators (G.E.C and I.S.G) will independently screen all articles focusing
13 14 15	253	the research on open versus robotic surgery. All available clinical trials, prospective and
15 16 17	254	retrospective studies (cohort or case-control series) comparing open vs. robotic surgery will be
17 18 19	255	included. Any disagreements about eligibility will be resolved by discussion between the paired
20 21	256	investigators until a consensus is reached.
22 23	257	
24 25	258	Quality Assessment
26 27	259	All papers will be categorized according to the Oxford Level of Evidence Working Group
28 29	260	2011 levels of evidence (LOEs) for therapy studies [12]. Two paired investigators (G.E.C and
30 31	261	I.S.G) will independently weigh the risk of bias for all the studies according to the Cochrane
32 33 34	262	Handbook for Systematic Reviews of Interventions for including non-randomized studies [13]. In
34 35 36	263	consideration of the design of studies, we will likewise examine the risk of preassigned
37 38	264	confounders identified as the possible predictors at the time of surgery. We will examine articles
39 40	265	for specific data on baseline characteristics that may have an impact on outcomes of interest
41 42	266	within their univariate analysis models.
43 44	267	
45 46	268	Statistical Analysis
47 48	269	Figure 1 summarizes the steps of the present systematic review. A cumulative meta-
49 50	270	analysis will be conducted using Review Manager®5.3 (Cochrane Collaboration, Oxford, UK).
51 52 53	271	Weighted mean difference (WMD) will be used to compare continuous variables and odds ratio
55 54 55	272	(OR), and Risk Ratio (RR) and Hazard Ratios (HR) will be used to compare dichotomous
56 57	273	variables, respectively. Baseline characteristics will be analyzed in the same fashion.
58 59		11

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1		
2 3 4	274	All results will be reported with 95% confidential intervals (CI). Statistical heterogeneity
5 6	275	between studies will be tested using the l^2 statistic [9]. Heterogeneity will be considered low,
7 8	276	moderate and high when the values are below 25%, between 25% and 75%, and above 75%,
9 10	277	respectively [9, 14].
11 12	278	Random and fixed effects will be used in case of the presence or absence of
13 14	279	heterogeneity, respectively [9]. A two-sided p-value < 0.05 will be considered statistically
15 16 17	280	significant. Pooled analysis of continuous variables is possible only when data are presented as
17 18 19	281	mean and standard deviation (SD). Since some studies may report continuous variables in
20 21	282	"median" and "interquartile range" or "min/max" range, we will use a validated mathematical
22 23	283	method to estimate "mean" and "SD" [15]. When available, we will use data reported in a
24 25	284	matched-pair comparison manner.
26 27	285	The use of the pooled graphical effect of a meta-analysis that includes RCTs and non-
28 29	286	RCTs allows assessment of the similarity between the studies. Forest plots allow the
30 31	287	presentation of estimates and standard errors for each study. Graphical representation of
32 33	288	pooled findings will be made according to the heterogeneity [9].
34 35 26	289	
30 37 38	290	Assessment of publication bias
39 40	291	Funnel plots will be visually inspected to assess both the degree of publication bias and
41 42	292	its effect on the study findings. Egger's weighted regression will be used to test for publication
43 44	293	bias, with p<0.1 considered indicative of statistically significant publication bias. When
45 46	294	asymmetry is found, extreme outliers (i.e. small studies) will be removed from the funnel plot,
47 48	295	Duval and Tweedie non-parametric 'trim and fill' analysis to formalize the use of funnel plot and
49 50	296	re-computing the effect size to correct for publication bias [13]. When necessary, to assess the
51 52	297	risk of bias in the non-RCTs included in our meta-analysis, we will independently weigh the risk-
55 55	298	of-bias for all studies according to the Cochrane Handbook for Systematic Reviews of
56 57	299	Interventions for including non-randomized studies [9]. In considering the design of studies, we
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2 3 1	300	will likewise examine the risk of preassigned confounders identified as possible predictors at the
- 5 6	301	time of surgery. We will examine all publications for specific data on baseline characteristics that
7 8	302	may impact outcomes of interest within their univariate analysis models.
9 10	303	
11 12	304	Sensitivity Analyses
13 14	305	a) Temporal Meta-Analysis
15 16 17	306	The chronologic time of publication may impact the reported outcomes of urologic oncologic
18	307	surgery; in other words, earlier publications that reflect the 'discovery' era of a novel technology
20 21	308	may demonstrate different/inferior outcomes than later publications, when the initial learning
22 23	309	curve has been surmounted. As such, we will perform a temporal meta-analysis to evaluate the
24 25	310	evolving impact of time-of-publication on reported outcomes of open and robotic uro-oncologic
26 27	311	surgery. First, a meta-regression model will be performed to assess the association between the
28 29	312	year-of-publication and the outcomes of interest. Then, we will divide all available comparative
30 31	313	studies into two equivalent temporal cohorts. Various outcomes of ORP vs. RRP, ORC vs. RRC
32 33	314	, OPN vs. RPN, ORN vs. RRN and ORLND vs. RRLND will be compared between these two
34 35 26	315	cohorts to assess the temporal impact of the robotic learning curve.
30 37 38	316	b) Proficiency Meta-Analysis
39 40	317	Similarly, surgical case volumes can impact the outcomes of urologic oncologic surgery; in
41 42	318	other words, because of presumed differences in surgical 'proficiency', low-volume centers may
43 44	319	deliver inferior outcomes compared to high-volume centers [16]. However, a clear definition of
45 46	320	low- and high-volume centres is still lacking. To evaluate the impact of surgical volumes on the
47 48	321	outcomes of interest, we will perform a "proficiency" meta-analysiss. We will exclude all multi-
49 50	322	centre studies, propensity score-matched studies and studies that do not report the surgical
51 52	323	period. The mean number of robotic procedures performed per month will be calculated by
55 54	324	dividing the total number of robotic procedures reported by the number of months in the study
55 56 57	325	period. First, a meta-regression model will be performed to assess the association between the
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3 4	326	number of robotic procedures/month and the outcomes of interest. Next, we will calculate the
5 6	327	mean number of procedures/month to determine the cut-off to distinguish between low-volume
7 8	328	(number of robotic procedures/month below the cut-off value) vs. high volume (number of
9 10	329	robotic procedures/month above the cut-off value) centres. Various outcomes of ORP vs. RRP,
11 12	330	ORC vs. RRC OPN vs. RPN, ORN vs. RRN and ORLND vs. RRLND will be compared between
13 14	331	low- and high-volume centers. Since data on single-surgeon experience in studies comparing
15 16	332	open vs. robotic uro-oncology surgery are sparse, those cut-offs will be considered as a
17 18 10	333	surrogate to evaluate the impact of surgical skill proficiency on perioperative, functional and
19 20 21	334	oncological outcomes.
21 22 23	335	
23 24 25	336	c) Assessment of Baseline Characteristics
26 27	337	Differences in baseline characteristics between cohorts may be present in the studies
28 29	338	included in a meta-analysis. Ignoring such substantial variability in one or more baseline
30 31	339	characteristics may lead to misleading conclusions, which can jeopardize the overall
32 33	340	applicability of the pooled estimates [17]. Therefore, comparability of baseline patient
34 35	341	characteristics between the two cohorts is crucial for minimizing the impact of heterogeneity on
36 37	342	study outcomes.
38 39 40	343	To account for the impact of baseline characteristics on a given outcome and explore the
40 41 42	344	possible relationship between baseline characteristics and outcomes-of-interest, we will perform
42 43 44	345	a pooled analysis of the baseline characteristics (Table 2). Then, we will perform a sensitivity
45 46	346	analysis of the pooled estimate of the baseline characteristics reported by the studies reporting
47 48	347	a given outcome to assess differences between the two cohorts. Sensitivity analyses will be
49 50	348	performed plotting only papers reporting comparable baseline characteristics estimates (mean
51 52	349	for continues variable and OR for dichotomous variable) defined as estimates with 95%
53 54	350	confidence interval for effect including the null value (such as an odds ratio of 1.0 or a risk
55 56	351	difference of 0) [13].
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4	352	
5 6	353	d) Risk of Incontinence and Erectile dysfunction after Radical Prostatectomy
7 8	354	For the analysis of continence and potency recovery rates following radical prostatectomy
9 10	355	(open versus robotic), we will assess the relative risk of incontinence and erectile dysfunction,
11 12 12	356	respectively. We will consider as "total" the number of men reporting to be continent or potent
13 14 15	357	before surgery or, if not specified, the total number of men evaluated at last follow up. We will
15 16 17	358	consider as "events" the total number of men who report having incontinence or erectile
18 19	359	dysfunction after surgery. This number will be calculated by the difference (Δ) between the total
20 21	360	of the "continent or potent patients following surgery" and the "total" (the number of patients that
22 23	361	are continent or potent before surgery or, if not specified, the total of patients evaluated at last
24 25	362	follow up). Inconsistency in the definition will be reported.
26 27	363	
28 29	364	e) Cost analyses
30 31 22	365	We will evaluate the costs of open versus robotic uro-oncologic surgery. We will select only
32 33 34	366	comparative studies (open vs. robotic) reporting operative and non-operative costs; studies
35 36	367	reporting charges, modeling and analyses of national databases will be excluded. We will
37 38	368	include the following items in operative costs: 1) labor (professional fees); 2) surgical
39 40	369	equipment; 3) robot-related costs (capital, maintenance); and 4) anesthesia supply/technician
41 42	370	labor cost. We will include the following items in non-operative costs: 1) post-anesthesia care; 2)
43 44	371	professional fees; 3) hospital stay costs (room/day, nursing costs); 4) drugs and supplies; 4)
45 46	372	blood transfusion costs; and 5) technical services (laboratory, radiology). Difference (Δ) in
47 48 40	373	overall operative cost will be calculated as overall robotic operative cost minus overall open
49 50 51	374	operative cost. Difference (Δ) in overall non-operative cost will be calculated as overall robotic
52 53	375	non-operative cost minus overall open non-operative cost. Percentages indicating the overall
54 55	376	total cost differential of robotic vis-a-vis open surgery will be considered. We will convert all
56 57	377	currencies to the 2020 exchange rate using the Consumer Price Index (CPI) inflation calculator
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2 3 4	378	(https://www.bls.gov/data/inflation_calculator.htm). Foreign currency will first be converted to					
5 6	379	dollars using historical exchange rates at the year of publication and then adjusted to the 2020					
7 8	380	exchange rate using the CPI inflation calculator.					
9 10	381						
11 12 13	382	Grade Of The Evidence					
14 15	383	The quality of scientific evidence and outcomes will be assessed using the Grading of					
16 17	384	Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE					
18 19 20 21	385	offers a specific definition of the quality of evidence that is different in the context of making					
	386	recommendations and in the context of summarizing the findings of a systematic review [18,					
22 23 24	387	19]. The GRADE methodology involves rating evidence for a given outcome by upgrading or					
24 25 26	388	downgrading the evidence. Indications for upgrading the quality of evidence include having a					
20 27 28	389	large effect size and dose-response gradient. Indications for downgrading the quality of					
29 30	390	evidence include serious risk of bias, serious inconsistency between studies, serious					
31 32 33 34 35 36 27	391	indirectness, serious imprecision and likely publication bias [18]. Summary of Findings (SoF)					
	392	tables will provide a summary of findings for each of the included outcomes and the quality of					
	393	evidence rating for each outcome [18]. The format of the Sof will include:					
37 38 39	394	1. A list of the outcomes of interest					
40 41	395	2. The assumed risk; a measure of the typical burden of the outcomes, i.e. illustrative risk or					
42 43	396	also called baseline risk, baseline score, or control group risk					
44 45	397	3. The corresponding risk; a measure of the burden of the outcomes after the intervention is					
46 47	398	applied, i.e. the risk of an outcome in treated/exposed people based on the relative					
48 49	399	magnitude of an effect and assumed (baseline) risk					
50 51	400	4. The relative effect; for dichotomous outcomes, the table will provide risk ratio, odds ratio, or					
52 53	401	hazard ratio					
55 56	402	5. The number of participants, the number of studies and their designs					
57 58		16					
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2 3 4	403	6. Rating of the overall quality of evidence for each outcome
5 6 7	404	Presentation of results and reporting
8 9	405	The PRISMA guidelines [10] will be used and the checklist will accompany the publication.
10 11 12	406	Quantitative data will be summarized and presented in tables and as forest plots where
13 14	407	necessary [9].
15 16 17	408	Potential amendments
18 19	409	We do not anticipate any amendments to the current protocol. However, should an amendment be
20 21 22	410	necessary, it will be notified, registered and reported.
23 24	411	Ethics and Dissemnination
25 26 27	412	No ethics clearance is necessary, as no primary data will be collected. Results will be published in a peer-
28 29	413	reviewed journal. These results will likely help inform directions and design of future studies.
30 31 32	414	
33 34 35	415	IMPLICATIONS OF THE REVIEW
36 37	416	We believe this aggregate information will be of interest and practical use to the general medica
38 39 40	417	community at large, who need to be aware of contemporary trends in urologic oncologic
41 42	418	surgery, thereby to better advise patients seeking care for urologic cancers.
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2 3 4	426	FOOTNOTES	
4 5 6	427	Contributorship statement: I.S.G and G.E.C conceptualised an	d designed the protocol,
7 8	428	drafted the initial manuscript and reviewed the manuscript. I.S.G a	nd G.E.C defined the
9 10	429	concepts and search items, data extraction process as well as met	thodological appraisal of the
11 12	430	studies. G.E.C, K.S.G and I.S.G planned the data extraction and s	tatistical analysis. I.S.G and
13 14	431	G.E.C, provided critical insights. All authors have approved and co	ntributed to the final written
15 16 17	432	manuscript	
18 19 20	433		
21 22	434	Competing interests: None declared.	
23 24 25	435		
26 27	436	Funding: The authors have not declared a specific grant for this re	esearch from any funding
28 29 30	437	agency in the public, commercial or not-for-profit sectors.	
31 32 33	438		
34 35 36	439	Data sharing statement: There are no data in this work	
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8 9	498	FIGURE CAPTATION
10 11	499	Figure 1. study design flow chart
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525	Table 1. Description of the PICOTS strategy as applied to this study
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	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:
001001120	•Operative time (min)
	•Estimated blood loss (ml)
	•Length of hospital stay (days)
	•Blood transfusion rate (%)
	•Overall complication rate (%)
	•Major and Minor nostonerative complication rate (%)
	•Farly and Late complication rate (%)
	Poodmission rate (%)
	Oncologic outcomos:
	• Positive margins
	•Lymph pade counts
	Concer specific survival
	•Cancer-specific survival
	Functional outcomes:
	•Potency recovery rate (n)
	•Continence recovery rate (n)
	Health-related quality of life Denot Evention (aCED change)
	• 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.
	Any time point and setting

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529 Table 2. Baseline characteristics evaluated for each comparison

Surgical Procedure	Baseline characteristics
Radical Prostatectomy	Age, years
(ORP vs. RRP)	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	Age, years
(ORC vs. RRC)	BMI, Kg/m ²
	ASA score
	Male, %
	Female, %
	NACH, %
	pT ≥ 3, %
	pN ≥ 1, %
	n of node removed, mean
Partial nephrectomy (OPN vs. RPN) and Radical	Age, years
Nephrectomy (ORN vs. RRN)	BMI, Kg/m ²
	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	Age, years
(ORLND vs. RRLND)	BMI, Kg/m ²
	ASA score
	Primary laterality Left/right side, %
	Preoperative AFP (ng/mL)
	Preoperative hCG (mIU/mL)
	Lympho vascular invasion. %
	pT ≥ 2. %
	$pN \ge 1.\%$

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Page 24 of 26



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address in a syste	emati	c review protocol*	ite
Section and topic	Item No	Checklist item for g 10	
ADMINISTRATIV	E INF	ORMATION B C	
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:		ind ind	
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical main address of corresponding author	5
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identing as such and list changes; otherwise, state plan for documenting important protocol amendments	٢
Support:			
Sources	5a	Indicate sources of financial or other support for the review	
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	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants anterventions, comparators, and outcomes (PICO)	
METHODS		gies 24, 2	
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	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, that registers or other grey literature sources) with planned dates of coverage	

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Search strategy	10	Precent draft of search strategy to be used for at least one electronic database, including planned mig such that it could be	10 and
Search Shalegy	10	repeated	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 the 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 independ Entry and uplicate), 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) aby 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 a get anal 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 the state of 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 at haddling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall'sa)	
	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	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	4

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred response for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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])

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