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Original Article

Misconduct in research integrity: Assessment the quality of systematic reviews in Cochrane urological cancer review group

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ABSTRACT

Objective: Cochrane Library provides a powerful and authoritative database to aid medical decision making. We aimed to evaluate the quality of clinical trials and systematic reviews recorded in the Cochrane urology cancers group.

Material and methods: This analytic cross-sectional study was conducted on 44 published systematic reviews of the Cochrane urology group which were published until May 2020. In the current study, we selected the urological cancer reviews. All types of biases in the understudied randomized controlled trials (RCTs) or quasi-RCTs of these systematic reviews were evaluated using the Cochrane appraisal checklist. We also separated and stratified the types of biases in the included studies. In addition, the quality of systematic reviews was assessed using the Joanna Briggs Institute (JBI) appraisal checklist.

Results: A total of 44 systematic reviews and their understudied 340 RCTs were evaluated. On the basis of the JBI appraisal checklist results, 93.2% of systematic reviews had high quality. In terms of the quality of understudied RCTs in these reviews, the common prevalent risk of bias of the understudied RCTs or quasi-RCTs was unclear selection bias (allocation concealment and random sequence generation). The highest risk of bias was seen in the blinding of participants and personnel (performance bias).

Conclusion: Although most Cochrane urological cancer reviews had high quality, performance bias was the highest one in their understudied RCTs. Regarding it and considering the increasing unclear risk of detection, attrition, and reporting biases, it is obvious that they have structural deficiencies; therefore, it is recommended to observe integrity principles for preventing research misconduct.

Keywords: Cochrane; randomized controlled trial; risk of bias; sstematic review.

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Introduction

In recent decades, the number of published journals and articles in medical sciences has dramatically increased.[1] With the expansion of medical sciences and the increase in the number of research journals, the structure of published articles and their compliance with reporting standards and research methods have received much attention than before. A low quality research has negative consequences and leads to incorrect conclusions, affecting healthcare at all levels from patients' treatment to the development of national health policies; therefore, it is crucial to maintain the quality as the quantities arise.[2]

The Cochrane Library provides a powerful and authoritative database to enhance medical knowledge and aid clinical decision making. This database consists of different review groups that each focus on a specific topic. One of these groups is the Cochrane urology group. This group focuses on many urological disorders, including prostatic diseases, male sexual dysfunction, urologic renal diseases, and urologic cancers.

Urological malignancies, including cancers of the bladder, prostate, kidneys, or testicles, have the highest morbidity and mortality in urological problems with a rising burden on low- and middle-income countries.[3,4] Worldwide, urologic cancer patient's composition has evolved due to population growth, aging, and changes in age-specific incidence and death rates. As kidney, bladder, and prostate cancers are more common in older age groups, these malignancies burden may substantially increase, especially in developing countries where gain in life expectancy is greater. Urological cancers constituted about 8% of cancer-related deaths in Iran in 2015.[5] Prostate cancer is the most prevalent malignancy among western men[6] and the second most commonly diagnosed cancer in men worldwide[7] and the third cause of cancer-related death in America.[6] Bladder cancers,[7] renal cancers,[8] testicular, and penile cancer[9] are the other urological cancers, which had been investigated in Cochrane urological cancer reviews.

Since urological cancers are common neoplasms in clinical settings and categorized as top-ten cancers in the community, they have a high impact on the economy. The medical literature is important resource to guide clinical decision making. Hence, incorrect reporting of clinical outcomes can affect healthcare at all levels, from patient treatment to the development of national public health policies. Since Cochrane contributors and groups produce high-quality systematic reviews on the effects of interventions for the prevention or treatment of diseases as well as rehabilitation, the quality assessment of published systematic reviews has great importance. Thus, we aimed to evaluate the quality of the studies utilized by the Cochrane urology group in urological cancers based on the types of biases presented in the risk of bias assessments in each Cochrane review. In addition, this study gives us an overview of the conducted trial and systematic review studies to address the possible sources of biases in this field of medical research.

Main Points

- Cochrane Library provides a powerful and authoritative database to aid medical decision making.
- Cochrane database consists of different review groups that each focus on a specific topic. One of these groups is the Cochrane urology group.
- The majority of systematic reviews in the Cochrane urology group had high quality (93.2%).
- The most prevalent risk of bias in the understudied RCTs in these reviews was unclear selection bias (allocation concealment and random sequence generation), and the highest risk of bias was seen in blinding of participants and personnel (performance bias).
- It is recommended to observe integrity principles for preventing research misconduct.

Material and Methods

This analytic cross-sectional study was conducted on 44 published systematic reviews of the Cochrane urology group until May 2020. We included all systematic reviews and meta-analysis which was published before May 2020. Our search was conducted on May 2020, and hence, the published reviews before this time point were included in our study. This study was approved by the regional ethic committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1396.578). All procedures has been carried out in accordance with The Code of Ethics. Since Cochrane urology cancer group systematic reviews or meta-analysis and their understudied RCTs were evaluated in the present study, the informed consent was not applicable as well.

The Cochrane Library is a collection of databases that contain different types of high-quality, independent evidence to inform healthcare decision making. The Cochrane urology group consists of 173 Cochrane reviews and 55 protocols at the search date. This group's related topics are incontinence, cancer, urological procedures, benign prostatic hyperplasia, sexual problems, pelvic organ prolapse, stones, prostatitis, and other voiding disorders. In the current study, after an electronic search in Cochrane Library, we selected the urological cancers reviews that focus on the urological malignancies, including bladder, prostate, kidneys, and testicles cancers. We have access to the Cochrane Library through a subscription managed by our organization.

First, general information, including title, year of publication, author name, study location, and other necessary information, was extracted from each study.

The risk of bias in each Cochrane review was evaluated by the Joanna Briggs Institute (JBI) Critical Appraisal tool comprising 11 questions[10] (Appendix 1). Two independent reviewers assessed quantitative papers selected for retrieving methodological validity before inclusion in the review using standardized critical appraisal instruments from the JBI Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI). Any disagreements that arise between the reviewers were resolved through discussion or with a third reviewer. JBI is an international research organization based on the Faculty of Health and Medical Sciences at the University of Adelaide, South Australia. JBI develops and delivers unique evidence-

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based information, software, education, and training to improve healthcare practice and health outcomes.[11]

The JBI critical appraisal tool is designed to assess the quality of systematic reviews using the JBI method. Factors, such as explicit review question, appropriate inclusion criteria, appropriate search and appraising tool, appropriate method for appraising, data extraction and combined studies, and publication bias and two questions of review quality, are investigated by this tool. Each question should be answered by anyone of the following choices: "yes," "no," "unclear," or "not applicable,"[12]

The preferred reporting items for systematic review and meta-analysis (PRISMA) are an evidence-based minimum set of items for reporting the systematic reviews and meta-analyses.[13]

PRISMA focuses on the reporting of reviews evaluating randomized trials but can also be used as a basis for reporting systematic reviews of other types of research studies, particularly evaluations of interventions.[14]

After critical appraisal of the included systematic reviews and meta-analysis, we extracted different biases of all understudied 340 RCTs that are included in these systematic reviews. All the included RCTs in Cochrane reviews were appraised by the authors of systematic reviews using the standard risk of bias tool developed by the Cochrane group.[15] This checklist includes all kinds of biases (selection, performance, detection, attrition, and reporting). This tool consisted of six dimensions, including random sequencing, random assignment of samples, selective report of the consequences, blindness, and the existence of any probabilistic suppression of results as well as reporting incomplete data. The questions had three possible answers, including "low risk of bias," "high risk of bias," and "unclear risk of bias." The standard risk of bias tool is a valid and reliable tool for evaluating all randomized clinical trials, regardless of the article's language, time, and location. We extracted the results of risk of bias assessment in each Cochrane review.

Statistical Analysis

Descriptive statistics were used to analyze the data. Data were analyzed using SPSS software, version 16, (SPSS Inc.; Chicago, IL, USA). (SPSS 16, SPSS Inc., Chicago, IL, USA).

Results

A total of 44 systematic reviews and meta-analyses and their understudied 340 RCTs were evaluated. According to our results, 20 studies were related to prostate, 19 bladder cancer, four renal carcinoma and one testicular tumor. The detailed characteristics of the included studies are presented in Supplementary File 1.

Quality of Systematic Reviews and Meta-Analysis and Their Understudied RCTs

Based on the JBI appraisal checklist results, 93.2% of systematic reviews had high quality. In addition, all the systematic reviews used PRISMA standard for reporting their results.

In terms of the quality of understudied RCTs in these reviews, the most prevalent risk of bias was unclear selection bias (allocation concealment and random sequence generation). Also, the highest risk of bias was seen in the blinding of participants and personnel (performance bias). Our results showed that the lowest risk of biases was those of incomplete outcome data (attrition bias) and selective reporting.

Risk of Bias in Different Time Points

We also analyzed the data according to the date of publishing. Before 2015, the most prevalent biases were unclear allocation concealment and unclear random sequence generation. However, in recent years, the most prevalent bias was performance bias. The results of the risk of bias assessment in Cochrane reviews are presented in Table 1, and the number of biases of the understudied RCTs is presented in Table 2. We categorized the study based on the recently published systematic reviews in the mentioned cancer group (2018-2020). Then, we introduced the different biases in the published articles with the three years interval. According to the date of publishing, the trends of all kinds of biases are summarized in Figure 1.

Included Study's Conclusion

Sixty six percent of studies suggested that further studies with high-quality methodology and greater sample size should be conducted (Supplementary File 2).

Discussion

Our results showed that the Cochrane urological cancer reviews had high quality based on appraise results using the JBI appraisal checklist. In addition, all the included reviews used PRISMA standard for reporting their results. However, in their understudied RCTs, the performance high risk of bias was the most prevalent. In addition, more than half of the published systematic reviews concluded that further studies with high-quality methodology and greater sample size should be conducted.

According to the statistics, in 2020, cancer is a leading cause of death worldwide.[16] Cancer can affect patients' quality of life at

Table 1. Risk of Bias in Cochrane Urological Cancer Review Group Using the Joanna Briggs Institute Critical Appraisal Tools for Use in Systematic Reviews

Question	1 Schmidt et al.[32]	2 Hickey et al.[33]	3 Kunath et al.[34]	4 Burden et al.[35]	5 Hwang et al.[36]	6 Hwang et al.[37]	7 Drost et al.[38]	8 Rai et al.[39]	9 Sathianathen et al.[40]	10 Narayan et al.[41]	11 Jung et al.[42]	12 Macherey et al.[43]	13 Ilic et al.[44]	14 Jung et al.[45]	15 Unverzaft et al.[46]	16 Kunath et al.[47]	17 Sultan et al.[48]	18 Shepherd et al.[49]	19 Nabi et al.[50]	20 Coppin et al.[51]	21 Shelley et al.[52]	22 Krogsboll et al.[53]
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				Y
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				Y
3	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y				Y
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				Y
5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Withdraw	Withdraw	Withdraw	U
7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				Y
8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				Y
9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				Y
10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				Y
11	Y	Y	Y	Y	Y	Y	Y	Y	Y	y	Y	Y	Y	Y	Y	Y	Y	Y				Y
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	90.90%	100%	81.80%	90.90%	100%	100%	100%	100%	100%				90.90%

Question	23 Kunath et al.[54]	24 Parahoo et al.[55]	25 Ilic et al.[56]	26 Jones et al.[57]	27 Daly et al.[58]	28 Ilic et al.[59]	29 Peinemann et al.[60]	30 Zani et al.[61]	31 Shang et al.[62]	32 Shelley et al.[63]	33 Rai et al.[64]	34 Ilic et al.[65]	35 Hegarty et al.[66]	36 Wilt et al.[67]	37 Coppin et al.[68]	38 De Conti et al.[69]	39 Shelley et al.[70]	40 Kumar et al.[71]	41 Vale et al.[72]	42 ABCMA Collaboration[73]	43 Shelley et al.[74]	44 Shelley et al.[75]
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	U	Y	Y	Y	Y	Y	Y	Y	Y
6	Y	U	Y	U	Y	Y	Y	Y	Y	U	U	N/A	Y	U	U	U	U	U	U	U	U	U
7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	U	Y	U	Y	Y	U	U	U	Y
8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N/A	N	N	Y	Y	N	N	N	N	N	N
10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total	100%	90.90%	100%	81.80%	100%	100%	100%	100%	100%	90.90%	63.60%	-	90.90%	36.40%	90.90%	81.80%	90.90%	81.80%	54.50%	54.50%	63.60%	81.8

Abbreviations: Y, yes; N, no; U, unclear; N/A, not applicable.

different levels raising the need for more effective management strategies.[17]

Since urological cancers are common neoplasms in clinical settings and categorized as top-ten cancers in the community, they have a high impact on the economy. All these cancers rank as prevalent human cancers. In addition, diagnosis and management of some urological cancers, such as renal tumors, are a challenge for multidisciplinary clinical teams due to the different pathogenetic mechanisms.[18,19] The medical literature is an important resource to guide clinical decision making. Hence, incorrect reporting of clinical outcomes can affect healthcare at all levels from patient's treatment to the development of national public health policies.[20] Hence, the evaluation of the study's methodological quality is an essential step in the process of the best clinical literature selection. The methodological quality assessment should be based on the evaluation of the internal and external validity, which represents the design conduction, analysis of the data, or the degree that the study results can be generalized.[21] In the evidence pyramid level, meta-analysis and systematic review of randomized controlled trials have the highest level.[22] These types of studies provide the best evidence for treatment efficacy in clinical research. Systematic reviews of homogeneous randomized controlled trials constitute the most robust form of clinical evidence. These studies had the greatest impact on the guidelines and decision making. Thus, misconduct could have a significant effect on the quality of caregiving. The high risk of bias studies can result in inaccurate evidence, which could harm both the patients and the healthcare system in different ways.

The Cochrane Library provides a powerful and authoritative database to enhance medical knowledge and help in making medical decisions.[23] Therefore, maintaining the quality of such studies, which will be utilized in developing related guidelines, is of high importance. According to the current study results, 93% of Cochrane reviews in urological cancer group had high quality using the JBI appraisal checklist for systematic reviews and meta-analysis. In addition, all of them used PRISMA for reporting systematic reviews. Previous studies in different medical disciplines have been assessed the quality of systematic reviews.[24–26] For example, Gagnier et al.,[27] in evaluating the reporting and methodological quality of systematic reviews in the top five orthopedic journals according to the 2010 ISI Thomson Reuters Journal Citation Reports, concluded that the validity of orthopedics published systematic reviews that were questionable. Otherwise, in another study in the field of internal medicine journals, results revealed that among 42 systematic reviews, only 4.6 out of 11 items gained a complete score on the Assessment of Multiple Systematic Reviews (AMSTAR)

Table 2. The Number of Different Biases in the Understudied RCTs in Systematic Reviews (n = 44)

Number	Study	No. of included RCTs	Random sequence generation (selection bias)			Allocation concealment (selection bias)			Blinding of participants and personnel (Performance bias)			Blinding of outcome assessor (Detection bias)			Incomplete outcome data (Attrition bias)			Selective reporting (Reporting data)			Other bias		
			Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear
1	Schmidt et al.[32]	14	6	1	7	2	1	11	-	11	3	5	-	9	9	2	3	-	1	13	10	3	1
2	Hickey et al.[33]	10	6	-	4	6	-	4	-	3	7	2	3	5	8	1	1	4	-	6	10	-	-
3	Kunath et al.[34]	10	3	-	7	6	-	4	-	-	10	10	-	-	5	-	5	3	4	3	-	-	10
4	Burden et al.[35]	8	3	1	4	1	1	6	8	-	-	2	-	6	7	-	1	3	-	5	8	-	-
5	Hwang et al.[36]	2	2	-	-	2	-	-	-	2	-	-	2	-	1	-	1	-	1	1	-	2	-
6	Hwang et al.[37]	1	1	-	-	1	-	-	-	1	-	-	1	-	1	-	-	1	-	-	1	-	-
7	Drost et al.[38]	18	15	2	5	The risk of bias was assessed using the QUADAS-2 tool																	
8	Rai et al.[39]	5	5	-	-	4	1	-	-	5	-	-	1	4	5	-	-	4	-	1	5	-	-
9	Sathianathen et al.[40]	3	3	-	-	3	-	-	-	3	-	3	-	-	3	-	-	3	-	-	3	-	-
10	Narayan et al.[41]	1	1	-	-	1	-	-	-	-	1	1	-	-	1	-	-	-	-	1	1	-	-
11	Jung et al.[42]	2	1	-	1	-	-	2	-	1	1	-	1	1	2	-	-	1	1	-	-	-	2
12	Macherey et al.[43]	18	5	-	13	4	-	14	12	5	1	2	-	16	8	3	7	3	3	12	6	2	10
13	Ilic et al.[44]	2	2	-	-	-	-	2	-	2	-	1	-	1	1	-	1	1	-	1	1	-	1
14	Jung et al.[45]	3	3	-	-	1	-	2	-	3	-	3	-	-	3	-	-	2	-	1	3	-	-
15	Unverzagt et al.[46]	8	5	-	3	4	-	4	2	6	-	5	3	-	8	-	-	6	2	-	2	6	-
16	Kunath et al.[47]	1	-	-	1	1	-	-	-	-	1	1	-	-	1	-	-	1	-	-	-	1	-
17	Sultan et al.[48]	1	1	-	-	-	-	1	1	-	-	1	-	-	1	-	-	1	-	-	1	-	-
18	Shepherd et al.[49]	5	2	-	3	2	-	3	-	2	3	-	2	3	1	1	3	1	3	1	2	1	2
23	Kunath et al.[54]	11	3	-	8	1	1	9	-	-	11	9	-	2	6	1	4	8	3	-	-	-	11
24	Parahoo et al.[55]	19	12	-	7	4	4	11	1	8	10	11	1	7	12	5	2	11	4	4	14	4	1
25	Ilic et al.[56]	5	2	1	2	1	3	1	-	-	-	-	-	-	3	-	2	3	-	2	2	2	1
26	Jones et al.[57]	6	3	-	3	2	-	4	1	-	5	-	-	6	5	-	1	5	-	-	-	-	4
27	Daly et al.[58]	3	3	-	-	3	-	-	-	-	-	-	-	-	-	1	2	-	1	2	2	-	1
28	Ilic et al.[59]	3	2	-	1	2	-	1	1	2	-	1	-	2	2	-	1	1	-	2	-	1	2
29	Peinemann et al.[60]	1	1	-	-	-	-	1	-	-	-	-	-	-	-	1	-	-	1	-	-	1	-
30	Zani et al.[61]	22	12	-	10	4	-	18	-	-	-	-	-	-	22	-	-	22	-	-	19	-	3
31	Shang et al.[62]	5	1	4	-	1	4	-	-	-	-	-	-	-	5	-	-	5	-	-	5	-	-
32	Shelley et al.[63]	7	-	-	-	-	2	5	-	-	-	-	4	3	-	-	-	-	-	-	-	-	-
33	Rai et al.[64]	1	-	1	-	-	-	1	-	-	-	-	-	1	-	-	1	-	1	-	-	-	1
35	Hegarty et al.[66]	2	1	-	1	1	-	1	-	-	-	-	-	-	1	1	-	1	-	1	1	1	-
36	Wilt et al.[67]	13	-	-	-	-	3	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
37	Coppin et al.[68]	25	11	-	14	8	-	17	-	-	-	-	-	-	16	-	9	19	-	6	6	-	18
38	De Conti et al.[69]	5	-	-	-	2	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
39	Shelley et al.[70]	47	-	-	-	17	-	30	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
40	Kumar et al.[71]	22	-	-	-	6	-	16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41	Vale et al.[72]	6	-	-	-	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42	ABCMA Collaboration[73]	14	-	-	-	14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
43	Shelley et al.[74]	5	-	-	-	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44	Shelley et al.[75]	6	-	-	-	4	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Total	340	115	10	94	119	20	193	26	54	53	57	18	66	137	16	44	109	25	62	102	24	68

Note: The risk of bias was assessed using the QUADAS-2 tool. The reported bias were as follow: Index test MRI (15 low), Reference standard (4 low, 8 High, 3 Unclear), Flow and Timing (13 low, 2 High).

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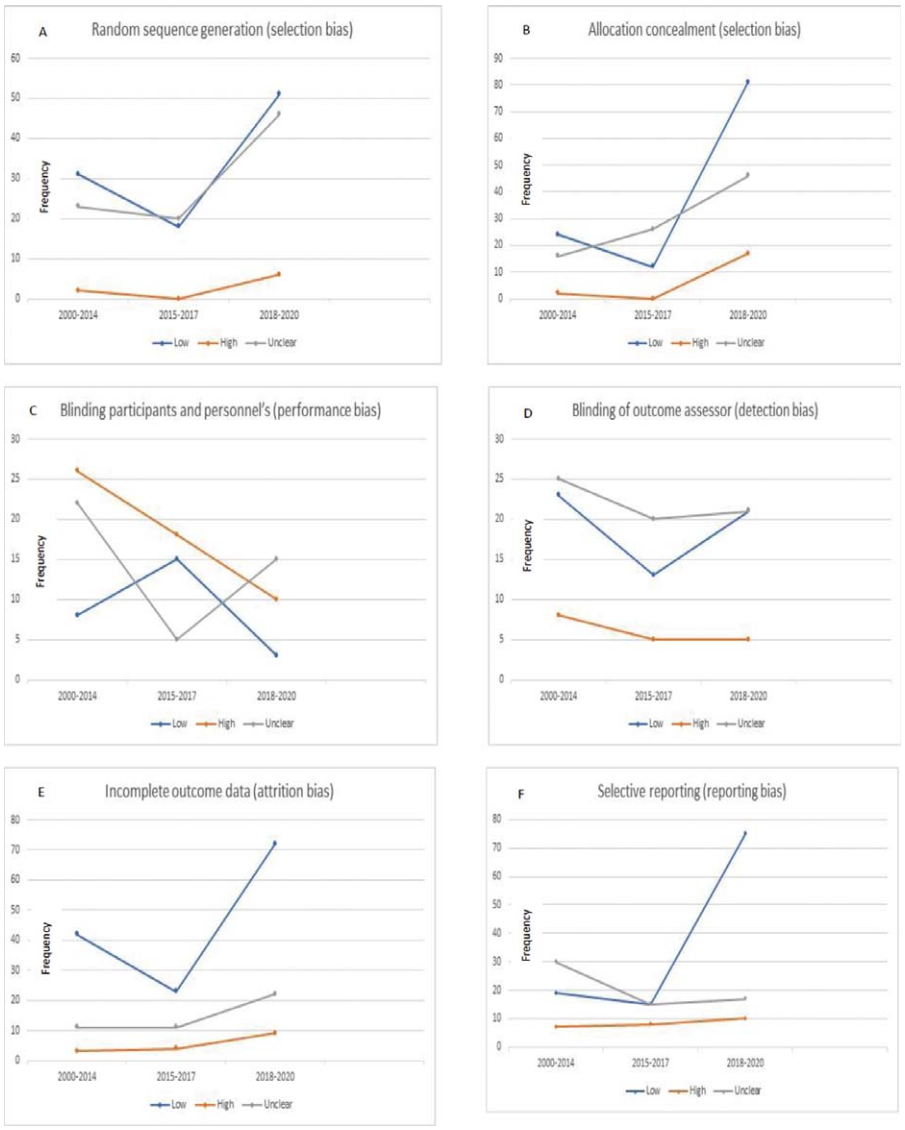

Figure 1. The trend of different bias in different time point in understudies RCTs of systematic reviews: (A) Random sequence generation (B) Allocation concealment (C) Performance bias (D) Detection bias (E) Attrition bias (F) Reporting bias.

guidelines.[28] Using the accepted reporting tools, such as the PRISMA statement, improves the reporting quality. In our study, the published articles in the urological cancer group used the PRISMA statement. However, Gagnier et al.[27] showed that only three orthopedic journals stated in the instructions for authors the PRISMA statement, which may justify the low quality of reporting in their included systematic reviews.

Despite the high quality of the systematic reviews, in the present study, in assessing the understudied RCTs' quality, they had some bias in different aspects. In this regard, the most prevalent bias was unclear selection bias.

Selection bias, which is defined as a systematic error due to a nonrandom sample of a population, is related to the randomization methods (random sequence generation) and the assignment process (Random Allocation).[29] Proper randomization eliminates selection bias and is an important part of a high-quality randomized clinical trial.[30] In the previously published studies of the Cochrane urology group, the most prevalent bias was unclear selection bias. However, in the last two years, it decreased. Thus, appropriate randomization and allocation concealment was respected. Among the surveyed dimensions of biases, the highest risk of bias was blinding participants and personnel (performance bias). Performance bias happens when

Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
1	Schmidt et al.[32]	Bladder	Participants with intermediate- and high-risk nonmuscle invasive bladder tumors	Comparing BCG versus MMC	2932	-Time to death from any cause -Serious adverse effects -Time to recurrence -Time to progression -Quality of life	14	*Based on our findings, BCG may reduce the risk of recurrence over time although the confidence intervals include the possibility of no difference. It may have no effect on either the risk of progression or risk of death from any cause over time. BCG may cause more serious adverse events although the confidence intervals once again include the possibility of no difference.*	*Three studies had at least one coauthor with a financial relationship with a company or the study was at least partly financed by a company.*	*Three studies had at least one coauthor with a financial relationship with a company or the study was at least partly financed by a company and Four studies provided no information on funding.*
2	Hickey et al.[33]	Prostate	Men with histologically confirmed, clinically localized prostate adenocarcinoma	Comparison of hypo fractionated versus conventionally fractionated RT	8278	-Prostate cancer-specific survival -Late gastrointestinal RT toxicity -Late genitourinary RT toxicity -Overall survival -Metastasis-free survival -Biochemical relapse-free survival -Acute GU RT toxicity	10	*These findings suggest that moderate hypofractionation (up to a fraction size of 3.4 Gy) results in similar oncologic outcomes in terms of disease-specific, metastasis-free and overall survival. There appears to be little to no increase in both acute and late toxicity.*	*BH: receivedReceived financial support from the Princess Alexandra Cancer Collaborative Group (PAH CCG), which funded a research assistant for hand searching and data management.*	*Princess Alexandra Cancer Collaborative Group, Australia.Financial support for a data manager and hand searching was provided*
3	Kunath et al.[34]	Prostate	Participants included had advanced hormone-sensitive prostate cancer receiving surgical or medical castration.	Direct comparison of early versus deferred standard AST	15374	-Time to death of any cause -Serious adverse events -Time to death from prostate cancer -Skeletal events -Fatigue -Heart failure -Global quality of life	10	*Early AST probably reduces the risk of death from any cause over time-Early versus deferred AST may have little or no effect on serious adverse events*	*The present work was supported by a grant from the German Federal Ministry of Education and Research.*	*University Hospital Erlangen, Germany. Salary support for Frank Kunath, Andreas Kahlmeyer, Verena LiebUniversity of Minnesota, Minneapolis, USA. Salary support for Philipp DahmDeutsche GesellschaF für Urologie (German Association of Urology), Germany. Salary support for Stefanie SchmidtWelch Medical Library, John Hopkins Medical Institution, Baltimore, Maryland, USA.*

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Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
4	Burden et al.[35]	Bladder	Adults undergoing RC for bladder cancer	-Parenteral nutrition (PN) versus oral nutrition -Immuno-enhancing nutrition versus standard nutrition -Preoperative oral nutritional support versus normal diet - Early postoperative feeding versus standard postoperative management -Amino acid with dextrose versus dextrose -Branch chain amino acids versus dextrose only -Perioperative oral nutritional supplements versus oral multivitamin and mineral supplement	500	-Complications -Length of hospital -Stay -Mortality	8	*Based on few, small and dated studies, with serious methodological limitations, we found limited evidence for a benefit of perioperative nutrition interventions. We rated the quality of evidence as low or very low, which underscores the urgent need for high-quality research studies to better inform nutritional support interventions for people undergoing surgery for bladder cancer*	*SB: receivedReceived a Macmillan Post-Doctoral Fellowship Award for postdoctoral research, which was paid to her institution and unrelated to this work.HAB: theThe author's institution, Central Manchester University Hospitals NHS Foundation Trust (CMFT) receives some funds in association with enteral feed procurement from Nutricia Ltd who have had no involvement with this Review.SL: receivedReceived honoraria and educational support from Baxter, B Braun and Fresenius Kabi which was unrelated to this work.KAO: theThe author's institution, Central Manchester University Hospitals NHS Foundation Trust (CMFT) receives some funds in association with enteral feed procurement from Nutricia Ltd who have had no involvement with this review.AM: receivedReceived honoraria and educational support from Eli Lilly and Bayer.*	*National Health Service (NHS), UK.All authors work in the NHS and receive salaries from the NHS*
5	Hwang et al.[36]	Bladder	Participants either received or did not receive single-dose intravesical chemotherapy instillation after nephroureterectomy.	Single dose of any intravesical chemotherapeutic agent instillation (eg, mitomycin, epirubicin, pirarubicin, gemcitabine, etc.) after RNU • Observation • Placebo Concomitant interventions had to be the same in the experimental and comparator groups to ensure fair comparisons.	361	-Time to bladder cancer recurrence -Time to death from UTUC -Serious adverse events -Time to death from any cause -Minor adverse events -Disease-specific quality of life	2	*-Our results indicate that single-dose intravesical chemotherapy instillation may reduce the risk of bladder cancer recurrence over time compared to no instillation-We found no trials that reported on the outcomes of time to death from upper tract urothelial carcinoma. The effect of single-dose intravesical chemotherapy instillation on serious adverse events is uncertain*	*Conflicts of interests were reported as 'none' in the included studies.*	*Included studies reported receiving funding from multiple sources, including hospitals, pharmaceutical companies, and their respective governments.*

Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
6	Hwang et al.[37]	Bladder	Participants with urothelial carcinoma of the bladder undergoing RC with PLND with curative intent	To assess the effects of extended versus standard PLND	401	-Time to death from any cause -Time to death from bladder cancer -Clavien-Dindo grade > 3 complications -Time to recurrence -Clavien-Dindo grade < 2 complications	1	*Our results indicate that extended PLND may reduce the risk of death from any cause over time as compared to standard PLND, but the confidence interval includes the possibility of no effect*	*No conflicts of interest*	*A pharmaceutical company supported the study*
7	Drost et al.[38]	Prostate	Men with a clinical suspicion of prostate cancer (based on PSA or digital rectal exam (DRE) outcome) in the biopsy-naïve or prior-negative biopsy setting (or a mix of both)	Systematic biopsy as compared to template-guided biopsy as the reference standard in detecting clinically significant prostate cancer as the target condition, defined as International Society of Urological Pathology (ISUP) grade 2 or higher.	-	MRI compared to template-guided biopsy -MRI-targeted biopsy compared to template-guided biopsy -The MRI pathway compared to template-guided biopsy -Systemic biopsy compared to template-guided biopsy -Agreement analyses	18	*Among the diagnostic strategies considered, the MRI pathway has the most favorable diagnostic accuracy in clinically significant prostate cancer detection. Compared to systematic biopsy, it increases the number of significant cancers detected while reducing the number of insignificant cancer diagnosed. The certainty in our findings was reduced by study limitations, specifically issues surrounding selection bias, as well as inconsistency. Based on these findings, further improvement of prostate cancer diagnostic pathways should be pursued.*	*-Frank-Jan H Drost: noneNone known-Daniel F Osses: noneNone known-Daan Nieboer: noneNone known-Ewout W Steyerberg reports the following relevant financial activities outside the submitted work: receivesReceives royalties from Springer for the textbook entitled Clinical Prediction Models-Chris H Bangma: noneNone known-Monique J Roobol: noneNone known*	*-Erasmus University Medical Center, Netherlands.-Evidence based research Grant 2014 (project 2014-14103)*
8	Rai et al.[39]	Bladder	Adult participants with a diagnosis of bladder malignancy who were undergoing radical cystectomy as part of their treatment for pathologically proven MIBC or high-grade NMIBC (T1-4/carcinoma in situ (CIS), N0M0).	Investigated the following comparison of experimental intervention versus comparator intervention.	541	-Time to recurrence -Major postoperative complications -Minor postoperative complications -Transfusion rate -Hospital stay -Quality of life -Positive margins	**5**	*There may be little to no difference in the time to recurrence, the rate of major complications or minor complications, quality of life, and rates of positive margins (signaling that cancer may have been left behind). Robotic surgery probably results in fewer blood transfusions and may lead to a slightly shorter hospital stay when compared with open surgery.*	*BR: noneNone known.JB: noneNone known.NV: noneNone known.JA: noneNone known.TL: noneNone known.KA: noneNone known.MSK: noneNone known.PD: noneNone known.KG: noneNone known.PLC: noneNone known.OMA: noneNone known.*	-Parekh 2018 was funded by the National Institutes of Health National Cancer Institute. -Bochner 2015 was supported by the Sidney Kimmel Center for Prostate and Urologic Cancers at Memorial Sloan Kettering Cancer Center, Pin Down Bladder Cancer, and the Michael and Zena Wienerfor Therapeutics Program in Bladder Cancer. -Khan 2016 was supported by the National Institute for Health Research (NIHR) Biomedical Research Center based at Guy's and St. Thomas' NHS Foundation Trust and King's College London. The remaining two studies did not report funding (Nix 2010; Parekh 2013).

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Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
9	Sathianathen et al.[40]	Prostate	Men with a confirmed histological diagnosis of adenocarcinoma of the prostate and radiologic evidence of metastases as determined by cross-sectional imaging with or without bone scans.	We considered the following interventions. Concomitant interventions had to be the same in the experimental and comparator groups to establish fair comparisons.	2261	-Time to death due to any cause -Grade III to V adverse events -Prostate cancer-specific death5 -Time to progression -Discontinuation due to adverse events -All adverse events -Quality of life at 12 months	3	*Compared to ADT alone, the early (within 120 days of beginning ADT) addition of taxane-based chemotherapy to ADT for hormone-sensitive prostate cancer probably prolongs both overall and disease-specific survival and delays disease progression.*	*Conflicts of interests with pharmaceutical companies were reported in all studies*	*All three included trials reported receiving funding from multiple sources including pharmaceutical companies and governments (Gravis 2013; James 2016; Sweeney 2015).*
10	Narayan et al.[41]	Bladder	Participants with locally advanced (>T2) or metastatic (M1) urothelial carcinoma of the bladder as determined by cross-sectional imaging or confirmed by biopsy, or both, whose disease progressed during or following platinum-containing chemotherapy (synonymous with second-/third-/fourth-line therapy).	This review focused on pembrolizumab (synonyms: MK-3475, lambrolizumab, Keytruda). We investigated the following comparisons of experimental intervention versus comparator intervention.	542	-Time to death from any cause -Quality of life -Response rate -Treatment-related mortality -Discontinuation due to adverse event -Serious adverse events	1	Pembrolizumab probably reduces the risk of death from any cause	VN: noneNone. AK: noneNone. PD: noneNone. NS: noneNone. MR: noneNone. CB: noneNone. NP: noneNone. JHJ: noneNone. ECH: noneNone GG: noneNone. FK: noneNone.	University of Erlangen, Germany: Salary support for Frank Kunath Minneapolis VAMC, Minneapolis, MN, USA: Salary support for Philipp Dahm
11	Jung et al.[42]	Prostate	Men with clinical stage T1-T3, node-negative (N0), nonmetastatic (M0) prostate cancer who have not received prior therapy.	To assess the effects of cryotherapy (whole gland or focal) compared with other interventions for primary treatment of clinically localized (cT1-T2) or locally-advanced (cT3) nonmetastatic prostate cancer.	307	-Time to death from prostate cancer -Quality of life - urinary function assessed with -Quality of life - bowel function -Quality of life - sexual function -Major adverse events -Time to death from any cause	2	-we are uncertain about the effect of whole gland cryotherapy compared to radiation therapy on time to death from prostate cancer -We are equally uncertain about the effect of quality of life-related urinary function and bowel function -We are also uncertain about sexual function-related QoL using a MCID of 8 points - Lastly, we are uncertain of the risk for major adverse events.	The first author in Chin 2008 and one of the coauthors in Donnelly 2010 disclosed relevant conflicts of interest.	Chin 2008 and Donnelly 2010 were supported by research grants from Astra-Zeneca and the National Cancer Institute of Canada and the Alberta Cancer Board, respectively.

Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
12	Macherey et al.[43]	Prostate	Men with bone metastases from prostate cancer	We included trials comparing bisphosphonates to control regimens for the treatment of bone metastases from prostate cancer.	4843	-Proportion of participants with pain response -Skeletal-related events: Any, composite outcome -Mortality -Quality of life -Adverse events: Nausea -Adverse events: Renal -Adverse events: Osteonecrosis of the jaw -Proportion of participants with disease progression	18	There was no clear difference in the proportion of participants with pain response	-SM: None known. -IM: None known. -FJ: Received payment for lectures from MSD, Riemser and Tesaro; received travel, accommodation or meeting expenses from Pfizer, Roche, Tesaro. -KJ: Received payment for lectures from Amgen. -KKY: None known. -AH: None known. -NS: None known.	
13	Ilic et al.[44]	Prostate	Adult men, 18 years of age or older, of any ethnicity, diagnosed with clinically localized prostate cancer were eligible for inclusion in this review.	We planned to investigate the following comparisons of experimental intervention versus comparator intervention.	446	-Prostate cancer-specific survival -Urinary quality of life -Sexual quality of life -Biochemical recurrence-free survival -Overall survival -Overall surgical complications	2	There is no high-quality evidence to inform the comparative eIectiveness of LRP or RARP compared to ORP for oncological outcomes.Urinary and sexual quality of life-related outcomes appear similar.	-Dragan Ilic: None declared -Sue Evans: None declared -Christie Allan: None declared -Jae Hung Jung: None declared -Declan Murphy: None declared -Mark Frydenberg: None declared	• Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Australia. • Center of Research Excellence in Patient Safety, School of Public Health and Preventive Medicine, Monash University, Australia. • Department of Urology, Yonsei University Wonju College of Medicine, Korea, South. • Cancer Surgery, Peter MacCallum Cancer Center, Australia. • Department of Surgery, Monash University, Australia.
14	Jung et al.[45]	Bladder	Participants with NMIBC (Ta, T1 or CIS), as determined by pathological evaluation of the TURBT, with no lymph node involvement and no metastases (clinically N0, M0). We considered studies of participants with both primary and recurrent disease.	- Postoperative MMC-EMDA induction versus postoperative Bacillus Calmette-Guérin (BCG) induction -Postoperative MMC-EMDA induction versus MMC-passive di4usion (PD) induction -Postoperative MMC-EMDA with sequential BCG induction and maintenance versus postoperative BCG induction and maintenance -Single-dose, preoperative MMC-EMDA versus single-dose, postoperative MMC-PD-Single-dose, preoperative MMC-EMDA versus TURBT alone	672	-Time to recurrence -Time to progression -Serious adverse events -Disease-specific survival -Disease-specific quality of life	3	While the use of EMDA to administer intravesical MMC may result in a delay in time to recurrence in select patient populations, we are uncertain about its impact on serious adverse events in all settings.	Two studies reported no conflicts of interests (Di Stasi 2006; Di Stasi 2011), and Di Stasi 2003 reported financial interest or other relationships with Physion Srl (or both).	Two studies specified funding sources (Di Stasi 2003: Tor Vergata University of Rome and Physion Srl, Medolla, Italy, Di Stasi 2011: none). Di Stasi 2006 did not report the funding sources.

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Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
15	Unverzagt et al.[46]	Renal	Participants diagnosed with all types of histologically confirmed mRCC including stage IV (T4 any N M0, any T any N M1)	We investigated comparisons of experimental intervention versus comparator interventions utilizing at least one immunotherapeutic agent. We included only studies that compared protocol-defined immunotherapeutic, experimental interventions to standard treatment options (comparator interventions) as defined in current, evidence-based guidelines for systemic therapy in people with mRCC	4732	-Year mortality -Quality of life -Adverse events	8	Evidence of moderate quality demonstrates that IFN-D monotherapy increases mortality compared to standard targeted therapies alone, whereas there is no difference if IFN is combined with standard targeted therapies.	-SU: Institution received support from the Federal Ministry of Education and Research, Germany (grant number: 01KG1024) and from the Wilhelm-Roux-Program, Martin Luther University Halle- Wittenberg, Germany, to write this review -IM: Institution received support from the Wilhelm-Roux-Program, Martin Luther University Halle-Wittenberg, Germany, for travel to meetings for this review. -MN: None known. -DR: Institution received support from the Wilhelm-Roux-Program, Martin Luther University Halle-Wittenberg, Germany, for travel to meetings for this review. AVH. FP. FG.BS.	***Internal sources:*** •Wilhelm-Roux-Program, Martin Luther University Halle-Wittenberg, Germany. Financial support (grant number 26/18) **External sources:** • Federal Ministry of Education and Research, Germany. Financial support (grant number: 01KG1402)
16	Kunath et al.[47]	Renal	Participants with small renal masses	-Experimental intervention -Comparator intervention Partial nephrectomy versus radical nephrectomy.	541	-Time-to-death of any cause -Serious adverse events -Time-to-recurrence -Permanent hemodialysis -Quality of Life	1	Partial nephrectomy may be associated with a decreased time-to-death of any cause. With regards to surgery-related mortality, cancer specific survival and time-to-recurrence, partial nephrectomy appears to result in little to no difference.	S. Schmidt receives salary by the German Society of Urology (DGU) but the DGU had no role in gathering, analyzing, or interpreting the data and has no right to approve or disapprove any submitted paper.	• Deutsche GesellschaH für Urologic (DGU), Germany.

Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
17	Sultan et al.[48]	Bladder	Male and female participants undergoing radical cystectomy for primary bladder cancer, including urothelial carcinoma, squamous carcinoma, or adenocarcinoma (or other rare histological types), and participants undergoing cystectomy or benign disease such as hemorrhagic cystitis.	Compared alvimopan to placebo.	280	- Time-to-tolerance of a solid diet and documented bowel movements - Time-to-hospital discharge - Major adverse events - Readmission - Any cardiovascular event	1	In patients undergoing radical cystectomy and urinary diversion, the use of alvimopan administered as part of an enhanced recovery pathway for a limited duration (up to 15 doses for up to seven days) probably reduces the time to tolerance of solid food, time to hospital discharge and rates of major adverse events. Readmission rates, rates of cardiovascular events and narcotic pain requirements are probably similar. The need for reinsertion of nasogastric tubes is reduced. We found no evidence for the impact on rates of parenteral nutrition within 30 postoperative days.	Shahnaz Sultan: None known.Bernadette Coles: None known.Philipp Dahm: None known.	Minneapolis VA Health Care System, USA. University of Minnesota Department of Urology, USA.
18	Shepherd et al.[49]	Bladder	Adults (over 18 years of age) of either gender with histologically confirmed Ta and T1 superficial bladder cancer, with or without CIS, treated with TUR.	-Intravesical BCG plus IFN-2 versus intravesical BCG alone-Intravesical BCG alternating with IFN-2 versus intravesical BCG alone	1231	-Recurrence -Progression -Discontinuation of therapy due to adverse Events -Disease-specific mortality -Disease-specific quality of life	5	We found low- to very low-quality evidence suggesting no clear differences in recurrence or progression with BCG plus IFN-B compared with BCG alone for people with NMIBC; there was no information to determine the effect on discontinuation of therapy due to adverse events. Low-quality evidence suggests BCG alternating with IFN-B compared with BCG alone may increase time-to-recurrence, however, low-quality evidence also suggests no clear differences for time-to-progression or discontinuation of therapy due to adverse events.	ARHS: None known ES: None known NRB: None known	-

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Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
19	Nabi et al.[50] (withdraw)	Renal		Partial nephrectomy versus radical nephrectomy for clinically localized renal masses						Cancer Research Wales, UK. Cancer Research Wales funded the library facilities.
20	Coppin et al.[51] (withdraw)									-BC cancer agency, Canada
21	Shelley et al.[52] (withdraw)									
22	Krogsbøll et al.[53]		Screening using urinary dipsticks performed as part of a health check, such as in general practice or at the community level, as well as studies of screening hospital in- or outpatients, and patients in nonhospital specialist clinics.	Comparing urinary dipstick screening with no dipstick screening were eligible for inclusion.	-	• All-cause mortality • Cardiovascular mortality • Cancer mortality • ESKD (patients requiring renal replacement therapy, i.e. dialysis or kidney transplantation).	-	We found no evidence to assess the benefits and harms of screening with urinary dipsticks, which remain unknown.	• Lasse T Krogsbøll: None known • Karsten Juhl Jørgensen: None known • Peter C Gøtzsche: None known.	
23	Kunath et al.[54]	Prostate	Men at advanced stages of prostate cancer who had not received prior androgen suppression therapy were eligible.	Comparing nonsteroidal antiandrogen monotherapy with medical or surgical castration monotherapy for men in advanced stages of prostate cancer.	3060	- Overall survival - Clinical progression - Treatment failure - Breast pain - Gynecomastia - Hot flashes	11	Currently available evidence suggests that use of nonsteroidal antiandrogen monotherapy compared with medical or surgical castration monotherapy for advanced prostate cancer is less effective in terms of overall survival, clinical progression, treatment failure and treatment discontinuation due to adverse events. Evidence quality was rated as moderate according to GRADE. Further research is likely to have an important impact on results for patients with advanced but nonmetastatic prostate cancer treated with nonsteroidal antiandrogen monotherapy.	This review was supported by a Ferdinand Eisenberger grant of the Deutsche GesellschaJ für Urologie (German Society of Urology; grant ID KuF1/FE-10).	External sources • Deutsche GesellschaJ für Urologie e.V., Germany.

Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
24	Parahoo et al.[55]	Prostate	Men with prostate cancer	• Cognitive behavioral therapy. • Psychoeducational therapy. • Supportive therapy. • Counseling.	3204	-General health-related quality of life: Physical component at end of intervention - General health-related quality of life: Mental component at end of intervention - Self-efficacy at end of intervention - Prostate cancer knowledge at end of intervention - Uncertainty at end of intervention - Distress at end of intervention - Depression at end of intervention	19	Overall, this review shows that psychosocial interventions may have small, short-term beneficial effects on certain domains of well-being, as measured by the physical component of GHQoL and cancer-related QoL when compared with usual care.	KP and CS received a grant that included support for travel from the Health and Social Care Research and Development Office (NorthernIreland) as part of the Cochrane Training Fellowship Scheme. JN received travel support unrelated to the review from the National Institute for Social Care and Health Research (NISCHR) Steering Group Wales and The Cochrane Collaboration to attend meetings, and received support from grants unrelated to the review from the National Institute for Health Research (NIHR), the NISCHR, The Cochrane Collaboration and Together for Short Lives.	Internal sources • The University of Ulster, UK. External sources • This review was funded by the Health and Social Care Research & Development Office (Northern Ireland) as part of the Cochrane Training Fellowship Scheme, UK.
25	Ilic et al.[56]	Prostate	All men enrolled in studies of prostate cancer screening were eligible for this review	-Digital rectal examination (DRE) -Prostate-specific antigen (PSA)test -Transrectal ultrasound (TRUS)-guided biopsy	341	-All cause mortality -prostate cancer specific mortality -prostate cancer diagnosis -tumor stage (localized T1, T2, NO, MO) tumor stage (advanced T3-4, N1, M1)	5	Prostate cancer screening did not significantly decrease prostate cancer-specific mortality in a combined meta-analysis of five RCTs. Only one study (ERSPC) reported a 21% significant reduction of prostate cancer-specific mortality in a pre-specified subgroup of men aged 55 to 69 years. Pooled data currently demonstrates no significant reduction in prostate cancer-specific and overall mortality.	-	Internal sources: Department of Urology, College of Medicine, University of Florida, USA -Malcom Randall Veterance Affairs Medical Center, Gainesville, Florida, USA

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Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
26	Jones et al.[57]	Bladder	Adult patients of any gender, with histologically confirmed Ta or T1 transitional cell carcinoma of the bladder, with or without carcinoma in situ (CIS).	All trials compared gemcitabine to active controls and varied in the reporting of outcomes	704	The primary outcome of interest was treatment efficacy as measured by the effect of intravesical gemcitabine on tumor recurrence.Outcome data presented as the time to first recurrence, recurrence-free survival or the incidence of tumor recurrence at 12- and 24-months following treatment were relevant.	6	A single dose immediately following surgery is ineffective based on one study. Gemcitabine may be more active than mitomycin C with a lower toxicity profile. Compared to intravesical BCG therapy, gemcitabine had similar effects in intermediate risk patients, less effective in high risk patient and superior in BCG refractory patients		Internal sources: Cancer Research Wale, Cardiff, UK Funded the library facilities
27	Daly et al.[58]	Prostate	Men with histologically confirmed invasive prostate adenocarcinoma without regional lymph node involvement or distant metastatic disease	Randomized controlled trials (RCT) comparing RP followed by RT with RP alone.	1815	The primary endpoint was overall mortality.	3	Adjuvant RT after RP improves overall survival and reduces the rate of distant metastases, but these effects are only evident with longer follow up. At 5 and 10 years it improves local control and reduces the risk of biochemical failure, although the latter is not a clinical endpoint. Moderate or severe acute and late toxicity is minimal. There is an increased risk of urinary stricture and incontinence, but no detriment to quality of life, based on limited data. Given that the majority of men who have undergone a RP have a longer life expectancy, radiotherapy should be considered for those with high-risk features following radical prostatectomy. The optimal timing is unclear.		Princess Alexandra Cancer Collaborative Group, Australia.

Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology								
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results		Conflict of interest	Funding
28	Ilic et al.[59]	Prostate	Adult (> 18 years) men of any ethnicity who had not previously been diagnosed with prostate cancer were eligible for inclusion in this review. Those with an increased risk of prostate cancer due to a family history of the disease or an elevated PSA level were included.	Intervention included: Dietary interventions aimed at increasing lycopene intake; lycopene supplements; and lycopene-containing products used to prevent the development of prostate cancer.Studies employing any quantity of lycopene, taken over any duration of time and in combination with any other ingested supplements were included.	154	The primary outcomes of this review were prostate cancer-specific mortality and incidence of prostate cancer.	3	None of the studies reported data on prostate cancer mortality. All of the included studies differed with respect to design, participants included and allocation of lycopene.	-		-
29	Peinemann et al.[60]	Prostate	Men with clinically localized prostate cancer	Randomized, controlled trials comparing LDR-BT versus RP, EBRT, and NPT	200	Overall survival, cause-specific mortality, or metastatic-free survival were not reported	1	Low-dose rate brachytherapy did not reduce biochemical recurrence-free survival versus radical prostatectomy at 5 years. For short-term severe adverse events, low-dose rate brachytherapy was significantly more favorable for urinary incontinence, but radical prostatectomy was significantly more favorable for urinary irritation. Evidence is based on one RCT with high risk of bias	-		Internal sources: -Institute for Quality and Efficiency in Health Care (IQWiG): computer and program, full text of articles, Germany.
30	Zani et al.[61]	Bladder	Male patients who required TRPB and received prophylactic antibiotics or placebo/no treatment.	• Antibiotic versus placebo or no treatment • antibiotic class A (quinolones, sulfonamides, aminoglycosides, cephalosporins, V-lactamase inhibitors, metronidazole) versus class B (quinolones, sulfonamides, aminoglycosides, cephalosporins, V-lactamase inhibitors, metronidazole) • single-dose versus multiple-dose treatment • short-course (one day) versus long-course treatment (three days) • oral versus systemic administration (intravenous (IV) and intramuscular (IM)) • antibiotic versus enema	3599	1. Bacteriuria 2. Bacteremia 3. Fever 4. Urinary tract infection 5. Sepsis	22	Antibiotic prophylaxis is effective in preventing infectious complications following TRPB. There is no definitive data to confirm that antibiotics for long-course (3 days) are superior to short-course treatments (1 day), or that multiple-dose treatment is superior to single dose.			

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Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
31	Shang et al.[62]	Bladder	Adults (> 18 years) with Ta and T1 bladder cancer treated with trans-urethral resection.	To compare the effectiveness and safety of BCG with EPI in the treatment of Ta and T1 bladder cancer.	1111	1. Frequency of tumors recurrence (relapse) 2. Disease progression by stage (> stage T2) 3. Mortality (overall and disease-specific) 4. Distant metastases	5	The data from the present meta-analysis indicate that intravesical BCG treatment is more efficacious than EPI in reducing tumors recurrence for Ta and T1 bladder cancer. However, BCG appears to be associated with a higher incidence of adverse effects, such as drug induced cystitis, hematuria and systemic toxicity, then EPI. The overall quality of the evidence is rather low. Well-designed, high quality randomized controlled trials with good allocation concealment are required.	We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in this review (eg, employment, consultancy, stock ownership, honoraria, and expert testimony).	Internal sources • Institute of Urology, The Second Hospital of Lanzhou University, China. • The Center of Evidence Based Medicine of Lanzhou University, China.
32	Shelley et al.[63]	Bladder	Patients of any age or gender, with measurable or evaluable histologically proven, unresectable locally advanced (T3b-T4b) or metastatic (N2, N3, M1) transitional cell carcinoma of the bladder.	-Single agent gemcitabine versus placebo; -gemcitabine combined with one cytotoxic versus the same cytotoxic alone; -gemcitabine combined with one cytotoxic versus gemcitabine combined with a different cytotoxic; -a multiple combination regime containing gemcitabine versus the same regime without gemcitabine; - A multiple combination regime containing gemcitabine versus a different multiple combination regime.	1340	Overall survival was the main outcome of interest. The data included the duration of overall survival, defined as the time from randomization or first drug administration to death of any cause, and the median survival values and survival rates at 1,2,3 and 5 years.	7	A review of the published evidence found that one trial reported gemcitabine plus cisplatin had a better safety profile than MVAC and may be considered the first choice for treatment of metastatic bladder cancer. However, the data are limited to one trial only. Patients unable to tolerate cisplatin may benefit from gemcitabine plus carboplatin.	-	Internal sources: -Cancer Research Wales, UK.

Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
33	Rai et al.[64]	Bladder	All adult patients with localized transitional cell carcinoma.Localized disease was defined as limited to the kidney or ureter, with no gross lymph nodal enlargement on imaging.	Any surgical method or approach for managing localized upper tract transitional cell carcinoma -		Overall and cancer-specific survival were primary outcomes. Surgery-related morbidity. Quality of life and health economics outcomes were secondary outcomes.	1	There is no high-quality evidence available from adequately controlled trials to determine the best surgical management of upper tract transitional cell carcinoma. However, one small randomized trial and observational data suggests that laparoscopic approach is associated with less blood loss and early recovery from surgery with similar cancer outcomes when compared to open approach. -		Internal sources • Velindre NHS Trust, Cardiff, UK. External sources • Cancer Research Wales, UK. Funded library facilities
34	Ilic et al.[65]	Testicular	Adult men enrolled in studies evaluating screening for testicular cancer were eligible for this review.	Studies that incorporated either physical examination by a physician or patient self-examination as a means of screening were eligible for inclusion in this review.		The primary outcome in this review was mortality, including testicular-cancer specific and all-cause.		Patients with increased clinical risk factors for testicular cancer, including a family history of testicular cancer, undescended testis (cryptorchidism) or testicular atrophy should be informed by their physicians of their potential increased risk of testicular cancer, along with potential benefits and harms associated with screening.		
35	Hegarty et al.[66]	Prostate	Men with confirmed prostate cancer	Randomized or quasi-randomized controlled trials comparing the effects of RP versus WW for clinically localized prostate cancer.	837	Overall survival.	2	The existing trials provide insufficient evidence to allow confident statements to be made about the relative beneficial and harmful effects of RP and WW for patients with localized prostate cancer. The results of ongoing trials should help to inform treatment decisions for men with screen-detected localized -		Internal sources • University College Cork, Ireland. External sources • Health Research Board, Ireland. • Grant no. 5R01DK63300-4, USA.

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Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

	Study	Cancer	Methodology: Target population	Methodology: Intervention and comparisons	Methodology: Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
								prostate cancer.		
36	Wilt et al.[67]	Prostate	Adult men, aged 45 years or older, who are at risk for prostate cancer and have a life expectancy of at least 10 years subgroups of interest include	5ARI (finasteride or dutasteride) versus placebo, no intervention, medical or herbal therapies, or surgical, device/minimally invasive therapies for nonmalignant prostate conditions.	-	The primary outcome was prostate cancer detected for-cause period prevalence. For-cause prostate cancers include those that: 1) were suspected clinically during the course of the trial because of symptoms, abnormal digital rectal exam, or abnormal PSA, and were confirmed on biopsy; or 2) during the trial, a recommendation was made for biopsy per the study protocol (eg, due to increasing PSA) which was never done, and end-of-study biopsy showed prostate cancer; or 3) end-of-study biopsy in the setting of a PSA > 4 ng mL^{-1} and/or suspicious digital rectal exam (DRE) showed prostate cancer.	13	Five-alpha-reductase inhibitors reduce prostate cancer risk but may increase the risk of high-grade disease in men who are undergoing regular screening for prostate cancer using prostate specific antigen and digital rectal examination. Effects are consistent across race, family history and age and possibly 5ARI but were limited to men with baseline PSA values $<$ 4.0 ng mL^{-1}. The impact of 5ARI on absolute or relative rates of prostate cancer in men who are not being regularly screened is not clear. Information is inadequate to assess the impact of 5ARI on mortality.	-	External sources • American Society of Clinical Oncology, USA. • American Urological Association, USA. • NIDDK Grant #1R01 DK063300-01A2, USA. • Grant no. 5R01DK63300-4, USA.
37	Coppin et al.[68] (withdraw)	Renal	Patients with advanced renal cell cancer	Agents with known or presumed molecular targets and known or presumed antiangiogenesis agents must have been part of the therapeutic regimen of at least one study arm. Classic immunotherapy agents, including recombinant cytokines and their predecessors, were excluded from this definition of targeted therapy, but may have been included as part of the regimen in any study arm. Studies in which maintenance therapy by a targeted agent was the randomized variable were eligible.		Studies reported at least one efficacy outcome by allocation arm to be eligible for inclusion. Eligible efficacy outcomes were categorical or time-dependent. Categorical efficacy outcomes included achievement of tumor shrinkage or disease stabilization according to commonly recognized criteria. Time-dependent outcomes included overall survival or progression-free survival from date of randomization. Quality-of-life outcomes were examined where available. Adverse events were examined in studies reporting superior efficacy or decreased toxicity for the investigational arm. Studies that reported only adverse events were not eligible.	25	Several agents with specified molecular targets have demonstrated clinically useful benefits over interferon-alfa, and also after either prior cytokine or initial antiangiogenesis therapy. More research is required to fully establish the role of targeted agents in this condition.	To be declared by each reviewer.	Internal sources • BC Cancer Agency, Canada. External sources • Prostate Diseases and Urologic Cancers CRG, USA. • Department of Veterans Affairs Health Services Research and Development (HSRD) Office, USA. • Cochrane Urological Cancers Subgroup, Velindre NHS Trust, Cardiff, UK.

Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
38	De Conti et al.[69]	Prostate	Patients will be eligible, regardless of any tumor stage or grade, if they have prostate cancer and have not received prior androgen suppression therapy.	1) intermittent androgen suppression, including LHRH, androgen ablation (AA) and maximum androgen blockade (MAB) (or combination therapy), and 2) continuous androgen suppression, including orchiectomy, LHRH, AA, and MAB.	1382	Overall mortality.	5	Data from RCTs comparing IAS to CAS are limited by small sample size and short duration. There are no data for the relative effectiveness of IAS versus CAS for overall survival, prostate cancer-specific survival, or disease progression. Limited information suggests IAS may have slightly reduced adverse events. Overall, IAS was also as effective as CAS for potency, but was superior during the interval of cycles (96%).	-	External sources • Brazilian Cochrane Center, Brazil. • Grant no. 5R01DK63300-4, USA.
39	Shelley et al.[70]	Prostate	Patients with advanced prostate cancer refractory to hormone therapy (HRPC).	Randomized comparisons of different chemotherapeutic regimens, chemotherapy versus best standard of care or placebo, were relevant to this review.	6929	The main outcome measures will be overall survival, disease specific survival, PSA response, and time to progression.	47	Patients with HRPC have not traditionally been offered chemotherapy as a routine treatment because of treatment-related toxicity and poor responses. Recent data from randomized studies, in particular those using docetaxel, have provided encouraging improvements in overall survival, palliation of symptoms, and improvements in quality of life. Chemotherapy should be considered as a treatment option for patients with HRPC.	-	Internal sources • Velindre NHS Trust, Cardiff, UK. • Minneapolis VA Center for Chronic Disease Outcomes Research, USA. External sources • National Collaborating Center for Cancer, Cardiff, UK.

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Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
40	Kumar et al.[71]	Prostate	Patients with localized or locally advanced prostate cancer	Comparing neo-adjuvant or adjuvant hormonal deprivation in combination with primary therapy (radical radiotherapy or radical prostatectomy) versus primary therapy alone were included in this review.		For neo-adjuvant studies, the primary outcome was overall survival	22	Hormone therapy combined with either prostatectomy or radiotherapy is associated with significant clinical benefits in patients with local or locally advanced prostate cancer. Significant local control may be achieved when given prior to prostatectomy or radiotherapy, which may improve patient's quality of life. When given adjuvant to these primary therapies, hormone therapy, not only provides a method for local control, but there is also evidence for a significant survival advantage. However, hormone therapy is associated with significant side effects, such as hot flushes and gynecomastia, as well as cost implications.	-	Internal sources • Velindre NHS Trust, Cardiff, UK. • Minneapolis VA Center for Chronic Disease Outcomes Research, USA. • Cardiff University, Cardiff, Wales, UK.External sources• National Collaborating Center For Cancer, Cardiff, UK.
41	Vale et al.[72]	Bladder	Patients with biopsy proven invasive (i.e. clinical stage T2 to T4a) transitional cell carcinoma of the bladder	Patients should have been randomized to receive local definitive treatment with or without adjuvant chemotherapy. The comparison had to be unconfounded by additional agents or Interventions. The same local treatment should have been used on each arm, i.e. control and experimental arms had to differ only by the addition of chemotherapy.	491	- overall survival - Overall disease-free survival - Locoregional disease-free survival - Metastases-free survival In each case, patients alive without disease were censored on the date of last follow up. For all endpoints, death was defined as death by any cause.	6	This IPD meta-analysis provides the best evidence currently available on the role of adjuvant chemotherapy for invasive bladder cancer. However, at present there is insufficient evidence on which to reliably base treatment decisions. These results highlight the urgent need for further research into the use of adjuvant chemotherapy. The results of appropriately sized randomized trials, such as the ongoing EORTC-30994 trial are needed before any definitive conclusions can be drawn.	-	Internal sources • Medical Research Council, UK.

Supplementary File 1. The Characteristics of Included Studies in Urological Cancer Groups of Cochrane Library (Data Extraction Table) (continued)

			Methodology							
	Study	Cancer	Target population	Intervention and comparisons	Sample size	Outcomes	No of included RCTs	Main results	Conflict of interest	Funding
42	ABCMA Collaboration[73]	Bladder	Patients with biopsy proven invasive (i.e. clinical stage T2 to T4a) transitional cell carcinoma of the bladder	Patients should have been randomized to receive local definitive treatment with or without neoadjuvant chemotherapy. The comparison had to be unconfounded by additional agents or interventions. The same local treatment should have been used on each arm, i.e. control and experimental arms had to differ only by the addition of chemotherapy.		- overall survival - Living patients - Overall disease-free survival - Loco-regional disease-free survival - Metastases-free survival Patients alive without disease were censored on the date of last follow up. For all endpoints, death was defined as death by any cause.	14	This improvement in survival encourages the use of platinum-based combination chemotherapy for patients with invasive bladder cancer.		Internal sources • Medical Research Council, UK. External sources • Grant no. 5R01DK63300-4, USA.
43	Shelley et al.[74]	Bladder	Both male and female patients of any age with histologically proven transitional cell carcinoma of the bladder	All randomized studies comparing radical cystectomy (with or without preoperative radiotherapy) to radiotherapy with surgical salvage.	439	- Overall survival - disease-specific survival	5	The analysis of this review suggests that there is an overall survival benefit with radical surgery compared to radical radiotherapy in patients with muscle-invasive bladder cancer. However, it must be considered that only three trials were included for analysis, the patients numbers were small and that many patients did not receive the treatment they were randomized to. It must also be noted that many improvements in both radiotherapy and surgery have taken place since the initiation of these trials.	-	Internal sources • Velindre NHS Trust Hospital, UK. • Minneapolis VA Center for Chronic Disease Outcomes Research, USA.
44	Shelley et al.[75]	Bladder	Adults with histologically confirmed Ta and T1 superficial bladder cancer	All randomized or quasi-randomized studies comparing intravesically administered BCG plus TUR with TUR alone. BCG of any strain, dose and schedule would be considered appropriate	585	The main outcome measure in this review was treatment efficacy, as measured by the time to recurrence after treatment, and the number of patients that recur at 12 months post-TUR. Local toxicities such as cystitis, hematuria and urinary frequency, and systemic	6	In patients with medium/high risk Ta or T1 bladder cancer, immunotherapy with intravesical BCG following TUR appears to provide a significant advantage over TUR alone in delaying tumor recurrence.	-	Internal sources • Velindre NHS Trust, UK. • Veterans Affairs Health Services Research and Development Office, USA.

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Supplementary File 2. "Implications for Research" Section in the Included Studies

	Study	Implications for research
1	Schmidt et al.[32]	High-quality randomized controlled trials in people with intermediate- and high-risk bladder cancer with adequate randomization and blinding are warranted.
2	Hickey et al.[33]	Updating data in published randomized controlled trials with longer follow-up will likely add precision to these findings.
3	Kunath et al.[34]	Conclusions are limited primarily by imprecision, and performance and detection bias, and further research is likely to have an important impact on credibility of results
4	Burden et al.[35]	This review highlights the need for better-quality research on the perioperative nutritional management for the bladder cancer.
5	Hwang et al.[36]	We found small number of studies with small sample size and possibility of selective reporting bias for harm outcomes. We found no RCT evidence for other patient important outcome such as survival and quality of life.
6	Hwang et al.[37]	This is the first systematic review based on the only available RCT in this field. Given that the certainty of evidence for the patient important outcomes considered in this review was only low or very low future studies are required.
7	Drost et al.[38]	This systematic review provides diagnostic accuracy evidence of MRI, MRI-targeted biopsy, the MRI pathway and systematic biopsy, with additional evidence by agreement analyses.
8	Rai et al.[39]	This review is based on five relatively small trials with methodological limitations that provided low-quality evidence for most outcomes. Only one trial has provided long-term oncological outcomes.
9	Sathianathen et al.[40]	Given the low to moderate certainty of evidence that characterizes most of the reported analyses, future trials should strive for higher methodological standards with regards to blinding to minimize concerns about performance and detection bias.
10	Narayan et al.[41]	This review identified only one randomized controlled trial to contribute to its findings, and conclusions are limited primarily by imprecision and performance or detection biases. More rigorous trials are necessary in the future.
11	Jung et al.[42]	In this update, we found two trials that investigated the comparison of primary whole gland cry therapy to EBRT but we rated the QoE, consistently, as very low. We found no trials for other whole gland treatment comparisons and no eligible trials investigating focal therapy.
12	Macherey et al.[43]	Our review enlightened the need for more patient-important data, especially for pain and quality of life.
13	Ilic et al.[44]	Evidence from previous systematic reviews of non-RCTs has uniformly concluded that the quality of the evidence base in observational studies is low.There is an urgent need to raise methodological standards for clinical research on new urologic procedures and devices.
14	Jung et al.[45]	The findings of this review that included 5 comparisons was informed by only 3 trials by one research team. These studies have important limitations that future studies should avoid.
15	Unverzagt et al.[46]	The most effective setting of new immunotherapeutic and target therapies are currently under investigation and results should be discussed in the update of this review.
16	Kunath et al.[47]	We included only one randomized controlled trial containing methodological limitations.
17	Sultan et al.[48]	Despite the existence of only a single trial, we are moderately confident in the effect size estimates reported, which likely lie close to the true effect. Longer-term follow-up data from this trial would be helpful to provide further assurance of safety.
18	Shepherd et al.[49]	There was low- to very low-quality evidence indicating no clear difference for recurrence, progression, or disease-specific mortality with BCG plus IFN-α compared with BCG alone.
19	Nabi et al.[50]	"Withdrawn"
20	Coppin et al.[51]	"Withdrawn"
21	Shelley et al.[52]	"Withdrawn"
22	Krogsbøll et al.[53]	We found no trials that investigates dipstick screening versus no dipstick screening.
23	Kunath et al.[54]	Best available evidence was investigated. The quality of evidence according to GRADE is only moderate. However, we believe that further research on nonsteroidal antian-drogen monotherapy is likely not necessary for the subgroup of men with metastatic prostate cancer.

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Supplementary File 2. "Implications for Research" Section in the Included Studies (continued)

	Study	Implications for research
24	Parahoo et al.[55]	The evidence from this review is not strong enough to permit meaningful conclusions about the effect of psychological interventions for male with prostate cancer.
25	Ilic et al.[56]	Given the variation in study design and quality across the five include studies it could be argued that pooling studies is not appropriate.
26	Jones et al.[57]	The number of randomized trials evaluating intravesical gemcitabine is limited to six. Further randomized trials are needed.
27	Daly et al.[58]	Studies designed to adequately address all-cause and prostate cancer specific mortality are needed.
28	Ilic et al.[59]	The findings of this systematic review conclude that there is insufficient evidence to either support, or refute, the use of lycopene for the prostate cancer.
29	Peinemann et al.[60]	Evidenced was based on one RCT with high risk of bias.
30	Zani et al.[61]	Following these results, it is unlikely that future trials will feature a no-treatment control group for antibiotic prophylaxis in prostate biopsy.
31	Shang et al.[62]	The evidence from the five RCTs clearly indicates that intravesical BCG is more effective than EPI in reducing tumor recurrence for Ta and T1 bladder cancer.
32	Shelley et al.[63]	The evidence from randomized trials suggested that the combination of gemcitabine plus cisplatin had a similar overall survival outcome compared to MAC.
33	Rai et al.[64]	Although voluminous literature exists comparing different surgical approaches for the management of upper tract TCC, the quality of the retrospective studies and the one small randomized controlled trial is poor.
34	Ilic et al.[65]	This systematic review identified no randomized controlled trials that have evaluated the effectiveness of screening for testicular cancer in reducing testicular-specific mortality.
35	Hegarty et al.[66]	There is a paucity of randomized controlled trials directly comparing radical prostatectomy (RP) versus watchful waiting (WW) for patients with clinically localized prostate cancer. Only two trials met the inclusion criteria for this review. Initial results from the PIVOT are expected within the next year. The results of the PIVOT trial will be incorporated into future update.
36	Wilt et al.[67]	The impact of 5ARI on absolute or relative rates of prostate cancer in men who are not being regularly screened is not clear.
37	Coppin et al.[68]	The first round of Phase III comparative trials is now mature and published, with validated first- and second-line targeted therapy options for patients with advanced clear cell subtype that comprise the majority of renal cancers.
38	De Conti et al.[69]	We will have to wait for the results of ongoing randomized trials to see whether IAS or CAS is more effective for the treatment of prostate cancer. Based on our results with little data, more studies are needed.
39	Shelley et al.[70]	However, the clinical benefits of chemotherapy can only be tested against patients without such treatment in a randomized trial, and should be further evaluated.
40	Kumar et al.[71]	The numbers of patients were small and additional studies are required about primary outcomes.
41	Vale et al.[72]	This IPD meta-analysis of all available data provides the best information. We conclude that the current evidence is clearly limited with too few trials and too few patients on which to base reliable treatment decisions.
42	ABCMA Collaboration[73]	Our findings show a clear survival benefit associated with neoadjuvant combination chemotherapy for patients with invasive bladder cancer.
43	Shelley et al.[74]	Further randomized trial of sufficient power be undertaken to provide convincing evidence that one modality is superior.
44	Shelley et al.[75]	The evidence from the RCTs clearly indicates that intravesical BCG following TUR is effective for the prophylaxis of recurrence in Ta and T1 bladder cancers. None of the regimes described in this review fulfilled all these. Criteria: Be efficacious, improve survival, palliate symptoms, be nontoxic and improve quality of life compared to best standard of care.

one group of subjects in an experiment group gets much attention from the investigators than in the other groups.[31] Hence, it is difficult or impossible to conclude that intervention caused an effect, as opposed to the level of care. The authors often did not report whether blinding was done or not, and if blinding was mentioned, they often did not provide details.

Although high-risk selection biases decreased in recent years, the high-risk performance bias of the surveyed Cochrane urology group increased dramatically. This type of bias is a major threat to internal validity. Even though blinding minimizes this bias, there still may be differences in care levels of study groups, but these are likely to be random, and not systematic, and should not affect the outcomes. Also, blinding is not always possible or ethical.

The other common types of biases, including detection, attrition, and reporting bias, were increased in recent years rather than those in the published papers before 2015. It is obvious that systematic reviews that are designed and conducted properly produce reliable treatment-effect estimates, which may greatly impact clinical decision making. The Cochrane urology group with high quality published systematic reviews may be a reliable database in this regard. However, the methodological or reporting quality of their understudied RCTs represents the structural deficiencies.

One of the strengths of the current study is evaluating the quality of published systematic reviews and their understudied RCTs in terms of six criterion risk of bias for the first time in this field. However, our study had some limitations. We evaluated only 44 articles in the Cochrane urology group. We did not assess other topics that were not related to urological cancers in terms of risk of bias that may have influenced the results of the current study. It is recommended to evaluate other similar topics, especially urogynecology and functional urology, for future studies. Although most Cochrane urological cancer reviews had high quality, performance bias was the highest in their understudied RCTs. Regarding it and considering the increasing unclear risk of detection, attrition, and reporting biases, they obviously have structural deficiencies. Therefore, it is recommended to observe integrity principles for preventing research misconduct.

Ethics Committee Approval: The regional ethic committee of Tabriz University of Medical Sciences approved this study (IR.TBZMED.REC.1396.578).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

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Appendix 1. The Joanna Briggs Institute Critical Appraisal Tools for Use in Systematic Reviews

JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses

Reviewer_____Date_____.

Author _____Year_____Record Number_____.

		Yes	No	Unclear	Not applicable
1.	Is the review question clearly and explicitly stated?	☐	☐	☐	☐
2.	Were the inclusion criteria appropriate for the review question?	☐	☐	☐	☐
3.	Was the search strategy appropriate?	☐	☐	☐	☐
4.	Were the sources and resources used to search for studies adequate?	☐	☐	☐	☐
5.	Were the criteria for appraising studies appropriate?	☐	☐	☐	☐
6.	Was critical appraisal conducted by two or more reviewers independently?	☐	☐	☐	☐
7.	Were there methods to minimize errors in data extraction?	☐	☐	☐	☐
8.	Were the methods used to combine studies appropriate?	☐	☐	☐	☐
9.	Was the likelihood of publication bias assessed?	☐	☐	☐	☐
10.	Were recommendations for policy and/or practice supported by the reported data?	☐	☐	☐	☐
11.	Were the specific directives for new research appropriate?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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