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Subject: Reasons for excluding PRO studies

Reasons for excluding studies on patient-reported outcomes in a systematic review

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Abstract

Background

Within the frame of a systematic review, we evaluated patient-reported outcomes of permanent interstitial low-dose rate brachytherapy in patients with localized prostate cancer.

Objective

To summarize qualitatively the reasons for exclusion of nonrandomized controlled trials reporting patient-reported outcomes.

Methods

We searched PubMed, MEDLINE, EMBASE, and The Cochrane Library without restrictions on 14 June 2010. We defined the inclusion criteria according to the PICO framework. The outcomes in the present publication concerned methodological issues and were different from the initial publication: fulfilment of basic inclusion criteria according to a PICO framework and accomplishment of requirements to contain high risk of bias.

Results

We found that 21 of 50 excluded nonrandomized controlled trials did not meet PICO inclusion criteria. The rest of 29 of 50 studies lacked quality of reporting. The resulting flaws included attrition bias due to loss of follow-up, lack of reporting baseline data, potential confounding due to unadjusted data, and lack of statistical comparison between groups.

Conclusion

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With respect to the reporting of patient-reported outcomes, active efforts are required to improve the quality of reporting in nonrandomized controlled trials concerning permanent interstitial low-dose rate brachytherapy in patients with localized prostate cancer.

Key words: systematic review, patient-reported outcome, risk of bias

Strengths and limitations of this study

- We conducted a comprehensive literature search and strictly adhered to the projected methodology.
- We identified a lack of quality in patient-reported studies, analysed the cause, and suggested possible improvements in designing studies in the future.
- The systematic review is confined to a single disease and conclusions drawn from its results may not be generalizable to other diseases.
- The limits for the inclusion of studies are arbitrarily set.

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Introduction

We have conducted a systematic review to evaluate the effectiveness and adverse events of permanent interstitial low-dose rate brachytherapy (LDR-BT) in patients with localized prostate cancer categorized T1 to T2 [1]. We have compared LDR-BT with radical prostatectomy (RP), external beam radiotherapy (EBRT), and 'no primary therapy' (NPT). We used the term NPT to accommodate different types of observation including active surveillance, watchful waiting, and observing without a distinctive management. We have included one randomized controlled trial (RCT) and 30 nonrandomized controlled trials (NRCT). The primary outcome was overall survival and cancer-specific survival. The secondary outcomes were clinically defined disease-free survival, biochemical recurrence-free survival, physician-reported severe adverse events, and patient-reported outcomes such as function and bother scores as well as generic and disease-related health-related quality of life. We concluded that the current evidence is insufficient to allow a definitive conclusion about overall survival. RP and EBRT can severely affect the structural integrity of neighboring organs and their functions and can cause considerable long-term impairment of health-related quality of life. In a view of expecting similar survival but a tremendous difference of adverse events between treatment alternatives, valid data on health-related quality of life could tip the balance. At least, we assume that shared-decision making and consideration of patients' preferences in searching for the best individual treatment would rely on information on health-related quality of life data. Of the 30 included nonrandomized studies, 13 studies reported patient-reported outcomes (PRO) [2]. During the study selection process, we experienced that we excluded another 50 nonrandomized PRO studies. We found it a pity that we could not use the many data. We had the impression that a considerable number of studies were excluded because of lack in reporting quality. Therefore, we wanted to summarize the reasons for excluding those PRO studies and make aware that authors of PRO studies should

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meet some basic requirements for reporting of comparative PRO data to achieve higher acceptance in the scientific community. The importance of reporting PRO has been addressed by CONSORT [3] that recently has published a PRO extension to their acclaimed previous statement with respect to RCT [4]. It may be wise to build a PRO extension to STROBE [5] also to deal with the specific problems of observational studies.

The first aim of this study is to assess whether the excluded studies met the basic inclusion criteria using the PICO framework. The second aim of this study is to whether the excluded studies met requirements to contain high risk of bias.

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Materials and Methods

While preparing this systematic review, we endorsed the PRISMA statement, adhered to its principles and conformed to its checklist [6].

Study inclusion criteria

We defined the inclusion criteria according to the PICO framework that should include four essential constituents, that is, the type of participants (P), intervention (I), comparator (C), and outcome (O) [7]. The four PICO items can be supplemented by timing (T) and setting (S), two other important features of a systematic review, to create the so-called PICOTS typology [8]. A further extension embraces the study design (SD) to complete all major items of a search strategy (PICOTS-SD) [9].

Population

Initial and present publication: Localized prostate cancer is defined by the categories T1 to T2 of the Tumor-Node-Metastasis (TNM) staging system [10] if combined with an absence of both regional lymph node metastasis (N0) and distant metastasis (M0).

Intervention

Initial and present publication: Brachytherapy [11] is short-distance radiotherapy placing radiation sources with different duration and rates of dose delivery in or near tumors [12]. LDR-BT means implanting of low-energy radioactive sources emitting radiation, which are contained in titanium pellets of the size of rice grains called seeds [13].

Comparator

Initial and present publication: The European Association of Urology (EAU) suggested 3

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different treatment concepts for localized prostate cancer in addition to LDR-BT [11]: Radical prostatectomy (RP), external beam radiotherapy (EBRT), and different types of observation including active surveillance, watchful waiting, and observing without a distinctive management.

Outcome

Initial publication: Overall survival, cancer-specific survival, disease-free survival, biochemical recurrence-free survival, severe adverse events, and patient-reported outcomes. Patient-reported outcomes comprised function and bother scores as well as generic and disease-related health-related quality of life.

Present publication: Fulfilment of basic inclusion criteria according to a PICO framework by the excluded NRCT. Accomplishment of requirements to contain superimposed risk of bias in addition to the high risk of bias caused by the lack of randomization framework by the excluded NRCT.

Timing

Initial and present publication: We did not set limits on the length of the observation period.

Setting

Initial and present publication: We did not set limits on the setting such as type of country, year of recruitment, or level of health care.

Study design

Initial publication: We included RCT and NRCT evaluating LDR-BT as monotherapy in patients with localized prostate cancer. The proportion of relevant patients was required to be at

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least 80% of the study population and the response rate of questionnaires was expected to be at least 70%. For NRCT to be included, comparable baseline characteristics between treatment groups or adjustment for imbalances of these data were required. Limits on year of publication or language were not applied.

Present publication: We included specifically the NRCT that were excluded in the initial publication.

Search strategy

We searched PubMed, MEDLINE, EMBASE, and The Cochrane Library without restrictions on study design, publication year, and language. We conducted the last database searches on 14 June 2010. We tailored the terms and syntax used for the search in MEDLINE via Ovid as shown Table 1 to the requirements of the other databases.

Study selection

In the present study, we selected only those 50 nonrandomized studies on PRO that were excluded from the evaluation in the initial publication. In the study selection process, two reviewers independently judged whether a study was included or excluded. Differences were resolved by discussion without the need for a third opinion.

Data collection and analysis

The reasons for exclusion were extracted independently by two reviewers. We sought for the following data: the inclusion criteria using the PICO framework, the proportion of response of participants to questionnaires, which was required to be at least 70%, the reporting of separate baseline characteristics for each treatment group, the reporting of comparable baseline characteristics or adjustment for imbalances of these data such as the use of a Cox proportional haz-

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ard model, and the reporting of statistics comparing treatment groups. Sufficient comparability was defined as a difference between baseline values that were not statistically significant. If a statistical test was not reported, we assumed two comparable values if the greater of the two values was less than 10% above the smaller one. We also required that authors reported effect measures and statistics testing the difference between treatment groups, for example, p-values or effect measures including 95% confidence intervals. Reporting of within group comparisons or before-and-after analyses were not deemed sufficient for inclusion. We did not apply a principal summary measure as we aimed at synthesize the information in a qualitative way.

Assessment of risk of bias and quality of reporting

Two reviewers independently assessed the quality of reporting of NRCT according to the criteria specified in the previous paragraph. We did not specifically assess the risk of bias because we decided to exclude all papers with regard to a lack of reporting essential data.

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Results

We documented the reasons for exclusion of all 50 nonrandomized studies that were identified as studies reporting on PRO (Table 2). In 42% (21 of 50) studies, simply the essential PICO framework was not met. In the majority of 58% (29 of 50) studies, the predefined requirement to apply measures to contain high risk of bias was not met. Of these 29 studies, 19 studies reported a proportion of patients responding to questionnaires of less than 70% or did not address this item. Baseline characteristics were not presented for treatment groups in 3 studies. In another 6 studies, baseline characteristics were not comparable between treatment groups or there was no confounder control in the analysis adjusting for important different factors such as mean age. The statistical comparison between treatment groups was deemed not appropriate in 1 study.

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Discussion

Main results

In summary, we found that roughly 4 of 10 excluded PRO studies did not meet the essential inclusion criteria using the PICO framework. This result is consistent with the problem of information retrieval aiming at a high recall and ending up with a low precision. The papers were obviously not relevant to the research question and we did not further examine the reporting quality. We also found that roughly 6 of 10 excluded PRO studies met the PICO framework but did not provide predefined requirements to care sufficiently enough for a low response of patients to questionnaires, for reporting baseline characteristics between treatment groups, for adjusting differences in those baseline characteristics between treatment groups, and to use appropriate statistics to compare the outcome between treatment groups.

Quality of reporting of patient-reported outcomes

We identified a lack of quality of reporting in many excluded NRCT and we want to stress the importance of considering a series of requirements while conducting a study on PRO. Other authors have reported recently that, concerning disease-specific mortality or disease-free survival, available studies did not show significant differences between treatment groups. [14,15]. In view of unknown or small differences in survival measures, the results of patient-reported outcomes studies could have a noticeable impact on medical decision making [16,17]. None of the 50 excluded studies reported a non-responder analysis, though it is known that non-responders may have different attitudes than responders. Etter 1997 concluded that low response rates may be associated with overestimating an effect and that the strength and direction of a non-response bias may depend on the mechanism of non-response [18]. Therefore, results may be confounded if the proportion of included data not available for

analysis such as data from non-responders or due to loss to follow-up is considerable. We believe that a value of 30% or more can be denoted as considerable. Lowering this threshold, for example to 20%, would have resulted in less included studies. However, others suggested that 20% or more loss would be sufficient for a high risk of bias threatening the validity of results [19]. Concerning questionnaires, we recommend taking measures that are known to improve response rates [20,21]. Edwards 2009 conducted a systematic review to identify effective strategies to increase the response to postal and electronic questionnaires [22]. The authors found several strategies to increase the response, for example, pre-notification, follow-up contact, shorter questionnaires, mentioning an obligation to respond, university sponsorship, non-monetary incentives, a statement that others had responded, an offer of survey results, giving a deadline. We did not use a strict algorithm to differentiate between comparable and not comparable baseline values between treatment groups. A statistically significant difference was judged as not comparable. Not significant differences were also regarded as not comparable if the difference was at least 10% of the lower of two values. Using this approach we tried to reduce subjective decisions. We are not aware of published strict algorithms in this matter.

High risk of bias inherent in nonrandomized controlled trials

In the view of including only 1 RCT, the initial publication was based almost exclusively on NRCT. However, the lack of randomization poses a very large challenge on the authors that are advised to deal with essential problems such as selection bias and confounding. Otherwise, the findings may not be valid and of limited usefulness and the many efforts may be in vain. We want to stress that the nonrandomized design is associated with a high risk of bias because known and unknown characteristics may be distributed unequally between groups [23]. Certain study characteristics such as prospective design, concurrent control group,

adjustment of results with respect to different baseline values, and confounder control can limit additional bias. For example, Ioannidis 2001 [24] reported that discrepancies between RCT and NRCT were less common when only NRCT with a prospective design were considered. The Cochrane Collaboration offers a guide for inclusion of nonrandomized studies [25] and it has developed a tool for assessing the risk of bias in both RCT and controlled NRS [26]. Guidelines for reporting observational studies have been published to improve their quality [5]. Cox regression analysis, propensity-score-based analysis, and instrumental variable analysis are methods that have been used for correction of confounding bias in non-randomized studies [27]. Different values of various outcome measures between groups may be simply caused by different baseline data in lieu of absent significant treatment effects. We accepted any type of method adjusting or stratifying for one or more known differences in baseline characteristics. Nevertheless, it should be kept in mind that methods of adjustment do not guarantee removal of bias and that residual confounding may remain high [23]. Concerning the non-randomized design, we strongly recommend the use of methods for adjusting the results for confounders to aim for a less biased estimation of the treatment effect [28] and the adoption of guidelines for the reporting of observational studies [5].

Strengths and limitations

The strengths of the present study are a comprehensive literature search, strict adherence to the projected methodology, the identification of lack of quality in PRO studies and addressing the specific problems of PRO studies. We should consider some limitations: The study is confined to a single disease and conclusions drawn from its results may not be generalizable to other diseases. The arbitrary limits set for inclusion of studies are responsible for the extent of excluded studies. These limits may be questioned by other investigators. During re-evaluation of study quality, we found that one study fulfilled all criteria, although, this study was exclud-

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ed in previous reports [29]. The minimum follow-up of 70% for inclusion was set arbitrarily and others might find this threshold too low. We did not endorse the recently published reporting of PRO in randomized trials, an extension of the CONSORT statement [4]. All included studies in the present review are nonrandomized. We think that the lack of randomization is the prevailing issue. We did not endorse the CONSORT PRO extension for another reason. The included studies were published many years before this extension was published. There might be a need to develop an extension of the STROBE statement [5] aiming to improve the reporting of PRO in nonrandomized studies. This extension could emphasize the specific challenges of reporting PRO with respect to lack of randomization.

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Conclusions

We found that a considerable number of non-randomized controlled reporting patient-reported outcomes were excluded from a systematic review because of a lack of predefined reporting requirements. The assumed overall risk of bias was regarded too high to consider the data of these studies for inclusion in the systematic review. With respect to the reporting of patient-reported outcomes, active efforts are required to improve the quality of reporting in nonrandomized controlled trials and to increase the number of randomized controlled trials.

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Contributorship Statement

Frank Peinemann: design, data analysis, writing of the manuscript

Alexander Michael Labeit: interpretation of data

Christian Thielscher: interpretation of data

Michael Pinkawa: urological advice

Data Sharing Statement

No additional unpublished data

Competing interests

No additional unpublished data

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Subject: Reasons for excluding PRO studies

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Subject: Reasons for excluding PRO studies

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Subject: Reasons for excluding PRO studies

Figure legends

Figure 1. Study flow
Abbreviation. PICO: population, intervention, comparator, outcome; PRO: patient-reported outcomes; RCT: randomised controlled trial

Subject: Reasons for excluding PRO studies

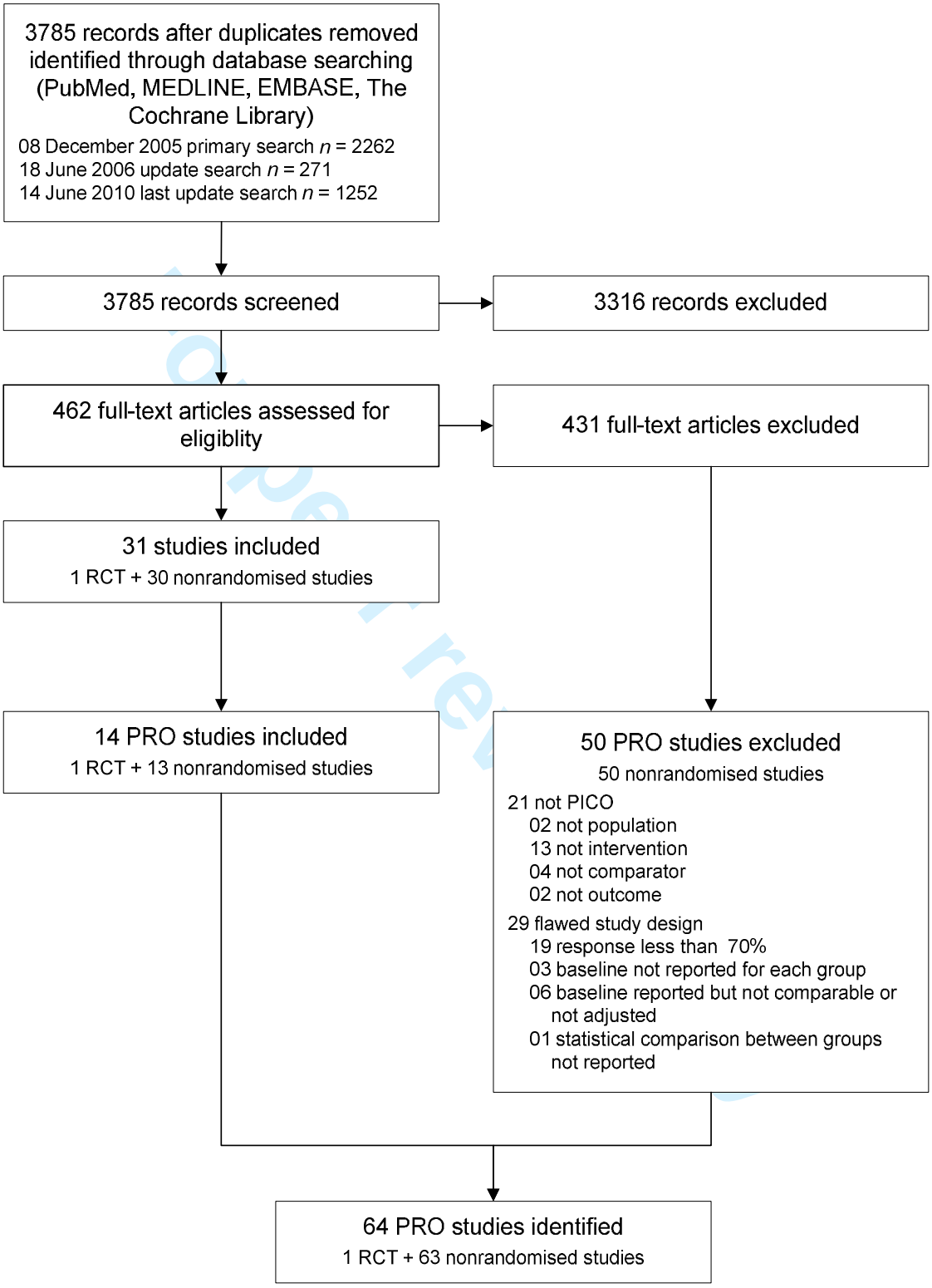


Figure 1. Study flow

Subject: Reasons for excluding PRO studies

Table 1. Search strategy.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1950 to Present>	
No	**Search term**
1	PROSTATIC NEOPLASMS/
2	(prostat* adj6 (cancer* or carcinom* or tumor* or tumour* or neoplasm* or adenocarcinom*)).ab,ti.
3	or/1-2
4	BRACHYTHERAPY/
5	brachytherap*.ab,ti.
6	((interstit* or implant*) adj6 (radiation* or radiotherapy*)).ab,ti.
7	((seed* or permanent*) adj6 implant*).ab,ti.
8	or/4-7
9	3 and 8
10	RANDOMIZED CONTROLLED TRIAL.pt.
11	CONTROLLED CLINICAL TRIAL.pt.
12	RANDOMIZED CONTROLLED TRIALS AS TOPIC/
13	RANDOM ALLOCATION/
14	DOUBLE BLIND METHOD/
15	SINGLE BLIND METHOD/
16	or/10-15
17	ANIMAL/ not HUMAN/
18	16 not 17
19	CLINICAL TRIAL.pt.
20	exp CLINICAL TRIALS AS TOPIC/
21	(clinic* adj25 trial*).tw.
22	((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw.
23	PLACEBOS/
24	placebo*.tw.
25	random*.tw.
26	RESEARCH DESIGN/
27	(latin adj square).tw.
28	or/19-27
29	28 not 17
30	29 not 18
31	COMPARATIVE STUDY.pt.
32	exp EVALUATION STUDIES/
33	FOLLOW UP STUDIES/
34	PROSPECTIVE STUDIES/
35	(control* or prospectiv* or volunteer*).tw.
36	CROSS-OVER STUDIES/
37	or/31-36
38	37 not 17
39	38 not (18 or 30)

Subject: Reasons for excluding PRO studies

40	18 or 30 or 39
41	exp CASE-CONTROL STUDIES/
42	exp COHORT STUDIES/
43	((compare* or comparison* or versus or evaluation or follow up or case-control*) adj8 (stud* or trial* or analy*)).ab,ti.
44	((cohort* or observation* or intervention*) adj3 (stud* or trial* or analy*)).ab,ti.
45	exp CONTROL GROUPS/
46	exp MULTICENTER STUDIES/
47	(multi center adj3 stud*).ab,ti.
48	or/41-47
49	40 or 48
50	search*.tw. or META ANALYSIS.mp,pt. or REVIEW.pt.
51	9 and (49 or 50)

Subject: Reasons for excluding PRO studies

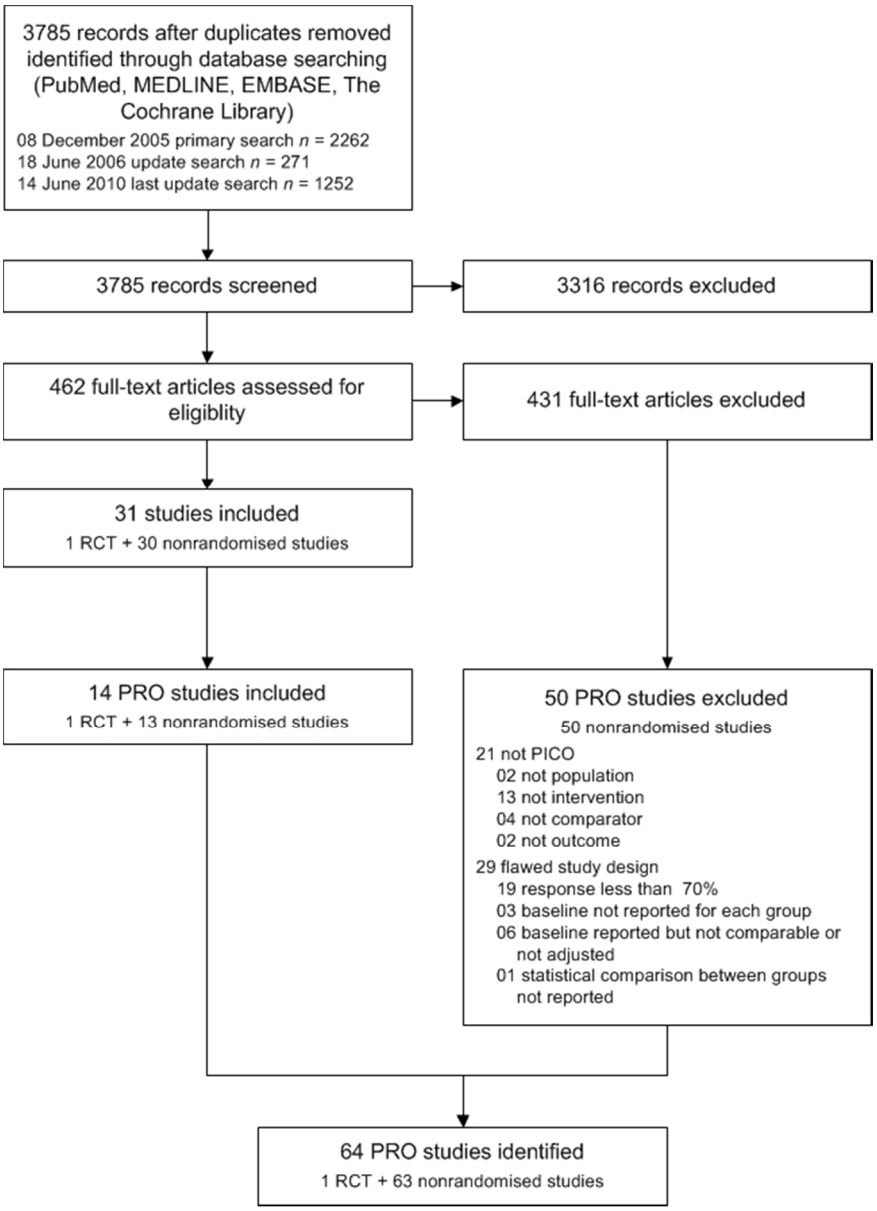
Table 1. Reasons for excluding PRO articles

Nonrandomized studies	Inclusion criteria				Requirements to contain high risk of bias				Comments
	P	I	C	O	Response ≥70%	Baseline each group	Baseline comparable/ or adjusted	Statistical comparison between groups	
Bacon 2001 [30]	yes	yes	NO	-	-	-	-	-	No concurrent group
Ball 2006 [31]	yes	yes	NO	-	-	-	-	-	Cryotherapy
Befort 2005 [32]	yes	yes	yes	yes	NO	-	-	-	Low response
Bergman 2009 [33]	yes	yes	yes	yes	yes	yes	yes	NO	No appropriate test
Bergman 2010 [34]	yes	yes	yes	yes	NO	-	-	-	Low response
Brandeis 2000 [35]	yes	NO	-	-	-	-	-	-	29% LDR-BT + EBRT
Brown 2007 [36]	yes	NO	-	-	-	-	-	-	EBRT
Burnett 2007 [37]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Chaikin 1996 [38]	NO	-	-	-	-	-	-	-	Staging not reported
Chen 2009 [39]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Choo 2010 [40]	yes	yes	yes	yes	yes	NO	-	-	Baseline not reported
Clark 2003 [41]	yes	yes	yes	yes	NO	-	-	-	Low response
Downs 2003 [42]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Eton 2001 [43]	yes	yes	yes	yes	NO	-	-	-	Low response
Frank 2007 [44]	yes	yes	yes	yes	NO	-	-	-	Low response
Fulmer 2001 [45]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Gore 2009 [46]	yes	yes	yes	yes	NO	-	-	-	Low response
Guedea 2009 [47]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Hashine 2008 [48]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Hashine 2009 [49]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Hervouet 2005 [50]	NO	-	-	-	-	-	-	-	≥20% T3-T4 in control groups
Hollenbeck 2002 [51]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Jo 2005 [52]	yes	NO	-	-	-	-	-	-	High-dose rate brachytherapy
Johnstone 2000 [53]	yes	NO	-	-	-	-	-	-	EBRT
Joly 1998 [54]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Kakehi 2007 [55]	yes	yes	yes	yes	yes	NO	-	-	Baseline not reported
Lev 2009 [56]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Lilleby 1999 [57]	yes	NO	-	-	-	-	-	-	EBRT
Litwin 2004 [58]	yes	yes	yes	yes	NO	-	-	-	Low response
Litwin 2007 [59]	yes	NO	-	-	-	-	-	-	25% LDR-BT + EBRT
Mehta 2003 [60]	yes	yes	yes	NO	-	-	-	-	"Fear of cancer"*

Subject: Reasons for excluding PRO studies

Nonrandomized studies	Inclusion criteria				Requirements to contain high risk of bias				Comments
	P	I	C	O	Response ≥70%	Baseline each group	Baseline comparable/ or adjusted	Statistical comparison between groups	
Miller 2005 [61]	yes	NO	-	-	-	-	-	-	44% LDR-BT + EBRT
Miller 2006 [62]	yes	yes	yes	yes	yes	NO	-	-	Baseline not reported
Monahan 2007 [63]	yes	yes	yes	yes	NO	-	-	-	Low response
Namiki 2006 [64]	yes	yes	yes	yes	NO	-	-	-	Low response
Namiki 2009 [65]	yes	yes	yes	yes	NO	-	-	-	Low response
Ohashi 2006 [66]	yes	yes	yes	yes	NO	-	-	-	Low response
Pinkawa 2006 [67]	yes	yes	NO	-	-	-	-	-	LDR-BT + hormones[†]
Roach 1996 [68]	yes	NO	-	-	-	-	-	-	EBRT, single-arm trial
Sanda 2008 [69]	yes	yes	yes	yes	NO	-	-	-	Low response
Schover 2002 [70]	yes	yes	yes	yes	NO	-	-	-	Low response
Soderdahl 2005 [71]	yes	yes	yes	yes	NO	-	-	-	Low response
Speight 2004 [72]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Stone 2010 [73]	yes	yes	NO	-	-	-	-	-	LDR-BT + hormones[†]
Trojan 2007 [74]	yes	yes	yes	yes	NO	-	-	-	Low response
Tward 2006 [75]	yes	yes	yes	NO	-	-	-	-	Mortality differs[§]
Valicenti 2002 [76]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Van de Poll-F 2008 [77]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Wyler 2009 [78]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Zagar 2007 [79]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
"NO" counts	2	13	4	2	19	3	6	1	Total: 50 studies
	PICO not met: 21				High risk of bias: 29				

-: not appropriate
[*]Mehta 2003: no appropriate endpoint
[†]Pinkawa 2006; Stone 2010: neoadjuvant hormonal therapy
[§]Tward 2006: non-disease-related mortality differs greatly
Abbreviations: C: comparison of interest is radical prostatectomy, external beam radiotherapy, or no primary therapy; EBRT: external beam radiotherapy; I: intervention of interest is low-dose rate brachytherapy as monotherapy; LDR-BT: low-dose rate brachytherapy; O: outcome of interest is function, bother, or generic health-related quality of life; P: patients with localized prostate cancer; PRO: patient-reported outcomes



Study flow
170x235mm (96 x 96 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	none
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	none
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	none
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	none
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	none
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	none
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	none
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Failure to address potential bias in nonrandomized controlled clinical trials may cause lack of evidence on patient-reported outcomes - a method study

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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Urology, Patient-centred medicine, Evidence based practice
Keywords:	Adult surgery < SURGERY, Radiation oncology < RADIOTHERAPY, Urological tumours < ONCOLOGY

Subject: bmjopen-2013-004720.R1.: Failure to address potential bias in CCT

Failure to address potential bias in nonrandomized controlled clinical trials may cause lack of evidence on patient-reported outcomes – a method study

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Word count, excluding title page, abstract, references, figures and tables: 6102

Subject: bmjopen-2013-004720.R1.: Failure to address potential bias in CCT

Abstract

Objectives: We conducted a workup of a previously published systematic review and aimed to analyse why most of the identified nonrandomized controlled clinical trials with patient-reported outcomes did not match a set of basic quality criteria.

Setting: There were no limits on the level of care and the geographical location.

Participants: The review evaluated permanent interstitial low-dose rate brachytherapy in patients with localized prostate cancer and compared that intervention to alternative procedures such as external beam radiotherapy, radical prostatectomy, and no primary therapy.

Primary outcome measure: Fulfilment of basic inclusion criteria according to a PICO framework and accomplishment of requirements to contain superimposed risk of bias.

Results: We found that 21 of 50 excluded nonrandomized controlled trials did not meet PICO inclusion criteria. The rest of 29 of 50 studies lacked quality of reporting. The resulting flaws included attrition bias due to loss of follow-up, lack of reporting baseline data, potential confounding due to unadjusted data and lack of statistical comparison between groups.

Conclusions: With respect to the reporting of patient-reported outcomes, active efforts are required to improve the quality of reporting in nonrandomized controlled trials concerning permanent interstitial low-dose rate brachytherapy in patients with localized prostate cancer.

Subject: bmjopen-2013-004720.R1.: Failure to address potential bias in CCT

Key words: systematic review, patient-reported outcome, risk of bias

Strengths and limitations of this study

- We conducted a comprehensive literature search and strictly adhered to the projected methodology.
- We identified a lack of quality in nonrandomized controlled clinical trials reporting patient-reported outcomes, analysed the cause, and suggested possible improvements in designing studies in the future.
- The analysis is confined to a single disease and a specific treatment and conclusions drawn from its results may not be generalizable to other diseases and treatments.
- The limits for the inclusion of studies are arbitrarily set.

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Abbreviation	Term
CCT	Nonrandomized controlled clinical trial
CONSORT	Consolidated standards of reporting trials
EBRT	External beam radiotherapy
EMBASE	Excerpta medica database
LDR-BT	Permanent interstitial low-dose rate brachytherapy
MEDLINE	Medical literature analysis and retrieval system online
PICO (TS-SD)	Participants, intervention, comparator, outcome (timing, setting, study design)
PRO	Patient-reported outcome
RCT	Randomized controlled trial
STROBE	Strengthening the reporting of observational studies in epidemiology
TNM	Tumor-Node-Metastasis

Subject: bmjopen-2013-004720.R1.: Failure to address potential bias in CCT

Introduction

The present paper reports a workup of a previously published systematic review [1]. It may be regarded as a methodological supplement adding information on a subset of excluded studies. We have compared permanent interstitial low-dose rate brachytherapy, with radical prostatectomy, external beam radiotherapy, and 'no primary therapy' in patients with localized prostate cancer categorized T1 to T2. We used the term 'no primary therapy' to accommodate different types of observation including active surveillance, watchful waiting, and observing without a distinctive management. As a result, we included one randomized controlled trial (RCT) and 30 nonrandomized controlled clinical trials (CCT). The primary outcome was overall survival. The secondary outcomes were clinically defined disease-free survival, biochemical recurrence-free survival, physician-reported severe adverse events, and patient-reported outcomes such as function and bother scores as well as generic and disease-related health-related quality of life. We concluded that the current evidence is insufficient to allow a definitive conclusion about overall survival. Radical prostatectomy and external beam radiotherapy can severely affect the structural integrity of neighboring organs and their functions and can cause considerable long-term impairment of health-related quality of life. In a view of expecting similar survival but a tremendous difference of adverse events between treatment alternatives, valid data on health-related quality of life could tip the balance. At least, we assume that shared-decision making and consideration of patients' preferences in searching for the best individual treatment would rely on information on health-related quality of life data. Of the 30 included nonrandomized studies, 13 studies reported patient-reported outcomes (PROs), that is, only the patients provided the information [2]. During the study selection process, we experienced that we excluded another 50 nonrandomized PRO studies. We found it a pity that we could not use the many data. We had the impression that a considerable number of studies were excluded because of lack in reporting quality. Therefore,

Subject: bmjopen-2013-004720.R1.: Failure to address potential bias in CCT

we wanted to summarize the reasons for excluding those PRO studies and make aware that authors of PRO studies should meet some basic requirements for reporting of comparative PRO data to achieve higher acceptance in the scientific community. The importance of reporting PRO has been addressed by the Consolidated Standards of Reporting Trials (CONSORT) group [3] that recently has published a PRO extension to their acclaimed previous statement [4]. It may be wise to build a PRO extension to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement [5] that addresses specific issues of observational studies.

The first aim of this study was to assess whether the excluded studies met the basic inclusion criteria using the PICO framework. The second aim of this study was whether the excluded studies met requirements to contain high risk of bias.

Subject: bmjopen-2013-004720.R1.: Failure to address potential bias in CCT

Materials and Methods

Study inclusion criteria

We defined the inclusion criteria according to the PICO framework that should include four essential constituents, that is, the type of participants (P), intervention (I), comparator (C), and outcome (O) [6]. The four PICO items can be supplemented by timing (T) and setting (S), two other important features of a systematic review, to create the so-called PICOTS typology [7]. A further extension embraces the study design (SD) to complete all major items of a search strategy (PICOTS-SD) [8].

Population

Initial and present publication: Localized prostate cancer is defined by the categories T1 to T2 of the Tumor-Node-Metastasis (TNM) staging system [9] if combined with an absence of both regional lymph node metastasis and distant metastasis.

Intervention

Initial and present publication: Brachytherapy [10] is short-distance radiotherapy placing radiation sources with different duration and rates of dose delivery in or near tumors [11]. Permanent interstitial low-dose rate brachytherapy means implanting of low-energy radioactive sources emitting radiation, which are contained in titanium pellets of the size of rice grains called seeds [12].

Comparator

Initial and present publication: The European Association of Urology suggested 3 different treatment concepts for localized prostate cancer in addition to permanent interstitial low-dose rate brachytherapy [10]: Radical prostatectomy, external beam radiotherapy, and different

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types of observation including active surveillance, watchful waiting, and observing without a distinctive management.

Outcome

Initial publication: Overall survival, cancer-specific survival, disease-free survival, biochemical recurrence-free survival, severe adverse events, and patient-reported outcomes. Patient-reported outcomes comprised function and bother scores as well as generic and disease-related health-related quality of life.

Present publication: Fulfilment of basic inclusion criteria according to a PICO framework by the excluded CCT. Accomplishment of requirements to contain superimposed risk of bias in addition to the high risk of bias caused by the lack of randomization framework by the excluded CCT.

Timing

Initial and present publication: We did not set limits on the length of the observation period.

Setting

Initial and present publication: We did not set limits on the setting such as type of country, year of recruitment, or level of health care.

Study design

Initial publication: We included RCT and CCT evaluating permanent interstitial low-dose rate brachytherapy as monotherapy in patients with localized prostate cancer. The proportion of relevant patients was required to be at least 80% of the study population and the response rate of questionnaires was expected to be at least 70%. For CCT to be included, comparable base-

line characteristics between treatment groups or adjustment for imbalances of these data were required. Limits on year of publication or language were not applied.

Present publication: We included specifically the CCT that were excluded in the initial publication.

Search strategy

The search strategy was reported previously [1].

Study selection

In the present study, we selected only those 50 nonrandomized studies on PRO that were excluded from the evaluation in the initial publication. In the study selection process, two reviewers independently judged whether a study was included or excluded. Differences were resolved by discussion without the need for a third opinion.

Data collection and analysis

The reasons for exclusion were extracted independently by two reviewers. We sought for the following data: the inclusion criteria using the PICO framework, the proportion of response of participants to questionnaires, which was required to be at least 70%, the reporting of separate baseline characteristics for each treatment group, the reporting of comparable baseline characteristics or adjustment for imbalances of these data such as the use of a Cox proportional hazard model, and the reporting of statistics comparing treatment groups. Sufficient comparability was defined as a difference between baseline values that were not statistically significant. If a statistical test was not reported, we assumed two comparable values if the greater of the two values was less than 10% above the smaller one. We also required that authors reported effect measures and statistics testing the difference between treatment groups, for example, p-

values or effect measures including 95% confidence intervals. Reporting of within group comparisons or before-and-after analyses was not deemed sufficient for inclusion. We did not apply a principal summary measure as we aimed at synthesize the information in a qualitative way.

Assessment of risk of bias and quality of reporting

Two reviewers independently assessed the quality of reporting of CCT according to the criteria specified in the previous paragraph. We did not specifically assess the risk of bias because we decided to exclude all papers with regard to a lack of reporting essential data.

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Results

Of a total of 462 full-text articles assessed for eligibility in the previously published systematic review, 31 studies were included and 431 studies were excluded. Among the 431 excluded articles, we identified 50 nonrandomised studies that were reporting on PRO (Figure 1). We evaluated the reasons for exclusion of those 50 studies and documented the results in Table 1. In 42% (21 of 50) studies, simply the essential PICO framework was not met. In the majority of 58% (29 of 50) studies, the predefined requirement to apply measures to contain high risk of bias was not met. Of these 29 studies, 19 studies reported a proportion of patients responding to questionnaires of less than 70% or did not address this item. Baseline characteristics were not presented for treatment groups in 3 studies. In another 6 studies, baseline characteristics were not comparable between treatment groups or there was no confounder control in the analysis adjusting for important different factors such as mean age. The statistical comparison between treatment groups was deemed not appropriate in 1 study.

Discussion

Main results

In summary, we found that roughly 4 of 10 excluded PRO studies did not meet the essential inclusion criteria using the PICO framework. This result is consistent with the problem of information retrieval aiming at a high recall and ending up with a low precision. The papers were obviously not relevant to the research question and we did not further examine the reporting quality. We also found that roughly 6 of 10 excluded PRO studies met the PICO framework but did not provide predefined requirements to care sufficiently enough for a low response of patients to questionnaires, for reporting baseline characteristics between treatment groups, for adjusting differences in those baseline characteristics between treatment groups, and to use appropriate statistics to compare the outcome between treatment groups.

Quality of reporting of patient-reported outcomes

We identified a lack of quality of reporting in many excluded CCT and we want to stress the importance of considering a series of requirements while conducting a study on PRO. Other authors have reported recently that, concerning disease-specific mortality or disease-free survival, available studies did not show significant differences between treatment groups. [13 14]. In view of unknown or small differences in survival measures, the results of patient-reported outcomes studies could have a noticeable impact on medical decision making [15 16]. None of the 50 excluded studies reported a non-responder analysis, though it is known that non-responders may have different attitudes than responders. Etter 1997 concluded that low response rates may be associated with overestimating an effect and that the strength and direction of a non-response bias may depend on the mechanism of non-response [17]. Therefore, results may be confounded if the proportion of included data not available for analysis

such as data from non-responders or due to loss to follow-up is considerable. We believe that a value of 30% or more can be denoted as considerable. Lowering this threshold, for example to 20%, would have resulted in less included studies. However, others suggested that 20% or more loss would be sufficient for a high risk of bias threatening the validity of results [18]. Concerning questionnaires, we recommend taking measures that are known to improve response rates [19 20]. Edwards 2009 conducted a systematic review to identify effective strategies to increase the response to postal and electronic questionnaires [21]. The authors found several strategies to increase the response, for example, pre-notification, follow-up contact, shorter questionnaires, mentioning an obligation to respond, university sponsorship, non-monetary incentives, a statement that others had responded, an offer of survey results, giving a deadline. We did not use a strict algorithm to differentiate between comparable and not comparable baseline values between treatment groups. A statistically significant difference was judged as not comparable. Not significant differences were also regarded as not comparable if the difference was at least 10% of the lower of two values. Using this approach we tried to reduce subjective decisions. We are not aware of published strict algorithms in this matter.

High risk of bias inherent in nonrandomized controlled trials

In the view of including only 1 RCT, the initial publication was based almost exclusively on CCT. However, the lack of randomization poses a very large challenge on the authors that are advised to deal with essential problems such as selection bias and confounding. Otherwise, the findings may not be valid and of limited usefulness and the many efforts may be in vain. We want to stress that the nonrandomized design is associated with a high risk of bias because known and unknown characteristics may be distributed unequally between groups [22]. Certain study characteristics such as prospective design, concurrent control group, adjustment

of results with respect to different baseline values, and confounder control can limit additional bias. For example, Ioannidis 2001 [23] reported that discrepancies between RCT and CCT were less common when only CCT with a prospective design were considered. The Cochrane Collaboration offers a guide for inclusion of nonrandomized studies [24] and it has developed a tool for assessing the risk of bias in both RCT and CCT [25]. Guidelines for reporting observational studies have been published to improve their quality [5]. Cox regression analysis, propensity-score-based analysis, and instrumental variable analysis are methods that have been used for correction of confounding bias in non-randomized studies [26]. Different values of various outcome measures between groups may be simply caused by different baseline data in lieu of absent significant treatment effects. We accepted any type of method adjusting or stratifying for one or more known differences in baseline characteristics. Nevertheless, it should be kept in mind that methods of adjustment do not guarantee removal of bias and that residual confounding may remain high [22]. Concerning the non-randomized design, we strongly recommend the use of methods for adjusting the results for confounders to aim for a less biased estimation of the treatment effect [27] and the adoption of guidelines for the reporting of observational studies [5].

Strengths and limitations

The strengths of the present study are a comprehensive literature search, strict adherence to the projected methodology, the identification of lack of quality in PRO studies and addressing the specific problems of PRO studies. We should consider some limitations: The study is confined to a single disease and conclusions drawn from its results may not be generalizable to other diseases. The arbitrary limits set for inclusion of studies are responsible for the extent of excluded studies. These limits may be questioned by other investigators. During re-evaluation of study quality, we found that one study fulfilled all criteria, although, this study was exclud-

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ed in previous reports [28]. The minimum follow-up of 70% for inclusion was set arbitrarily and others might find this threshold too low. We did not endorse the recently published reporting of PRO in randomized trials, an extension of the CONSORT statement [4]. All included studies in the present review are nonrandomized. We think that the lack of randomization is the prevailing issue. We did not endorse the CONSORT PRO extension for another reason. The included studies were published many years before this extension was published. There might be a need to develop an extension of the STROBE statement [5] aiming to improve the reporting of PRO in nonrandomized studies. This extension could emphasize the specific challenges of reporting PRO with respect to lack of randomization.

Conclusions

We found that a considerable number of non-randomized controlled reporting patient-reported outcomes were excluded from a systematic review because of a lack of predefined reporting requirements. The assumed overall risk of bias was regarded too high to consider the data of these studies for inclusion in the systematic review. With respect to the reporting of patient-reported outcomes, active efforts are required to improve the quality of reporting in nonrandomized controlled trials and to increase the number of randomized controlled trials.

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Figure legends

Figure 1. Study flow
Abbreviation. PICO: population, intervention, comparator, outcome; PRO: patient-reported outcomes; RCT: randomised controlled trial

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Table 1. Reasons for excluding PRO articles

Nonrandomized studies	Inclusion criteria				Requirements to contain high risk of bias				Comments
	P	I	C	O	Response ≥70%	Baseline each group	Baseline comparable/ or adjusted	Statistical comparison between groups	
Bacon 2001 [29]	yes	yes	NO	-	-	-	-	-	No concurrent group
Ball 2006 [30]	yes	yes	NO	-	-	-	-	-	Cryotherapy
Befort 2005 [31]	yes	yes	yes	yes	NO	-	-	-	Low response
Bergman 2009 [32]	yes	yes	yes	yes	yes	yes	yes	NO	No appropriate test
Bergman 2010 [33]	yes	yes	yes	yes	NO	-	-	-	Low response
Brandeis 2000 [34]	yes	NO	-	-	-	-	-	-	29% LDR-BT + EBRT
Brown 2007 [35]	yes	NO	-	-	-	-	-	-	EBRT
Burnett 2007 [36]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Chaikin 1996 [37]	NO	-	-	-	-	-	-	-	Staging not reported
Chen 2009 [38]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Choo 2010 [39]	yes	yes	yes	yes	yes	NO	-	-	Baseline not reported
Clark 2003 [40]	yes	yes	yes	yes	NO	-	-	-	Low response
Downs 2003 [41]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Eton 2001 [42]	yes	yes	yes	yes	NO	-	-	-	Low response
Frank 2007 [43]	yes	yes	yes	yes	NO	-	-	-	Low response
Fulmer 2001 [44]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Gore 2009 [45]	yes	yes	yes	yes	NO	-	-	-	Low response
Guedea 2009 [46]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Hashine 2008 [47]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Hashine 2009 [48]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Hervouet 2005 [49]	NO	-	-	-	-	-	-	-	≥20% T3-T4 in control groups
Hollenbeck 2002 [50]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Jo 2005 [51]	yes	NO	-	-	-	-	-	-	High-dose rate brachytherapy
Johnstone 2000 [52]	yes	NO	-	-	-	-	-	-	EBRT
Joly 1998 [53]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Kakehi 2007 [54]	yes	yes	yes	yes	yes	NO	-	-	Baseline not reported
Lev 2009 [55]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Lilleby 1999 [56]	yes	NO	-	-	-	-	-	-	EBRT
Litwin 2004 [57]	yes	yes	yes	yes	NO	-	-	-	Low response
Litwin 2007 [58]	yes	NO	-	-	-	-	-	-	25% LDR-BT + EBRT
Mehta 2003 [59]	yes	yes	yes	NO	-	-	-	-	"Fear of cancer"*

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Nonrandomized studies	Inclusion criteria				Requirements to contain high risk of bias				Comments
	P	I	C	O	Response ≥70%	Baseline each group	Baseline comparable/ or adjusted	Statistical comparison between groups	
Miller 2005 [60]	yes	NO	-	-	-	-	-	-	44% LDR-BT + EBRT
Miller 2006 [61]	yes	yes	yes	yes	yes	NO	-	-	Baseline not reported
Monahan 2007 [62]	yes	yes	yes	yes	NO	-	-	-	Low response
Namiki 2006 [63]	yes	yes	yes	yes	NO	-	-	-	Low response
Namiki 2009 [64]	yes	yes	yes	yes	NO	-	-	-	Low response
Ohashi 2006 [65]	yes	yes	yes	yes	NO	-	-	-	Low response
Pinkawa 2006 [66]	yes	yes	NO	-	-	-	-	-	LDR-BT + hormones†
Roach 1996 [67]	yes	NO	-	-	-	-	-	-	EBRT, single-arm trial
Sanda 2008 [68]	yes	yes	yes	yes	NO	-	-	-	Low response
Schover 2002 [69]	yes	yes	yes	yes	NO	-	-	-	Low response
Soderdahl 2005 [70]	yes	yes	yes	yes	NO	-	-	-	Low response
Speight 2004 [71]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Stone 2010 [72]	yes	yes	NO	-	-	-	-	-	LDR-BT + hormones†
Trojan 2007 [73]	yes	yes	yes	yes	NO	-	-	-	Low response
Tward 2006 [74]	yes	yes	yes	NO	-	-	-	-	Mortality differs§
Valicenti 2002 [75]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Van de Poll-F 2008 [76]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Wyler 2009 [77]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Zagar 2007 [78]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
"NO" counts	2	13	4	2	19	3	6	1	Total: 50 studies
	PICO not met: 21				High risk of bias: 29				

-: not appropriate

*Mehta 2003: no appropriate endpoint

†Pinkawa 2006; Stone 2010: neoadjuvant hormonal therapy

§Tward 2006: non-disease-related mortality differs greatly

Abbreviations: C: comparison of interest is radical prostatectomy, external beam radiotherapy, or no primary therapy; EBRT: external beam radiotherapy; I: intervention of interest is low-dose rate brachytherapy as monotherapy; LDR-BT: permanent interstitial low-dose rate brachytherapy; O: outcome of interest is function, bother, or generic health-related quality of life; P: patients with localized prostate cancer; PRO: patient-reported outcomes

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Failure to address potential bias in nonrandomized controlled clinical trials may cause lack of evidence on patient-reported outcomes – a method study

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Abstract

Objectives: We conducted a workup of a previously published systematic review and aimed to analyse why most of the identified nonrandomized controlled clinical trials with patient-reported outcomes did not match a set of basic quality criteria.

Setting: There were no limits on the level of care and the geographical location.

Participants: The review evaluated permanent interstitial low-dose rate brachytherapy in patients with localized prostate cancer and compared that intervention to alternative procedures such as external beam radiotherapy, radical prostatectomy, and no primary therapy.

Primary outcome measure: Fulfilment of basic inclusion criteria according to a PICO framework and accomplishment of requirements to contain superimposed risk of bias.

Results: We found that 21 of 50 excluded nonrandomized controlled trials did not meet PICO inclusion criteria. The rest of 29 of 50 studies lacked quality of reporting. The resulting flaws included attrition bias due to loss of follow-up, lack of reporting baseline data, potential confounding due to unadjusted data and lack of statistical comparison between groups.

Conclusions: With respect to the reporting of patient-reported outcomes, active efforts are required to improve the quality of reporting in nonrandomized controlled trials concerning permanent interstitial low-dose rate brachytherapy in patients with localized prostate cancer.

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Key words: systematic review, patient-reported outcome, risk of bias

Strengths and limitations of this study

- We conducted a comprehensive literature search and strictly adhered to the projected methodology.
- We identified a lack of quality in nonrandomized controlled clinical trials reporting patient-reported outcomes, analysed the cause, and suggested possible improvements in designing studies in the future.
- The analysis is confined to a single disease and a specific treatment and conclusions drawn from its results may not be generalizable to other diseases and treatments.
- The limits for the inclusion of studies are arbitrarily set.

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Abbreviation	Term
CCT	Nonrandomized controlled clinical trial
CONSORT	Consolidated standards of reporting trials
EBRT	External beam radiotherapy
EMBASE	Excerpta medica database
LDR-BT	Permanent interstitial low-dose rate brachytherapy
MEDLINE	Medical literature analysis and retrieval system online
PICO (TS-SD)	Participants, intervention, comparator, outcome (timing, setting, study design)
PRO	Patient-reported outcome
RCT	Randomized controlled trial
STROBE	Strengthening the reporting of observational studies in epidemiology
TNM	Tumor-Node-Metastasis

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Introduction

The present paper reports a workup of a previously published systematic review [1]. It may be regarded as a methodological supplement adding information on a subset of excluded studies. We have compared permanent interstitial low-dose rate brachytherapy, with radical prostatectomy, external beam radiotherapy, and 'no primary therapy' in patients with localized prostate cancer categorized T1 to T2. We used the term 'no primary therapy' to accommodate different types of observation including active surveillance, watchful waiting, and observing without a distinctive management. As a result, we included one randomized controlled trial (RCT) and 30 nonrandomized controlled clinical trials (CCT). The primary outcome was overall survival. The secondary outcomes were clinically defined disease-free survival, biochemical recurrence-free survival, physician-reported severe adverse events, and patient-reported outcomes such as function and bother scores as well as generic and disease-related health-related quality of life. We concluded that the current evidence is insufficient to allow a definitive conclusion about overall survival. Radical prostatectomy and external beam radiotherapy can severely affect the structural integrity of neighboring organs and their functions and can cause considerable long-term impairment of health-related quality of life. In a view of expecting similar survival but a tremendous difference of adverse events between treatment alternatives, valid data on health-related quality of life could tip the balance. At least, we assume that shared-decision making and consideration of patients' preferences in searching for the best individual treatment would rely on information on health-related quality of life data. Of the 30 included nonrandomized studies, 13 studies reported patient-reported outcomes (PROs), that is, only the patients provided the information [2]. During the study selection process, we experienced that we excluded another 50 nonrandomized PRO studies. We found it a pity that we could not use the many data. We had the impression that a considerable number of studies were excluded because of lack in reporting quality. Therefore,

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we wanted to summarize the reasons for excluding those PRO studies and make aware that authors of PRO studies should meet some basic requirements for reporting of comparative PRO data to achieve higher acceptance in the scientific community. The importance of reporting PRO has been addressed by the Consolidated Standards of Reporting Trials (CONSORT) group [3] that recently has published a PRO extension to their acclaimed previous statement [4]. It may be wise to build a PRO extension to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement [5] that addresses specific issues of observational studies.

The first aim of this study was to assess whether the excluded studies met the basic inclusion criteria using the PICO framework. The second aim of this study was whether the excluded studies met requirements to contain high risk of bias.

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Materials and Methods

Study inclusion criteria

We defined the inclusion criteria according to the PICO framework that should include four essential constituents, that is, the type of participants (P), intervention (I), comparator (C), and outcome (O) [6]. The four PICO items can be supplemented by timing (T) and setting (S), two other important features of a systematic review, to create the so-called PICOTS typology [7]. A further extension embraces the study design (SD) to complete all major items of a search strategy (PICOTS-SD) [8].

Population

Initial and present publication: Localized prostate cancer is defined by the categories T1 to T2 of the Tumor-Node-Metastasis (TNM) staging system [9] if combined with an absence of both regional lymph node metastasis and distant metastasis.

Intervention

Initial and present publication: Brachytherapy [10] is short-distance radiotherapy placing radiation sources with different duration and rates of dose delivery in or near tumors [11]. Permanent interstitial low-dose rate brachytherapy means implanting of low-energy radioactive sources emitting radiation, which are contained in titanium pellets of the size of rice grains called seeds [12].

Comparator

Initial and present publication: The European Association of Urology suggested 3 different treatment concepts for localized prostate cancer in addition to permanent interstitial low-dose rate brachytherapy [10]: Radical prostatectomy, external beam radiotherapy, and different

types of observation including active surveillance, watchful waiting, and observing without a distinctive management.

Outcome

Initial publication: Overall survival, cancer-specific survival, disease-free survival, biochemical recurrence-free survival, severe adverse events, and patient-reported outcomes. Patient-reported outcomes comprised function and bother scores as well as generic and disease-related health-related quality of life.

Present publication: Fulfilment of basic inclusion criteria according to a PICO framework by the excluded CCT. Accomplishment of requirements to contain superimposed risk of bias in addition to the high risk of bias caused by the lack of randomization framework by the excluded CCT.

Timing

Initial and present publication: We did not set limits on the length of the observation period.

Setting

Initial and present publication: We did not set limits on the setting such as type of country, year of recruitment, or level of health care.

Study design

Initial publication: We included RCT and CCT evaluating permanent interstitial low-dose rate brachytherapy as monotherapy in patients with localized prostate cancer. The proportion of relevant patients was required to be at least 80% of the study population and the response rate of questionnaires was expected to be at least 70%. For CCT to be included, comparable base-

line characteristics between treatment groups or adjustment for imbalances of these data were required. Limits on year of publication or language were not applied.

Present publication: We included specifically the CCT that were excluded in the initial publication.

Search strategy

The search strategy was reported previously [1].

Study selection

In the present study, we selected only those 50 nonrandomized studies on PRO that were excluded from the evaluation in the initial publication. In the study selection process, two reviewers independently judged whether a study was included or excluded. Differences were resolved by discussion without the need for a third opinion.

Data collection and analysis

The reasons for exclusion were extracted independently by two reviewers. We sought for the following data: the inclusion criteria using the PICO framework, the proportion of response of participants to questionnaires, which was required to be at least 70%, the reporting of separate baseline characteristics for each treatment group, the reporting of comparable baseline characteristics or adjustment for imbalances of these data such as the use of a Cox proportional hazard model, and the reporting of statistics comparing treatment groups. Sufficient comparability was defined as a difference between baseline values that were not statistically significant. If a statistical test was not reported, we assumed two comparable values if the greater of the two values was less than 10% above the smaller one. We also required that authors reported effect measures and statistics testing the difference between treatment groups, for example, p-

values or effect measures including 95% confidence intervals. Reporting of within group comparisons or before-and-after analyses was not deemed sufficient for inclusion. We did not apply a principal summary measure as we aimed at synthesize the information in a qualitative way.

Assessment of risk of bias and quality of reporting

Two reviewers independently assessed the quality of reporting of CCT according to the criteria specified in the previous paragraph. We did not specifically assess the risk of bias because we decided to exclude all papers with regard to a lack of reporting essential data.

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Results

Of a total of 462 full-text articles assessed for eligibility in the previously published systematic review, 31 studies were included and 431 studies were excluded. Among the 431 excluded articles, we identified 50 nonrandomised studies that were reporting on PRO (Figure 1). We evaluated the reasons for exclusion of those 50 studies and documented the results in Table 1. ~~We documented the reasons for exclusion of all 50 nonrandomized studies that were identified as studies reporting on PRO (Table 1).~~ In 42% (21 of 50) studies, simply the essential PICO framework was not met. In the majority of 58% (29 of 50) studies, the predefined requirement to apply measures to contain high risk of bias was not met. Of these 29 studies, 19 studies reported a proportion of patients responding to questionnaires of less than 70% or did not address this item. Baseline characteristics were not presented for treatment groups in 3 studies. In another 6 studies, baseline characteristics were not comparable between treatment groups or there was no confounder control in the analysis adjusting for important different factors such as mean age. The statistical comparison between treatment groups was deemed not appropriate in 1 study.

Discussion

Main results

In summary, we found that roughly 4 of 10 excluded PRO studies did not meet the essential inclusion criteria using the PICO framework. This result is consistent with the problem of information retrieval aiming at a high recall and ending up with a low precision. The papers were obviously not relevant to the research question and we did not further examine the reporting quality. We also found that roughly 6 of 10 excluded PRO studies met the PICO framework but did not provide predefined requirements to care sufficiently enough for a low response of patients to questionnaires, for reporting baseline characteristics between treatment groups, for adjusting differences in those baseline characteristics between treatment groups, and to use appropriate statistics to compare the outcome between treatment groups.

Quality of reporting of patient-reported outcomes

We identified a lack of quality of reporting in many excluded CCT and we want to stress the importance of considering a series of requirements while conducting a study on PRO. Other authors have reported recently that, concerning disease-specific mortality or disease-free survival, available studies did not show significant differences between treatment groups. [13 14]. In view of unknown or small differences in survival measures, the results of patient-reported outcomes studies could have a noticeable impact on medical decision making [15 16]. None of the 50 excluded studies reported a non-responder analysis, though it is known that non-responders may have different attitudes than responders. Etter 1997 concluded that low response rates may be associated with overestimating an effect and that the strength and direction of a non-response bias may depend on the mechanism of non-response [17]. Therefore, results may be confounded if the proportion of included data not available for analysis

such as data from non-responders or due to loss to follow-up is considerable. We believe that a value of 30% or more can be denoted as considerable. Lowering this threshold, for example to 20%, would have resulted in less included studies. However, others suggested that 20% or more loss would be sufficient for a high risk of bias threatening the validity of results [18]. Concerning questionnaires, we recommend taking measures that are known to improve response rates [19 20]. Edwards 2009 conducted a systematic review to identify effective strategies to increase the response to postal and electronic questionnaires [21]. The authors found several strategies to increase the response, for example, pre-notification, follow-up contact, shorter questionnaires, mentioning an obligation to respond, university sponsorship, non-monetary incentives, a statement that others had responded, an offer of survey results, giving a deadline. We did not use a strict algorithm to differentiate between comparable and not comparable baseline values between treatment groups. A statistically significant difference was judged as not comparable. Not significant differences were also regarded as not comparable if the difference was at least 10% of the lower of two values. Using this approach we tried to reduce subjective decisions. We are not aware of published strict algorithms in this matter.

High risk of bias inherent in nonrandomized controlled trials

In the view of including only 1 RCT, the initial publication was based almost exclusively on CCT. However, the lack of randomization poses a very large challenge on the authors that are advised to deal with essential problems such as selection bias and confounding. Otherwise, the findings may not be valid and of limited usefulness and the many efforts may be in vain. We want to stress that the nonrandomized design is associated with a high risk of bias because known and unknown characteristics may be distributed unequally between groups [22]. Certain study characteristics such as prospective design, concurrent control group, adjustment

of results with respect to different baseline values, and confounder control can limit additional bias. For example, Ioannidis 2001 [23] reported that discrepancies between RCT and CCT were less common when only CCT with a prospective design were considered. The Cochrane Collaboration offers a guide for inclusion of nonrandomized studies [24] and it has developed a tool for assessing the risk of bias in both RCT and CCT [25]. Guidelines for reporting observational studies have been published to improve their quality [5]. Cox regression analysis, propensity-score-based analysis, and instrumental variable analysis are methods that have been used for correction of confounding bias in non-randomized studies [26]. Different values of various outcome measures between groups may be simply caused by different baseline data in lieu of absent significant treatment effects. We accepted any type of method adjusting or stratifying for one or more known differences in baseline characteristics. Nevertheless, it should be kept in mind that methods of adjustment do not guarantee removal of bias and that residual confounding may remain high [22]. Concerning the non-randomized design, we strongly recommend the use of methods for adjusting the results for confounders to aim for a less biased estimation of the treatment effect [27] and the adoption of guidelines for the reporting of observational studies [5].

Strengths and limitations

The strengths of the present study are a comprehensive literature search, strict adherence to the projected methodology, the identification of lack of quality in PRO studies and addressing the specific problems of PRO studies. We should consider some limitations: The study is confined to a single disease and conclusions drawn from its results may not be generalizable to other diseases. The arbitrary limits set for inclusion of studies are responsible for the extent of excluded studies. These limits may be questioned by other investigators. During re-evaluation of study quality, we found that one study fulfilled all criteria, although, this study was exclud-

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ed in previous reports [28]. The minimum follow-up of 70% for inclusion was set arbitrarily and others might find this threshold too low. We did not endorse the recently published reporting of PRO in randomized trials, an extension of the CONSORT statement [4]. All included studies in the present review are nonrandomized. We think that the lack of randomization is the prevailing issue. We did not endorse the CONSORT PRO extension for another reason. The included studies were published many years before this extension was published. There might be a need to develop an extension of the STROBE statement [5] aiming to improve the reporting of PRO in nonrandomized studies. This extension could emphasize the specific challenges of reporting PRO with respect to lack of randomization.

Conclusions

We found that a considerable number of non-randomized controlled reporting patient-reported outcomes were excluded from a systematic review because of a lack of predefined reporting requirements. The assumed overall risk of bias was regarded too high to consider the data of these studies for inclusion in the systematic review. With respect to the reporting of patient-reported outcomes, active efforts are required to improve the quality of reporting in nonrandomized controlled trials and to increase the number of randomized controlled trials.

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Figure legends

Figure 1. Study flow
Abbreviation. PICO: population, intervention, comparator, outcome; PRO: patient-reported outcomes; RCT: randomised controlled trial

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Table 1. Reasons for excluding PRO articles

Nonrandomized studies	Inclusion criteria				Requirements to contain high risk of bias				Comments
	P	I	C	O	Response ≥70%	Baseline each group	Baseline comparable/ or adjusted	Statistical comparison between groups	
Bacon 2001 [29]	yes	yes	NO	-	-	-	-	-	No concurrent group
Ball 2006 [30]	yes	yes	NO	-	-	-	-	-	Cryotherapy
Befort 2005 [31]	yes	yes	yes	yes	NO	-	-	-	Low response
Bergman 2009 [32]	yes	yes	yes	yes	yes	yes	yes	NO	No appropriate test
Bergman 2010 [33]	yes	yes	yes	yes	NO	-	-	-	Low response
Brandeis 2000 [34]	yes	NO	-	-	-	-	-	-	29% LDR-BT + EBRT
Brown 2007 [35]	yes	NO	-	-	-	-	-	-	EBRT
Burnett 2007 [36]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Chaikin 1996 [37]	NO	-	-	-	-	-	-	-	Staging not reported
Chen 2009 [38]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Choo 2010 [39]	yes	yes	yes	yes	yes	NO	-	-	Baseline not reported
Clark 2003 [40]	yes	yes	yes	yes	NO	-	-	-	Low response
Downs 2003 [41]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Eton 2001 [42]	yes	yes	yes	yes	NO	-	-	-	Low response
Frank 2007 [43]	yes	yes	yes	yes	NO	-	-	-	Low response
Fulmer 2001 [44]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Gore 2009 [45]	yes	yes	yes	yes	NO	-	-	-	Low response
Guedea 2009 [46]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Hashine 2008 [47]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Hashine 2009 [48]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Hervouet 2005 [49]	NO	-	-	-	-	-	-	-	≥20% T3-T4 in control groups
Hollenbeck 2002 [50]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Jo 2005 [51]	yes	NO	-	-	-	-	-	-	High-dose rate brachytherapy
Johnstone 2000 [52]	yes	NO	-	-	-	-	-	-	EBRT
Joly 1998 [53]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Kakehi 2007 [54]	yes	yes	yes	yes	yes	NO	-	-	Baseline not reported
Lev 2009 [55]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Lilleby 1999 [56]	yes	NO	-	-	-	-	-	-	EBRT
Litwin 2004 [57]	yes	yes	yes	yes	NO	-	-	-	Low response
Litwin 2007 [58]	yes	NO	-	-	-	-	-	-	25% LDR-BT + EBRT
Mehta 2003 [59]	yes	yes	yes	NO	-	-	-	-	"Fear of cancer"*

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Nonrandomized studies	Inclusion criteria				Requirements to contain high risk of bias				Comments
	P	I	C	O	Response ≥70%	Baseline each group	Baseline comparable/ or adjusted	Statistical comparison between groups	
Miller 2005 [60]	yes	NO	-	-	-	-	-	-	44% LDR-BT + EBRT
Miller 2006 [61]	yes	yes	yes	yes	yes	NO	-	-	Baseline not reported
Monahan 2007 [62]	yes	yes	yes	yes	NO	-	-	-	Low response
Namiki 2006 [63]	yes	yes	yes	yes	NO	-	-	-	Low response
Namiki 2009 [64]	yes	yes	yes	yes	NO	-	-	-	Low response
Ohashi 2006 [65]	yes	yes	yes	yes	NO	-	-	-	Low response
Pinkawa 2006 [66]	yes	yes	NO	-	-	-	-	-	LDR-BT + hormones†
Roach 1996 [67]	yes	NO	-	-	-	-	-	-	EBRT, single-arm trial
Sanda 2008 [68]	yes	yes	yes	yes	NO	-	-	-	Low response
Schover 2002 [69]	yes	yes	yes	yes	NO	-	-	-	Low response
Soderdahl 2005 [70]	yes	yes	yes	yes	NO	-	-	-	Low response
Speight 2004 [71]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Stone 2010 [72]	yes	yes	NO	-	-	-	-	-	LDR-BT + hormones†
Trojan 2007 [73]	yes	yes	yes	yes	NO	-	-	-	Low response
Tward 2006 [74]	yes	yes	yes	NO	-	-	-	-	Mortality differs§
Valicenti 2002 [75]	yes	yes	yes	yes	NO	-	-	-	Response not reported
Van de Poll-F 2008 [76]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
Wyler 2009 [77]	yes	yes	yes	yes	yes	yes	NO	-	No confounder control
Zagar 2007 [78]	yes	NO	-	-	-	-	-	-	LDR-BT + EBRT
"NO" counts	2	13	4	2	19	3	6	1	Total: 50 studies
	PICO not met: 21				High risk of bias: 29				

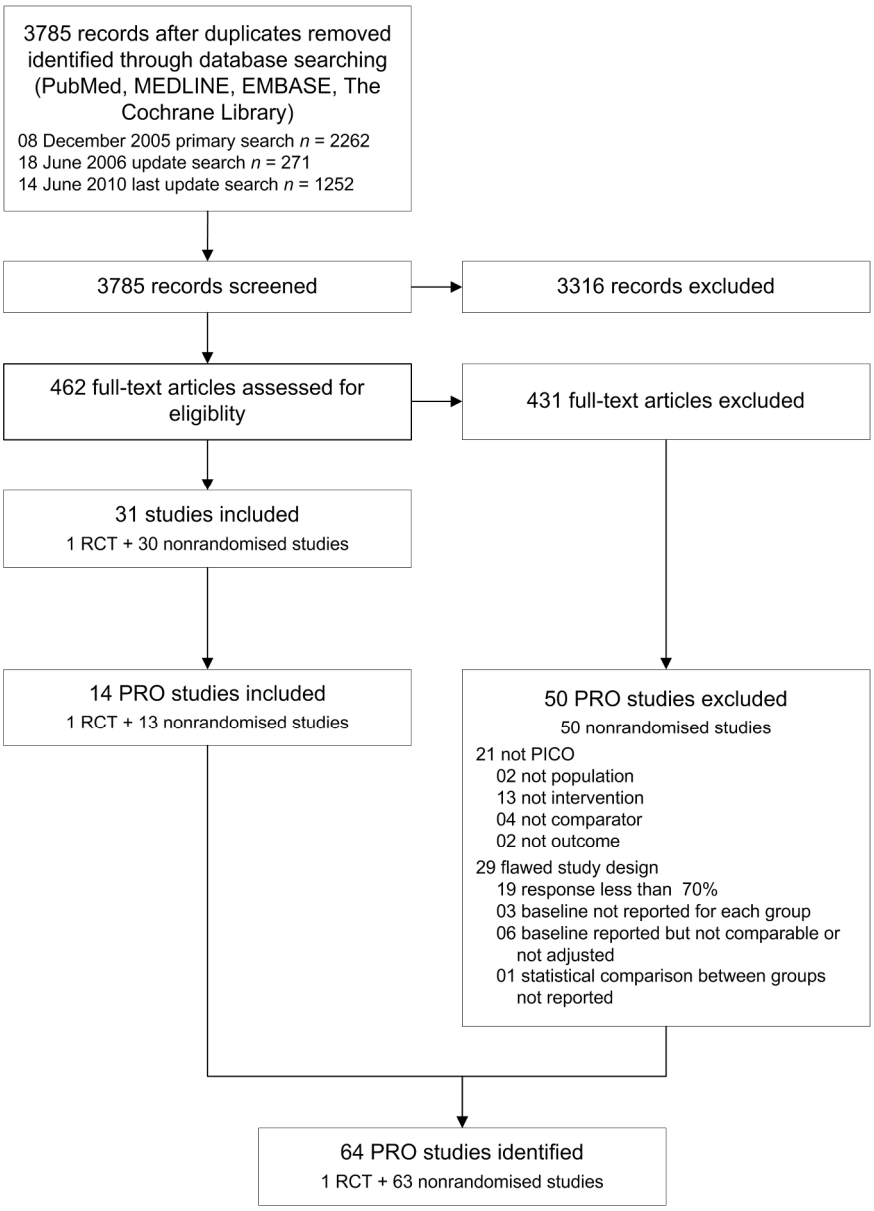
-: not appropriate

*Mehta 2003: no appropriate endpoint

†Pinkawa 2006; Stone 2010: neoadjuvant hormonal therapy

§Tward 2006: non-disease-related mortality differs greatly

Abbreviations: C: comparison of interest is radical prostatectomy, external beam radiotherapy, or no primary therapy; EBRT: external beam radiotherapy; I: intervention of interest is low-dose rate brachytherapy as monotherapy; LDR-BT: permanent interstitial low-dose rate brachytherapy; O: outcome of interest is function, bother, or generic health-related quality of life; P: patients with localized prostate cancer; PRO: patient-reported outcomes



Abbreviation. PICO: population, intervention, comparator, outcome; PRO: patient-reported outcomes; RCT: randomised controlled trial
170x235mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	figure 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9-10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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