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Does Gleason score of positive surgical margin after radical prostatectomy affect biochemical recurrence and oncological outcomes? – Protocol for systematic review

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Title: Does Gleason score of positive surgical margin after radical prostatectomy affect biochemical recurrence and oncological outcomes? – Protocol for systematic review

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Keywords:
prostatic neoplasms, prostatectomy, Positive surgical margin, Gleason score, Biochemical recurrence

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Abstract

Introduction:
Positive surgical margins (PSM) in cancer patients are commonly associated with worse prognosis and a higher risk of secondary treatment. However, the relevance of this parameter in prostate cancer patients undergoing radical prostatectomy(RP) remains controversial, given the inconsistencies in its ability to predict biochemical recurrence(BCR) and oncological outcomes. Hence, further assessment of the utility of surgical margins for prostate cancer prognosis is required to predict these outcomes more accurately. Over the last decade, studies have used the Gleason score(GS) of positive margins to predict outcomes. Herein, the authors aim to conduct a systematic review investigating the role of GS of PSM after radical prostatectomy in predicting BCR and oncological outcomes

Methods and analysis:
We will perform a search using MEDLINE, EMBASE, SCOPUS and COCHRANE databases. The review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We will screen titles and abstracts to select articles appropriate for full-text review. Studies discussing GS of PSM after RP will be included. Given the change in reporting of GS, only articles from 2004-2019 will be included. The quality of the studies chosen will be assessed using the Newcastle Ottawa tool for non-randomized and Cochrane risk of bias for randomized control studies. We will adopt the grading of recommendations, assessment, development and evaluation (GRADE) framework to comment on quality of cumulative evidence. The primary outcome measure will be time to BCR. Secondary outcome measures include secondary treatment, disease-specific survival, disease progression-free and overall mortality at follow up period. We aim to perform a meta-analysis if the level of heterogeneity is acceptable (I2<50%).

Ethics and dissemination
We will follow the PRISMA protocol checklist to maintain methodological and ethical standards. The findings of the review will be submitted for peer-reviewed publications and presented at scientific meetings.

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Strengths and limitations of this study:

- Positive surgical margin after radical prostatectomy remains controversial in its ability to predict long-term outcomes after surgery.
- To our knowledge, this is the first systematic review and meta-analysis investigating outcomes of patients after radical prostatectomy based on Gleason score of positive surgical margin site.
- A major limitation of the study is lack of randomised controlled trials, and the majority of expected studies are likely to be retrospective cohort studies.
- Quality assessment of included studies will also be reported.
- The PRISMA protocol checklist will be followed when reporting the findings.

Introduction:

Positive surgical margins in cancer patients are commonly associated with worse prognosis and a higher risk of secondary treatment. However, its role in patients undergoing radical prostatectomy remains controversial since only 30-35% and 19-48% of men with positive surgical margins develop metastatic disease or biochemical recurrence after radical prostatectomy, respectively(1, 2). Positive surgical margins have been reported in 11–40 % of men undergoing radical prostatectomy. Given the apparent inaccuracy of positive surgical margins as a means to predict prostate cancer progression, further evaluation of this parameter is required to improve its predictive value.

Recently, there have been multiple studies investigating Gleason score of positive surgical margins and its impact on biochemical recurrence(1-6). As a result, some studies recommend mandatory reporting of Gleason score of positive surgical margin. This is in contrast to the current ISUP recommendation, which leaves the decision up to the discretion of the pathologist (International society of urological pathology). However, very few studies report oncological outcomes and the relationship between biochemical recurrence and long-term survival rates are still poorly defined. Hence, the authors aim to conduct a systematic review investigating the role of Gleason score of positive surgical margins after radical prostatectomy in predicting biochemical recurrence and oncological outcomes (e.g. cancer-specific survival and all-cause survival). To the authors' knowledge, no systematic reviews have explored this topic previously.

Review question

In men who have positive surgical margins after radical prostatectomy, how does the Gleason score of positive surgical margin affect biochemical recurrence and long term oncological outcomes?

Objective

To conduct a systematic review investigating the role of Gleason score at positive surgical margin site in men who have undergone radical prostatectomy for prostate cancer, in predicting biochemical recurrence and long term oncological outcomes.

Methods

Eligibility criteria:

The search strategy aims to find published studies exploring the role of Gleason score of positive surgical margins after radical prostatectomy in predicting biochemical recurrence and oncological outcomes. The review will consider all published studies, including meta-analysis and Randomised Controlled Trials; however, we will also consider observational cohort studies and case-controlled studies if level 1 evidence is not available.
Language will be restricted to English. Studies with men who underwent radical prostatectomy without reporting of Gleason score at positive surgical margin site will be excluded. Grey literature, including conference abstracts and editorials, will be excluded.

Patient and Public Involvement:

No patient involved

Information sources:

The review will involve searching the MEDLINE, SCOPUS, EMBASE and COCHRANE databases. Given the change in Gleason reporting in 2004, the review will only include studies published between 1st January 2004 and 31st September 2019 (7). A further comprehensive literature search will also involve examining reference lists of included studies identified from the search. Authors will be contacted if the published study does not contain sufficient details to extract data.

Search strategy:

The search strategy will be created with the assistance of health sciences librarians with previous expertise in conducting systematic searches. The search strategies will be modified to accommodate the requirements of different databases used for the search.

A draft of MEDLINE (OVID interface) search strategy is shown below(See Table 1):

Table 1: Search terms for MEDLINE

Population Men with Prostate cancer	**Intervention** Radical prostatectomy	**Comparators** Gleason score at positive surgical margin site	**Outcomes** Biochemical recurrence and oncological outcomes
"prostatic neoplasms"[mh] OR prostate neoplasm*[tiab] OR prostatic neoplasm*[tiab] OR cancers of the prostate[tiab] OR cancer of the prostate[tiab] OR adenocarcinoma of the prostate[tiab] OR prostatic cancer*[tiab] OR prostate cancer*[tiab] OR	"prostatectomy"[mh] OR prostatectomy*[tiab] OR prostate removal[tiab] OR resection of prostate[tiab] OR prostate surger*[tiab]	(((Gleason[tiab] OR Gleeson[tiab]) AND (score[tiab] OR status[tiab] OR grade[tiab] OR grading[tiab] OR grade group[tiab])) AND (Positive surgical margin*[tiab] OR margin[tiab] OR margin status[tiab] OR PSM[tiab]))	Oncological outcome*[tiab] OR survival[tiab] OR mortality[tiab] OR metastases[tiab] OR metastasis[tiab] OR metastatic recurrence*[tiab] OR biochemical recurrence*[tiab] OR BCR[tiab] OR biochemical failure*[tiab] OR biochemical relapse*[tiab] OR

prostate gland cancer*[tiab] OR cancer of the prostate[tiab] OR prostate tumour*[tiab] OR prostatic tumour*[tiab] OR prostate tumor*[tiab] OR prostatic tumor*[tiab] OR tumors of the prostate*[tiab] OR tumours of the prostate[tiab] OR prostate adenocarcinoma*[tiab]			biochemical freedom from failure[tiab] OR disease progression[tiab] OR clinical recurrence[tiab] OR clinical progression[tiab] OR PSA failure[tiab] OR PSA relapse[tiab] OR PSA recurrence[tiab] OR relapse free survival[tiab] OR recurrence free survival[tiab] OR local failure[tiab] OR local failure[tiab] OR mortality rate[tiab] OR prostate specific antigen*[tiab]

Study records

Data management

A preformulated data extraction template will be used to keep track of information obtained from each study. Software including Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) and EndNote X8.2 will be used to track studies included and excluded from the review. Covidence will also be used to assist with tracking the quality of assessment and extracted information. This data will be tabulated using Microsoft Excel (Redmond, Washington, USA).

Data collection and selection process

A comprehensive search strategy aims to find published studies in various electronic databases, including the MEDLINE, SCOPUS, EMBASE, and COCHRANE databases. Studies will be screened by two authors by titles and abstracts to determine if it is appropriate. Once screened, the full-text article will be retrieved. If inclusion criteria is fulfilled, it will be selected for the review. Hand searching of reference lists of the selected studies will also be conducted and be considered for inclusion based on inclusion criteria based on the same criteria. Any disagreements between authors will be discussed with a third reviewer. Once included, the authors aim to extract, tabulate and summarise details of the eligible studies.

Data items:

Study characteristics to be extracted by the review include title, study design and type, financial supports, first authors, Year study published, inclusion criteria, follow up period, and the period of enrolment for the study. Population characteristics include Sample size, average age of men, Year of surgery, age at diagnosis, Body mass index and Median postoperative follow up. Intervention characteristics to be extracted type of procedure (Robot-assisted, Laparoscopic or open), year of surgery and additional interventions.

Comparator characteristics include primary Gleason score at positive surgical margin, overall Gleason score at margin, surgical margin length of invasion, Gleason score on biopsy, extent of margin, lobe of prostate cancer, location of margin, Extraprostatic extension, perineural invasion, lymphadenopathy, pT stage and PSA at diagnosis. Outcome characteristics include Biochemical recurrence, Secondary treatment rate, Survival post-surgery, number of individuals with metastasis and Systemic progression at median/mean follow up, systemic progression-free survival.

Outcomes and prioritisation:

Primary outcomes measure:
Time to biochemical recurrence after radical prostatectomy. Biochemical recurrence is defined by two consecutive PSA values of > 0.2 ng/mL and rising (8). This is one of the main indicators used in clinical practise to commence secondary treatment and to commence assessment of metastatic spread.

Secondary outcome measures:
Prostate cancer-related Mortality. This is defined as death as a result of prostate cancer in the cohort. Given the chronicity prostate cancer, studies should look specifically at prostate cancer-related mortality rate to avoid other confounders which may also cause death in individuals involved in the cohort study. This may also be reported as a hazards ratio. This will be more beneficial than the overall survival rate.

Secondary treatment/intervention rate. The number of individuals who required additional treatment for prostate cancer such as Androgen deprivation therapy or external beam radiotherapy after the radical prostatectomy. This outcome is dependent on biochemical recurrence. Repeated treatments have been associated with worse comorbidities; hence, this outcome is important to establish so that patients can be counselled appropriately.

Cancer-free Survival at follow up
Number of participants that are alive and have no biochemical recurrence at follow up period of the study.

Metastasis free survival or Systemic progression-free at follow up
Number of participants that are alive have no evidence of prostate cancer metastasis or systemic progression at follow up period of the study.

Outcome follow up periods:
All mean and median follow up period will be noted. Based on initial searches, studies are likely to have significant variability in the short term, and long term follow up periods. Studies with identical follow up periods will be considered for a meta-analysis. If time-specific estimates are not provided, we hope to report hazard ratios. The authors agree that a median follow up of less than 12 months is inadequate in regards to detecting biochemical recurrence post radical prostatectomy.

Risk of bias in individual studies

The quality of the studies chosen would be assessed using the Newcastle Ottawa tool which is used for assessing the quality of non-randomized studies included in a systematic review by assessing domains such as selection of study groups, comparability of the groups and based on exposure or outcome of interest. Stars are awarded for each domain which allows the study to be graded into poor, fair or good quality. (9) For randomised control trials, Cochrane risk of bias tools will be used to assess the bias. A funnel plot will be used to represent an assessment of publication bias.

Data synthesis

The authors aim to summarise the role of Gleason score of positive surgical margins after radical prostatectomy in predicting biochemical recurrence and long-term oncological outcomes. The heterogeneity of the selected studies would be calculated using the I^2 score. If heterogeneity is not significant (I^2<50%), the data sets from studies would be used to conduct a metanalysis. If there is considerable heterogeneity, sources of heterogeneity will be explored, and further subgroup analysis would be conducted using various Gleason scores at positive surgical margin. (10)The outcome measures would be summarised in a tabular format. We will use the PRISMA checklist when writing our report. (11)

Confidence in cumulative evidence:

The authors believe oncological outcomes such as cancer-free survival, disease progression and survival should be followed up for a minimum of five years post radical prostatectomy. The authors would also evaluate and critically appraise studies adjusted for confounders such as age of diagnosis, pre-diagnosis PSA and biopsy Gleason grade and any additional therapy before surgery. Overall, the authors aim to adopt the grading of recommendations, assessment, development and evaluation (GRADE) framework to assess each outcome measure to comment on quality of cumulative evidence. (12)

Dissemination plans:

The authors aim to publish the review in a peer-reviewed scientific journal and present the findings at relevant national and international scientific meetings.

Authors's statement:

AJ and MOC drafted the manuscript and created the study concept of the systematic review. RC and LS provided supervision and guidance during the formulation of the study. All authors were also involved in reviewing and critically appraising the protocol in its current form. The authors acknowledge Vikki Langton for her assistance with the formulation of search strategy.

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Competing interests statement:

The authors have no conflict of interest to declare.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list	n/a

		changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	7
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Pathology
Keywords:	Gleason score, positive surgical margin, prostatectomy, prostate cancer, outcomes, biochemical recurrence

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Word count 3624

Abstract

Introduction:
Positive surgical margins (PSM) in cancer patients are commonly associated with worse prognosis and a higher risk of secondary treatment. However, the relevance of this parameter in prostate cancer patients undergoing radical prostatectomy(RP) remains controversial, given the inconsistencies in its ability to predict biochemical recurrence(BCR) and oncological outcomes. Hence, further assessment of the utility of surgical margins for prostate cancer prognosis is required to predict these outcomes more accurately. Over the last decade, studies have used the Gleason score(GS) of positive margins to predict outcomes. Herein, the authors aim to conduct a systematic review investigating the role of GS of PSM after radical prostatectomy in predicting BCR and oncological outcomes

Methods and analysis:
We will perform a search using MEDLINE, EMBASE, SCOPUS and COCHRANE databases. The review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We will screen titles and abstracts to select articles appropriate for full-text review. Studies discussing GS of PSM after RP will be included. Given the change in reporting of GS, only articles from 2005-2019 will be included. The quality of the studies chosen will be assessed using the Newcastle Ottawa tool for non-randomized and Cochrane risk of bias for randomized control studies. We will adopt the grading of recommendations, assessment, development and evaluation (GRADE) framework to comment on quality of cumulative evidence. The primary outcome measure will be time to BCR. Secondary outcome measures include secondary treatment, disease-specific survival, disease progression-free and overall mortality at follow up period. We aim to perform a meta-analysis if the level of heterogeneity is acceptable (I2<50%).

Ethics and dissemination
The review does not require ethics approval as it is a review of published literature. The findings of the review will be submitted for peer-reviewed publications and presented at scientific meetings.

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Strengths and limitations of this study:

- Positive surgical margin after radical prostatectomy remains controversial in its ability to predict long-term outcomes after surgery.
- To our knowledge, this is the first systematic review and meta-analysis investigating outcomes of patients after radical prostatectomy based on Gleason score of positive surgical margin site.
- A major limitation of the study is lack of randomised controlled trials, and the majority of expected studies are likely to be retrospective cohort studies.
- Quality assessment of included studies will also be reported.
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Introduction:

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Recently, there have been multiple studies investigating Gleason score of positive surgical margins and its impact on biochemical recurrence(1-6). As a result, some studies recommend mandatory reporting of Gleason score of positive surgical margin. This is in contrast to the current ISUP recommendation, which leaves the decision up to the discretion of the pathologist (International society of urological pathology). However, very few studies report oncological outcomes and the relationship between biochemical recurrence and long-term survival rates are still poorly defined. Hence, the authors aim to conduct a systematic review investigating the role of Gleason score of positive surgical margins after radical prostatectomy in predicting biochemical recurrence and oncological outcomes (e.g. cancer-specific survival and all-cause survival). To the authors' knowledge, no systematic reviews have explored this topic previously.

Review question

In men who have positive surgical margins after radical prostatectomy, does a low Gleason score at the margin compared with a high Gleason score affect biochemical recurrence and long term oncological outcomes?

Objective

To conduct a systematic review investigating the role of Gleason score at positive surgical margin site in men who have undergone radical prostatectomy for prostate cancer, in predicting biochemical recurrence and long term oncological outcomes.

Methods

Eligibility criteria:

The search strategy aims to find published studies exploring the role of Gleason score of positive surgical margins after radical prostatectomy in predicting biochemical recurrence and oncological outcomes. The review will consider all published studies, including meta-analysis and Randomised Controlled Trials; however, we will also consider observational cohort studies and case-controlled studies if level 1 evidence is not available.
Language will be restricted to English. Studies with men who underwent radical prostatectomy without reporting of Gleason score at positive surgical margin site will be excluded. Grey literature, including conference abstracts and editorials, will be excluded.

Patient and Public Involvement:

No patient involved

Information sources:

The review will involve searching the MEDLINE, SCOPUS, EMBASE and COCHRANE databases. Given the change in Gleason reporting in 2005, the review will only include studies published between 1st January 2005 and 31st September 2019 (7). A further comprehensive literature search will also involve examining reference lists of included studies identified from the search. Authors will be contacted if the published study does not contain sufficient details to extract data.

Search strategy:

The search strategy will be created with the assistance of health sciences librarians with previous expertise in conducting systematic searches. The search strategies will be modified to accommodate the requirements of different databases used for the search.

A draft of MEDLINE (OVID interface) search strategy is shown below(See Table 1):

Table 1: Search terms for MEDLINE

Population Men with Prostate cancer	**Intervention** Radical prostatectomy	**Comparators** Gleason score at positive surgical margin site	**Outcomes** Biochemical recurrence and oncological outcomes
"prostatic neoplasms"[mh] OR prostate neoplasm*[tiab] OR prostatic neoplasm*[tiab] OR cancers of the prostate[tiab] OR cancer of the prostate[tiab] OR adenocarcinoma of the prostate[tiab] OR prostatic cancer*[tiab] OR prostate cancer*[tiab] OR	"prostatectomy"[mh] OR prostatectomy*[tiab] OR prostate removal[tiab] OR resection of prostate[tiab] OR prostate surger*[tiab]	(((Gleason[tiab] OR Gleeson[tiab]) AND (score[tiab] OR status[tiab] OR grade[tiab] OR grading[tiab] OR grade group[tiab])) AND (Positive surgical margin*[tiab] OR margin[tiab] OR margin status[tiab] OR PSM[tiab]))	Oncological outcome*[tiab] OR survival[tiab] OR mortality[tiab] OR metastases[tiab] OR metastasis[tiab] OR metastatic recurrence*[tiab] OR biochemical recurrence*[tiab] OR BCR[tiab] OR biochemical failure*[tiab] OR biochemical relapse*[tiab] OR

prostate gland cancer*[tiab] OR cancer of the prostate[tiab] OR prostate tumour*[tiab] OR prostatic tumour*[tiab] OR prostate tumor*[tiab] OR prostatic tumor*[tiab] OR tumors of the prostate*[tiab] OR tumours of the prostate[tiab] OR prostate adenocarcinoma*[tiab]			biochemical freedom from failure[tiab] OR disease progression[tiab] OR clinical recurrence[tiab] OR clinical progression[tiab] OR PSA failure[tiab] OR PSA relapse[tiab] OR PSA recurrence[tiab] OR relapse free survival[tiab] OR recurrence free survival[tiab] OR local failure[tiab] OR local failure[tiab] OR mortality rate[tiab] OR prostate specific antigen*[tiab]

Study records

Data management

A preformulated data extraction template will be used to keep track of information obtained from each study. Software including Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) and EndNote X8.2 will be used to track studies included and excluded from the review. Covidence will also be used to assist with tracking the quality of assessment and extracted information. This data will be tabulated using Microsoft Excel (Redmond, Washington, USA).

Data collection and selection process

A comprehensive search strategy aims to find published studies in various electronic databases, including the MEDLINE, SCOPUS, EMBASE, and COCHRANE databases. Studies will be screened by two authors by titles and abstracts to determine if it is appropriate. Once screened, the full-text article will be retrieved. If inclusion criteria is fulfilled, it will be selected for the review. Hand searching of reference lists of the selected studies will also be conducted and be considered for inclusion based on inclusion criteria based on the same criteria. Any disagreements between authors will be discussed with a third reviewer. Once included, the authors aim to extract, tabulate and summarise details of the eligible studies.

Data items:

Study characteristics to be extracted by the review include title, study design and type, financial supports, first authors, Year study published, inclusion criteria, follow up period, and the period of enrolment for the study. Population characteristics include Sample size, average age of men, Year of surgery, age at diagnosis, Body mass index and Median postoperative follow up. Intervention characteristics to be extracted type of procedure (Robot-assisted, Laparoscopic or open), year of surgery and additional interventions.

Comparator characteristics include primary Gleason score at positive surgical margin, overall Gleason score at margin, Gleason grade group of specimen, Gleason grade group at margin, surgical margin length of invasion, Gleason score on biopsy, extent of margin, lobe of prostate cancer, location of margin, Extraprostatic extension, perineural invasion, lymphadenopathy, pT stage and PSA at diagnosis. Outcome characteristics include Biochemical recurrence, Secondary treatment rate, Survival post-surgery, number of individuals with metastasis and Systemic progression at median/mean follow up, systemic progression-free survival.

Outcomes and prioritisation:

The review will aim to extract and report following outcome measures in the following patterns.

Primary outcomes measure:

Time to biochemical recurrence after radical prostatectomy. Biochemical recurrence is defined by two consecutive PSA values of > 0.2 ng/mL and rising (8). This is one of the main indicators used in clinical practise to commence secondary treatment and to commence assessment of metastatic spread.

Secondary outcome measures:

Prostate cancer-related Mortality. This is defined as death as a result of prostate cancer in the cohort. Given the chronicity prostate cancer, studies should look specifically at prostate cancer-related mortality rate to avoid other confounders which may also cause death in individuals involved in the cohort study. This may also be reported as a hazards ratio. This will be more beneficial than the overall survival rate.

Secondary treatment/intervention rate. The number of individuals who required additional treatment for prostate cancer such as Androgen deprivation therapy or external beam radiotherapy after the radical prostatectomy. This outcome is dependent on biochemical recurrence. Repeated treatments have been associated with worse comorbidities; hence, this outcome is important to establish so that patients can be counselled appropriately.

Cancer-free Survival at follow up

Number of participants that are alive and have no biochemical recurrence at follow up period of the study.

Metastasis free survival or Systemic progression-free at follow up

Number of participants that are alive have no evidence of prostate cancer metastasis or systemic progression at follow up period of the study.

Outcome follow up periods:

All mean and median follow up period will be noted. Based on initial searches, studies are likely to have significant variability in the short term, and long term follow up periods. Studies with identical follow up periods will be considered for a meta-analysis. If time-specific estimates are not provided, we hope to report hazard ratios. The authors agree that a median follow up of less than 12 months is inadequate in regards to detecting biochemical recurrence post radical prostatectomy.

Risk of bias in individual studies

The quality of the studies chosen would be assessed using the Newcastle Ottawa tool which is used for assessing the quality of non-randomized studies included in a systematic review by assessing domains such as selection of study groups, comparability of the groups and based on exposure or outcome of interest. Stars are awarded for each domain which allows the study to be graded into poor, fair or good quality. (9) For randomised control trials, Cochrane risk of bias tools will be used to assess the bias. A funnel plot will be used to represent an assessment of publication bias.

Data synthesis

The authors aim to summarise the role of Gleason score of positive surgical margins after radical prostatectomy in predicting biochemical recurrence and long-term oncological outcomes. Cox proportional-hazard ratios of both multivariate and univariate analysis data on primary and secondary outcomes would be extracted. This data will be presented as forest plots. The heterogeneity of the selected studies would be calculated using the I^2 score. Meta-analysis will use a random-effects model as the studies extracted are likely to have some differences in the way Gleason score is grouped. If there is considerable heterogeneity, sources of heterogeneity will be explored, and further subgroup analysis would be conducted using various Gleason scores at positive surgical margin(10). The outcome measures would be summarised in a tabular format. We will use the PRISMA checklist when writing our report. (11)

Confidence in cumulative evidence:

The authors believe oncological outcomes such as cancer-free survival, disease progression and survival should be followed up for a minimum of five years post radical prostatectomy. The authors would also evaluate and critically appraise studies adjusted for confounders such as age of diagnosis, pre-diagnosis PSA and biopsy Gleason grade and any additional therapy before surgery. Overall, the authors aim to adopt the grading of recommendations, assessment, development and evaluation (GRADE) framework to assess each outcome measure to comment on quality of cumulative evidence. (12)

Dissemination plans:

The authors aim to publish the review in a peer-reviewed scientific journal and present the findings at relevant national and international scientific meetings.

Authors' statement:

AJ and MOC drafted the manuscript and created the study concept of the systematic review. RC and LS provided supervision and guidance during the formulation of the study. All authors were also involved in reviewing and critically appraising the protocol in its current form. The authors acknowledge Vikki Langton for her assistance with the formulation of search strategy.

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Competing interests statement:
The authors have no conflict of interest to declare.

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments			

	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5

Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	7
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7