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Impact of surgical margin status on the survival outcome after surgical resection of gastric cancer: a protocol for systematic review and meta-analysis

Zhiyuan Jiang ,[1] Zhaolun Cai ,[1] Yuan Yin,[1] Chaoyong Shen,[1] Jinming Huang,[2] Yiqiong Yin,[1] Bo Zhang[1]

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ZJ and ZC contributed equally.

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[1]Department of Gastrointestinal Surgery, Sichuan University West China Hospital, Chengdu, Sichuan, China
[2]Department of Rehabilitation Medicine, Sichuan University West China Hospital, Chengdu, Sichuan, China

Correspondence to
Professor Bo Zhang; hxwcwk@126.com and Yiqiong Yin; yiqiong489@163.com

ABSTRACT

Introduction Generally, complete resection with cancer cell negative (R0) margin has been accepted as the most effective treatment of gastric cancer and positive resection (R1/R2) margin has been associated with decreased survival to varied degrees. However, the independent impact of microscopical positive (R1) margin on long-term survival may be confounded. No meta-analysis has worked at the association between R1 margin and outcomes of gastric cancer and the available evidence are scant. Therefore, we plan to conduct a systematic review and meta-analysis to quantitatively explore the role of R1 margin on gastric (including oesophagogastric junction) cancer survival after curative intent resection.

Methods and analysis The protocol was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guideline. A systematic search of PubMed, Embase and the Cochrane Central Register of Controlled Trials databases will be performed from their inceptions to 30 April 2020 to identify randomised controlled trials (RCTs), cohort studies and case–control studies focusing on the impact of R1 margin on survival of gastric cancer after curative intent resection. The primary outcome will be the overall survival (OS) and disease-free survival (DFS) and the secondary outcomes will be 5-year OS rate and 5-year DFS rate. The Cochrane tool for bias assessment in randomised trials and Risk Of Bias In Non-randomised Studies-I for the assessment of bias in non-randomised studies (NRS) will be used. Statistical heterogeneity will be assessed by visual inspection of forest plots and measured using the I^2 statistics. A fixed-effect model will be used when heterogeneity is low, otherwise, a random-effect model will be chosen. Publication bias will be assessed by funnel plots, subgroup analysis and sensitivity analysis will be performed in the right context. For each outcome, we will perform data synthesis separately for RCTs and NRS using Rev Man V.5.3 software and compile 'summary of findings' tables separately for RCTs and NRS using GRADEpro software. Grading of Recommendations, Assessment, Development and Evaluations considerations will also be used to make an overall assessment of the quality of evidence.

Ethics and dissemination There is no requirement for ethics approval because no patient data will be collected at an individual level in this systematic review and meta-analysis.

Strengths and limitations of this study

- This present protocol will provide transparency to the development process of our systematic review and accountability for the authors such that bias is minimised.
- To the best of our knowledge, this will be the first meta-analysis to explore influence of R1 margin on gastric cancer survival after curative intent resection.
- Our findings might provide relevant evidence to help surgeons to determine whether their patients with R1 margins need reresections or other aggressive treatments.
- Risk of bias will be evaluated at both study and outcome levels.
- The quality of evidence and grading of recommendation of our systematic review may be limited by a potential lack of randomised controlled trials that meet the inclusion criteria.

The results of this systematic review will be published in a peer-reviewed journal and presented at relevant conferences, any deviations from the protocol will be clearly documented and explained in its final report.

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INTRODUCTION

Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of death from cancer in the world.[1] Although adjuvant therapies can improve outcomes of some patients, surgical resection is considered to be the first line and only possible radical treatment for gastric cancer.[2–4] Complete resection with cancer cell negative (R0) margin (no cancer cells identified at the resection margin by pathological examination) has been accepted as the most effective treatment based on the surgical philosophy and even minimal remaining cancer cells will develop recurrences.[5 6] The recently reported rate of

positive resection, which included both positive resection (R1) margin (cancer cells presented at the resection margin by pathological examination) and R2 margin (tumour tissue seen at the resection margin on gross examination by the naked eye) was 24.2%.[7] Although the influence of R1 margin on gastric cancer survival has been the topics of many studies, inconsistent conclusions have been reached.[2 5 8–18] For example, Kim *et al*[17] and Postlewait *et al*[14] found that R1 margin was not independently associated with survival while Woo *et al*[13] and Nagata *et al*[5] revealed R1 margin boded ill for survival. Bickenbach *et al*[11] found that R1 margin was an independent predictor of worse survival, but not in patients with >3 positive nodes or T3–4 disease. Schoenfeld *et al*[18] found R1 margins were associated with disease-free survival (DFS) but not overall survival (OS).

Raziee *et al*[19] conducted a systematic review in 2012 examining R1 and R2 margins of gastric cancer by exploring their predictive factors, impact on survival and optimal strategies for reresection, but it did not perform meta-analysis. It was still uncertain whether R1 margin had negative influence on survival and whether it is worth performing reresection to eliminate R1 margin. Therefore, we plan to conduct a systematic review and meta-analysis to quantitatively explore the impact of R1 margin on gastric cancer survival after curative intent resection. Since the preformal study literature search found that original studies on this topic were almost non-randomised studies (NRS), our systematic review will consider both randomised controlled trials (RCTs) and NRS. The protocol for our research is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P),[20 21] its PRISMA-P checklist file is attached in online supplemental file 1. The findings of the review will be sought published in a peer-reviewed journal, also in the event of insignificant results or null results, and thereby it will be disseminated to clinicians and public available.

OBJECTIVES

The aim of this systematic review and meta-analysis is to explore the following:

1. Whether R1 margin negatively influences the survival of gastric cancer after curative intent resection.
2. Which subgroups are most impacted by R1 margin and which are not?

The study will be conducted based on the following requirements.

Population

Patients who have undergone curative intent resection for gastric cancer diagnosed by pathological examination will be included.

Gastric cancer patients underwent palliative intent resection will be excluded.

Exposure

The exposure will be postoperative R1 margin, which means that cancer cells are identified by pathological examination at the linear, circular, proximal or distal resection margin.

Margin status identified as R1 by intraoperative frozen section but R0 by pathological examination and R2 margin will be excluded.

Control

R0 margin is confirmed by pathological examination.

Outcomes

Primary outcome: time-to-event OS and time-to-event DFS or relevant data to estimate them.

Secondary outcome: 5-year OS rate and 5-year DFS rate or relevant data to estimate them.

Studies in which relevant data about these outcomes are impossible to extract will be excluded.

METHODS

This systematic review and meta-analysis will be conducted according to the PRISMA guidelines.[22]

Criteria for considering studies

Inclusion criteria

1. RCTs, cohort studies or case–control studies estimating the impact of margin status on gastric cancer survival after curative intent resection.
2. Studies with a minimum of 60 months follow-up reporting time-to-event OS or DFS or reporting 5-year OS rate or 5-year DFS rate.
3. Studies including only human participants.
4. There will be no restrictions on language and publication year.

Exclusion criteria

1. Studies with overlapping data.
2. Studies researching endoscopic submucosal dissection and endoscopic mucosal resection of gastric cancer.

Search strategy

The search strategy will be conducted in two stages.

Bibliographic database searches

A systematic search of PubMed, Embase and the Cochrane Central Register of Controlled Trials databases will be performed from their inceptions to 30 April 2020 to identify all relevant studies. The details of PubMed database search strategy and syntax are shown in table 1.

Searching for other sources

We will manually search the references of relevant articles to further identify eligible studies, and their full texts will be retrieved.

Study selection and data extraction

Records identified according to search strategy will be collated and exported to EndNote V.X8 software. Two

Table 1 Search strategy for PubMed

Search	Search terms
#1	"Neoplasm, Stomach" or "Stomach Neoplasm" or "Neoplasms, Stomach" or "Gastric Neoplasms" or "Gastric Neoplasm" or "Neoplasm, Gastric" or "Neoplasms, Gastric" or "Cancer of Stomach" or "Stomach Cancers" or "Gastric Cancer" or "Cancer, Gastric" or "Cancers, Gastric" or "Gastric Cancers" or "Stomach Cancer" or "Cancer, Stomach" or "Cancers, Stomach" or "Cancer of the Stomach" or "Gastric Cancer, Familial Diffuse"
#2	"Excision Margin" or "Excision Margins" or "Resection Margin" or "Margin, Resection" or "Margins, Resection" or "Resection Margins" or "Surgical Margins" or "Margin, Surgical" or "Margins, Surgical" or "Surgical Margin" or "Positive Surgical Margins" or "Positive Surgical Margin" or "Surgical Margin, Positive" or "Surgical Margins, Positive" or "Negative Surgical Margins" or "Negative Surgical Margin" or "Surgical Margin, Negative" or "Surgical Margins, Negative" or "Tumor-Free Margins" or "Margin, Tumor-Free" or "Margins, Tumor-Free" or "Tumour Free Margins" or "Tumor-Free Margin"
#3	#1 AND #2 Limits: Publication date to 2020/4/30, Humans species.

reviewers (ZJ and ZC) will independently screen their titles and abstracts. Subsequently, the two independent reviewers will reassess the full texts of the identified studies, verifying the reasons for inclusion and exclusion. Disagreements will be resolved by team consensus.

Data extraction for included studies will be conducted by two reviewers (ZJ and either ZC or YY) independently using a standardised electronic data extraction form (listed in table 2). This form was piloted by all reviewers. The following data will be extracted from all the included studies: first author, publication year, study design, study period, country(region), male rate, age (mean or median), follow-up (mean or median), sample size, R1 margin rate, R0 margin rate, tumour size, tumour site, tumour stage, histologic grade, type of surgery, lymphadenectomy, neoadjuvant or adjuvant treatments, survival outcomes. If outcomes were reported in multiple data sets, the one with more adjusted confounders will be used. All disputes in the process of data extraction will be resolved through team negotiation.

Dealing with missing data

To pool HRs of OS or DFS, when an HR and its upper or lower limit of 95 CI are provided by a trial, we can calculate lnHR (the natural logarithm of HR) and its SE and then merge HRs. When the above data are incomplete, we will attempt to contact the authors to retrieve it. If do not get an effective response in 10 days, we will try to estimate some or all of the lnHR, the logrank observed minus expected events (O-E), the logrank variance and the variance of the lnHR by indirect methods.[23] If even these indirect methods cannot be applied, we will consider to generate the necessary statistics from published Kaplan-Meier curves.[23] When a trial fails to provide necessary statistics by mentioned methods, it will be omitted from pooling HRs. To pool ORs of 5-year OS rate or DFS rate, we will record data on the total number of participants and the incidence of events in each arm of every trial. When these data in the full text are incomplete, we will contact the authors to extract more, trials that fail to provide these necessary data will be excluded from pooling ORs.

Risk of bias assessment

Two independent reviewers (ZJ and ZC) will assess the methodological quality/risk of bias of included studies, disagreements will be resolved by discussion, where necessary, in consultation with the third reviewer (YY). For RCTs, the risk of bias will be assessed using the Cochrane Collaboration's risk of bias tool[24]. For NRS, we will use the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool[25] . Results of this meta-analyses will be interpreted in light of risk of bias assessment of the included studies.

Measurements

As for time-to-event outcome, the HR will be used to pool overall effects. Dichotomous outcome will be analysed by calculating the OR. Results will be presented as summary relative effect sizes (HR or OR) with 95% CIs.

Strategy for data synthesis

We will import extracted data into Rev Man V.5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for data synthesis by the first reviewer and checked by the second one. The overall pooled estimates for the association between resection margin status and survival will be calculated in the meta-analysis. Due to the nature of survival analysis, we will first try to extract HR-related data from each included study and then estimate pooled HRs for OS and DFS with 95% CI according to methods introduced by Parmar *et al* and Tierney *et al*.[23 26] If multiple HRs for a same outcome are presented in a paper, we will choose the one adjusted for the greatest number of confounders.[27] Subsequently, we will try to extract the 5-year OS rate and DFS rate of the two groups from each included study and estimate pooled ORs with 95% CI. NRS with large sample sizes pooling with small RCTs could dominate the pooled effect estimates, thus we will perform data synthesis separately for RCTs and NRS. Statistical heterogeneity will be assessed by visual inspection of forest plots and measured using the I^2 statistics. I^2 < 50% or ≥50% indicates low or high heterogeneity, respectively. A fixed effect model will be used when heterogeneity is low, otherwise, a random

Table 2 Data extraction form

Study details	
General information	
First author	
Year of publication	
Region	
Study period	
Study eligibility	
Study design	
Participants	
Exposure	
Control	
Outcome diagnostic criteria	
Confounding variables	
Include or exclude	Include □ exclude □
Reason(s) for exclusion	
Characteristics of included studies	
Sample size	
R1 margin group	
R0 margin group	
Data source	
Age (mean or median)	
Gender (male rate)	
Follow-up (mean and range) (months)	
R1 margin rate (%)	
R0 margin rate (%)	
Tumour size (cm)	
Tumour site	
Tumour stage	
Histologic grade	
Type of surgery	
Lymphadenectomy	
Neoadjuvant or adjuvant treatment for R1 margin group	
Neoadjuvant or adjuvant treatment for R0 margin group	
Subgroups	
Key conclusion(s)	
Primary outcomes	
HRs (comparing R1 and R0 group) with 95% CI	
OS	
DFS	
Relevant data to calculate HRs	
OS	
DFS	
Other data	
Second outcomes	
5 year OS rate	R1 group: R0 group:
5 year DFS rate	R1 group: R0 group:
Other data	R1 group: R0 group:

effect model will be chosen. When substantial heterogeneity is detected, subgroup analysis and sensitivity analysis will be performed to investigate its possible sources. In case of considerable clinical heterogeneity, a narrative review rather meta-analysis will be conducted.

Sensitivity analysis and subgroup analyses

We will apply the leave-one-out sensitivity analysis to evaluate the robustness of the results.

Subgroup analyses are planned as follows:

1. Study carried out in: Asia and other regions.
2. Tumour stage: early gastric cancer and advanced gastric cancer.
3. Lymphadenectomy: ≤D1 and ≥D2.
4. HR (estimating OS or DFS) extracted from: multivariate analysis and univariate analysis.
5. Proximal cancer (tumour in the gastro-oesophageal junction, cardia or fundus).

Publication bias assessment

Since detecting and overcoming publication bias are problematic and firm guidance is not yet offered, we will use visual inspection of funnel plots to assess publication bias, with results being interpreted cautiously.[28 29]

Quality of the evidence

Two reviewers (ZC and YY) will assess overall quality of evidence for each outcome independently using the five Grading of Recommendations, Assessment, Development and Evaluations (GRADE) considerations. In this approach, direct evidence from RCTs begins at high quality, while observational study begins at low; however, the overall quality will be analysed on five down-grade considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) and three up-grade considerations (large magnitude of effect, dose–response relation and plausible confounders or biases), and finally rate it as high, moderate, low or very low.[30–37] Disagreements will be solved by discussion. Whenever necessary, we will provide all decisions to down grade or up grade the quality of studies with clear arguments in footnotes to aid the reader's understanding of the table and the process.

Presentation and reporting of results

We will summarise the study selection process by a flow diagram with reasons for exclusions (figure 1). The characteristics of each included study will be tabulated in detail. We will use forest plots to present the pooled

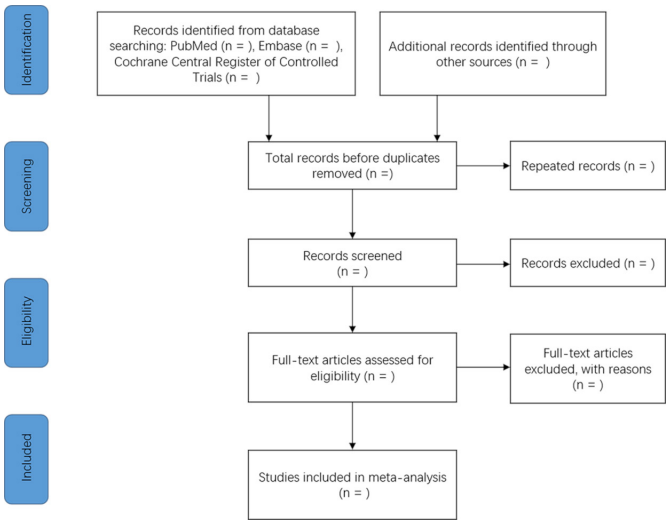

Figure 1 Flow diagram of studies selected for inclusion in this systematic review.

estimates. Additionally, for each outcome, 'summary of findings' tables compiled by GRADEpro software (GRADEpro GDT 2015) will be presented separately for both RCTs and NRS.

Patient and public involvement

This systematic review and meta-analysis will be based on published studies, raw patient data will not be collected. As a result, patients and the public will not be involved in the design, or conduct, or reporting or dissemination plans of this research.

Ethics and dissemination

There is no ethics approval required for this systematic review due to no patient data being collected at an individual level. We will seek to present the findings of this systematic review at relevant conferences and publish in an influential open access journal, any deviations from the protocol will be clearly documented and explained in its final report.

SUMMARY

This is a protocol for a systematic review and meta-analysis reported according to the PRISMA-P guidelines. This systematic review and meta-analysis will explore the influence of R1 margin comparing with R0 margin on gastric cancer survival by summarising the published studies and reveal which subgroups are most affected by R1 margin and which are not. It will be conducted according to PRISMA guidelines and with robust methodological processes and statistical analyses. Risk of bias will be evaluated at study level using Cochrane Collaboration's risk of bias tool and ROBINS-I tool as well as at outcome level using the GRADE approach. As a result, its findings might provide relevant evidence and help surgeons to determine whether their patients with R1 margins need reresections or other aggressive treatments.

Contributors The original idea of this research was conceived by BZ. JZ and ZC designed the protocol and drafted the manuscript. JZ, ZC, YY and CS participated in developing the eligibility criteria, search strategy, data extraction methods and data summary plan. JZ, ZC and JH will search for studies, extract and analyse the data. BZ and YYQ supervised the work. All authors approved the final version of this manuscript.

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ORCID iDs
Zhiyuan Jiang http://orcid.org/0000-0003-2483-3413
Zhaolun Cai http://orcid.org/0000-0002-3706-6703

REFERENCES

1 Ajani JA, D'Amico TA, Almhanna K, *et al*. Gastric cancer, version 3.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2016;14:1286–312.
2 Chen J-D, Yang X-P, Shen J-G, *et al*. Prognostic improvement of reexcision for positive resection margins in patients with advanced gastric cancer. *Eur J Surg Oncol* 2013;39:229–34.
3 Liang Y, Ding X, Wang X, *et al*. Prognostic value of surgical margin status in gastric cancer patients. *ANZ J Surg* 2015;85:678–84.
4 Cai Z, Yin Y, Yin Y, *et al*. Comparative effectiveness of adjuvant treatments for resected gastric cancer: a network meta-analysis. *Gastric Cancer* 2018;21:1031–40.
5 Nagata T, Ichikawa D, Komatsu S, *et al*. Prognostic impact of microscopic positive margin in gastric cancer patients. *J Surg Oncol* 2011;104:592–7.
6 Cai Z, Yin Y, Shen C, *et al*. Comparative effectiveness of preoperative, postoperative and perioperative treatments for resectable gastric cancer: a network meta-analysis of the literature from the past 20 years. *Surg Oncol* 2018;27:563–74.
7 Koumarianou A, Krivan S, Machairas N, *et al*. Ten-Year survival outcomes of patients with potentially resectable gastric cancer: impact of clinicopathologic and treatment-related risk factors. *Ann Gastroenterol* 2019;32:99–106.
8 Cho BC, Jeung HC, Choi HJ, *et al*. Prognostic impact of resection margin involvement after extended (D2/D3) gastrectomy for advanced gastric cancer: a 15-year experience at a single Institute. *J Surg Oncol* 2007;95:461–8.
9 Wang S-Y, Yeh C-N, Lee H-L, *et al*. Clinical impact of positive surgical margin status on gastric cancer patients undergoing gastrectomy. *Ann Surg Oncol* 2009;16:2738–43.
10 Sun Z, Li D-ming, Wang Z-ning, *et al*. Prognostic significance of microscopic positive margins for gastric cancer patients with potentially curative resection. *Ann Surg Oncol* 2009;16:3028–37.
11 Bickenbach KA, Gonen M, Strong V, *et al*. Association of positive transection margins with gastric cancer survival and local recurrence. *Ann Surg Oncol* 2013;20:2663–8.
12 Liang Y, Ding X, Wang X, *et al*. Prognostic value of surgical margin status in gastric cancer patients. *ANZ J Surg* 2015;85:678–84.
13 Woo J-W, Ryu KW, Park JY, *et al*. Prognostic impact of microscopic tumor involved resection margin in advanced gastric cancer patients after gastric resection. *World J Surg* 2014;38:439–46.

14 Postlewait LM, Squires MH, Kooby DA, *et al*. The importance of the proximal resection margin distance for proximal gastric adenocarcinoma: a multi-institutional study of the US gastric cancer collaborative. *J Surg Oncol* 2015;112:203–7.
15 Bissolati M, Desio M, Rosa F, *et al*. Risk factor analysis for involvement of resection margins in gastric and esophagogastric junction cancer: an Italian multicenter study. *Gastric Cancer* 2017;20:70–82.
16 Kim BS, Oh ST, Yook JH, *et al*. Appropriate gastrectomy resection margins for early gastric carcinoma. *J Surg Oncol* 2014;109:198–201.
17 Kim Y, Squires MH, Poultsides GA, *et al*. Impact of lymph node ratio in selecting patients with resected gastric cancer for adjuvant therapy. *Surgery* 2017;162:285–94.
18 Schoenfeld JD, Wo JY, Mamon HJ, *et al*. The impact of positive margins on outcome among patients with gastric cancer treated with radiation. *Am J Clin Oncol* 2016;39:243–7.
19 Raziee HR, Cardoso R, Seevaratnam R, *et al*. Systematic review of the predictors of positive margins in gastric cancer surgery and the effect on survival. *Gastric Cancer* 2012;15:116–24.
20 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
21 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
22 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
23 Tierney JF, Stewart LA, Ghersi D, *et al*. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
24 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
25 Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
26 Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815–34.
27 Hunink MG, Wong JB. Meta-Analysis of failure-time data with adjustment for covariates. *Med Decis Making* 1994;14:59–70.
28 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
29 Li F, Liu G, Roudi R, *et al*. Do statins improve outcomes for patients with non-small cell lung cancer? A systematic review and meta-analysis protocol. *BMJ Open* 2018;8:e022161.
30 Balshem H, Helfand M, Schünemann HJ, *et al*. Grade guidelines: 3. rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6.
31 Guyatt GH, Oxman AD, Kunz R, *et al*. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol* 2011;64:1283–93.
32 Guyatt GH, Oxman AD, Kunz R, *et al*. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol* 2011;64:1303–10.
33 Guyatt GH, Oxman AD, Kunz R, *et al*. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *J Clin Epidemiol* 2011;64:1294–302.
34 Guyatt GH, Oxman AD, Montori V, *et al*. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin Epidemiol* 2011;64:1277–82.
35 Guyatt GH, Oxman AD, Sultan S, *et al*. Grade guidelines: 9. rating up the quality of evidence. *J Clin Epidemiol* 2011;64:1311–6.
36 Guyatt GH, Oxman AD, Vist G, *et al*. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011;64:407–15.
37 Kien C, Gartlehner G, Kaminski-Hartenthaler A, *et al*. [GRADE guidelines: 9. Rating up the quality of evidence]. *Z Evid Fortbild Qual Gesundhwes* 2013;107:249–55.