Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Clinical Evidence for Association of Neoadjuvant Chemotherapy or Chemoradiotherapy with Efficacy and Safety in Patients With Resectable Esophageal Carcinoma (NewEC Study)

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

14/11/2018

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/12/2019

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Yun-Fang Yu

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr. Yun-Fang Yu

7. * Named contact email.

Give the electronic mail address of the named contact.

yuyf9@mail.sysu.edu.cn

8. Named contact address

Give the full postal address for the named contact.

Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Department of Medical Oncology, Phase I Clinical Trial Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, No. 107 Yanjiang West Road, Guangzhou 510120, China

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+86 13660238987

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Sun Yat-sen Memorial Hospital, Sun Yat-sen University

Organisation web address:

https://www.syshospital.com/Category_155/Index.aspx

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**

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Professor Herui Yao. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University
Dr Yun-Fang Yu. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

This study was supported by grants from the National Science and Technology Major Project (2020ZX09201021), the National Natural Science Foundation of China (81572596, 81972471, U1601223), the Natural Science Foundation of Guangdong Province (2017A030313828, 2018A0303130113), the Guangzhou Science and Technology Major Program (201704020131, 201903010028), the Medical artificial intelligence project of Sun Yat-Sen Memorial Hospital (YXRGZN201902), the Guangdong Science and Technology Department (2017B030314026), and the Guangdong Province Medical Scientific Research Foundation (A2015333, B2018148).

Grant number(s)

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13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

Is surgery or neoadjuvant therapy, specifically, chemoradiotherapy (NCRT) or chemotherapy (NCT), better for resectable esophageal carcinoma?

16. * Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

We searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for randomized clinical trials (RCTs) up to May 2019 using the following terms: “esophageal cancer”, “chemotherapy”, “surgery”, “chemoradiotherapy”, and “neoadjuvant therapy”. The proceedings of the American Society of Clinical Oncology, European Society for Medical Oncology and American Society for Therapeutic Radiology and Oncology as well as the references in the included RCTs and relevant meta-analyses were also reviewed manually.

For inclusion, RCTs had to evaluate the efficacy and safety of NCRT or NCT followed by surgery versus surgery alone or NCRT versus NCT as the primary schedule among patients with esophageal carcinoma or gastroesophageal junction carcinoma. Trials involving patients who had histologically proven adenocarcinoma or SCC of the stomach or lower third of the esophagus but did not separate the available data for esophageal cancer patients were excluded. We excluded studies whose abstracts or full texts were

not in English and studies that did not have available data. Three investigators (S-PZ, A-LL, Y-YF) screened the titles and abstracts to choose relevant studies, and the eligibility of the studies that seemed to meet the inclusion criteria was confirmed by a full-text review. The data collected included the recruitment period, sample size, follow-up time, treatment group allocation, details regarding the chemotherapy and radiotherapy regimens, and patient and tumor characteristics.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Resectable Esophageal Carcinoma

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

For inclusion, RCTs had to evaluate the efficacy and safety of NCRT or NCT followed by surgery versus surgery alone or NCRT versus NCT as the primary schedule among patients with esophageal carcinoma or gastroesophageal junction carcinoma. Trials involving patients who had histologically proven adenocarcinoma or SCC of the stomach or lower third of the esophagus but did not separate the available data for esophageal cancer patients were excluded. We excluded studies whose abstracts or full texts were not in English and studies that did not have available data. Three investigators (S-PZ, A-LL, Y-YF) screened the titles and abstracts to choose relevant studies, and the eligibility of the studies that seemed to meet the inclusion criteria was confirmed by a full-text review. The data collected included the recruitment period, sample size, follow-up time, treatment group allocation, details regarding the chemotherapy and radiotherapy regimens, and patient and tumor characteristics.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Neoadjuvant chemoradiotherapy, neoadjuvant chemotherapy, surgery

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be

compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy versus surgery

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Randomized clinical trials.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The primary endpoint was overall survival (OS).

* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

The treatment effect on the time-to-event outcome was estimated by the hazard ratio (HR) with 95% confidence interval (CI).

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

The secondary end points included disease-free survival (DFS), R0 resection rate, pathologic complete response (pCR) and 30-day postoperative or in-hospital mortality.

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

The treatment effect on the time-to-event outcome was estimated by the hazard ratio (HR) with 95% confidence interval (CI), and the dichotomous outcomes were evaluated by the risk ratio (RR) and risk difference (RD).

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

For inclusion, RCTs had to evaluate the efficacy and safety of neoadjuvant chemoradiotherapy (NCRT) or neoadjuvant chemotherapy (NCT) followed by surgery versus surgery alone or NCRT versus NCT as the primary schedule among patients with esophageal carcinoma or gastroesophageal junction carcinoma. Trials involving patients who had histologically proven adenocarcinoma or squamous cell carcinoma (SCC) of the stomach or lower third of the esophagus but did not separate the available data for esophageal cancer patients were excluded. We excluded studies whose abstracts or full texts were not in English and studies that did not have available data. We screened the titles and abstracts to choose relevant studies, and the eligibility of the studies that seemed to meet the inclusion criteria was confirmed by a full-text review. The data collected included the recruitment period, sample size, follow-up time, treatment group allocation, details regarding the chemotherapy and radiotherapy regimens, and patient and tumor characteristics.

The study selection, data extraction and methodological quality assessment were conducted independently by three investigators (Y-FY, S-PZ, and A-LL). If an inconsistency arose, consensus was reached via discussion among all the investigators.

27. * Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

We rigorously assessed the risk of bias based on the following seven domains as recommended by the Cochrane Collaboration Handbook: generation of the allocation sequence; concealment of the allocation; blinding of the participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.1 Each item was categorized as having a low, unclear, or high risk of bias, and a risk of bias graph and the corresponding summary graph were generated by Review Manager 5.3 software.

The study selection, data extraction and methodological quality assessment were conducted independently by three investigators (Y-FY, S-PZ, and A-LL). If an inconsistency arose, consensus was reached via discussion among all the investigators.

28. * Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

Direct and indirect evidence for OS and DFS were combined using random or fixed effects on the hazard ratio (HR) scale, and risk ratio (RR) for OS rate, and absolute 30-day or in-hospital mortality, along with corresponding 95% confidence intervals (CIs). P 0.05 was considered to be statistically significant.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

Prespecified subgroup analyses were performed to examine the effects of NCT or NCRT according to tumor histology (SCC or adenocarcinoma), the timing of chemotherapy and radiotherapy (concurrent or sequential), and the chemotherapy regimen (platinum plus taxanes or platinum plus fluorouracil).

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
Yes

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
Yes

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology

No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

China

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data

will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

The meta-analysis part of this study is registered with PROSPERO CRD42017072242 and the cohort study part is registered with ClinicalTrials.gov. NCT04027543.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Oesophageal cancer

Neoadjuvant chemoradiotherapy

Neoadjuvant chemotherapy

Surgery

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s) or preprints if available.

This field should be left empty until details of the completed review are available OR you have a link to a preprint.

Give the link to the published review.