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Immune checkpoint inhibitors for advanced oesophageal cancer treated with surgery, radiotherapy or chemotherapy (Protocol)

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[Intervention Protocol]

Immune checkpoint inhibitors for advanced oesophageal cancer treated with surgery, radiotherapy or chemotherapy

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the effectiveness and safety of immune checkpoint inhibitors (ICIs) for people with advanced, unresectable or metastatic oesophageal cancer.

BACKGROUND

Description of the condition

According to the morbidity and mortality rates of global cancers estimated by GLOBOCAN in 2018, oesophageal cancer ranked seventh in incidence, with 572,000 new cases, and sixth in terms of mortality, with 509,000 deaths (Bray 2018). Oesophageal cancer can be divided into two dominant histological subtypes: oesophageal squamous cell carcinoma and oesophageal adenocarcinoma. Epidemiological studies have demonstrated that low socioeconomic status (Wu 2016), cigarette smoking (Xu 2018), alcohol drinking (Yang 2017), and hot tea drinking (Yang 2018) are risk factors with consistent evidence for oesophageal squamous cell carcinoma. The oesophageal adenocarcinoma incidence rate has risen sharply in high-income countries over the past four decades (Smyth 2017; Xie 2017). Overall, the outcome of oesophageal cancer is poor, with a five-year survival rate of only 19% (Siegel 2019). Localised and regional oesophageal cancer have five-year survival rates of 46.7% and 25.1%, respectively (Howlader 2019). However, the five-year survival rate of distant oesophageal cancer is as low as 4.8% (Howlader 2019).

In the early stages, oesophageal cancer is often asymptomatic. As it progresses, people may present with progressive dysphagia, unintentional weight loss, odynophagia, new-onset dyspepsia, heartburn or chest pain, and other such symptoms (Short 2017). The National Comprehensive Cancer Network recommends that people with these symptoms undergo upper endoscopy (Ajani 2019).

The diagnosing and staging of oesophageal malignancy is crucial for predicting prognosis and assigning proper treatment. The current staging system uses the tumor-node-metastasis (TNM) classification along with other prognostic variables, including histologic grade criteria (Rice 2010). Clinical staging is often performed according to imaging modalities, including computed tomography (CT), positron emission tomography-CT (PET-CT), and endoscopic ultrasound (El 2019).

Currently, the treatment for oesophageal cancer mainly involves endoscopic therapy, surgery, radiotherapy and chemotherapy (Rustgi 2014). Endoscopic submucosal dissection and endoscopic mucosal resection are two types of endoscopic eradication therapy. Endoscopic submucosal dissection appears to be superior to endoscopic mucosal resection, as evidenced by significantly higher curative resection rates and obviously lower local recurrence rates (Guo 2014). When malignancies occur in the submucosal layers, esophagectomy is more curative (Molena 2017). The current standard curative treatment for resectable oesophageal cancer is open transthoracic esophagectomy, with or without neoadjuvant or adjuvant therapies (Haverkamp 2017). Patients may experience complications and operative mortality remains relatively high, with impaired quality of life (Findlay 2015; Patel 2015). Neoadjuvant and adjuvant therapy are two types of chemotherapy that may increase resectability and curative (R0) resection, and improve locoregional control and long-term survival (Mota 2018; Tu 2019). However, these two therapies may cause therapeutic adverse effects or complications (Markar 2018; Sabra 2017). In summary, treating oesophageal cancer is challenging and patients generally have a poor prognosis.

The traditional therapies mentioned above provide only a moderate prognosis for oesophageal cancer. The five-year overall survival rate was only 28% for regional disease and 6% for distant disease between 2013 and 2019, according to the Surveillance, Epidemiology and End Results (SEER) database (American Cancer Society 2024). Immunotherapeutic approaches have led to considerable clinical benefits in various cancers, including melanoma and lung cancer. Ongoing investigations are exploring the therapeutic utility of immunotherapies in other types of cancers. In oesophageal cancer, multiple clinical trials have proven that immune checkpoint inhibitors (ICIs) improve overall survival and progression-free survival for people with advanced and metastatic oesophageal cancer (Doki 2022; Kojima 2020; Kato 2019). For example, KEYNOTE-181 reported a median overall survival of 9.3 months in the ICI arm, in contrast to 6.7 months in the chemotherapy arm (Kojima 2020). It is important to evaluate the efficacy and safety of ICIs.

Description of the intervention

The pace of immune checkpoint inhibitors' development is accelerating. In the past three years, multiple phase III clinical trials of KEYNOTE-181, ATTRACTION-03, Checkmate 648 and others have demonstrated the efficacy of ICIs for oesophageal cancer (Doki 2022; Kato 2019; Kojima 2020). Numerous immune checkpoint pathways suppress T cell activation at multiple checkpoints during an immune response to prevent autoimmunity. However, tumours may exploit the endogenous immune checkpoint pathways to actively evade immune destruction (Topalian 2012). In this process, the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) immune checkpoint pathways are critical, where tumours use PD-1 and CTLA-4 inhibitory pathways to silence the immune system (Buchbinder 2016; Duraiswamy 2014). CTLA-4 primarily functions by impairing the early activation of memory and naive T cells, whereas PD-1 plays a pivotal role in modulating T cell function in peripheral tissues (Wang 2016). A strong preclinical basis for using PD-1 and CTLA-4 antibodies alone and in combination overcame checkpoint inhibition in cancer treatment, and it has been suggested that these antibodies may augment the efficacy of other antibodies, cytokines, radiation, and adoptive cell therapy in human cancer (Baksh 2015). PD-1 inhibitor drugs, including pembrolizumab and nivolumab, are recognised as a potential treatment when traditional therapies fail to control cancer (Kudo 2017; Shah 2018). Regarding the CTLA-4 pathway, ipilimumab and tremelimumab are the two most researched drugs in cancer immunotherapy, where the relevant clinical trials have shown promising results with survival benefits (Janjigian 2018; Ralph 2010).

How the intervention might work

Mechanism of checkpoint signalling inhibition

The PD-1 and CTLA-4 inhibitory pathways are among the most critical immune checkpoint pathways. When a T cell recognises the antigen expressed by the major histocompatibility complex (MHC) on the target cell, an inflammatory process is initiated, resulting in PD-L1 (PD-1 ligand 1) expression in the tissue and PD-1 protein activation on the T cell. The PD-1–PD-L1 interaction leads to immune tolerance, where the immune system fails to mount an inflammatory response (Hashem 2017). CTLA-4 interacts with CD80/CD86 on target cells, subsequently limiting T cell activation (Dyck 2017). Blocking these two pathways with antibodies is

effective for activating the immunisation suppressed by tumours. Blocking the CTLA-4 pathway increases T cell infiltration into tumours and reduces tumour growth (Dyck 2017). Blocking the PD-L1–PD-1 interaction increases effector T cell numbers, augments tumour-specific T cell cytolytic activity, draws effector T cells to the tumour site, and enhances pro-inflammatory cytokine production (Ma 2016). Checkpoint blockade of the CTLA-4 pathway supports the induction phase of anti-tumour T cell responses while checkpoint blockade of the PD-1–PD-L1 pathway maintains the effector phase of anti-tumour T cell responses (Hargadon 2018).

Why it is important to do this review

Conventional treatments for oesophageal cancer include endoscopic therapy, surgery, chemotherapy and radiotherapy, and adjuvant and neoadjuvant therapy. Despite the progress made in its treatment, the five-year survival rate for oesophageal cancer remains relatively low, at 5% to 34% for different stages (Rustgi 2014). With chemotherapy as first-line treatment, people with recurrent or metastatic oesophageal cancer had a median overall survival of 6.7 months to 13.2 months in one study (Lee 2015). In contrast, another study reported that median overall survival reached 15.3 months in people treated with ICIs combined with chemotherapy, versus 12.0 months in the chemotherapy arm (Luo 2021). Oesophageal cancer treatment may be revolutionised by the emergence and rapid progress of checkpoint inhibitors. Different investigators use multiple strategies based on complex rationales. In the meantime, immune-related adverse events (irAEs) are different from adverse effects of chemotherapy. Such irAEs include myocarditis, pneumonitis, hypothyroidism and may lead to non-cancer-related death in severe circumstances (Tan 2022). The overall incidence of irAEs can reach 26% with PD-1/L1 inhibitors (Wang 2017). Therefore, it is necessary to systematically assess the safety and effectiveness of oesophageal cancer immune checkpoint inhibitors to provide oncologists with comprehensive evidence-based guidelines for reference.

OBJECTIVES

To evaluate the effectiveness and safety of immune checkpoint inhibitors (ICIs) for people with advanced, unresectable or metastatic oesophageal cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) will be eligible for this review, including those with and without blinding, reported in full text or abstract form, or unpublished. We will exclude cross-over design studies, as advanced oesophageal cancer is not a stable condition. We will not include cluster-randomised trials or quasi-RCTs.

Types of participants

We will include participants aged 18 years or over with confirmed advanced oesophageal cancer, including gastro-oesophageal junction cancers. Advanced oesophageal cancer generally means locally unresectable (locally advanced), metastatic or recurrent carcinomas. It is associated with T1b-SM2, T1b-SM3 and more advanced stages in the TMN staging system. We will include studies in which participants are described by authors as 'advanced', 'unresectable' or 'metastatic'. We will also contact the authors of identified trials to confirm the staging. If it is not possible to determine whether participants have been previously treated with immunotherapies or whether they meet the inclusion criteria, we will categorise these studies awaiting classification. Then we will contact the authors by email for enquiries. If it is determined that the participants of the trials do not meet the inclusion criteria or the authors cannot be reached, we will exclude the trials. We will exclude studies in which participants receive immunotherapies without checkpoint inhibitors or have received immunotherapies previously.

Types of interventions

Conventional treatments are defined as the guideline-recommended non-immune-based treatments, which usually include surgery, chemotherapy, radiotherapy, supportive treatments, and treatment plans combining these options.

We will include studies with the following checkpoints.

- PD-1/PD-L1/PD-L2 inhibitors: nivolumab, pembrolizumab and other PD-1/PD-L1/PD-L2 inhibitors (Kudo 2017)
- CTLA-4
- TIGIT
- Other immune checkpoint inhibitors

We will evaluate immune checkpoint inhibitors as a whole group, including PD-1 or PD-L1 or CTLA-4 antibodies, regardless of the subtypes. We will exclude studies in which participants receive vaccines rather than immune checkpoint inhibitors.

The comparisons will be as follows.

- Experimental treatment: immune checkpoint inhibitors plus conventional therapies.
- Control: conventional therapies alone.

Studies that include identical co-interventions in both groups will be eligible, e.g. studies that compare immunotherapy and chemotherapy with chemotherapy alone. Studies that include participants with previous systemic treatments are also eligible.

Types of outcome measures

Primary outcomes

The primary outcome is overall survival (OS): the interval between the date of randomisation and the time of death or when observation ceased.

Secondary outcomes

1. Objective response: the proportion of participants who have a partial or complete response to therapy, assessed by independent central review on the basis of the Response Evaluation Criteria In Solid Tumors (RECIST). Objective response will be collected from the date of randomisation up to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first.
2. Adverse effects: adverse events should be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) classification, and will be reported as the percentages of participants who had treatment-related

adverse events of grade 3 or 4 and the percentage of those who had a treatment-related adverse event of any grade that led to discontinuation. Adverse effects will be collected from the date of randomisation up to the date of the documented adverse effect.

3. Progression-free survival (PFS): defined as the interval between randomisation and disease progression, death, or the end of the trial, according to RECIST (Eisenhauer 2009).
4. Health-related quality of life (HRQoL): the multidimensional concept commonly used to examine the impact of health status on quality of life, measured using questionnaires such as the 36-Item Short Form Survey Instrument (SF-36) or EQ-5D. HRQoL will be collected from the date of randomisation up to 12 months. If studies report data for more than one time point for HRQoL, we will select data for the time point closest to 12 months.
5. Duration of response: the interval from response initiation (when either complete response or partial response is first determined), to progression or death. The response is assessed according to RESIST, and we will only include the duration of response assessed by independent central review.

Search methods for identification of studies

There will be no restrictions on the publication language for the electronic database search or when reviewing the reference lists of identified studies. Searches will not be limited by date or publication status.

Electronic searches

We will conduct a literature search to identify all published and unpublished RCTs relevant to our topic. The aim is to identify and use literature published in any language, with translation if necessary. The search strategies will meet the requirements of the *Cochrane Handbook for Systematic Reviews of Interventions* (subsequently referred to as the *Cochrane Handbook*) (Higgins 2024). We will search the following databases (via Ovid).

- Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 1)
- MEDLINE (from inception to present) (Appendix 2)
- Embase (from inception to present) (Appendix 3)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (inception to present) (Appendix 4)
- ClinicalTrials.gov and the EU Clinical Trials Register for information on ongoing trials

Searching other resources

- In addition to the online database search, we will conduct a thorough exploration of the references of the review and identify unpublished trials by contacting authors of the literature and oesophageal cancer and immunotherapy specialists.
- We will search for grey literature using the OpenGrey database (www.opengrey.eu).

Data collection and analysis

Selection of studies

Two review authors (NC, YC) will import all titles and abstracts retrieved from the electronic search to EndNote, remove duplicates, and examine all references independently. They will screen the titles and abstracts, marking studies as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve' (irrelevant studies to be excluded). Subsequently, the authors will read the full texts of the trials and determine inclusions separately. They will document the reasons for exclusion. Any disagreements will be discussed between the authors, and if necessary, a third review author (CS) will be consulted. We will initiate correspondence with investigators if the eligibility requires clarification. The process of selecting studies will be reported in a PRISMA flow diagram and the characteristics of excluded studies table will provide details of studies assessed in full text that did not meet the review criteria.

Data extraction and management

After studies have been selected, we will use a standard form to record their methodological characteristics and outcomes. Two authors (NC and YC) will extract data independently using a prepiloted data extraction form. If there are disagreements between the two authors (NC and YC), a third author (SC) will be involved. Review authors will extract the following information.

1. Methods: study design, duration of study, duration of follow-up period, number of study centres and location, study setting, withdrawals, date of study.
2. Participants: sample size, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, exclusion criteria, previous treatments.
3. Interventions: intervention, comparison, concomitant medications, excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors.

In the characteristics of included studies table, if outcome data are not reported in a usable way, we will note them. One review author will copy data from the forms to the Review Manager file. A second review author will spot-check study characteristics for accuracy against the trial report. If participants withdraw from the randomised controlled trials, for example, due to an inability to tolerate the intervention, adverse events occurring during the study, or other issues, we will extract the reasons for withdrawal.

Assessment of risk of bias in included studies

Two review authors (NC and YC) will independently assess the risk of bias for each included study, using the criteria outlined in Chapter 7 and Chapter 8 of the *Cochrane Handbook* (Higgins 2024) and RoB 2 tool (Sterne 2019). Any disagreements will be resolved through discussion between authors and, if necessary, a third review author (CS) will be consulted. We will focus on the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (the 'intention-to-treat effect'; ITT).

In order to assess the risk of bias for each study, we will assess the following domains.

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome

- Bias in selection of the reported result

We will use the Rob 2 Excel tool to manage the assessment of bias, available at www.riskofbias.info (current version). We will use the RoB 2 tool to assess the primary outcome (overall survival) and secondary outcomes (objective response, safety/adverse effects, progression-free survival, health-related quality of life at 12 months, duration of response). Each domain of the RoB 2 tool for each trial will be rated as 'low risk of bias', 'some concerns', or 'high risk of bias' through algorithms and criteria outlined in the *Cochrane Handbook*, and we will provide a quote from the study report or a justification for our judgement in the risk of bias tables. We will present a risk of bias graph and summary. Based on the assessment of each domain, we will use an algorithm to reach an overall risk of bias judgement for each study and predict the direction of bias. For details, see Table 8.2.b and Section 8.2.4 of the *Cochrane Handbook* (Higgins 2024).

Measures of treatment effect

We will analyse the primary outcome based on ITT analysis. Based on Section 6.8 of the *Cochrane Handbook*, we will use survival analysis to synthesise time-to-event outcomes and express the treatment effect as hazard ratios (HRs) with 95% confidence intervals (CIs) for time-to-event variables (Higgins 2024). For dichotomous variables, we will use risk ratios (RRs) with 95% CIs as summary statistics and use odds ratios (ORs) with 95% CIs for sensitivity analysis. HR-QoL is a continuous outcome. If included studies use a similar questionnaire to measure this outcome, we will use mean differences (MDs) between treatment arms; we will use standardised mean differences (SMDs) for studies using different questionnaires to measure this outcome.

Unit of analysis issues

For studies that compare more than one treatment arm with a control arm in the same randomised controlled trial, we will divide the number of participants in the control group by the number of treatment arms.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain and address missing outcome data (e.g. when a study is identified as abstract only), as indicated in Chapter 10 of the *Cochrane Handbook* (Higgins 2024). To evaluate the potential effect that such trials may introduce, we will conduct sensitivity analysis by excluding studies with missing data. We will follow the principles of ITT, as guided by MECIR standard C64 (Higgins 2023).

Assessment of heterogeneity

In order to assess clinical and methodological heterogeneity, we will inspect the characteristics of the included studies, including the types of studies, participants, and interventions. We will assess whether observed differences in the results are compatible with chance alone using the Chi^2 test and will quantify inconsistency across studies using the I^2 statistic. Substantial statistical heterogeneity will be considered if the Chi^2 test P value is less than 0.10 or if the I^2 statistic is over 50% (Higgins 2024). If we detect moderate or higher heterogeneity (I^2 = 50% to 100%), we will perform a thorough exploration of the possible sources of heterogeneity via subgroup and sensitivity analyses (as stated below). Given the limitations of the test statistics, we will use the Chi^2 test P value and the I^2 value as a guide only, and interpret the results with caution. We will use random-effects analysis by default.

Assessment of reporting biases

Pooling more than 10 trials will enable the creation and examination of a funnel plot (intervention effect estimate versus standard error of intervention effect estimate) to explore possible publication biases (Peters 2008). If a funnel plot is asymmetric, we will investigate the diversity of clinical factors as a suspected explanation. With sufficient studies (>10), we will use the contour-enhanced funnel plot to distinguish asymmetry due to publication bias from other factors. If there are insufficient trials to generate a funnel plot assessing reporting bias, we will compare the findings of eligible studies with their published protocols and reports, when available.

Data synthesis

If a number of sufficiently similar studies are selected, we will perform a meta-analysis. The primary analysis will include all eligible studies, and we will conduct sensitivity analysis to include only studies with overall low risk of bias ratings. We will perform the meta-analysis using RevMan 2024 and use the random-effects model by default. For time-to-event outcomes, we will use generic inverse-variance methods (random-effects model), calculating the log hazard ratios and standard errors from the results of Cox proportional-hazards regression models. For dichotomous outcomes, we will use DerSimonian and Laird inverse variance method (random-effects model).

Subgroup analysis and investigation of heterogeneity

If we can pool a sufficient number of trials (at least three for each subgroup), we will perform the following exploratory subgroup analyses.

- Participants previously treated with systemic therapies or previously untreated. Participants with different expression levels of PD-L1, at cutoffs of 1%, 5% and 10%.
- Disease status at immunotherapy initiation, including unresectable advanced, metastatic, locoregionally recurrent and distant recurrent.
- Treatments of PD-1/L1 combined with chemotherapy and PD-1/L1 alone.
- Participants with different pathological subtypes, i.e. squamous carcinomas and adenocarcinoma.
- Different immune checkpoint inhibitors, including PD-1, PD-L1, CTLA-4 and others.

Moreover, we only plan to undertake subgroup analyses for primary outcomes. To ensure comparability between the results of the main analyses and subgroup analyses, we will apply the same model (random-effects).

We will examine differences between subgroups via visual inspection of confidence intervals (CIs), i.e. non-overlapping CIs indicate a statistically significant difference in treatment effects between subgroups. To investigate differences between two or more subgroups, we will use a significance test (Borenstein 2013).

Sensitivity analysis

To assess the robustness of our conclusions, we will perform sensitivity analyses. This is achieved by repeating the analyses to explore the influence of the following factors on effect size.

- Exclusion of unpublished studies.
- Exclusion of studies at high risk of bias. A study is considered to have low risk of bias only when all domains are at low risk of bias, as assessed using the RoB 2 tool (Sterne 2019).
- The main analysis will use a random-effects model. In the case of divergence between the random-effects model and the fixed-effect model, we will also report the fixed-effect model.

Furthermore, if RCTs assess PFS or response rate in an unblinded manner, we will conduct a sensitivity analysis for PFS or response rate to evaluate the potential effect that unblinded trials may introduce.

Summary of findings and assessment of the certainty of the evidence

We will focus on the following comparisons.

- PD-1/PD-L1/PD-L2 inhibitors versus traditional therapies (e.g. chemotherapy, surgery)
- The combination of CTLA4 and PD-1/PD-L1 inhibitors versus traditional therapies (e.g. chemotherapy, surgery)
- Novel immunotherapies including TIGIT versus traditional therapies (e.g. chemotherapy, surgery)

We will create a summary of findings table that includes the following outcomes.

- Overall survival
- Objective response
- Safety/adverse effects
- Progression-free survival
- Health-related quality of life: we will report EQ-5D or SF-36 at the 12-month time point as the default.
- Duration of response

Two review authors (NC and YC) will independently assess the certainty of the evidence. We will resolve any disagreement by discussion, or by involving a third review author (CS). Based on the studies that contribute data to the respective meta-analyses, we will assess the certainty of the body of evidence using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias). The certainty of evidence will be classified as high, moderate, low, or very low. We will use methods and recommendations described in Chapter 14 of the *Cochrane Handbook* (Higgins 2024), and use GRADEpro GDT software (GRADEpro GDT). We will justify all decisions to downgrade or upgrade the certainty of evidence, presenting the rationale and comments in footnotes. We will downgrade surrogate outcomes for indirectness during the GRADE assessment, according to the GRADE guideline (Guyatt 2011). Moreover, we will also use the overall risk of bias evaluations to inform the GRADE assessment.

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Editorial and peer-reviewer contributions

Cochrane Gut supported the authors in the development of this protocol.

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Toby Lasserson, Cochrane Acting Editor-in-Chief
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Anne-Marie Stephani and Jo Duffield, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks and supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service
- Copy Editor (copy-editing and production): Andrea Takeda, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Anthony C Uwandu-Uzoma, University of Bradford (clinical/content review); Shun Yamamoto, National Cancer Center Hospital, Japan (clinical/content review); Ionut Negoi, Emergency Hospital of Bucharest, Romania; Andrew Bäck, Cochrane (methods review); Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (Methods review); Ina Monsef (search review).

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APPENDICES

Appendix 1. Glossary of terms

ACT: adoptive cell therapy

CTA: cancer-testis antigen

CTLA-4: cytotoxic T-lymphocyte-associated antigen 4

DC: dendritic cells

DSS: disease-specific survival

ESD: endoscopic submucosal dissection

EMR: endoscopic mucosal resection

PD-1: programmed death 1

PFS: progression-free survival

RFS: recurrence-free survival

Appendix 2. MEDLINE search strategy (via Ovid)

1. exp Esophageal Neoplasms/
2. ((esophag* or oesophag*) adj3 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or adenocarcinoma*)).tw,kw.
3. 1 or 2
4. exp immunomodulation/
5. (immuonmodulation* or immunomodulatory or Immune modulation* or Immunotherap* or immunization* or immunisation* or immunologic* or immunosuppression* or immunoradiotherap* or radioimmunotherap* or Immunosuppressive or immunity).tw,kw.
6. ((checkpoint* or PD-1 or PD1 or PD-L1 or PDL1 or Cytotoxic T-lymphocyte-associated protein or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIGIT) adj5 (inhibitor* or block* or antagon* or anti-bod* or antibod*)).tw,kw.
7. (anti adj3 (PD-1 or PD1 or PD-L1 or PDL1 or Cytotoxic T-lymphocyte-associated protein or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3 or TIGIT)).tw,kw.
8. exp Ipilimumab/
9. (Ipilimumab or Yervoy or strentarga or bms 734016 or bms734016 or "mdx 010" or mdx010 or mdx 101 or mdx101 or mdx ctla 4).tw,kw.
10. (Tremelimumab or ticilimumab or cp 675 206 or cp 675206 or cp675 206 or cp675206).tw,kw.
11. (Nivolumab or Opdivo or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538).tw,kw.
12. (Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475).tw,kw.
13. (Pidilizumab or "ct 011" or ct011).tw,kw.
14. (Atezolizumab or Tecentriq or tecntriq or MPDL3280A or mpdl 3280a or rg 7446 or rg7446).tw,kw.
15. (Durvalumab or Imfinzi or MEDI 4736 or medi4736 or medi 4736).tw,kw.
16. (Avelumab or Bavencio or "msb 0010682" or msb 0010718c or msb 10682 or msb 10718c or msb0010682 or msb0010718c or msb10682 or msb10718c).tw,kw.
17. (BMS-936559 or mdx1105 or mdx1105).tw,kw.
18. (Indoximod or D-1MT or D1MT).tw,kw.
19. ((IDO or Indoleamine) adj5 (inhibitor* or block* or antagon* or antibod*)).tw,kw.
20. (Camrelizumab or SHR-1210).tw,kw.
21. (SHR-8068).tw,kw
22. (Tiragolumab or CITYSCAPE).tw,kw.
23. (Candonilimab or AK104).tw,kw.
24. or/4-25
25. 3 and 26
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. random*.mp.
29. placebo.ab.
30. drug therapy.fs.
31. trial.ab.
32. groups.ab.
33. or/28-34
34. exp animals/ not humans/
35. 33 not 34
36. 3 and 35

Note: Lines 28-37, RCT filter, “Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format”, Cochrane handbook version 5.1. We made the following minor revisions: we used “random*” instead of “randomized.ab” or “randomly.ab.” to capture word variations such as “randomised, randomization, random”.

Appendix 3. Cochrane Central Register of Controlled Trials (CENTRAL) (via Ovid)

1. exp Esophageal Neoplasms/
2. ((esophag* or oesophag*) adj3 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or adenocarcinoma*)).tw,kw.
3. 1 or 2
4. exp immunomodulation/

5. (immunmodulation* or immunomodulatory or Immune modulation* or Immunotherap* or immunization* or immunisation* or immunologic* or immunosuppression* or immunoradiotherap* or radioimmunotherap* or Immunosuppressive or immunity or immuno modulation* or immuno modulatory or Immune modulation* or Immun?therap* or immunization* or immunisation* or immunologic* or immuno suppression* or immuno radiotherap* or radio immunotherap* or Immuno suppressive or immunity).tw,kw,nm.
6. ((checkpoint* or PD-1 or PD1 or PD-L1 or PDL1 or Cytotoxic T-lymphocyte-associated protein or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3 or TIGIT) adj5 (inhibitor* or block* or antagon* or anti-bod* or antibod*)).tw,kw,nm.
7. (anti adj3 (PD-1 or PD1 or PD-L1 or PDL1 or Cytotoxic T-lymphocyte-associated protein or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3 or TIGIT)).tw,kw,nm.
8. exp Ipilimumab/
9. (Ipilimumab or Yervoy or strentarga or bms 734016 or bms734016 or "mdx 010" or mdx010 or mdx 101 or mdx101 or mdx ctla 4).tw,kw,nm.
10. (Tremelimumab or ticilimumab or cp 675 206 or cp 675206 or cp675 206 or cp675206).tw,kw,nm.
11. (Nivolumab or Opdivo or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538).tw,kw,nm.
12. (Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475).tw,kw,nm.
13. (Pidilizumab or "ct 011" or ct011).tw,kw,nm.
14. (Sintilimab or Tyvyt).tw,kw,nm.
15. (Atezolizumab or Tecentriq or tecntriq or MPDL3280A or mpdl 3280a or rg 7446 or rg7446).tw,kw.
16. (Durvalumab or Imfinzi or MEDI4736 or medi 4736 or medi4736).tw,kw.
17. (Avelumab or Bavencio or "msb 0010682" or msb 0010718c or msb 10682 or msb 10718c or msb0010682 or msb0010718c or msb10682 or msb10718c).tw,kw.
18. (BMS-936559 or mdx1105 or mdx1105).tw,kw.
19. (Indoximod or D-1MT or D1MT).tw,kw.
20. ((IDO or Indoleamine) adj5 (inhibitor* or block* or antagon* or antibod*)).tw,kw.
21. (Camrelizumab or SHR-1210).tw,kw.
22. (SHR-8068).tw,kw
23. (Tiragolumab or CITYSCAPE).tw,kw.
24. (Candonilimab or AK104).tw,kw.
25. or/4-34
26. 3 and 25

Appendix 4. Embase search strategy (via Ovid)

1. exp esophagus tumor/
2. ((esophag* or oesophag*) adj3 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or adenocarcinoma*)).tw,kw.
3. 1 or 2
4. exp immunomodulation/
5. (immuonmodulation* or immunomodulatory or Immune modulation* or Immunotherap* or immunization* or immunisation* or immunologic* or immunosuppression* or immunoradiotherap* or radioimmunotherap* or Immunosuppressive or immunity).tw,kw.
6. ((checkpoint* or PD-1 or PD1 or PD-L1 or PDL1 or Cytotoxic T-lymphocyte-associated protein or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3 or TIGIT) adj5 (inhibitor* or block* or antagon* or antibod*)).tw,kw.
7. (anti adj3 (PD-1 or PD1 or PD-L1 or PDL1 or Cytotoxic T-lymphocyte-associated protein or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3 or TIGIT)).tw,kw.
8. exp ipilimumab/
9. exp ticilimumab/
10. exp nivolumab/
11. exp pembrolizumab/
12. exp pidilizumab/
13. exp atezolizumab/
14. exp durvalumab/
15. exp avelumab/
16. exp bms 936559/
17. (Ipilimumab or Yervoy or strentarga or bms 734016 or bms734016 or "mdx 010" or mdx010 or mdx 101 or mdx101 or mdx ctla 4).tw,kw.
18. (Tremelimumab or ticilimumab or cp 675 206 or cp 675206 or cp675 206 or cp675206).tw,kw.
19. (Nivolumab or Opdivo or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538).tw,kw.

20. (Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475).tw,kw.
21. (Pidilizumab or "ct 011" or ct011).tw,kw.
22. (Atezolizumab or Tecentriq or tecntriq or MPDL3280A or mpdl 3280a or rg 7446 or rg7446).tw,kw.
23. (Durvalumab or Imfinzi or MEDI4736 or medi4736).tw,kw.
24. (Avelumab or Bavencio or "msb 0010682" or msb 0010718c or msb 10682 or msb 10718c or msb0010682 or msb0010718c or msb10682 or msb10718c).tw,kw.
25. (BMS-936559 or mdx1105 or mdx1105).tw,kw.
26. Indoximod.tw,kw.
27. ((IDO or Indoleamine) adj5 (inhibitor* or block* or antagon* or antibod*)).tw,kw.
28. (Camrelizumab or SHR-1210).tw,kw.
29. (SHR-8068).tw,kw
30. (Tiragolumab or CITYSCAPE).tw,kw.
31. (Candonilimab or AK104).tw,kw.
32. or/4-33
33. 3 and 34
34. random:.tw.
35. placebo:.mp.
36. double-blind:.tw.
37. or/36-38
38. exp animal/ not exp human/
39. 37 not 38
40. 32 and 39

Note: Lines 36-40, RCT filter, Hedge Best balance of sensitivity and specificity filter for identifying randomised trials in Embase.

https://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx

Appendix 5. WHO ICTRP search strategy

Basic searches:

1. esophageal cancer AND immune checkpoint inhibitor*

2. esophageal cancer AND immunotherap*

3. esophageal cancer AND Cytotoxic T-lymphocyte-associated protein 4*

Advanced searches:

1. Condition: esopahgeal cancer*

Intervention: Immunotherap* OR immune therap* OR vaccin* OR immune checkpoint inhibitor*

Recruitment status: All

2. Condition: esopahgeal cancer*

Intervention: PD-1 inhibitor *OR PD-L1 inhibitor* OR Programmed Cell Death Protein 1 inhibitor *OR Programmed Death-Ligand 1 inhibitor* OR nivolumab OR pembrolizumab OR Opdivo OR bms 936558 OR bms936558 OR mdx1106 OR mdx1106 OR ono 4538 OR ono4538 OR Keytruda OR lambrolizumab OR mk 3475 OR mk3475 OR Camrelizumab OR SHR-1210 OR SHR-8068 OR Tiragolumab OR CITYSCAPE OR Candonilimab OR AK104

Recruitment status: All

3. Condition: esopahgeal cancer*

Intervention: Cytotoxic T-lymphocyte-associated protein OR CTLA-4 OR CTLA4 Ipilimumab OR Yervoy OR strentarga OR bms 734016 OR bms734016 OR "mdx 010" OR mdx010 OR mdx 101 OR mdx101 OR mdx ctla 4 OR Tremelimumab OR ticilimumab OR cp 675 206 OR cp 675206 OR cp675 206 OR cp675206 OR Camrelizumab OR SHR-1210 OR SHR-8068 OR Tiragolumab OR CITYSCAPE OR Candonilimab OR AK104

Recruitment status: All

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: CS, XC

Designing the protocol: CS, XC

Coordinating the protocol: CS, HS, YS

Designing search strategies: NC, YC, YS

Writing the protocol: NC, YC, CS, HD

Providing general advice on the protocol: HS, XC

Securing funding for the protocol: CS, XC, HS

Performing previous work that was the foundation of the current study: HS, CS

Dr Xingdong Chen and Dr Chen Suo contributed equally to the correspondence work, Ning Cai and YiFung Chau contributed equally to the protocol, and Yurou Xu will contribute to data management and analysis in the full review. All authors agree to be acknowledged.

DECLARATIONS OF INTEREST

NC: none

YC: none

YX: none

YS: none

HS: none

CS: none

XC: none

HD: none

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