INPLASY PROTOCOL

To cite: Yu et al. Neoadjuvant immunotherapy for resectable esophageal cancer: A protocol of meta-analysis. Inplasy protocol 202120026. doi: 10.37766/inplasy2021.2.0026

Received: 07 February 2021

Published: 07 February 2021

Corresponding author:
Kan Xu

langyazhenlou@163.com

Author Affiliation:
Affiliated Hangzhou Chest Hospital, Zhejiang University School of Medicine

Support: **20201203B179.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Neoadjuvant immunotherapy for resectable esophageal cancer: A protocol of meta-analysis

Yu, G[1]; Yu, W[2]; Xu, X[3]; Ye, B[4]; Xu, K[5].

Review question / Objective: **Esophageal cancer is a highly malignant cancer with a very poor prognosis. For resectable esophageal cancer, neoadjuvant treatment could improve the prognosis of esophageal cancer. However, current clinical neoadjuvant treatment options for esophageal cancer are still limited. The application of immunotherapy is a potentially beneficial new neoadjuvant treatment option for esophageal cancer.**
Information sources: **We will search Wanfang Database, SinoMed, China National Knowledge Infrastructure (CNKI), Embase, Web of Science, Pubmed, and Cochrane Library for relevant articles that may be eligible for inclusion published before July, 2021. We will also identify other articles from the review's references that meet the criteria. we will also search the unpublished clinical trials of neoadjuvant immunotherapy in esophageal cancer in Chinese Society of Clinical Oncology (CSCO), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) up to July, 2021.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 February 2021 and was last updated on 07 February 2021 (registration number INPLASY202120026).

INTRODUCTION

Review question / Objective: **The objective of this meta-analysis is to evaluate the efficacy and safety of immunotherapy for the neoadjuvant treatment of esophageal cancer.**

Rationale: **Esophageal cancer is a highly malignant cancer with a very poor prognosis. For resectable esophageal**

cancer, neoadjuvant treatment could improve the prognosis of esophageal cancer. However, current clinical neoadjuvant treatment options for esophageal cancer are still limited. The application of immunotherapy is a potentially beneficial new neoadjuvant treatment option for esophageal cancer.

Condition being studied: Esophageal cancer is one of the most common malignant tumors, and has the seventh highest morbidity rate and the sixth highest mortality rate among all malignancies in the world. Esophageal cancer is a tumor with high degree of malignancy and is prone to invasion and metastasis. Surgery is still the radical treatment for esophageal cancer. However, for resectable locally advanced esophageal cancer, a direct surgery is sometimes difficult. In such cases, preoperative neoadjuvant therapy is usually used. Several studies have demonstrated that neoadjuvant chemoradiotherapy improves the survival rate of patients with esophageal cancer. However, the treatment-related adverse events (TRAEs) of neoadjuvant chemoradiotherapy are severe and poorly tolerated by patients. For this group of patients, there is an urgent need for a new and more effective and safer neoadjuvant therapy. In recent years, immunotherapy has opened up a whole new field for the treatment of esophageal cancer. However, the role of immunotherapy in the neoadjuvant treatment of esophageal cancer is still lacking in the evidence of evidence-based medicine. For this purpose, we will conduct a meta-analysis to evaluate the efficacy and safety of neoadjuvant immunotherapy in the treatment of resectable esophageal cancer.

METHODS

Search strategy: #1 “Immunotherapy "[Mesh] OR Immunotherapies OR #2 "Programmed Cell Death 1 Receptor"[Mesh] OR “Antigens, CD279” OR “CD279 Antigens” OR “CD279 Antigen” OR “PD1 Receptor” OR “Receptor, PD1” OR “Programmed Cell Death Protein 1” OR “Programmed Cell Death 1 Protein” #3 "Immune Checkpoint Inhibitors"[Mesh] OR “Checkpoint Inhibitors, Immune” OR “Immune Checkpoint Inhibitor” OR “Checkpoint Inhibitor, Immune” OR “Immune Checkpoint Blockers” OR “Checkpoint Blockers, Immune” OR “Immune Checkpoint Blockade” OR “Checkpoint Blockade, Immune” OR “Immune Checkpoint Inhibition” OR “Checkpoint Inhibition, Immune” OR “PD-L1 Inhibitors” OR “PD L1 Inhibitors” OR “PD-L1 Inhibitor” OR “PD L1 Inhibitor” OR “Programmed Death-Ligand 1 Inhibitors” OR “Programmed Death Ligand 1 Inhibitors” OR “PD-1 Inhibitors” OR “PD 1 Inhibitors” OR “PD-1 Inhibitor” OR “Inhibitor, PD-1” OR “PD 1 Inhibitor” OR “Programmed Cell Death Protein 1 Inhibitor” OR “Programmed Cell Death Protein 1 Inhibitors” OR “PD-1-PD-L1 Blockade” OR “Blockade, PD-1-PD-L1” OR “PD 1 PD L1 Blockade” #4 #1 OR #2 OR #3 #5 "Esophageal Neoplasms"[Mesh] OR “Esophageal Neoplasm” OR “Neoplasm, Esophageal” OR “Esophagus Neoplasm” OR “Esophagus Neoplasms” OR “Neoplasm, Esophagus” OR “Neoplasms, Esophagus” OR “Neoplasms, Esophageal” OR “Cancer of Esophagus” OR “Cancer of the Esophagus” OR “Esophagus Cancer” OR “Cancer, Esophagus” OR “Cancers, Esophagus” OR “Esophagus Cancers” OR “Esophageal Cancer” OR “Cancer, Esophageal” OR “Cancers, Esophageal” OR “Esophageal Cancers” #6 "Neoadjuvant Therapy"[Mesh] OR “Neoadjuvant Therapies” OR “Therapy, Neoadjuvant” OR “Neoadjuvant Treatment” OR “Neoadjuvant Treatments” OR “Treatment, Neoadjuvant” OR “Neoadjuvant Systemic Therapy” OR “Neoadjuvant Systemic Therapies” OR “Systemic Therapy, Neoadjuvant” OR “Therapy, Neoadjuvant Systemic” OR “Neoadjuvant Systemic Treatment” OR “Neoadjuvant Systemic Treatments” OR “Systemic Treatment, Neoadjuvant” OR “Treatment, Neoadjuvant Systemic” OR “Neoadjuvant Chemotherapy” OR “Chemotherapy, Neoadjuvant” OR “Neoadjuvant Chemotherapies” OR “Neoadjuvant Chemotherapy Treatment” OR “Neoadjuvant Chemotherapy Treatments” OR “Treatment, Neoadjuvant Chemotherapy” OR “pre-surgical” OR

"presurgical" OR "pre-operative" OR "preoperative" OR neoadjuvant #7 #4 AND #5 AND #6.

Participant or population: Participants with resectable esophageal cancer confirmed by histopathology or cytopathology and immune checkpoint inhibitors (ICIs) were used as neoadjuvant therapy. There will be no restrictions on age, gender, and ethnicity.

Intervention: Immunotherapy (including all currently known ICIs) alone or immunotherapy plus other therapy as neoadjuvant treatment for resectable esophageal cancer.

Comparator: Other treatments as neoadjuvant therapy (not mandatory).

Study designs to be included: Clinical randomized controlled trials (RCTs), quasi-RCTs, and prospective cohort studies.

Eligibility criteria: Types of studies Published or unpublished clinical randomized controlled trials (RCTs), quasi-RCTs, and prospective cohort studies, which must have been completed and evaluated efficacy and safety of neoadjuvant immunotherapy in resectable esophageal cancer. Review, repeated publications, articles published not using Chinese or English, studies with less than 10 patients were included, and case reports will be excluded. Types of participants Participants with resectable esophageal cancer confirmed by histopathology or cytopathology and immune checkpoint inhibitors (ICIs) were used as neoadjuvant therapy. There will be no restrictions on age, gender, and ethnicity. Types of interventions Immunotherapy (including all currently known ICIs) alone or immunotherapy plus other therapy as neoadjuvant treatment for resectable esophageal cancer. Outcomes Major pathological response (MPR), pathological complete response (pCR), the incidence of TRAE, surgical resection rate, the incidence of surgical complications, and surgical delay rate will be the key clinical outcomes.

Information sources: We will search Wanfang Database, SinoMed, China National Knowledge Infrastructure (CNKI), Embase, Web of Science, Pubmed, and Cochrane Library for relevant articles that may be eligible for inclusion published before July, 2021. We will also identify other articles from the review's references that meet the criteria. we will also search the unpublished clinical trials of neoadjuvant immunotherapy in esophageal cancer in Chinese Society of Clinical Oncology (CSCO), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) up to July, 2021.

Main outcome(s): Major pathological response (MPR), pathological complete response (pCR), the incidence of TRAE, surgical resection rate, the incidence of surgical complications, and surgical delay rate will be the key clinical outcomes.

Data management: Study selection Endnote X9.2 software will be used to manage the articles obtained by searching the relevant databases. In the first step, two reviewers (Guocan Yu and Wenfeng Yu) will independently filter duplicate articles through Endnote and exclude them, then exclude articles that do not meet the inclusion criteria by investigating the title and abstract, and finally screen the full text of remaining articles to finalize the eligible articles. If there are disagreements between the two reviewers, a discussion with the third reviewer (Kan Xu) will be conducted as a way to resolve the disagreements. Data extraction The same two reviewers (Guocan Yu and Wenfeng Yu) as in the study selection phase will independently extract the necessary data from the articles included. Cross-check will be done to find controversial data and resolve by discussing with a third author (Kan Xu). The following data from the included articles will be extracted: first author name, year of publication, countries, study type, article type, clinical trial, registration number, study phase, intervention model, masking, randomization method, main inclusion criteria, type of pathology, the ICI drug, ICIs

dose, expected inclusion, size of sample, male, median age, MPR, pCR, incidence of TRAE, surgical resection rate, incidence of surgical complication, and surgical delay rate.

Quality assessment / Risk of bias analysis: Two authors (Guocan Yu and Wenfeng Yu) will independently assess the risk of bias of each article included. The Cochrane Handbook for Systematic Reviews of Interventions will be used for the evaluation of the risk of bias. We will assess the risk of bias according to the following ranges: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Each domain will be assessed as high, low or uncertain risk of bias. The risk of bias graph will be reported to demonstrate the results and details of assessment. The risks of nonrandomized controlled trials will be assessed using EPOC guidelines.

Strategy of data synthesis: We will use Review Manager software, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for statistical analysis of the meta-analysis. If all of the included studies were RCTs, we will calculate pooled odds ratios (ORs) for MPR, pCR, incidence of TRAE, surgical resection rate, incidence of surgical complication, and surgical delay rate with comparative binary data in RevMan 5.3. If most of the included studies were single-arm studies with main outcome indicators (such as MPR, pCR), we performed meta-analysis with noncomparative binary data in RevMan 5.3. The vaule of p and standard error (SE (P)) were calculated with the following formula: $p = \ln(odds) = \ln(X/(n-x))$. $SE(P) = SE(\ln(odds)) = \sqrt{(1/X + 1/(n-x))}$. OR with 95 % confidence interval (CI) were the effect measures. The statistical heterogeneity between studies were evaluated by the Q-statistic (22). The P-value of the Q-statistic < 0.1 or an I2 > 50% will be considered as statistically significant heterogeneity between studies (23). Data will be analyzed using a fixed-effects model if the heterogeneity is insignificant and a random-effects model if the heterogeneity is significant. A $P < 0.05$ was considered statistically different.

Subgroup analysis: When significant heterogeneity exists and sufficient data are available, we will conduct subgroup analysis to further explore the sources of heterogeneity. We will conduct subgroup analysis of each parameter (such as study type, article type, intervention model, randomization method, masking, type of pathology, the ICI drug, sex, age), when the extracted data are sufficient.

Sensitivity analysis: Sensitivity analysis will be conducted to evaluate the reliability and robustness of the aggregation results via eliminating studies with high bias risk.

Language: No restriction.

Country(ies) involved: China.

Other relevant information: Publication bias We will use funnel plots and Egger test to assess publication bias when more than 10 eligible articles are included. If publication bias is suspected in a study, we will consult the corresponding author for more information. If publication bias does exist, we will use the fill and trim method to further analyze publication bias in the studies. Evidence evaluation We will evaluate all the strength of the body of evidence according to The Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline. The quality of evidence will be classified into 4 levels: high, moderate, low, and very low.

Keywords: neoadjuvant treatment, immunotherapy, esophageal cancer, efficacy, safety, meta-analysis.

Contributions of each author:

Author 1 - Guocan Yu - The author drafted the manuscript, searched databases, selected literatures, managed data and assessed quality.
Email: dabaitwo@163.com

Author 2 - Wenfeng Yu - The author searched databases, selected literatures, managed data and evaluated quality.
Email: ywf1078@163.com
Author 3 - Xudong Xu - The author drafted and revised the manuscript.
Email: xuxudong234@163.com
Author 4 - Bo Ye - The author provided statistical expertise and read feedback and approved the final manuscript.
Email: yeboboye@126.com
Author 5 - Kan Xu - The author provided statistical expertise and read feedback and approved the final manuscript.
Email: xukanmed@163.com