INPLASY PROTOCOL

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None declared.

The difference of prognosis between gastric carcinoma with neuroendocrine components and pure gastric neuroendocrine carcinoma compared with gastric carcinoma: a meta-analysis

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Review question / Objective: **The aim of this study is to analyze the clinicopathologic characteristics and prognosis of gastric carcinoma with neuroendocrine components and pure gastric neuroendocrine carcinoma compared with gastric carcinoma.**
Condition being studied: **According some studies reported, the difference of prognosis between GCNED,MANEC,NEC and GC is still controversial, mostly gastric carcinoma was better prognosis, some suggested worse. Therefore, we need to do a meta analysis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 September 2021 and was last updated on 06 September 2021 (registration number INPLASY202190016).

INTRODUCTION

Review question / Objective: **The aim of this study is to analyze the clinicopathologic characteristics and prognosis of gastric carcinoma with neuroendocrine components and pure gastric neuroendocrine carcinoma compared with gastric carcinoma.**

Rationale: **Gastric cancer is one of the common malignant tumors. Studies have**

found that neuroendocrine differentiation (NED) occurs along with the occurrence and development of gastric cancer. However, there is no clear standard for the definition and diagnosis of gastric cancer with neuroendocrine differentiation (GCNED). WHO 2010 proposed that GCNED was a kind of gastric tumors, and neuroendocrine cells were scattered in gastric cancer in the form of single cells or cell clusters. The diagnosis was mainly depends on both histological features of neuroendocrine neoplasms and immunohistochemical (IHC) positivity for neuroendocrine markers, such as synaptophysin (SYN), chromogranin A (CGA), neuron cell adhesion molecule (NCAM or CD56), neuron-specific enolase and Leu7 (CD57). While mixed adenoneuroendocrine carcinoma (MANEC) is clearly defined as an epithelial neoplasms with the morphological and immunophenotypic characteristics of both classic adenocarcinoma and neuroendocrine neoplasms. The two components were not mixed, but separated cancer cell groups, and each component accounts for at least 30% or more respectively. Neuroendocrine carcinoma (NECs) are poorly differentiated, high-grade malignant neoplasms that encompass small cell and large cell types. Although the part of less than 30% was classified in GCNED, but the 30% threshold is partly arbitrary because there is not enough data to prove its prognostic significance .In fact, the difference of prognosis between GCNED,MANEC,NEC and GC is still controversial. Therefore, it is necessary to study the difference of prognosis between them in order to identify the key prognostic factors , to provide better clinical treatment methods. In this study, a systematic review and meta-analysis was performed.

Condition being studied: According some studies reported, the difference of prognosis between GCNED,MANEC,NEC and GC is still controversial, mostly gastric carcinoma was better prognosis, some suggested worse. Therefore, we need to do a meta analysis.

METHODS

Search strategy: We selected relevant studies published until July 5, 2021, by searching PubMed (MEDLINE), Embase databases, Web of Science, Cochrane library. We applied no language restrictions.

Participant or population: Patients who underwent gastric surgery.

Intervention: Patients who diagnosed GC with GCNED or MANEC or NEC.

Comparator: Patients who diagnosed GC.

Study designs to be included: No study restrictions.

Eligibility criteria: Newcastle-Ottawa Quality Assessment Scale (NOS) was used as a methodological quality assessment. Studies with a score equal to or higher than six were considered as high-quality studies.

Information sources: All intended information sources will come from electronic databases.

Main outcome(s): Overall survival data between GC with GCNED or MANEC or NEC and GC.

Additional outcome(s): Clinicopathologic characteristics between GC with GCNED or MANEC or NEC and GC.

Data management: Two independent investigators (Yan Meng, JunRen MA) reviewed study titles and abstracts, and studies that satisfied the inclusion criteria were retrieved for full text assessment. Trials selected for detailed analysis and data extraction were analyzed by two investigators (Yan Meng, JunRen MA), disagreements were resolved by a third investigator (Xin Zhou). We extracted the following data from each selected study: author name, publication year, country of patients, date of accrual, total number of participants, survival data, age (mean±SD), gender, tumor location, T stage, lymph

node metastatic states, TNM stage and OS (HR, 95%CIs).

Quality assessment / Risk of bias analysis: Two reviewers will be involved in quality assessment independently. Any disagreements between reviewers will be resolved by a third reviewers. The publication bias was tested by Begg's funnel plot and Egger's test of the intercept.

Strategy of data synthesis: This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. The estimated odds ratio (OR) or weighted mean difference (WMD) was used to summarize the clinicopathological characteristics between GC with NED, NEC and GC. The hazard ratio (HR) was pooled to analyze the OS results as demonstrated by Parmar et al. Heterogeneity was assessed using the χ^2 test and quantified using the I2 statistic, with values greater than 50% regarded as being indicative of moderate-to-high heterogeneity. We assessed funnel plot asymmetry using Begg tests, and defined significant publication bias as a p value$<$0.05. We used Revman 5.3, SPSS version 24.0 and Stata 16.0 for statistical analyses. Data synthesis will include survival and other clinicopathologic characteristics between GC with GCNED or MANEC or NEC and GC.

Subgroup analysis: If necessary, we will analyze between GC with GCNED and MANEC or NEC.

Sensitivity analysis: Sensitivity analysis was conducted mainly by changing the inclusion criteria.

Language: English.

Country(ies) involved: China.

Keywords: gastric cancer, prognosis, neuroendocrine tumor.

Contributions of each author:

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