INPLASY PROTOCOL

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Corresponding author:
Na Gao

Gaonaedu@163.com

Author Affiliation:
Liaoning Cancer Hospital

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None declared.

Long-term outcomes and clinical safety of expanded indication early gastric cancer treated with endoscopic submucosal dissection versus surgical resection: a meta-analysis

Xu, X[1]; Zheng, G[2]; Zheng, Z[3]; Gao, N[4].

Review question / Objective: **Endoscopic submucosal dissection (ESD) remained an investigational issue for expanded indication early gastric cancer (EGC)due to the risk of lymph node metastasis. We aim to evaluate the clinical outcomes and safety of ESD versus surgery resection (SR) for EGC within expanded indication.**

Eligibility criteria: **We included studies that involved a comparison of endoscopic submucosal resection (ESD) vs surgery resection (SR) for EGC within expanded indication: (1)mucosal cancer without ulceration, irrespective of tumor size (2) differentiated submucosal cancer with ulceration and diameter ≤ 30 mm; (3) differentiated submucosal penetrative cancer in diameter ≤ 500 μm (SM1); (4) undifferentiated type submucosal cancer without ulceration and diameter ≤ 20 mm and explicitly reported data on at least one of the outcomes: enbloc resection, complete resection, metachronous cancer, synchronous cancer, procedure-related adverse event, short- and long-term prognosis. The types of include studies were clinical randomized or non-randomized control trials or observational studies of adequate quality. Duplicate publications, secondary literature, conference papers, abstracts, letters, editorials and expert opinions, case report and studies lacking clinical endpoints data were excluded.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 May 2021 and was last updated on 02 May 2021 (registration number INPLASY202150011).

INTRODUCTION

Review question / Objective: **Endoscopic submucosal dissection (ESD) remained an investigational issue for expanded indication early gastric cancer (EGC)due to the risk of lymph node metastasis. We aim to evaluate the clinical outcomes and**

safety of ESD versus surgery resection (SR) for EGC within expanded indication.

Condition being studied: Endoscopic resection (ER) has been accepted as the standard treatment for patients with EGC with a negligible risk of metastatic lymph node in eastern countries. According to Japanese Gastric Cancer treatment Guidelines 2010, the absolute indication for EGC was strictly limited to mucosa lesion with differentiated histopathologic type and without ulceration or lymphatic-vascular invasion and its size was smaller than 2.0 cm. Thanking to the development of endoscopic devices and technique, ESD can achieve the enbloc resection and complete resection, which would reduce postoperative residual lesion and local region recurrence. The expanded indication included: (1)mucosal cancer without ulceration, irrespective of tumor size (2) differentiated submucosal cancer with ulceration and diameter ≤ 30 mm; (3) differentiated submucosal penetrative cancer in diameter ≤ 500 μm (SM1); (4) undifferentiated type submucosal cancer without ulceration and diameter ≤ 20 mm. Prior cohort reports demonstrated the long-term favorable outcomes of ESD for EGC in patients meeting the expanded indication criteria when compared with those meeting the absolute indication. According to the Japanese gastric cancer treatment guidelines 2010, ESD was still regarded as the investigational treatment for EGC lesions meeting the expanded indication criteria.

METHODS

Search strategy: The search strategy was: ((((((((((((((((((((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)) AND ((((((((((((((endoscopic mucosal resections) OR ucosal resection, endoscopic) OR ucosal resection, endoscopic) OR resection, endoscopic mucosal) OR resections, endoscopic mucosal) OR strip biopsy) OR biopsies, strip) OR biopsy, strip) OR strip biopsies) OR endoscopic mucous membrane resection) OR endoscopic submucosal dissection) OR dissection, endoscopic submucosal) OR dissections, endoscopic submucosal) OR endoscopic submucosal dissections) OR submucosal dissection, endoscopic) OR submucosal dissection, endoscopic))) AND ((surgery) OR gastrectomy).

Participant or population: Expanded indication early gastric cancer treated with endoscopic submucosal dissection. versus surgical resection.

Intervention: Treated with endoscopic submucosal dissection.

Comparator: Treated with gastrectomy.

Study designs to be included: We included studies that involved a comparison of endoscopic submucosal resection (ESD) vs surgery resection (SR) for EGC within expanded indication: (1)mucosal cancer without ulceration, irrespective of tumor size (2) differentiated submucosal cancer with ulceration and diameter ≤ 30 mm; (3) differentiated submucosal penetrative cancer in diameter ≤ 500 μm (SM1); (4) undifferentiated type submucosal cancer without ulceration and diameter ≤ 20 mm.

Eligibility criteria: We included studies that involved a comparison of endoscopic submucosal resection (ESD) vs surgery resection (SR) for EGC within expanded indication: (1)mucosal cancer without ulceration, irrespective of tumor size (2) differentiated submucosal cancer with ulceration and diameter ≤ 30 mm; (3) differentiated submucosal penetrative cancer in diameter ≤ 500 μm (SM1); (4) undifferentiated type submucosal cancer without ulceration and diameter ≤ 20 mm and explicitly reported data on at least one of the outcomes: enbloc resection, complete resection, metachronous cancer, synchronous cancer, procedure-related

adverse event, short- and long-term prognosis. The types of include studies were clinical randomized or non-randomized control trials or observational studies of adequate quality. Duplicate publications, secondary literature, conference papers, abstracts, letters, editorials and expert opinions, case report and studies lacking clinical endpoints data were excluded.

Information sources: The systematic review of PubMed, Embase, Cochrane, Web of Science databases was performed from 2010 to 2020 for studies comparing survival data and clinical safety of ESD versus surgery resection for EGC with in expanded indication.

Main outcome(s): Complete resection was regarded as resection of a tumor without histological evidence of tumor cell involvement on the lateral and vertical resection margins. Enbloc resection refers to resection of a tumor in one piece without visible residual tumor. If patients received no-curative resection, he or she would undergo the additional surgery (ESD or gastrectomy plus lymphadenectomy). Synchronous gastric cancer was regarded as one new cancer at a previously uninvolved site in the remnant stomach occurring in 1 year after treatment and metachronous gastric cancer occurred more than 1 year after treatment. Procedure-related adverse event was associated with bleeding, ileus, intra-abdominal abscess, anastomosis site leakage, et al.

Quality assessment / Risk of bias analysis: In order to assess the validity of eligible studies, Newcastle-Ottawa Quality Assessment Scale and the Scottish Intercollegiate Guidelines Network checklist was used to measure the risk of bias for cohort studies. The GRADE tool (GRADEpro, https://gradepro.org/) was used to assessed the quality of evidence provided by the pooled results. Automatically, the evidence was graded as very low, low, moderate, and high quality.

Strategy of data synthesis: Assuming the homogeneity of individual existed, hazard ratio estimates of individual study were incorporated into an overall HR using a fixed-effects model. If there was a significant heterogeneity, the random model would take palace of it. Heterogeneity across studies was assessed by $\chi 2$ and I2. Heterogeneity was to be present if the I2 statistic was > 50%.

Subgroup analysis: We investigated sources of heterogeneity by the subgroup hypotheses: type of study design (propensity score matching (PSM) group versus non-propensity-score matching group).

Sensitivity analysis: Excluding one study at each time from included studies, sensitivity analysis associated with metachronous data, synchronous data, survival data showed robustness of the pooled effect estimates.

Country(ies) involved: China.

Keywords: gastric cancer; endoscopic submucosal resection; surgery.

Contributions of each author:

Author 1 - Xing Xu.
Email: drxuxing@163.com
Author 2 - Guoliang Zheng.
Email: drzhengboren1@163.com
Author 3 - Zhichao Zheng.
Email: zhengzhichaoedu@163.com
Author 4 - Na Gao.
Email: Gaonaedu@163.com