Digestive and Liver Disease 47 (2015) 37–44

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Digestive Endoscopy

Clinical outcomes of endoscopic submucosal dissection for early stage esophagogastric junction cancer: A systematic review and meta-analysis

Chan Hyuk Park[a], Eun Hye Kim[a], Ha Yan Kim[b], Yun Ho Roh[b], Yong Chan Lee[a,*]

[a] Division of Gastroenterology, Department of Internal Medicine, Severance Hospital, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 6 July 2014
Accepted 10 October 2014
Available online 12 November 2014

Keywords:
Barrett's adenocarcinoma
Endoscopic submucosal dissection
Esophagogastric junction cancer
Gastric cancer
Meta-analysis

ABSTRACT

Background: Although endoscopic submucosal dissection has become widely used for the management of selected cases of early gastric cancer, the effects of endoscopic submucosal dissection for esophagogastric junction cancer have not been fully evaluated.
Methods: Medline, Embase, and the Cochrane Library were searched using the primary keywords "endoscopic submucosal dissection," "ESD," "endoscopic resection," "esophagogastric junction," "gastroesophageal junction," and "Barrett." Six short-term clinical outcomes and three long-term oncologic outcomes were extracted.
Results: A total of six studies provided data on 359 early stage esophagogastric junction cancers treated with endoscopic submucosal dissection. The pooled estimate of en bloc resection and complete resection was 98.6% (95% confidence interval 95.9–99.6%) and 87.0% (95% confidence interval 79.7–92.0%), respectively. The pooled estimate of stenosis was 6.9% (95% confidence interval 3.2–14.0%). In 269 lesions with curative resection, there was no local recurrence or distant metastasis. In contrast, three local recurrences and two distant metastases occurred in 90 lesions with non-curative resection.
Conclusions: Endoscopic submucosal dissection for early stage esophagogastric junction cancer is a feasible treatment option with high en bloc resection, complete resection rates and an acceptable range of complications. When curative resections are achieved, good oncologic outcomes are likely in the management of early stage esophagogastric junction cancer by endoscopic submucosal dissection.

1. Introduction

Endoscopic submucosal dissection (ESD) has been accepted as a standard treatment for differentiated gastric adenocarcinoma without ulceration in which the depth of invasion is clinically diagnosed as T1a and the diameter is ≤2 cm [1]. In addition, Gotoda et al. proposed criteria that suggest a low-risk for lymph node metastasis in gastric cancer [2]. Based on these observations, an expanded indication for gastric ESD was suggested. The expansion of indication has allowed many patients with early gastric cancer (EGC) to undergo ESD rather than surgery. Many reports have shown excellent oncologic outcomes of ESD in patients with EGC that fulfilled expanded indication criteria [3–7]. ESD especially has advantages in patients with proximal gastric cancer, as these patients would usually undergo total gastrectomy if surgery was to be performed. The ESD method can preserve the whole stomach and provide better quality of life compared with surgery.

Two questions have been raised regarding ESD in patients with esophagogastric junction (EGJ) cancer, which is a tumour occurring at the mucosa between the lower oesophagus and cardia. The first question concerns curative resection criteria of ESD for EGJ cancer. EGJ cancer may have clinicopathological characteristics of both esophageal and gastric malignancies [8–10]. Due to differences in the curative resection criteria for ESD were different between esophageal cancer and gastric cancer, the concern is which criteria should be applied. Generally, ESD indication for esophageal cancer is stricter than for gastric cancer. While ESD indications for esophageal cancer include differentiated mucosal cancer of <20 mm without lymphovascular invasion [11], those for gastric cancer have been expanded by Gotoda et al. [2] as follows: (a) differentiated intramucosal adenocarcinoma smaller than

* Corresponding author at: Division of Gastroenterology, Department of Internal Medicine, Severance Hospital, Institute of Gastroenterology, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea. Tel.: +82 2 2228 1960; fax: +82 2 393 6884.
E-mail address: leeyc@yuhs.ac (Y.C. Lee).

http://dx.doi.org/10.1016/j.dld.2014.10.011
1590-8658/

3 cm in diameter without lymphovascular invasion, irrespective of ulcer findings; (b) differentiated intramucosal adenocarcinoma without lymphovascular invasion and negative for ulceration, irrespective of tumour size; (c) undifferentiated intramucosal cancer smaller than 2 cm without lymphovascular invasion and ulcer findings; and (d) differentiated adenocarcinomas which are smaller than 3 cm with minimal submucosal invasion (<500 μm) and without lymphovascular invasion. Oncologic outcomes of patients who underwent ESD for early stage EGJ cancer that fulfilled the ESD indication for gastric cancer but did not fulfil the ESD indication for esophageal cancer have not been fully evaluated. Although several studies have reported treatment outcomes of ESD for early stage EGJ cancer, all of these studies were retrospective, single-centre studies that included only a relatively small number of lesions [12–17]. The second question concerns short-term clinical outcomes, including complications of ESD for EGJ cancer. Difficult location for ESD in early stage EGJ cancer may affect complete resection and curative resection, which are related to long-term oncologic outcomes. Major complications of ESD, such as post-operative bleeding and perforation, may be influenced by the difficulty of the procedure. Stenosis at the post-ESD site is also a concern after ESD for EGJ cancer.

To answer the above questions and provide more reliable estimates of the efficacy of ESD for EGJ cancer, we performed a systematic review and meta-analysis. This study was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [18].

2. Methods

2.1. Search strategy

We searched for all relevant studies that performed ESD for EGJ cancer published between January 1990 and March 2014 through MEDLINE, EMBASE, and the Cochrane Library. The medical terms "endoscopic submucosal dissection," "ESD," "endoscopic resection," "esophagogastric junction," "gastroesophageal junction," and "Barrett" were used in the search (Appendix 1). We also searched the references of screened articles to identify any additional studies. All human studies published in English were considered. The latest date for updating the search was March 24, 2014.

2.2. Study selection

In the first stage of the study selection, titles and abstracts of papers searched by keywords were examined to exclude irrelevant articles. Next, the full text of all selected studies was screened according to inclusion and exclusion criteria. The inclusion criteria specified (1) studies about ESD for EGJ cancer, and (2) studies reporting at least one of the appropriate clinical outcomes, including en bloc resection, complete resection, curative resection, post-ESD bleeding, perforation, stenosis, local recurrence, distant metastasis, and cause-specific death. The exclusion criteria ruled out (1) studies including participants without cancer, such as adenoma, (2) studies including participants who underwent endoscopic mucosal resection rather than ESD (3) non-original articles, (4) animal testing or preclinical trials, (5) abstract-only publications or unpublished studies, and (6) publications in a language other than English. Two investigators (C.H.P. and E.H.K.) independently evaluated studies for eligibility and subsequently resolved any disagreements through discussion and consensus. If no agreement could be reached, a third investigator (Y.C.L.) decided eligibility.

To understand the risk of bias in individual studies, a formal quality assessment of studies was performed, along with subgroup analysis. The methodological quality of observational studies was independently assessed by two investigators (C.H.P. and E.H.K.), using the Newcastle-Ottawa scale [19,20]. Using this scale, observational studies were scored across three categories: selection (4 questions), comparability of study groups (2 questions), and ascertainment of the exposure or outcome (3 questions). All questions were assigned a score of one point, with the exception of comparability of study groups, in which a maximum of two points were awarded. In addition, a subgroup analysis was performed after excluding studies that included patients who had undergone ESD during the initial introduction period of ESD in Japan, because ESD requires a high level of endoscopic skill to achieve desirable oncologic outcomes and has an obvious learning curve [2,21,22].

2.3. Data extraction

Using a data extraction form developed in advance, two reviewers independently extracted the following information: first author, year of publication, study design, institution, country, enrollment period, number of patients and lesions, age and sex of patients, Siewert classification of lesions [23], histologic type of lesions (Barrett's adenocarcinoma or gastric cardia cancer), tumour size, deep submucosal invasion, lymphovascular invasion, device for ESD, result of main outcomes, follow-up period, and criteria for curative resection. Main outcomes consisted of six short-term clinical outcomes, including en bloc resection, complete resection, curative resection, post-ESD bleeding, perforation, and stenosis, and three long-term oncologic outcomes, including local recurrence, distant metastasis, and cause-specific death.

2.4. Outcomes assessed

Our primary analysis focused on assessing the clinical outcomes and long-term oncologic outcomes of ESD for patients with early stage EGJ. Our *a priori* hypothesis posited that the procedures performed in the initial introduction period of ESD would be indicative of heterogeneity of the main outcomes.

2.5. Statistical analysis

Meta-analyses were performed by calculating pooled estimates of clinical outcomes, including complications. Taking a conservative approach, we used a random effects model [24], producing wider confidence intervals than a fixed effect model would produce. In all meta-analyses, we assessed heterogeneity with Cochran's Q test and the inconsistency index (I^2) [25]. If heterogeneity was found, we conducted sensitivity analyses. Statistical analyses were conducted using the statistical software Comprehensive Meta Analysis (version 2.2.064; Biostat Inc., Englewood, NJ, USA).

3. Results

3.1. Study selection

A flow diagram of this systematic review is shown in Fig. 1. In summary, 172 studies were identified by our literature search. After scanning titles and abstracts, we discarded 58 identical articles retrieved through multiple search engines. Additionally 97 irrelevant articles were excluded based on the titles and abstracts. Full texts of the 17 remaining articles were reviewed, and ten non-pertinent articles were excluded. In addition, one study was excluded due to cohort overlap between studies.

Finally, six studies were appropriate for the meta-analysis. These studies described a total of 353 patients with 359 lesions. All studies had been published in the past 4 years, from 2010 to 2014.