



Long-term prognosis of expanded-indication differentiated-type early gastric cancer treated with endoscopic submucosal dissection or surgery using propensity score analysis

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Background and Aims: Although endoscopic submucosal dissection (ESD) for expanded-indication lesions of differentiated-type early gastric cancer (EGC) has been widely accepted, no prospective randomized study has been conducted on this subject. This study aimed to evaluate the long-term outcomes of ESD and surgery for expanded-indication lesions of differentiated-type EGC.

Methods: Between 1997 and 2012, 1500 consecutive patients with EGC were treated in Osaka City University Hospital. Using propensity score matching and inverse probability of treatment weighting (IPTW), we retrospectively evaluated the long-term outcomes, risk factors for mortality, and adverse events for patients with expanded-indication lesions of differentiated-type EGC who underwent ESD or surgical treatments.

Results: A total of 308 patients with expanded-indication lesions of differentiated-type EGC confirmed by pathologic examination after ESD or surgery met the eligibility criteria. After matching, the 5-year overall survival rate was higher in the ESD group than in the surgery group (97.1% vs 85.8%; $P = .01$). We also found that surgery was significantly associated with mortality using both the IPTW method (hazard ratio [HR], 10.89; 95% confidence interval [CI], 1.37–86.6; $P < .01$), and Cox analysis (HR, 8.60; 95% CI, 1.11–66.52; $P = .04$) after matching. Significantly fewer adverse events were associated with ESD than with surgery (6.8% vs 28.4%; $P < .01$). No cause-specific mortality was observed in either group.

Conclusions: Our results indicate that ESD might be an alternative treatment modality for expanded-indication lesions of differentiated-type EGC. (Gastrointest Endosc 2017;85:143-52.)

Early gastric cancer (EGC) has a favorable prognosis, and the standard treatment has traditionally consisted of gastrectomy with lymph node dissection. Endoscopic resection for EGC without lymph node metastasis has

been widely accepted as a therapeutic alternative.¹⁻⁴ Compared with those for surgery, the long-term outcomes of EMR are favorable for the treatment of EGC that meets the following absolute indications: an intramucosal,

Abbreviations: ASA-PS, American Society of Anesthesiologists Physical Status; ASD, absolute standardized differences; CI, confidence interval; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; QOL, quality of life.

DISCLOSURE: Dr Watanabe has served on an advisory committee for Eisai Co., Ltd.; Dr Fujiwara has served on an advisory committee for Ono Pharmaceutical Co. Ltd.; Dr Arakawa has served on advisory committees for Otsuka Pharmaceutical Co., Ltd. and Eisai Co., Ltd. All other authors disclosed no financial relationships relevant to this publication.

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differentiated-type cancer ≤ 2 cm in size, without ulceration or lymphatic-vascular invasion.^{5,6} Endoscopic submucosal dissection (ESD) has enabled en bloc resection for EGC regardless of size, location, or coexisting ulcerative findings,^{2,3} which was impossible using conventional EMR. En bloc resection prevents residual disease and local recurrence because of precise histologic assessment of the resected specimen.³

Previous studies noted an absence of lymph node metastasis in patients undergoing surgery for expanded-indication lesions.⁷⁻⁹ Therefore, several reports on cohorts demonstrated long-term favorable outcomes of ESD for EGC in patients meeting the expanded-indication criteria.¹⁰⁻¹⁹ Although ESD has become generally accepted for routine treatment of expanded-indication lesions of EGC, ESD is still classified as an investigational procedure under the Japanese gastric cancer treatment guidelines 2010.⁷ This is attributable to the fact that there has been no randomized study of the long-term outcomes comparing ESD with surgery for EGC in this setting. Although a few studies using propensity score matching reported the long-term outcomes for ESD and surgery, these included absolute-indication lesions and undifferentiated adenocarcinomas.^{11,20} Although absolute-indication lesions generally have lower potential for metastasis than expanded-indication lesions, undifferentiated-type EGC has a higher potential for metastasis and a worse prognosis than differentiated-type EGC.^{21,22} Thus, the long-term outcomes may be affected. In addition, most expanded-indication lesions were treated recently with ESD because ESD is less invasive and leads to a better quality of life (QOL) than gastrectomy, in particular for patients in poor general condition.

We therefore conducted the present comparative study of long-term outcomes in patients in whom expanded-indication lesions of differentiated-type EGC were treated by ESD or surgery using propensity score matching and inverse probability of treatment weighting (IPTW) analysis to support our hypothesis that ESD offers a more favorable prognosis than surgery.

METHODS

Patients

This retrospective study conducted at a single referral hospital compared the outcomes of 2 groups of patients: those who had ESD and were found on pathology to have expanded-indication lesions of differentiated-type EGC, and those who had surgery who were found to have the same type of lesions. A propensity score approach was used for the analysis to adjust for various confounding variables. A total of 1500 consecutive patients with EGC underwent ESD or surgery between January 1997 and December 2012 and were observed until August 2014. In patients who underwent multiple treatments for different

lesions, the first treated lesion was considered to be the representative lesion. All lesions including surgically treated lesions were assessed pathologically according to the expanded histologic criteria for endoscopic resection in the Japanese gastric cancer treatment guidelines 2010.⁷ Patients with EGC who did not fulfill all eligibility requirements and the expanded histologic criteria of differentiated-type EGC were excluded from this study. Patients who underwent curative resection for an absolute indication, those with undifferentiated-type EGC, and those with histories of other malignant neoplasms were excluded because these variables could affect long-term outcomes. Patients who were diagnosed as non-curative resection were also excluded because additional surgical treatment was recommended in these patients, and many of these patients underwent additional surgical resection. The protocol of this study was approved by the ethics committee of the Osaka City University Graduate School of Medicine.

ESD

Experienced endoscopists performed all procedures with the patients under intravenous sedation. We analyzed the margin of EGC via chromoendoscopy with indigo-carmin dye or magnified endoscopy with narrow-band imaging.²³ A single-channel upper GI endoscope and a standard electrosurgical generator were used. We mainly used an insulation-tipped diathermic knife (KD-611L, Olympus, Tokyo, Japan). Marking dots were placed. Then, glycerol and/or 0.4% hyaluronate sodium solution were injected. A circumferential mucosal incision and submucosal dissection was performed.

Perforation was defined as endoscopic observation of a hole in the gastric wall exposing the peritoneal cavity or free air seen on an abdominal radiograph or CT image. Delayed bleeding was defined as hemorrhage resulting in hematemesis, melena, or hemoglobin drop >2 g/dL that required endoscopic re-intervention or transfusion after the ESD procedure.

Surgery

Radical gastrectomy with D1 + β (N1 stations plus stations 7, 8a, and 9) lymph node dissection was performed as standard treatment. A gross resection margin of 2 cm was obtained.⁷ When the tumor border was unclear, preoperative endoscopic clip-marking was often performed based on biopsy results. A distal, total, proximal, or segmental gastrectomy was performed depending on the tumor location. The reconstruction methods were Billroth I, II, or Roux-en-Y. Based on the patient's informed consent, open surgery or laparoscopic surgery was performed.

Pathologic examination

Fixed ESD specimens were sectioned perpendicularly at 2-mm intervals and surgical specimens at 5-mm intervals;

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