Prospective comparative study of endoscopic submucosal dissection and gastrectomy for early neoplastic lesions including patients’ perspectives

Authors
Diogo Libânio1,2, Vânia Braga1, Silvia Ferraz1, Rui Castro1, Jorge Lage1, Inês Pita1, Cátia Ribeiro3, Joaquim Abreu De Sousa3, Mário Dinis-Ribeiro1,2, Pedro Pimentel-Nunes1,2

Institutions
1 Gastroenterology Department, Instituto Português de Oncologia do Porto, Porto, Portugal
2 CINTESIS – Center for Health Technology and Services Research, Faculty of Medicine, University of Porto, Porto, Portugal
3 Surgical Oncology Department, Instituto Português de Oncologia do Porto, Porto, Portugal

submitted 26.11.2017
accepted after revision 24.4.2018

Bibliography
DOI https://doi.org/10.1055/a-0628-6601
Published online: 3.7.2018 | Endoscopy 2019; 51: 30–39
© Georg Thieme Verlag KG Stuttgart · New York
ISSN 0013-726X

Corresponding author
Diogo Libânio, MD, Gastroenterology Department, Instituto Português de Oncologia do Porto, 4200-072 Porto, Portugal
Fax: +351-225-084001
diogolibanionmonteiro@gmail.com

Online content viewable at: https://doi.org/10.1055/a-0628-6601

ABSTRACT
Background There are no prospective studies comparing endoscopic submucosal dissection (ESD) and gastrectomy, especially evaluating patient-reported outcomes. Our aim was to compare the safety and impact on quality of life (QoL) of ESD and gastrectomy in patients with early gastric neoplasia.

Methods This prospective study included consecutive patients presenting with early gastric neoplasia in a tertiary center from January 2015 to August 2016. Data collection included curative resection, adverse events (AEs), and patient-reported outcomes (questionnaires: EORTC QLQ-C30, EORTC STO-22, EQ-5D-5 L, and Assessment of Survivor Concerns) before and after interventions (after 1 month, 3–6 months, and 1 year).

Results 254 patients with early lesions were included: 153 managed by ESD and 101 by gastrectomy, the former being significantly older and with less advanced lesions. Mean procedural time and length of stay were significantly higher in the surgery group (164 vs. 72 minutes and 16.3 vs. 3.5 days; \( P < 0.001 \)). Complete resection was higher in the surgical group (99% vs. 90%; \( P = 0.02 \)); ESD was curative in 79% of patients. Severe AEs and surgical re-intervention were significantly more frequent in the gastrectomy group (21.8% vs. 7.8% and 11% vs. 1%, respectively). Endoscopic treatment was associated with a positive impact on global health-related QoL at 1 year (net difference +9.9; \( P = 0.006 \)), role function and symptom scales (fatigue, pain, appetite, eating restrictions, dysphagia, and body image). Concerns about recurrence did not differ between the groups.

Conclusions In patients with early gastric neoplasia, ESD is safer and is associated with a positive impact on health-related QoL when compared with gastrectomy, without increasing fear of recurrence and new lesions.

Introduction
Gastric cancer is a major health problem, being the fourth most common cancer and the second commonest cause of cancer-related death [1]. Early gastric neoplasms can be treated by endoscopic submucosal dissection (ESD) or gastrectomy with lymphadenectomy [2–5].

Although gastric ESD is widely performed in Eastern countries, the majority of guidelines are not straightforward in their recommendation of ESD as the first-line treatment. This absence of clear recommendations about the first-line treatment...
is related to the absence until recently of long-term follow-up after ESD and to the lack of comparative studies between endoscopic and surgical treatment. ESD is a minimally invasive treatment with the theoretical advantage of minimal impact on health-related quality of life (HR-QoL), and recent studies with long-term follow-up have proven its efficacy, reporting low rates of local (<2%) and distant recurrence (0.15%), and high overall and disease-specific survival [6,7]. On the other hand, the risk of metachronous lesions is increased and regular endoscopic surveillance is recommended, which may negatively affect HR-QoL (namely psychological dimensions).

Studies comparing the outcomes of the two treatments are important in order to define the first-line therapy and to provide patients with better information. However, there are few comparative studies [8–11], all being retrospective, and no study has compared the impact of the treatments in terms of HR-QoL using patient-reported outcomes (PROs). As it is difficult to randomize patients with early gastric neoplasms to endoscopic or surgical treatment, prospective studies are probably the best study design to compare the safety and impact of treatments on HR-QoL. Although acknowledging that, in a setting where both treatments are available, lesions in the two groups may not be strictly comparable, the morphological and histopathological characteristics of the lesions do not affect the comparability of safety and PROs. The main aim of this study was to prospectively compare the safety and impact on HR-QoL of ESD and gastrectomy in patients with early gastric neoplasia.

Methods
Selection of participants
This was a prospective cohort study including consecutive patients with gastric neoplasia (dysplastic lesions or adenocarcinoma) referred to the Gastroenterology and Surgical Departments of the Portuguese Oncology Institute of Porto (Porto), a tertiary referral center, between January 2015 and August 2016. The decision between endoscopic or surgical treatment was made by the assistant physician and/or the multidisciplinary team according to the endoscopic description of the lesion and the histology of the biopsies, without influence of the research team. Endoscopic ultrasound was not routinely performed, in line with European recommendations [2].

After resection, patients with adenocarcinoma invading beyond the submucosa were excluded from the study population, with all patients with dysplastic lesions and early gastric cancers being included in the efficacy and safety analysis. Criteria for exclusion from the quality-of-life analysis were: (i) prior gastric surgery; (ii) refusal to answer or not delivering questionnaires; (iii) inability to answer questionnaires because of illiteracy or mental illness; (iv) adjuvant chemotherapy; (v) major illness unrelated to ESD/gastrectomy during follow-up with significant impact on HR-QoL (e.g. bone fractures, stroke with sequelae). ESD patients not meeting curative criteria were also excluded from the quality-of-life analysis beyond 1 month and could be included in the gastrectomy group thereafter if the surgery was performed in our institution.

Procedures
ESD was performed by two expert endoscopists with previous experience with the technique, with the patients under general anesthesia and orotracheal intubation (Fig. 1). Virtual chromoendoscopy with narrow-band imaging (HQ-190, with dual-focus magnification) was used to assess the margins of the lesions; saline and methylene blue were used to inject the submucosa; a Needle Knife and IT Knife (both Olympus) were used for mucosal incision and submucosal dissection, respectively. After ESD, visible vessels were coagulated, mainly with hemostatic forceps using soft coagulation mode and, in a minority of cases, with the IT knife (in case of small caliber vessels). ERBE VIO 300 D was the electrosurgical device. Procedure duration was defined as the time between scope insertion and withdrawal, after coagulation of vessels and specimen retrieval.

Gastrectomies were performed by an experienced surgical team performing>200 gastrectomies/year; the extent of gastric resection and lymphadenectomy were determined by tumor location and clinical stage (D1 or D1+ was performed in cT1N0 and D2 in cT≥2 or if there was suspicion of N+ ) [3]. Surgical approach (open or laparoscopic) was determined by the surgical team.

Follow-up and data collection
Clinical and demographic variables were collected at baseline, and patients were asked to answer three quality-of-life questionnaires (see below). Efficacy and safety end points were monitored and included en bloc resection (removal of the lesion in one piece), complete resection (horizontal and vertical margins free of tumor), curative endoscopic criteria (assessed by two gastrointestinal pathologists) according to the Japanese Gastric Cancer Treatment and European Society of Gastrointestinal Endoscopy (ESGE) guidelines [2,3], and the occurrence of adverse events (AEs).

AEs were classified according to the Accordion Severity Classification of Postoperative Complications (0 = no AE; 1 = mild AE requiring only pharmacological measures [e.g. antipyretics, antiemetics] or minor invasive procedures [e.g. nasogastric drainage, drainage of wound infections]; 2 = moderate AE requiring antibiotics, transfusions, or parenteral nutrition; 3 = severe AE requiring intervention (surgical, endoscopic, or radiological) not under general anesthesia; 4 = severe AE requiring operation under general anesthesia; 5 = severe AE with organ failure; 6 = postoperative death) [12]. AEs of ESD were also classified with this classification, with post-ESD bleeding requiring hemostasis being classified as grade 3 as endoscopies were performed without anesthesia.

After treatment, ESD patients were evaluated after 1 month to discuss their histopathology and the need for additional surgery. If the curative criteria were met, a gastroscopy was scheduled 3–6 months after resection (and an abdominal computed tomography scan in case of expanded criteria) and at 1 year. Patients not meeting the curative criteria were subsequently submitted to gastrectomy unless they were considered unfit for surgery or refused additional treatments.
Gastrectomy patients were evaluated 1 month after surgery to review their histopathology and decide on adjuvant treatment. Patients with an indication for adjuvant chemotherapy were excluded from the analysis beyond this time point. The remainder were clinically evaluated 3–6 months and 1 year after surgery. The decision to request follow-up diagnostic tests was at the discretion of the assistant surgeon.

**Patient-reported outcomes (PROs)**

Patients were asked to self-answer three questionnaires (EORTC QLQ-C30, EORTC STO-22, and EQ-5D-5L) at baseline (in the month before treatment), and at 1 month, 3–6 months, and 1 year after treatment. At 1 year, patients were also asked to answer a questionnaire concerning fear of cancer recurrence and cancer death (Assessment of Survivor Concerns).

The EORTC QLQ-C30 questionnaire is scored in one global health scale, five functional dimensions, and nine symptom scales [13]. The EORTC STO-22 is composed of five multi-item scales and four single measures and is validated in patients with gastric cancer [14]. These questionnaires are scored from 0 to 100 points, with higher scores in functional dimensions corresponding to higher functionality, while higher symptom scale scores correspond to greater symptom severity.

The EQ-5D-5L is composed by five dimensions (mobility, self-care, usual activities, pain, anxiety/depression) and the EQ visual analogue scale (EQ-VAS) [15]. The dimensions have five levels (1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems), which were recoded as ‘no problems’ (1) or ‘problems’ (2–5). The EQ-VAS records the respondents’ self-rated health on a 20-cm vertical VAS with end points labelled “the best health you can imagine” (100 points) and “the worst health you can imagine” (0 points). The Assessment of Survivor Concerns is a brief validated five-item questionnaire that assesses patients’ concerns about the need to undergo diagnostic tests, development of new tumors, tumor recurrence, fear of dying, and fear of health issues in general [16].

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of IPO-Porto (CES.282/2014). Written informed consent was obtained from all patients included in the study. Permission to use questionnaires was obtained from the developers.

**Statistical analysis**

The defined primary end point for sample size calculation was the mean change in global health status (EQ-AVS) at 1 year. We calculated that 36 patients with baseline and 1-year response had to be included in each group to demonstrate a 10-point net difference between the groups (assuming no reduction in global HR-QoL in the gastrectomy group [17–19] and estimating an improvement of 10 points in the ESD group [assuming a minimal impact in physical HR-QoL dimensions and an improvement in psychological dimensions], with a standard deviation of 15 points) with 80% power and a type I error probability of 0.05 (two-sided).

The EORTC QLQ-C30 and STO-22 questionnaires were scored according to developers’ norms. Statistical analysis was performed with SPSS ver. 22 (IBM; Armonk, New York, USA). Descriptive statistics included mean and standard deviation or median and interquartile range for quantitative variables and

**Fig. 1** Endoscopic submucosal dissection of a 0-IIa+c 12-mm lesion in the lesser curvature of the antrum.
proportions for categorical variables. Paired comparisons within groups at different time points were performed with paired-samples t test or Wilcoxon signed-rank test, while between-group comparisons were performed with independent-samples t test or Mann-Whitney U test. Between-group proportions were compared with the chi-squared test (with Bonferroni adjustment for multiple comparisons), while within-group proportions were compared with the McNemar test. Significance level was defined as \( P < 0.05 \).

Results

The flowchart of patients within the study is shown in Fig. 2. After excluding 272 patients with non-early gastric neoplasia, 254 patients were included in the study (153 ESD, 101 gastrectomy). ESD patients were significantly older (68 vs. 63 years; \( P < 0.001 \)), although no differences were found in American Society of Anesthesiologists classification status (Table 1). Lesions resected by gastrectomy were more frequently located in the upper and middle third, were significantly larger (mean diameter 25.3 vs. 21.1 mm; \( P < 0.007 \)), and more frequently ulcerated (44.4% vs. 3.3%; \( P < 0.001 \)).

In the surgical group, total gastrectomy was performed in 52.5% of patients and subtotal gastrectomy in 47.5%, with Roux-en-Y bypass being the preferred reconstruction in the latter (75.0%). Laparoscopic gastrectomy was performed in 13.9% of patients, with no necessity for conversion in any case. Lymphadenectomy extent was D1 in 36.6% of patients, D1 + in 26.8%, and D2 in 36.6%; ≥15 lymph nodes were resected in 98.0% of patients (mean 26 ± 10).

In the ESD group, en bloc resection was achieved in 94.8% of patients. Mean anesthesia and procedure duration were significantly higher in the surgical group (+113 and +92 minutes, respectively; \( P < 0.001 \)), as was median inpatient stay (11 days [interquartile range (IQR) 9–17] vs. 3 days [IQR 3–4]; \( P < 0.001 \)) (Table 2). Surgical drains were placed at surgery in 80.2% of patients (being in place for a median of 7 days [IQR 6–9]), while nasogastric tubes were placed in 32.7% of the surgery group and 2.0% of the ESD group.

Efficacy and safety

The rate of complete resection was significantly higher in the surgical group (99.0% vs. 90.2%; \( P = 0.02 \)) (Table 2), although four of the cases of incomplete ESD resection corresponded to dysplasia at the resection margins alone. In the ESD group, the resection was curative in 121 cases (79%), of which 14% met the expanded criteria. No local recurrences occurred during a median follow-up of 20 months (IQR 13–26). Of the 32 patients not meeting the curative criteria, 22 subsequently underwent gastrectomy (of which 20 were included in the gastrectomy arm). In the gastrectomy group, 17 patients (16.9%) had nodal involvement and 10 underwent adjuvant chemotherapy. No local recurrences or distant metastases were detected, although the patient with incomplete resection was submitted to subsequent surgical resection.

Intraprocedural AEs occurred in 10.9% of the surgical group (vs. 1.3% in the ESD group; \( P < 0.001 \)). Intraprocedural AEs in the surgery group included seven splenic injuries, two vascular injuries, one significant hemorrhage, and one hollow viscus laceration; all were controlled during surgery, although one patient was submitted to non-planned splenectomy during surgery. The two intraoperative perforations during ESD were closed endoscopically and successfully managed conservatively (fasting and intravenous antibiotics).

The most frequent AEs in the surgery group were postoperative respiratory or urinary tract infections (n = 16), followed by dehiscence and/or fistula (n = 12), persistent vomiting and/or oral feeding intolerance (n = 6), and intra-abdominal abscesses.
In the ESD group, delayed post-ESD bleeding occurred in 13 patients (8.5%: all managed with endoscopic hemostasis and/or transfusions) and delayed perforation in two patients (1 in the body–antrum transition managed conservatively and 1 in the gastric fundus that led to peritonitis and surgery). Severe AEs and surgical re-intervention were more frequent in the surgery group (21.8% vs. 7.8%, \(P = 0.003\); and 10.9% vs. 0.7%, \(P < 0.001\), respectively). AEs requiring procedures under general anesthesia or leading to multiorgan dysfunction were also significantly more frequent in the gastrectomy group, although mortality was similar (1 patient in the ESD group died 4 days after surgery for delayed perforation and 1 patient in the gastrectomy group died with sepsis and decompensated cirrhosis).

Impact on health-related quality of life

Pretreatment PROs were similar in the surgical and endoscopic group in the majority of dimensions and symptom scales, although ESD patients had higher scores in pain scales and lower HR-QoL (mean EQ-AVS 63.4 vs. 70.3; \(P = 0.02\)).

The impact of gastrectomy and ESD on EORTC QLQ-C30 dimensions is shown in Fig. 3 and Table 3. Gastrectomy was associated with significant worsening in physical function and role function at 1 month (mean change −11.7 and −18.8 points, respectively; \(P < 0.001\)) and at 3–6 months (mean change −9.3 and −17.8, respectively; \(P < 0.001\)). Role function remained significantly lower at 1 year, although the difference in physical function was no longer statistically significant (mean change −4.9; \(P = 0.10\)). In the ESD group there was no worsening in any dimension, and a significant improvement in emotional function was seen at 1 month and 3–6 months. Between-group
comparison showed a significant benefit of ESD when compared with gastrectomy in physical, role, emotional, and social functioning at 1 month, physical and role functioning at 3–6 months, and role function at 1 year.

Gastrectomy was also associated with significantly higher mobility, self-care, and usual activity problems at 1 month and 3–6 months (▶Table e4). At 1 year, problems with pain increased significantly in the gastrectomy group (P=0.04), while anxiety/depression problems improved significantly in both groups (P=0.02 in the gastrectomy group; P=0.04 in the ESD group) (▶Fig. 4; ▶Table e4).

Regarding symptom scales, several symptoms deteriorated in the gastrectomy group at the different time points (▶Table e5), the majority remaining significantly worse at 1 year. Dyspnea, insomnia, dry mouth, and hair loss were the only symptoms that did not significantly worsen at any time point, while nausea/vomiting and reflux were aggravated at 3–6 months but returned towards baseline at 1 year. On the other hand, fatigue, pain, appetite loss, diarrhea, dysphagia, eating restrictions, taste, and body image were significantly worse at 1 year when compared with baseline (▶Table e5). In the ESD group, no symptom scale worsened and, at 1 year, there was a significant improvement in epigastric pain and anxiety.

With respect to the worry of recurrence, there were no significant differences between the groups regarding fear of recurrence, new tumors, or death, and the proportion of patients

### Table 2 Efficacy and safety outcomes of the two different treatment modalities.

<table>
<thead>
<tr>
<th></th>
<th>Gastrectomy (n = 101)</th>
<th>ESD (n = 153)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure duration, mean (SD), minutes</td>
<td>163.9 (56.4)</td>
<td>71.8 (59.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anesthesia duration, mean (SD), minutes</td>
<td>207.5 (62.1)</td>
<td>94.6 (64.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean (SD)</td>
<td>16.3 (12.9)</td>
<td>3.5 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• Median (IQR)</td>
<td>11 (9 – 16.5)</td>
<td>3.0 (3 – 4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resection / margins, n (%)</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>• R0</td>
<td>100 (99.0)</td>
<td>138 (90.2)</td>
<td></td>
</tr>
<tr>
<td>• Rx</td>
<td>0 (0)</td>
<td>5 (3.3)</td>
<td></td>
</tr>
<tr>
<td>• R1</td>
<td>1 (1.0)</td>
<td>10 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Curative endoscopic resection, n (%)</td>
<td>–</td>
<td>121 (79.1 %)</td>
<td>NA</td>
</tr>
<tr>
<td>Intraprocedural AEs, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• No</td>
<td>50 (49.5)</td>
<td>136 (88.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>• Mild</td>
<td>5 (5.0)</td>
<td>0 (0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>• Moderate</td>
<td>24 (23.8)</td>
<td>5 (3.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>• Severe (1)</td>
<td>7 (6.9)</td>
<td>11 (7.2)</td>
<td>ns</td>
</tr>
<tr>
<td>• Severe (2)</td>
<td>6 (5.9)</td>
<td>0 (0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>• Severe (3)</td>
<td>8 (7.9)</td>
<td>0 (0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>• Death</td>
<td>1 (1.0)</td>
<td>1 (0.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Re-intervention, n (%)</td>
<td>21 (20.8)</td>
<td>12 (7.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Type of re-intervention, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• Endoscopic</td>
<td>1 (1.0)</td>
<td>11 (7.2)</td>
<td></td>
</tr>
<tr>
<td>• Radiological</td>
<td>4 (4.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>• Surgical</td>
<td>11 (10.9)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>• Endoscopic and radiological</td>
<td>2 (2.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>• Radiological and surgical</td>
<td>3 (3.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

ESD, endoscopic submucosal dissection; SD, standard deviation; IQR, interquartile range; R0, negative vertical and horizontal margins; Rx, indeterminate vertical or horizontal margins; R1, positive vertical or horizontal margins; ns, non-significant (Bonferroni adjustment).
reporting grade 3 or grade 4 concerns was slightly higher in the gastrectomy group (▶ Fig. 5).

Regarding global health status (EQ-AVS), ESD was associated with an improvement at 1 year (+ 5.58; \( P = 0.007 \)), while in the gastrectomy group there was a decrease in global health at 1 year (−4.35; \( P = 0.17 \)), corresponding to a net benefit of 9.93 points in the mean global health change favoring ESD (\( P = 0.006 \)) (▶ Fig. 6). The same pattern of HR-QoL improvement was seen at 1 and 3–6 months. Weight change was also significantly different, with gastrectomy patients losing a mean of 9.3 kg (95% confidence interval [CI] −11.3 to −7.3 kg) and ESD patients having a mean change of 0 kg (95%CI −0.82 to +0.91 kg).

In subgroup analysis including only patients with T1a/T1b carcinomas, the same pattern of changes was found, although some differences did not reach statistical significance (▶ Table e6). With regard to surgical approach, there were no significant differences at 1 year in the majority of dimensions, symptoms, and weight loss between subtotal and total gastrectomy (data not shown).

Discussion

The decision between two different treatments is one of the most difficult tasks in medicine and should include consideration of the efficacy, safety, effectiveness, and costs. Early gastric neoplasms can be treated by endoscopic or surgical resection, each with advantages and disadvantages.

To our knowledge, this is the first prospective study comparing ESD and gastrectomy in patients with early gastric neoplasia, and the first study to evaluate the impact of both treatments on HR-QoL. We found that ESD has a significantly better safety profile, being associated also with shorter procedure duration and inpatient stay. Our findings are in line with retrospective studies that have also found a lower AE risk, although the rates of AEs were slightly higher in both arms in our study, which may be related to the prospective design. Indeed, the curative rate of ESD was slightly lower than our previous reports [20–22], which is probably related to the higher difficulty associated with the lesions, and the higher rate of delayed bleeding is probably related to the high proportion of patients on antithrombotic medication (22%).
With regard to the impact of the treatments on HR-QoL at 1 year, we found that ESD has significant advantages over gastrectomy in global health status, role function, and on several symptom scales. Patients submitted to gastrectomy had a decrease of 4.3 points in HR-QoL, while patients submitted to ESD had a mean increase of 5.6 points (net benefit of 9.9 points with ESD \( P = 0.006 \)). The increase in HR-QoL after ESD is probably related to a decrease in anxiety and depression associated with the disease state. In the gastrectomy group, anxiety and depression also decreased, although our findings suggest that this improvement in well-being is not enough to overcome the negative impact of surgical treatment in other symptom scores. In fact, although some dimensions deteriorated in the first months but improved at 1 year, others (like role function and the majority of symptom scales) remained significantly worse at 1 year. In the ESD group, there was no significant deterioration in any symptom scale at any time point and, at 1-year, epigastric pain and anxiety were improved.

Psychological dimensions improved in both treatment groups. Moreover, answers to the five questions related to concerns about health and disease were similar in both groups; fear of recurrence and of new cancers was even slightly higher in the gastrectomy group. Therefore, the higher risk of metachronous lesions in ESD patients does not seem to significantly influence emotional and psychological dimensions. This might be explained by an underestimation of the risk of metachronous lesions, which may be related to inclusion in a regular endoscopic surveillance program, as patients perceive that, if a new lesion develops, it will be detected and treated in a timely fashion. However, a cross-sectional study evaluating worry of cancer recurrence with a different questionnaire found a higher worry of cancer recurrence in ESD patients [23].

This study has some limitations. The response rate to questionnaires was lower than desirable, although more than 60% of the patients who answered pretreatment questionnaires responded to follow-up questionnaires (and the proportion of respondents was similar in both groups).

Another limitation is that the two cohorts are not strictly comparable as we did not perform a randomized controlled trial. Patients in the ESD group were significantly older, had a lower baseline HR-QoL (although ASA classification was similar between groups), and had less advanced lesions. Nevertheless, first, we may argue that, from a patients’ perspective, this may not be truly a confounder. In fact, both groups included only early gastric lesions and the histological differences are not expected to influence QoL per se. Secondly, the pre-and-post design decreases the impact of these differences on the outcomes. However, if we accept that this is a potential bias, the differences observed in our study would probably be smaller than the true differences. That is, we estimate that older patients may experience a more pronounced worsening of QoL owing to treatment when compared with younger patients.
Additionally, there was a higher proportion of submucosal carcinomas in the surgical group, and it is clear that some patients included in the surgical group could not have been effectively treated by endoscopic resection. However, we believe that the differences in lesions characteristics do not affect the comparability of endoscopic and surgical treatment in terms of safety and PROs, which were the main end points of this study. Furthermore, subgroup analysis including only patients with adenocarcinomas showed similar impact of the treatments. It is also important to note that the differences in characteristics of the lesions do not allow comparisons with regard to efficacy and we acknowledge that lesions with the suspicion of deep submucosal invasion should be treated by surgery; however, our results support the recommendation that ESD should be the first-line treatment for early gastric lesions that are expected to have a minimal risk of lymph node metastasis because of its safety and better impact in HR-QoL. In this context, early gastric lesions should probably be evaluated by a gastroenterologist experienced in endoscopic resection before surgery is considered. Surgery would then be reserved for lesions with a very low probability of curative endoscopic resection, although patients’ preferences should be taken into account.

Additional details can be found in the tables and figures provided.
In conclusion, we have shown for the first time in a prospective comparative study that ESD is effective in approximately 80% of patients, with a significantly better safety profile and a significant benefit in HR-QoL when compared with gastrectomy, without increasing patients’ worry about new lesions or recurrence. These findings suggest that ESD should be considered the first-line treatment whenever feasible and, given the advantages of this minimally invasive treatment modality, efforts should be made towards early diagnosis and ESD training and expertise in Western countries, even from the patients’ perspective.

Acknowledgments

The authors acknowledge the contribution of all of the nurses in the gastroenterology department, digestive clinic, and preoperative clinic, especially nurses Natália Silva, Fátima Teixeira, Brigitte Macedo, and Paula Pereira for their contribution in the delivery of questionnaires.

Competing interests

None

References