Gastroenterology Research and Practice

Endoscopic Submucosal Dissection: The Western Experience

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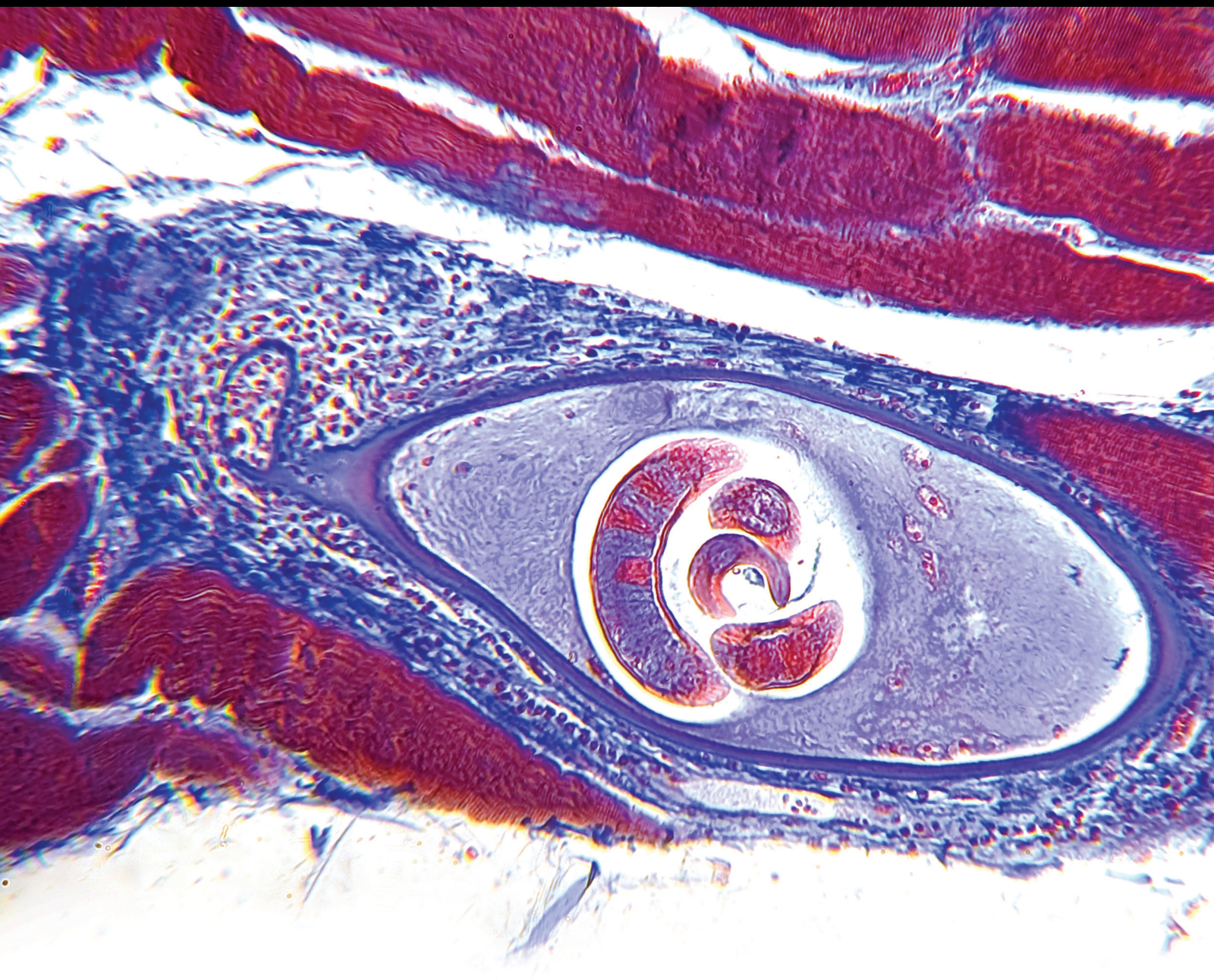

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Research Article

Stricture Prevention after Extensive Endoscopic Submucosal Dissection of Neoplastic Barrett's Esophagus: Individualized Oral Steroid Prophylaxis

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Guest Editor: Amit Bhatt

Introduction. Endoscopic resection (ER) exceeding ≥75% of the esophageal circumference is accompanied with a high stricture risk regardless of the resection method. The ideal strategy for stricture prevention is not well defined today. Different approaches have been reported but data are limited to the resection of squamous cell neoplasia. The aim of this study was to assess the efficacy of an individualized oral steroid regimen to prevent strictures after extensive ER in neoplastic Barrett's esophagus (NBE). *Materials and Methods*. Over a 50-month period, endoscopic submucosal dissection (ESD) was performed in 193 patients with NBE. 23 patients with resections exceeding 75% of the circumference were included. 19 resection ulcers were noncircumferential (NCR) while 4 were circumferential (CR). Stricture prevention was performed using oral prednisolone starting with a daily dose of 50 mg and standard tapering over 8 weeks (50/40/30/25/20/15/10/5 mg). Tapering was individualized according to the ulcer healing process (assessed endoscopically in the first tapering period and before stopping the steroids). Data were analyzed retrospectively. *Results*. Stricture rates were 5.3% (1/19) for NCR and 100% (4/4) for CR ($p < 0.001$). The only stricture in the NCR group was seen in a patient who had stopped steroids without any reason after few days. 12/19 patients received standard tapering over 8 weeks (63.1%). According to the individual ulcer healing, treatment was prolonged to 9-10 weeks in 4/19 (21.1%) and shortened to 7 weeks in another 2/19 (10.5%). After CR, all patients needed endoscopic balloon dilatation (median 6.5 sessions; range 3-14 sessions for 8-40 weeks). Side effects of the steroid therapy were not noted. *Conclusion*. Oral prednisolone therapy with an endoscopy-based individualized tapering regimen is effective in avoiding strictures after NCR of Barrett's neoplasia. After CR, the stricture risk is not sufficiently decreased. CR should be restricted to circumferential neoplasia which is a very rare scenario in neoplastic BE.

1. Introduction

The incidence of esophageal adenocarcinoma (EAC) is rising in Western countries [1]. Progress in endoscopic technology and surveillance programs for patients with Barrett's esophagus (BE) have improved the diagnosis of EAC in early stages allowing endoscopic resection (ER) as a curative treatment option. Endoscopic mucosal resection (EMR) of visible neoplastic lesions and additional ablation of the residual Barrett's are the standard treatment of neoplastic BE today. In selected neoplasia (lesion diameter exceeding 15 mm, poor-lifting lesions, and lesions at risk for submucosal invasion), endoscopic submucosal dissection (ESD) can be considered as a treatment option in order to achieve R0 resection and to improve histopathological assessment of R0 resection [2]. When ER is performed circumferentially or the resection area exceeds three quarters of the circumference, a substantial stricture risk has been reported for EMR (49.7-88%) and also for ESD (60.0%) in BE [3–5]. Different strategies have been introduced to prevent stricture development (balloon dilatation, stenting, local or systemic steroid therapy in fixed-dosage regimens, and tissue-shielding techniques).

These techniques have been shown to reduce but not to eliminate the stricture risk, and the ideal strategy for stricture prevention remains undefined. In our previous study on ESD for neoplastic BE and early esophageal squamous cell cancers (SCCs), we performed prophylactic endoscopic balloon dilatation (EBD) in the first study period and used a fixed-dose regimen of oral steroids in the second. In the dilatation group, a high number of EBD sessions (mean 8.2) were needed to prevent strictures and perforation was noted during EBD in one patient. In the steroid group, 62.5% developed a stricture during the steroid tapering period and EBD was required also in these patients [6]. Data on stricture prevention, published mainly by Asian authors, are restricted to ER of SCCs due to the rareness of Barrett's esophagus in Asia. The aim of this study was to evaluate the efficacy of a modified stricture prevention strategy after extensive ER in neoplastic BE (oral steroid treatment regimen with endoscopy-based control of dosage and duration).

2. Patients and Methods

The study was conducted as a single-center uncontrolled study in a German referral center (Department of Gastroenterology, Klinikum Augsburg, Germany). All patients who underwent ESD of Barrett's neoplasia from May 2014 to July 2018 were screened. All patients had given written informed consent after receiving detailed information about the ESD procedure and alternative treatment options (EMR, surgery). Data were analyzed retrospectively. The study was approved by the Institutional Review Board of Klinikum Augsburg, Germany (IRB number BKF-A-2018-24).

2.1. Inclusion Criteria. Inclusion criteria are as follows:

(i) ESD in neoplastic BE

(ii) Resection ulcer ≥ 75% of the esophageal circumference

(a) Noncircumferential resection (NCR)

(b) Resection involving the entire circumference (CR)

(iii) Stricture prevention performed with oral steroids

2.2. Exclusion Criteria. Exclusion criteria are as follows:

(i) Stricture prevention with other treatment regimens than oral steroids (local steroid injection into the resection ulcer, combination of oral and local steroids)

(ii) Patients receiving steroid therapy for other indications

2.3. Study End Points. The primary end point was the stricture rate after ESD. Secondary end points were procedural characteristics (procedure time, R0 resection rate, curative resection rate, and other complications than stricture).

2.4. ESD Procedure. All patients had been referred for ER, and biopsies had shown high-grade dysplasia or EAC. Video endoscopy with white light and narrow band imaging was performed with a video gastroscope (GIF-HQ190; Olympus Medical Systems, Tokyo, Japan). When the lesion lateral margin was unclear, chromoendoscopy with acetic acid and indigo carmine was added. Lesions were classified according to the Paris classification [7]. EUS was not performed routinely. A transparent cap at the tip of the scope (D-201-11804, Olympus) and insufflation with carbon dioxide were used routinely. Resection margins were marked using the tip of a hook knife (KD-620LR; Olympus). The standard solution for submucosal injection was a mixture of saline, epinephrine (1 : 100.000), glycerol (10%), and a slight amount of indigo carmine. In cases with severe fibrosis, hyaluronic acid (Sigmavisc™, Hyaltech Ltd., Livingston, UK) was injected. A VIO 300D electrosurgical generator (ERBE Elektromedizin, Tübingen, Germany) was used (spray coag mode 25 W for marking; endo cut I mode 60–80 W for cutting and spray coag mode 60 W for coagulation during dissection). Mucosal incision and submucosal dissection were performed with the hook knife. ESD was performed under general anesthesia. Patients stayed in the hospital for 48–96 hours after ESD. Routine control endoscopies were not performed before discharge. Anticoagulants, except aspirin, had been stopped before ESD and were restarted 5-7 days after the procedure depending on endoscopist's decision.

2.5. Histopathologic Workup. Intramucosal lesions were classified as low-grade dysplasia (LGD), high-grade dysplasia (HGD), or mucosal cancer. Invasion depth, grading, and the presence or absence of lymphovascular invasion were described. Regarding their invasion depth, lesions were classified mucosal (pT1a) or submucosal (pT1b). Grading was categorized into G1 (well differentiated), G2 (moderately differentiated), and G3 (poorly differentiated). R0 or R1 was diagnosed for the vertical margin (VM) and the horizontal margin (HM). Curative resection was defined as R0 resection of a well- or moderately differentiated intramucosal cancer without lymphovascular invasion.

2.6. Complications. Stricture was defined as a complication when it was impossible to pass the esophagus using a standard gastroscope (e.g., GIF-HQ190; diameter 9.9 mm). Delayed bleeding was defined as when clinical bleeding signs were observed after ESD (hematemesis, melena, and hemoglobin drop > 2 g/dl). In these cases, endoscopic treatment was performed. Perforation was defined as an endoscopic view into the mediastinum or the peritoneal cavity.

2.7. Regimen for Stricture Prevention and Follow-Up. Based on the results of our previous study and based on the published literature on preventive steroid treatment, we developed a modified steroid-based regimen and used it from 2014 [6, 8–12]. Taking Asian data into account, we chose a starting dose of 50 mg prednisolone daily and tapered this gradually over 8 weeks (50/40/30/25/20/15/10/5 mg) resulting in a cumulative dose of 1365 mg. Prednisolone was started on the first day after ESD when the resection ulcer

Week	Standard regimen oral prednisolone (daily dose), mg
1	50
2	40
3	30
4	25
5	20
6	15
7	10
8	5
9	Modified regimen
10	Modified regimen
11	Modified regimen

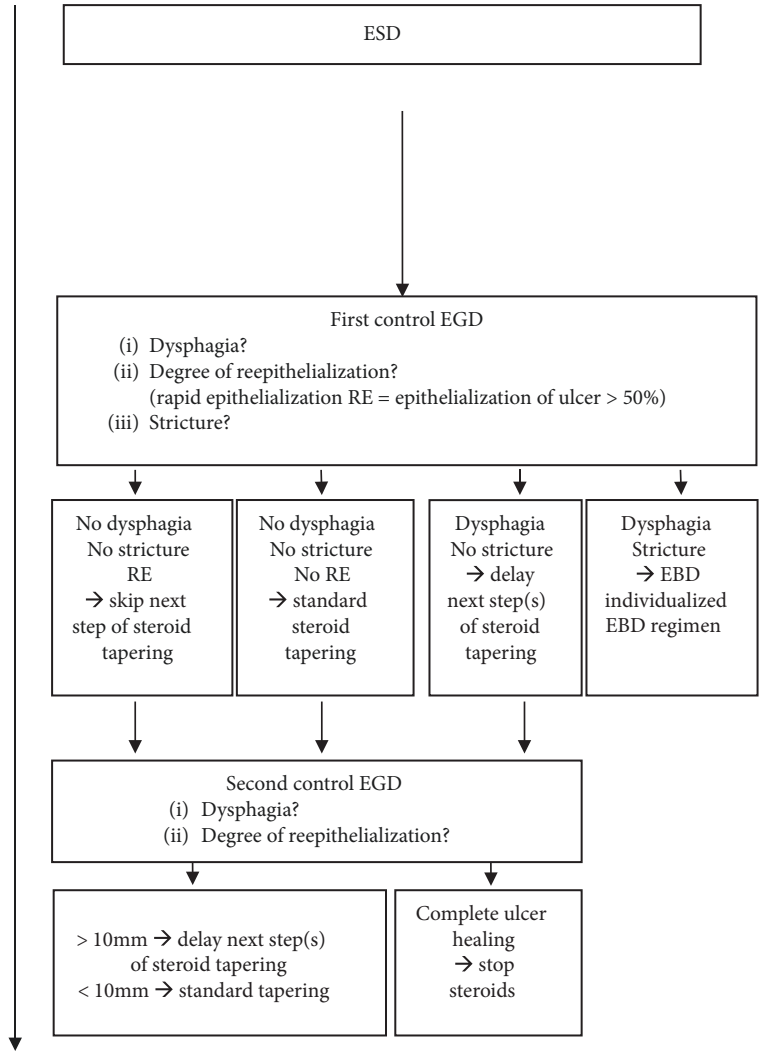

Figure 1: Regimen for stricture prevention (EBD: endoscopic balloon dilatation).

exceeded three quarters of the esophageal circumference. Extension of the resection ulcer was estimated at the end of the ESD procedure. We performed a first control endoscopy in the third week after ESD (days 15-22) under a daily prednisolone dose of 30 mg. Patients' symptoms, the extent of ulcer healing (reepithelialization from the ulcer margins), and the presence of stricture were assessed. Reepithelialization was defined as rapid (RE) when it exceeded 50% of the initial resection area. When patients denied dysphagia, the steroid treatment was tapered according to the degree of reepithelialization. When RE was noted, the next step of steroid tapering was skipped. When reepithelialization was not rapid, steroids were continued using the standard tapering regimen. When passage with the gastroscope was possible but patients reported any kind of dysphagia, the next step of steroid tapering was delayed for one or two weeks. When stricture had developed, EBD was started and continued according to the endoscopist's recommendation. In patients without stricture, a second control endoscopy was recommended in week eight. When complete healing of the ulcer was seen, steroids were stopped. When small residual ulcers ($\leq$10 mm) were diagnosed, completion of the steroid treatment was recommended according to the standard tapering regimen. When large ulcers (>10 mm) were present, a daily prednisolone dose of 5 mg was recommended for another 1-2 weeks. The treatment algorithm is shown in Figure 1. When patients reported dysphagia, endoscopy was performed on demand at any time to rule out strictures. Acid suppression with proton pump inhibitors (PPI) was started at the latest on the day before ESD and was continued for three months in all patients (pantoprazole 40 mg twice daily). When residual Barrett's epithelium was seen in the second control endoscopy, patients were scheduled for ablative therapy later and PPI therapy was continued until then.

2.8. Statistical Analysis. Calculations were performed using the software package Sigma Plot 13.0 (Systat Software, San Jose, USA). Numeric values were compared using the Mann-Whitney test. For the comparison of categorical data, a chi-squared test was employed. p values <0.05 were considered statistically significant.

Table 1: Patients and lesion characteristics.

	$n = 23$
Clinical characteristics	
Age, median (range) (years)	67 (45-84)
Sex, male/female, *n*	21/2
ASA grade, 1/2/3, *n*	8/12/3
Barrett's extent	
C (median, range) (cm)	2 (0-9)
M (median, range) (cm)	5 (2-10)
Hiatal hernia, *n* (%)	21 (91.3)
Lesion characteristics	
Paris classification, *n* (%)	
0-Is	2 (8.7)
0-IIa	11 (47.8)
0-IIb	9 (39.1)
0-IIc	1 (4.3)
Endoscopic estimation of neoplasia	
Single lesion, *n* (%)	13 (56.5)
Estimated diameter of single lesion; median (range), mm	40 (20-60)
Multifocal neoplasia (≥1 visible lesion), *n* (%)	10 (43.5%)
Pretreated lesions	0

3. Results

3.1. Patients and Lesion Characteristics. Over a 50-month period, 193 ESD procedures were performed for neoplastic BE. 27 resection ulcers exceeded ≥75% of the circumference (13.7%). Three patients were excluded because they had received additional intralesional triamcinolone injection during the first study period. Another patient was excluded because of permanent steroid treatment performed for rheumatoid arthritis. 23 patients who started the proposed stricture prevention regimen were included for further analysis. The reason for extensive ESD was a large neoplasia in 13 patients (56.5%) and multifocal visible lesions in another 10 patients (43.5%) (Table 1).

3.2. Procedure Characteristics. Table 2 shows the procedure characteristics. Resections were NCR in 19 patients (82.6%) and CR in another four (17.4%). 21 resections were judged curative (91.3%). In two patients (G3 sm1 L1 Rx at the VM and G3 sm1 L0 V0 R0, respectively), surgery was recommended but both patients refused. Both patients remained free of recurrence during follow-up of 40 months and 37 months, respectively.

3.3. Strictures. 23 patients started oral steroid therapy on the day after ESD. Patients' course is shown in Figure 2. One patient stopped steroid treatment without reasons and without notable side effects on the fourth day after ESD. He refused a scheduled control endoscopy and presented with a symptomatic stricture on day 27. Stricture was treated with three sessions of EBD. 17/19 patients with NCR and all four patients with CR underwent the recommended first control endoscopy after 2-3 weeks. At that time, all patients with CR had developed symptomatic strictures despite continued daily prednisolone dose of 30-40 mg. Repeated EBD was performed (median 6.5 sessions; range 3-14 sessions for 8-40 weeks). The length of the resection ulcer was not significantly different between the NCR and CR groups (median 42.5 vs. 50 mm; $p = 0.19$). None of the patients who continued steroid prophylaxis after NCR had developed a stricture at first control endoscopy, and steroids were tapered according to the degree of reepithelialization of the ESD ulcer. In ten patients, second control endoscopy was performed before stopping the steroid therapy. In another eight patients, second control endoscopy was not performed in time because of patient's refusal. In these patients, prednisolone was stopped according to the standard tapering regimen. In summary, 12 patients received the standard prednisolone regimen over 8 weeks. Treatment duration was prolonged to nine weeks in two patients and to ten weeks in another two. Decision to delay the treatment was made after the first control endoscopy in two and after the second control in the other two. In two patients, treatment was shortened to seven weeks after the first control endoscopy. The first control endoscopy was delayed on days 23-27 in three patients. None of these patients needed modification of the treatment. One patient had refused any control endoscopy and completed the standard steroid regimen over 8 weeks without a stricture. In summary, no stricture was seen in the NCR group when

Table 2: Procedure characteristics (*R0 for neoplasia was defined as R0 for cancer and high-grade dysplasia. **Rx resection was diagnosed at the HM in one lesion and at the HM in another).

Procedure time, median (range) (minutes)	150 (75-300)
Resection rates,n(%)	
En bloc resection	23 (100)
R status for neoplasia*, R0/R1/Rx	21 (91.3)/0/2** (8.7)
R status for Barrett's metaplasia, R0/R1/Rx	8 (34.8)/15 (65.2)/0
Resection ulcer	
75-89% of the circumference, *n* (%)	12 (52.2)
90-99% of the circumference, *n* (%)	7 (30.4)
100% of the circumference, *n* (%)	4 (17.4)
Resection specimen	
Horizontal diameter, median (range) (mm)	70 (43-110)
Vertical diameter, median (range) (mm)	45 (20-65)
Histopathological diagnosis	
Adenocarcinoma, *n* (%)	23 (100)
Single lesion, *n* (%)	16 (69.6%)
Diameter of single lesion; median (range) (mm)	40 (10-60)
Multifocal neoplasia, *n* (%)	7 (30.4%)
Histopathology,n	
Invasion depth, mucosal (pT1a)/submucosal (pT1b)	21/2
Grading, G1/G2/G3	14/6/3
Lymphatic invasion	1
Vascular invasion	0

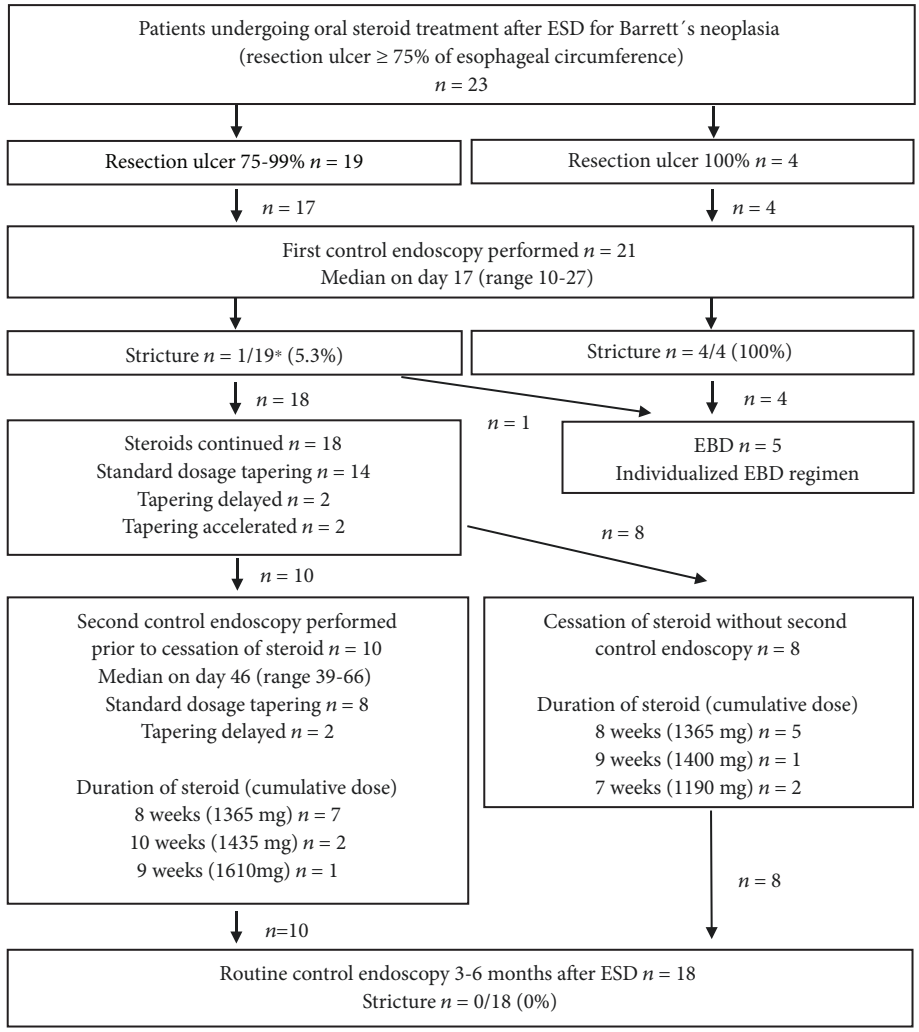

Figure 2: Clinical course of patients receiving oral prednisolone prophylaxis. EBD: endoscopic balloon dilatation. *The patient with the stricture had stopped steroid treatment without reasons and without side effects.

steroid prophylaxis was completed. In contrast, the stricture rate was significantly higher in the CR group (100% vs. 5.3%; $p < 0.001$). None of the patients developed infections or other side effects during steroid treatment. Three patients had concomitant type 2 diabetes mellitus (DM) and used oral antidiabetics at the time of ESD. Adjustment of the antidiabetic medication was not needed in any of them. None of the patients without DM at the time of ESD developed DM during steroid treatment.

Figure 3 shows examples of different courses after extensive ESD.

3.4. Other Complications. The bleeding rate was 4.3% (1/23). The patient presented with hematemesis 20 hours after circumferential ESD, and a small nonbleeding vessel was treated with endoscopic clip application. Blood transfusion was not indicated. No perforation- or procedure-related mortality was observed.

3.5. Follow-Up. In eight patients, complete elimination of BE was achieved with ESD. In one patient, a small metachronous mucosal cancer (diameter 10 mm) was resected with EMR six months after ESD, and residual Barrett's was ablated using radiofrequency ablation (RFA) another three months later. One patient, who had developed stricture after circumferential ESD, underwent repeated EBD for 6 months and refused RFA afterwards. Metachronous mucosal cancer (diameter 8 mm) was detected close to the stricture 20 months after ESD and repeated ESD was performed. Residual nonneoplastic Barrett's was treated with radiofrequency ablation in two patients, with APC in another three and with a combination of RFA and APC in another two patients.

None of the patients who received ablative therapies developed a stricture after ablation. One patient died six months after ESD because of metastatic renal cell carcinoma. Another patient died 12 months after ESD because of multiple myeloma. Median follow-up was 21 months (range 3-54).

4. Discussion

If ER exceeds 75% of the esophageal circumference, the risk for postinterventional stricture is reported to be as high as

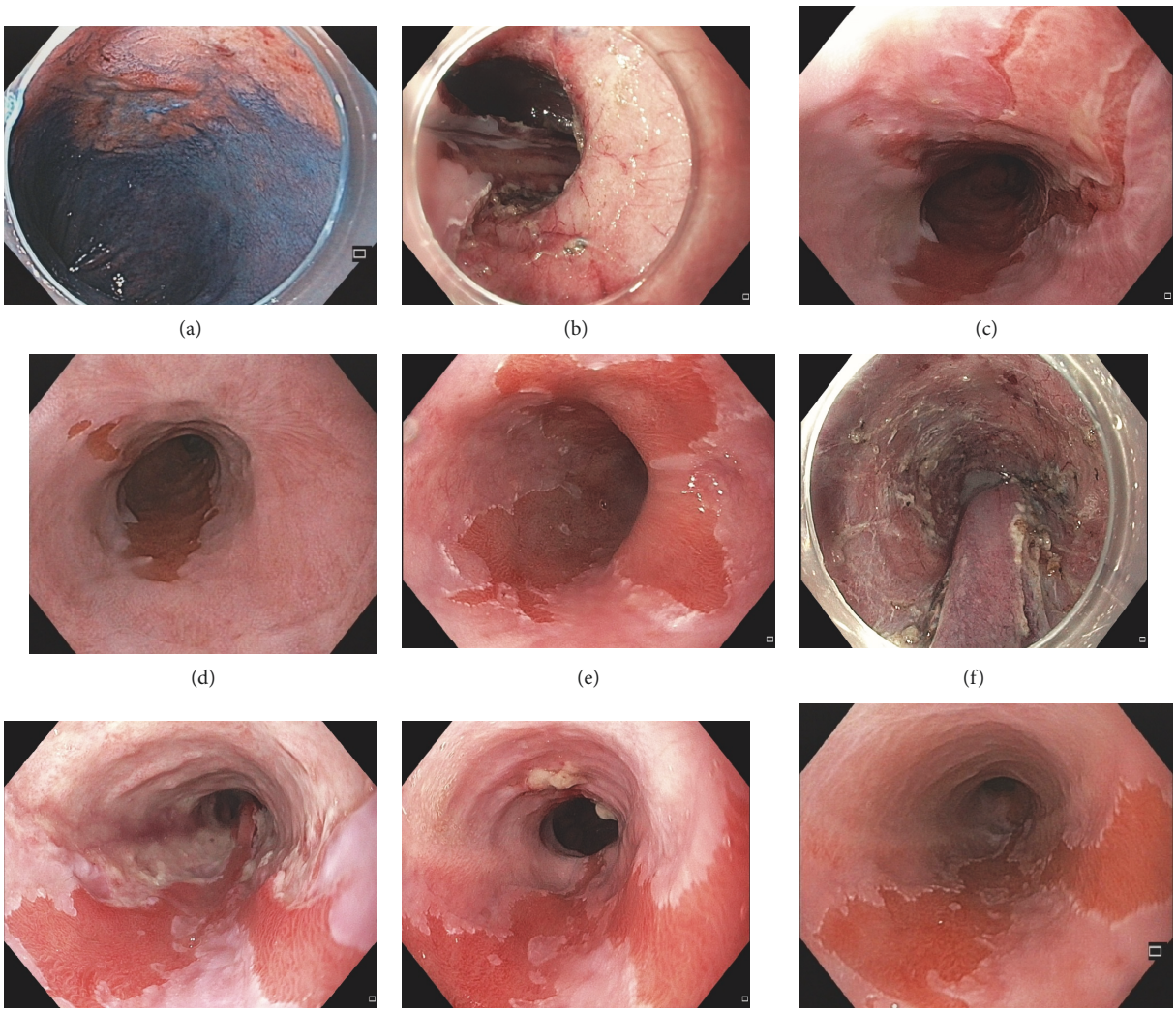

Figure 3: Examples for ESD and stricture prevention in large Barrett's neoplasia. (a) Early adenocarcinoma 40 mm in diameter within BE C7M8. (b) Resection ulcer after ESD involving 80% of the circumference. (c) First control endoscopy on d16 after ESD (prednisolone dose 30 mg): rapid reepithelialization, no stricture, mild dysphagia, and standard steroid tapering. (d) Second control endoscopy on d43 after ESD (prednisolone dose 10 mg): complete ulcer healing without stricture, standard steroid tapering (duration 8 weeks). (e) Multifocal early adenocarcinoma within BE C4M6. (f) Resection ulcer after ESD involving 90% of the circumference. (g) First control endoscopy on d12 after ESD (prednisolone dose 40 mg): no rapid reepithelialization, no stricture, no dysphagia, and standard steroid tapering. (h) Second control endoscopy on d47 after ESD (prednisolone dose 10 mg): residual ulcer without narrowing of the lumen. Prolongation of steroid tapering (duration 10 weeks). (i) Endoscopy on day 80 after ESD: complete ulcer healing without stricture.

66-100% [13–15]. Today, orally administered or locally injected steroids are first-line treatment options for stricture prevention [14, 15]. These techniques have been shown to reduce but not to eliminate the stricture risk, and the ideal treatment modality for stricture prevention remains undefined. Available data, published mainly by Asian authors, are restricted to ESD of superficial SCCs. In contrast, in Western countries, early SCC is rare and EAC arising within BE is the predominant indication for esophageal ER. EMR is the endoscopic resection method of choice for small Barrett's neoplasia and rarely causes strictures. Pech et al. reported 12 strictures in 1000 EMRs for early EAC [16]. ESD can be considered in lesions exceeding 15 mm, poor-lifting lesions, and lesions at risk for submucosal invasion [2]. Following this strategy, resections exceeding three quarters of the esophageal circumference are infrequent but unavoidable in some cases with large or multifocal neoplasia. In our study, 27/197 resections exceeded three quarters of the circumference (13.7%) and four resections were performed circumferentially (2.0%).

In 2015, we published our first data on ESD in early esophageal cancer which included nine EAC resections exceeding 75% of the circumference [6]. In the first six patients, prophylactic EBD was performed. Stricture developed in five of them (83.3%) and further EBD was required. During the later study period, three patients received a fixed-dose 8-week oral steroid prophylaxis according to the Japanese SCC data (starting with prednisolone 40 mg daily

followed by a weekly reduction of 5 mg). However, two of them (66.7%) developed dysphagia during the steroid tapering period and EBD was required. In 2011, Yamaguchi et al. had reported a stricture rate of 5.3% after oral steroid prophylaxis for ESD exceeding three quarters of the esophageal circumference [8]. Isomoto et al. reported a 50% stricture rate after circumferential ESD using the same regimen [9]. In both studies, a fixed-dose prednisolone regimen was used after ESD for SCC without routine control endoscopies (starting with 30 mg daily and tapering 30/30/25/25/20/15/10/5 mg weekly over eight weeks). Kataoka et al. described a 17.6% stricture rate for a shortened prednisolone regimen (starting with 30 mg daily and weekly tapering 30/20/10 mg over three weeks) [10]. So far, only one retrospective study using steroids after EMR in BE is available. Ratone et al. reported a 13% stricture rate using Yamaguchi's regime in 31 patients. However, he included resection ulcers exceeding 50% that makes interpretation of the data difficult [17]. Today, local injection of triamcinolone into the resection ulcer immediately after ESD is the preferred treatment strategy in Asia. Local injection is preferred in order to avoid potential side effects of systemic steroid treatment. Hanaoka et al. could reach a 10% stricture rate after injecting 100 mg triamcinolone in the ESD ulcer (one injection, fixed dose) while Hashimoto et al. reported a 19% stricture rate after repeated triamcinolone injection (days 3, 7, and 10; dose 18-62 mg) [11, 12]. A Japanese prospective randomized control trial is ongoing to compare systemic prednisolone therapy (Yamaguchi's regime) and local triamcinolone injection (Hanaoka's regime) [18]. The results are awaited and the ideal treatment regime remains undefined today, especially in Barrett's resections.

During our first study, we had seen different courses of ulcer healing and stricture development during routine endoscopies in patients undergoing prophylactic EBD [6]. We proposed that the stricture risk could be minimized when the individual scarring process would be taken into account for tapering the steroid dose and when epithelialization of the resection area would be completed before stopping the steroids. Taking these considerations into account, we decided to use a steroid regimen with a higher starting dose (prednisolone 50 mg) and individualized tapering according to the individual ulcer healing process (assessed endoscopically during the first tapering period and before stopping the steroids). Using this strategy, we could avoid strictures in all patients with NCR. 95% of our patients underwent a first control endoscopy 2-3 weeks after ESD, and the steroid tapering was modified in 21% according to different courses of ulcer healing. It remains speculative if the higher steroid dose or the endoscopy-based individualization of the tapering regimen has influenced the stricture development. In particular, the role of the second control endoscopy which was not performed in most patients seems questionable.

In contrast to patients with NCR, all patients with CR developed a symptomatic stricture within the first 2-3 weeks and repeated EBD was required. The stricture risk after CR has been addressed in Asian publications on ESD of SCCs. Hanaoka et al. described a stricture in 11/12 patients treated with local triamcinolone and up to 40 sessions of EBD were required. CR was an independent risk factor for stricture in his study (adjusted OR 19.77; 95% CI 4.67-8.72) [19]. Recently, Iizuka et al. reported a modified oral steroid regimen starting with 30 mg prednisolone and reducing the daily dose by 5 mg every three weeks (resulting in a prolonged treatment duration of 18 weeks). However, 10/11 patients had received additional local triamcinolone injections. The stricture rate after CR of SCCs was 36.4% and significantly lower compared to 82% after using Yamaguchi's regimen over 8 weeks [19]. Potential side effects of oral steroid prophylaxis regimens are feared but discussed controversially. Using a fixed-dose oral regimen over 8 weeks, Yamaguchi et al. did not report any side effects in 22 patients [8]. In contrast, Iizuka et al. reported three infections when nine patients were treated with the same regimen (pneumonia, oral herpes infection) [19]. Ishida et al. reported a case with severe disseminated nocardiosis during oral steroid prophylaxis [20]. In our study, we could confirm Yamaguchi's data and did not find infectious complications or other serious side effects in any patient. Patients should be informed about potential side effects and should be monitored carefully during the steroid treatment. Sufficient data not only on stricture prevention but also on steroid side effects are awaited from the ongoing Japanese multicenter study [18].

Today, it remains unclear if the risk of postinterventional stricture development is different for SCC and EAC and if Asian results are transferable to Western countries where EACs represent the vast majority of esophageal lesions.

Limitations of the study are the retrospective design, the small patient number, and the missing control group. Some patients did not undergo the second control endoscopy which is another limitation. Randomized controlled trials comparing different strategies are needed to define the ideal prevention strategy after extensive ER in neoplastic BE.

5. Conclusion

In our small study, oral steroid administration with an endoscopy-based individualization of dosage and treatment duration was sufficient to prevent strictures after extensive but noncircumferential ER of EAC. The stricture rate was lower compared to all previous studies reporting on steroid prophylaxis [14, 15]. In contrast, strictures could not be avoided after circumferential resection. After circumferential resection of neoplastic Barrett's esophagus, EBD should be started early. Circumferential extension of EAC is a very rare scenario and CR should be restricted to these rare lesions. The strategy for stricture prevention after CR needs to be further improved.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

There are no conflicts of interest to declare.

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Research Article

Wirelessly Powered Endoscopically Implantable Devices into the Submucosa as the Possible Treatment of Gastroesophageal Reflux Disease

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Gastroesophageal reflux disease (GERD) is a rather common disease with a prevalence reaching up to 10 or 20% in the western world. The most specific symptoms which point to the diagnosis of GERD are feelings of heartburn and the regurgitation of acidic stomach contents into the esophagus. However, a certain number of patients do not respond to standard therapy, and in these cases, it is necessary to resort to other treatment methods, such as laparoscopic fundoplication or electrostimulation of the lower esophageal sphincter. The aim of our work was to design and manufacture a miniature, battery-less stimulator to provide electric stimulation of the lower esophageal sphincter, which could be implanted deep into the submucosa of the distal esophagus. The main goal was to provide a battery-less system as opposed to traditional battery neurostimulators to reduce the size and weight of the device. An electronic prototype of a wirelessly powered implantable device was developed. We used animal models for the experiments. The device is designed to treat GERD via electrical stimulation of the muscularis propria. It is implanted into the submucosal pocket by the lower esophageal sphincter with an endoscope. This method of implantation is superior to esophageal stimulators used today because of very low invasiveness of the surgery. Bipolar neurostimulation via two gold-plated leads is provided. The device does not have any source of energy; it is powered wirelessly which reduces the risk of potential battery leakage and reduces the overall dimensions.

1. Introduction

The gastrointestinal tract (GIT) nervous system is a complex, independent network of neurons and glial cells which is responsible for controlling the functions of the gastrointestinal tract, including its motility, secretory function, and its role in immunoregulation. This network is made up of small ganglia and neurons interconnected by bundles of nerve fibers, which run along the entire gastrointestinal tract. Interstitial Cajal cells, as well as neurons, are also an important part of the enteric neural system. These are nonglial cells which can be found inside the entire gastrointestinal tract. They function much like a cardiostimulator and produce electrical activity, which leads to a peristaltic motion of the intestine in the form of slow waves [1]. The lower esophageal sphincter is made up of smooth muscles and keeps its contraction due to neurological and myogenic factors. Recent studies [2–4] suggest that electric stimulation of the gastrointestinal nervous system may represent a significant benefit for patients suffering from disorders such as gastroparesis (being effective for more than 10 years [5]), GERD, and constipation, or those who are not responding to therapy [6]. GERD and/or dysphagia is prevented by a correctly functioning lower esophageal sphincter. The LES is controlled by paracrine, hormonal, and neural factors, and it as well as the diaphragmatic sphincter works to stop gastric contents being refluxed into the esophagus [7].

Although electrostimulation therapy of the lower esophageal sphincter is a relatively new concept for the treatment of patients who are resistant to medication and also, the therapy is safe and effective in short-term and long-term studies in humans [3, 4, 6, 8], there have been no negative side effects

to this form of the treatment and it has been proven to provide both significant and sustained relief from the symptoms of GERD while at the same time eliminating the need for PPI medication and reducing esophageal acid exposure. Canine models were first used to study the effects of electrostimulation of the LES in the treatment of GERD [9, 10]. Reports have stated that electric stimulation (20 Hz, pulse width of 3 ms) with 2 pairs of electrodes causing a contraction and increase of the pressure of the sphincter complex was effective in preventing gastroesophageal reflux. The effects of electrostimulation of the LES in patients with GERD using both high (20 Hz, pulse width of 200 μs) and low (6 cycles per minute, pulse width of 375 ms) frequencies have also been examined. Both high- and low-frequency electrostimulation increased LES pressure but did not affect LES relaxation or residual pressure when swallowing [2]. It has been shown that high-frequency stimulation is preferable as it requires less energy and therefore extends the life of the battery. There are only two GIT stimulators currently in use, the Enterra II [11] and EndoStim [12], which use intramuscular catheters to stimulate gastric muscle tissue. Both of these require surgical implantation under general anesthesia and have a large unwieldy unit attached. As such, the option of a device implanted into the gastric submucosal layer which communicates wirelessly would be a large step forward in patient comfort. Neurostimulation of LES using endoscopically implanted leads exteriorized transnasally was also assessed and was successful, resulting in significant increase in LES pressure with no complaints of dysphagia [4]. Research has already proven that it is possible to implant a miniature neurostimulator into the submucosa [13, 14]. This research provides a scope for further improvements regarding power management (especially the option of wireless power device without battery), conforming to the rules and regulations for medical implants and wireless communication and the possibility of bipolar neuroelectrostimulation.

2. Material and Methods

2.1. Implantable Device Prototype Construction. The device which was constructed to assess the technology consists of 4 main components—printed circuit board (PCB) with electrical components, wireless power receiving coil, liquid-resistant enclosure, and stimulation electrodes.

The main PCB is manufactured on a FR4 material and the thickness is 0.8 mm. The electronics comprises of two main parts—control and power management.

The control part is integrated into a single microcontroller—PIC16LF1783—which is used to generate the electrical stimulation impulses. Two timer modules are used to generate stimulation pulses—the first timer sets the frequency of pulses and the second timer is used to turn on and off the stimulation at predefined times. The pulses generated by the logic part of the microcontroller is then amplified by on-chip operational amplifier and outputted to the stimulation electrodes.

The power management circuitry contains 3 main parts—voltage doubler with Avago HSMS282P zero-bias Schottky diodes, parallel LC resonant circuit with receiving coil, and low-drop regulator. A 5.1 V Zener diode is placed across the rectified voltage to protect the capacitor bank against damage due to overvoltage. The rectified voltage is converted to a stable 2.5 V DC power rail with a TPS70625 low-drop voltage regulator. This power rail is used to power the microcontroller. TLV803 voltage supervisor is utilized to avoid undervoltage lockout condition.

The main PCB is protected from the surrounding space using a technique which is today used in implantable medical devices like breast implants—by coating with functional biopolymers. In this case, multiple dip-coating of skin-colored 3Dresyn-MF UV-cured monomer-free resin for 3D printing was used. Between each coating, a curing schedule of 1 minute of 500 mW/cm^2 UV light with a wavelength of 405 nm from each side was performed. A total of 4 coatings were required to fully cover the device.

On the outside, the stimulation electrodes are connected. To reduce the thickness, the electrodes are manufactured on a polyimide substrate as a flexible printed circuit board. The electrodes are gold plated to limit corrosion and enhance biocompatibility. The electrodes are glued to the encapsulated electronics with the coil, and two straps are wound around the electronics and soldered on the other side, securing the electrodes against separation which occurred during first experiments. The completed device is depicted in Figure 1.

2.2. The Wireless Powering Device. The powering device was energised by an alternating magnetic field with a frequency of 1 MHz. This magnetic field was created by a custom-developed device intended for this task. This device comprised of a printed circuit board, a heatsink, and a rectangular coil composed of 3 turns. The coil was connected in series with a capacitor bank and tuned to a resonance frequency of 1 MHz. This was done to maximize the current flowing through the coil. The magnetic field strength in a constant distance from a wire is proportional to the current flowing through the wire.

$$B = \frac{\mu_0 I}{2\pi r}. \quad (1)$$

By measuring the impedance of the coil at target frequency, the resonance capacitor value was determined. The alternating current at predefined resonance frequency is then generated by an H bridge formed by four N-MOSFET transistors. The control signals for the MOSFET transistors are generated by a dedicated microcontroller.

2.3. Energy Propagation through Tissue. One of the major concerns in wireless power transfer is the influence of surrounding materials, especially materials in between a receiving and transmitting device. In this case, the energy is transferred via air coupling of a transmitting and receiving coil. This is commonly referred to as "near-field" communication. The second type of energy transfer is far-field which uses electromagnetic waves to transmit energy. The antenna size is then proportional to the wavelength. For 1 GHz, the wavelength in vacuum is around 30 cm. However, electromagnetic waves are significantly attenuated at these

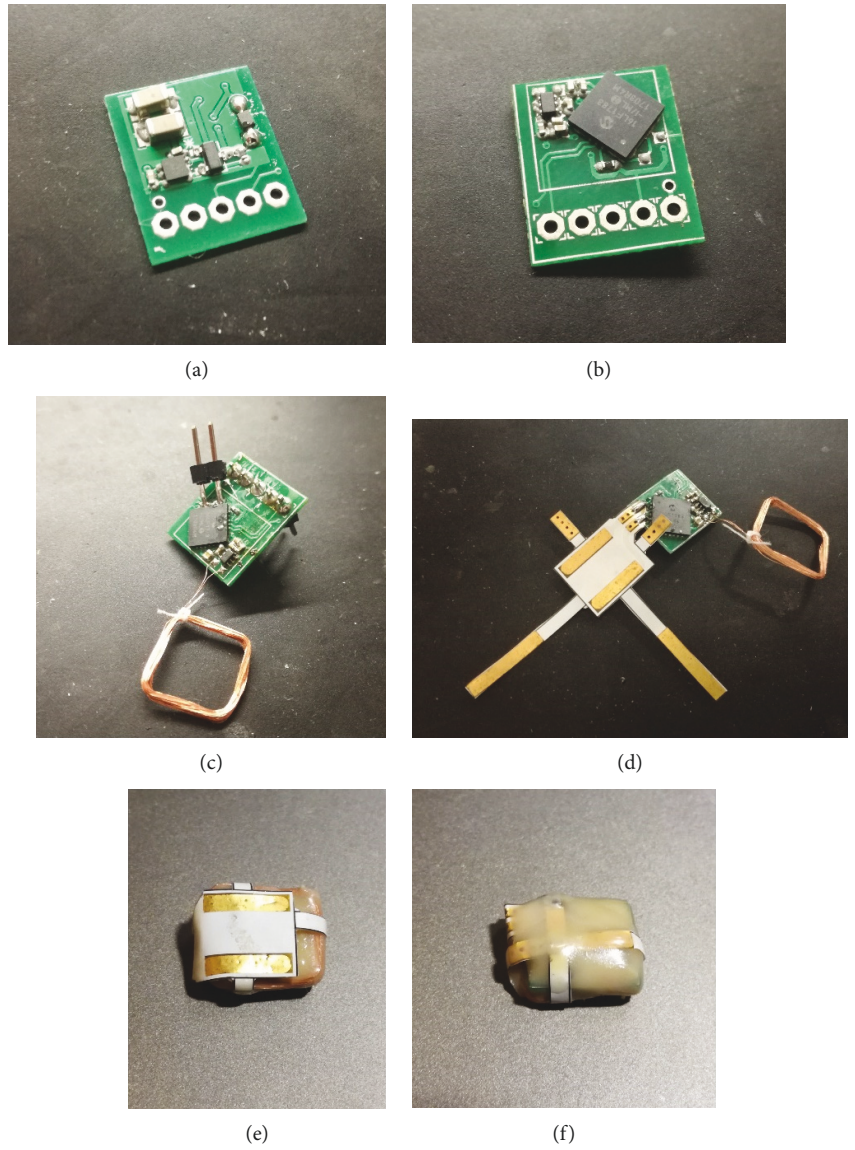

Figure 1: Composite picture of the implantable device prior to implantation: (a) back side of the PCB, (b) front side of the PCB, (c) PCB prepared for programming and testing, (d) trimmed PCB with stimulation electrodes ready for encapsulation, (e) encapsulated PCB—front side, and (f) encapsulated PCB—back side.

frequencies. The requirement of using high frequencies to achieve good antenna gain, attenuation by tissue, and regulatory requirements renders far-field energy transfer to wireless implant impractical.

The near-field wireless power transfer in this frequency range can be significantly affected only by materials with high conductivity by creating eddy currents in them (metals) or materials with high magnetic permeability (e.g., mu-metal or permalloy). To support this statement, an experiment was conducted (Figure 2). We have secured a wireless receiver coil with a parallel resonant capacitor and wireless transmitter 11 cm apart each other. The first measurement was done with no object placed between the coils. A 1 kOhm resistor was placed across the receiving coil resonant circuit to simulate an electric load. The voltage across the resistor with energy transfer active was measured, and received power was calculated using Ohm's law. After that, the experiment was repeated but in between transmitting and receiving coil, an 8 cm thick porcine tissue was placed. The average power (averaged over 10 seconds) received with and without animal tissue in between was 0.560 mW and 0.588 mW, respectively. This is in accordance with the theory that the effect of tissue on this type of wireless power transfer is minimal (4.7% decrease). One of the possible explanations of the decrease is detuning of the transmitting LC circuit. This may be compensated for during development, and the effect of the tissue presence will be further minimized (at the same distance and angular position of the coils, the power transferred will be smaller without the presence of the tissue).

2.4. Animal Model. A porcine model made of the stomach and a long segment of the esophagus was used. It is a

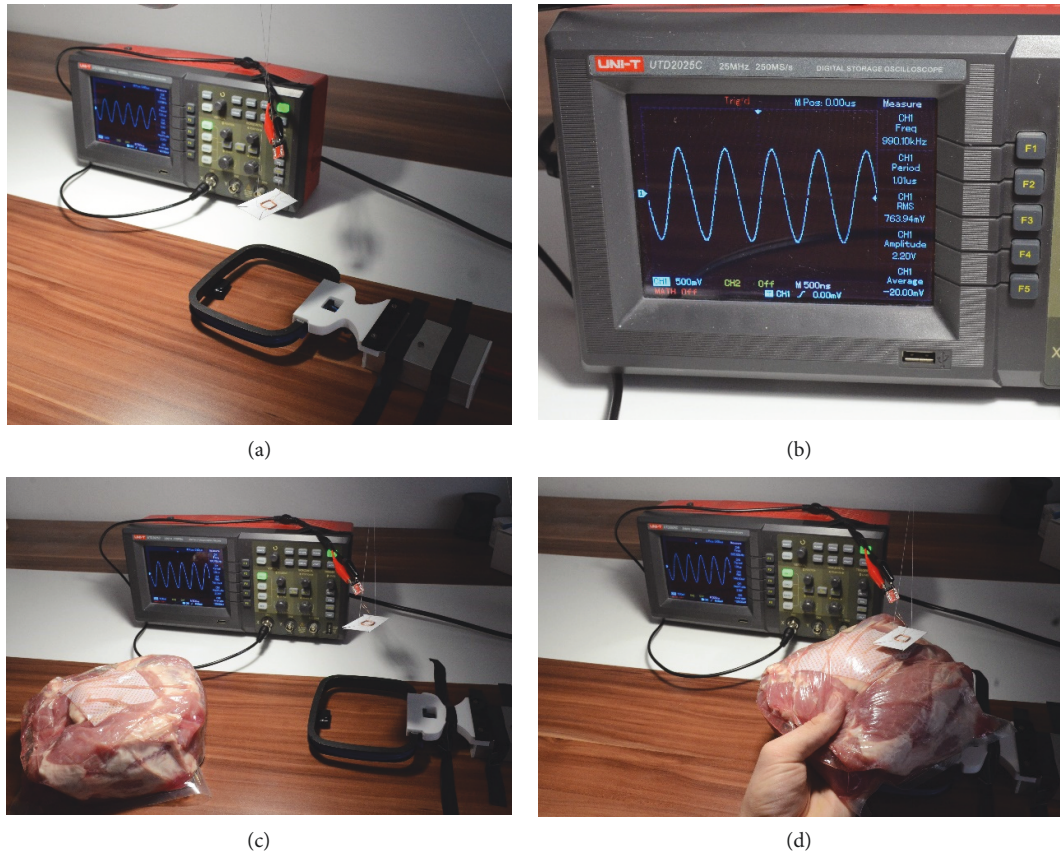

Figure 2: Composite picture of the experiment which evaluates effectivity of wireless power transfer through tissue: (a) measurement setup (receiving coil hovers 11 cm above transmitter coil), (b) detail of oscilloscope screen, (c) testing without the presence of porcine tissue, and (d) testing with the presence of porcine tissue.

commonly used model for training of techniques such as ESD (endoscopic submucosal dissection), tunnelisation, and POEM (peroral endoscopic myotomy). The overall view of the model with the implanted device and inserted endoscope is provided in Figure 3.

2.5. Endoscopic Implantation of the Device. Using the same endoscopic submucosal tunnelling method usually used for POEM, first described by Inoue et al. [15], the device was implanted into the submucosa. This procedure is documented in Figure 4. A combination of methylene blue and saline solution is first injected about 5 cm above the LES into the submucosal layer with a therapy needle catheter (25G). An electrosurgical knife is used to make an opening into the submucosa. This submucosal pocket is then dilated and disrupted, thus creating a 5 cm long tunnel large enough for the implantation of the device. Using a grasper, the device is moved into the area of the pocket and released. Grasping forceps then move the device into the submucosal tunnel. The opening made by the initial incision is then closed with haemostatic clips.

After implantation, a transmitter coil, which produces an alternating magnetic field of 1 MHz frequency, is powering the implantable device (Figure 5).

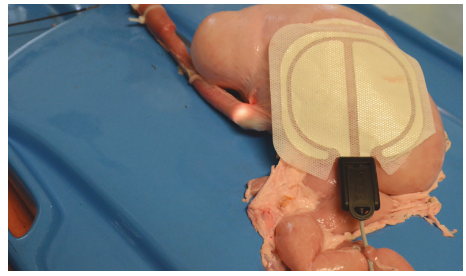

Figure 3: Animal model with the highlighted place of the implantation of the device near the lower esophageal sphincter.

3. Results

The prototype of the esophageal neurostimulator was successfully endoscopically implanted in a pig model. We used the tunnelisation method. The prototype was attached in the vicinity of the muscular layer of the LES. The entire procedure took approximately 30 minutes in total and was without any perforation or other complications. The device and its functions were tested with an oscilloscope ex vivo.

The wireless energy transfer device was successfully able to power the implant from approx. 12 cm. This means that

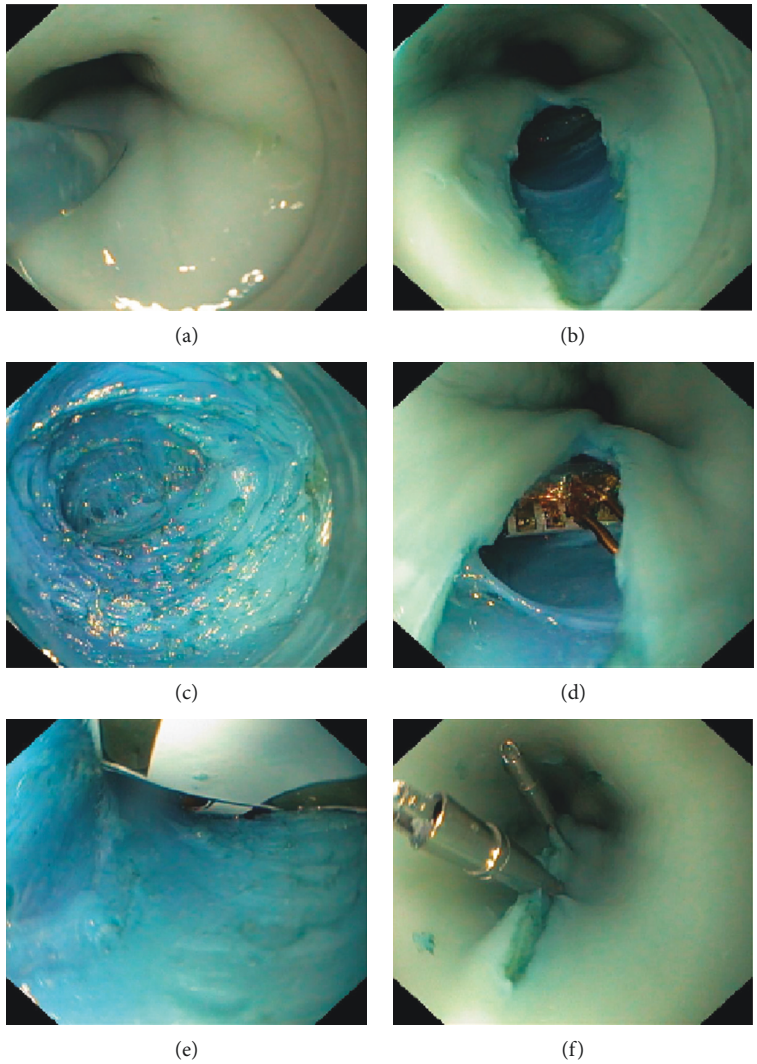

Figure 4: The process of implanting the device as shown in a composite picture: (a) submucosal injection; (b) vertical opening; (c) view of submucosal tunnel; (d) device inside the tunnel; (e) final implant positioning; (f) opening closure.

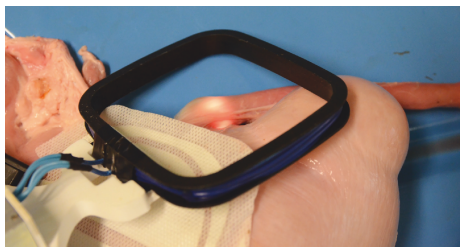

Figure 5: Powering the implant using wireless inductive power transfer.

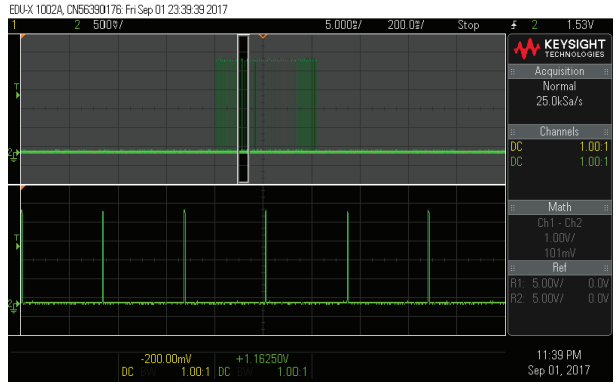

Figure 6: Stimulation pattern waveform generated by the implantable neurostimulator.

the microcontroller in the device was able to power up correctly and start generating stimulation patterns (Figure 6).

Next, the presented design of electrodes does not separate from the device which was one of the main issues during previous experiments. The electrodes are also constructed from intrinsically biocompatible materials (polyimide and gold, respectively).

A novel method of dip-coating of the device in biocompatible monomer-free resin was used which is a major improvement over previous research which did not use biocompatible coatings for device prototypes.

The weight of the neurostimulator is 1.22 grams (60% decrease over the previous experiment), and the volume is 0.74 cm^3 (40% decrease over the previous experiment).

4. Discussion

This test proves that a tiny implantable device without a battery may be used for LES neurostimulation. This innovative neurostimulator could provide patients with a reliable and comfortable solution to currently used surgical methods. The device has very low power requirements in standby, in terms of tens of microwatts, because it has no wireless communication. Through power cycling of the energising coil externally, the rate of neurostimulation can be controlled.

Endoscopically implanted battery-less devices which control neurostimulation have potential uses not only in the general population but also in problems caused by other sphincter dysfunctions. Although endoscopically implanted electrodes are proven to be effective [8], the determination of the efficacy of the neurostimulator on live animals will require further experimentation to be confirmed. Based on previous experiments with implantation of a device to the stomach and esophagus, we have found a size limit of the device. This was the primary motivation for the development of battery-less version of the device. The battery and charging electronics form a significant portion of the volume of the device. Also, any battery always represents a hazard, when any explosion or leakage in this specific area could result in serious injury or death. Thus, putting the energy source outside of the implant was a logical step to reduce the size and increase safety. In this experiment, we have confirmed that this topology of an implantable neurostimulator is feasible.

The new method of creating a biocompatible housing around the device is suitable for short-term experiments. When performing longer experiments (i.e., weeks), there is a possibility that moisture could leak into the implant via the interface between the PCB and outside of the implant where the stimulation electrodes are located. In that case, a layer of conformal coating of the PCB before coating the PCB with biocompatible 3D printing resin could add sufficient protection. In the case of a not biocompatible material, there is a significant risk of implant rejection. Also, the implant could be prone to migration, requiring additional solution for fixation.

5. Conclusions

This research has proven that the lower esophageal sphincter can receive controlled neurostimulation from a miniature implantable device without a battery. The neurostimulation can be provided by our solution which makes a relatively simple and, most importantly, reliable device. Its wireless nature means that it has very low power needs, only tens of microwatts. By power cycling the energy coil externally, we can regulate the power and rate of neurostimulation.

This technology presents a promising option for use in the general public with such problems as GERD. In both cases, the size of the device, its ease of implantation, its longevity, and its safety offer a leap forward when compared with contemporary neurostimulation solutions. On the other hand, the endoscopic implantation is quite a challenging procedure comparable to POEM. Our opinion is that the implantation procedure is easier because it does not require myotomy. But in almost every country, a high-volume centre for POEM is present. Thus, the accessibility of the treatment should be high. Periprocedural complications like bleeding and perforation can occur. On the other hand, data which supports high safety of POEM procedure is available [16]. On the other hand, fundoplication which was examined as a possible solution for GERD has worse track record according to literature [17].

Based on these results, we plan to confirm the effect of the stimulation of the device on a living pig with an esophageal manometry. For these experiments, it is planned to make a special enclosure for biocompatible materials as the device is expected to stay in the submucosa for extended durations of time (at least several weeks). The enclosure will be either machined from biocompatible polymer (i.e., PEEK) or made using additive manufacturing from medical-grade resins. The position of the neurostimulator close to the lower esophageal sphincter creates an opportunity to place a pH sensor outside of the submucosa. A feedback-controlled neurostimulator which would use real-time data from a pH sensor to control the neurostimulation could offer significant power savings as the stimulation would be active only when a reflux episode occurs.

Data Availability

The detailed description of the hardware as well as the implantation technique used is described in the article. The images which demonstrate successful implantation of the device into the submucosa and ex-vivo test of the implantable device (which are the results of the research) are also included within the article.

Conflicts of Interest

The authors declare that they have no conflict of interests.

Acknowledgments

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