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RESEARCH ARTICLE

Endoscopic-Assisted Electrochemotherapy Versus Argon Plasma Coagulation in Non-Curable Esophageal Cancer – A Randomized Clinical Trial

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Abstract

Background: In this randomized clinical trial, we compared endoscopic-assisted electrochemotherapy (ECT) with argon plasma coagulation (APC) in patients suffering from esophageal cancer. We hypothesized that an initial, local tumor treatment could prevent or prolong the time to severe, obstructive dysphagia. Previous studies suggest that ablative therapies might have survival advantages compared with placing an esophageal stent. Methods: We aimed to include 50 patients with non-curable esophageal cancer. Patients were randomized to ECT or APC (1:1) as an upfront treatment and hereafter referred for standard treatment. The primary endpoint was the difference in time to interventional treatment demanding dysphagia. Secondary endpoints included side effects, symptom palliation, tumor response, and survival. Results: Ten patients were included (the study was prematurely terminated due to recruitment challenges), and the results are, therefore, mainly exploratory. Five patients received ECT, and four patients received APC. The median survival time among all patients was ten months. Two patients in the APC group and no patients in the ECT group had an esophageal stent placed during the follow-up period. One month after treatment, dysphagia relief was observed in five patients (two patients in the ECT group), and four patients had a partial response evaluated from CT imaging (three patients from the ECT group). No severe adverse events were registered in either group. Conclusion: ECT and ACP were administrated as initial therapy with few side effects, and none of the patients in the ECT group developed interventional treatment demanding dysphagia during their remaining lifetime. Future studies with ECT should focus on both symptom palliation, the need for re-intervention, and survival.

Introduction

Dysphagia is the dominant symptom in patients with non-curable esophageal cancer. Recent data from our center showed that 76% of the patients suffered from dysphagia when diagnosed, whereas 8% suffered from complete dysphagia. 1 Dysphagia leads to malnutrition and weight loss and might also impair the patient's likelihood of receiving oncological treatment and increase treatment toxicity. 2 Therefore, relieving the symptom burden in these patients as quickly as possible, but without compromising oncological outcomes, is of high clinical importance.

Today, the most common approach in patients with obstructive tumors is to place an esophageal stent. Placing a stent includes the risk of adverse events, such as pain, discomfort, dislocation, or perforation of the esophagus. 3 Some studies suggest that stent placement might negatively affect survival and oncological outcomes. 1,4,5 Argon plasma coagulation (APC) has been used to induce hemostasis since the 1970s. Still, its role in tumor debulking is debated 6,7 since the procedure must be repeated in intervals from 6-12 weeks to maintain lumen patency. 7,8 Some studies have demonstrated APC (and other non-stent treatments) to be superior to stenting in regard to survival 7,9,10, while another study found no survival differences. 8 Overall, there are no current effective local treatment options with long-lasting responses.

Electrochemotherapy (ECT) is a well-established therapy and the first-line treatment for different cutaneous malignant lesions. 11,12 In ECT, locally applied electrical pulses cause temporary openings in the cell membrane, increasing the intracellular uptake of otherwise poorly or impermeable molecules. 13 Combined with chemotherapeutic drugs, this leads to increased cytotoxicity and cell death. 14 A novel electrode makes it possible to treat tumors in the gastrointestinal tract endoscopically. In the first pilot study 15, six patients with non-curable esophageal cancer were successfully treated with endoscopic-assisted ECT without serious complications. A visual tumor response was observed in five patients, which was further confirmed with magnetic resonance imaging in two patients. Next, in 2022, we evaluated calcium electroporation 16 as a potential palliative treatment in eight patients with non-curable esophageal cancer. 17 Furthermore, ECT and calcium electroporation have been evaluated in colorectal cancer with promising results. 18,19

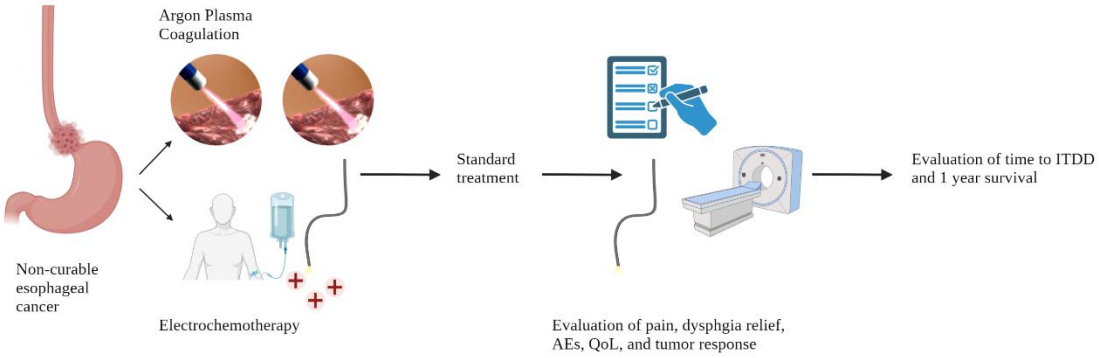
In this trial, we hypothesized that ECT or APC, as an initial add-on treatment in patients with non-curable esophageal cancer, could improve the patient's ability to intake food and fluids and prevent complete dysphagia. An early, local treatment was believed to lead to a better tolerance towards standard treatment and possibly better oncological outcomes. We further hypothesized that ECT would be superior to APC regarding maintaining esophageal luminal patency for an extended period.

Methods

STUDY DESIGN

This study was performed at the Department of Surgery and Transplantation, Copenhagen University Hospital, Rigshospitalet, from August 2021 to June 2023. Data are reported according to CONSORT guidelines. The study was a sponsor-investigator-initiated, open-label, phase 2 clinical randomized trial (simple randomization, 1:1) comparing ECT with APC as initial palliative treatment in patients with non-curable esophageal cancer, including tumors in the gastroesophageal junction. The primary endpoint was the difference in time to Interventional Treatment Demanding Dysphagia (ITDD). Time to ITDD was defined as the time from diagnosis to when the patient underwent an endoscopic intervention due to progressive dysphagia (including re-treatment, esophageal stent, endoscopic assisted feeding tube, percutaneous gastrostomy, or balloon dilatation). The second endpoints included palliation (dysphagia and pain), quality of life, Adverse Events (AEs), and tumor response. The tertiary endpoints were 90-day and 1-year survival. After the trial treatment, all patients were referred for standard care. In case of increasing dysphagia after the treatment, the patients were referred to the surgical department and evaluated according to clinical guidelines. To ensure correct registration of early side effects, but without compromising standard treatment, the patients were referred for oncologic therapy at the earliest seven days after study treatment (a maximum of 21 days). Figure 1 presents a study overview.

Figure 1 – Study overview



Patients with non-curable esophageal cancer were randomized to Electrochemotherapy or Argon Plasma Coagulation. After the treatment, patients were referred for standard oncological care and followed in the outpatient clinic for up to three months. Upper endoscopy and a CT scan were performed. Time to Interventional Treatment Demanding Dysphagia (ITDD) and survival were registered until the end of the trial (minimum of one year). AEs = Adverse Events, QoL = Quality of Life questionary (EORCT QLQ C-30). This figure was created with BioRender.com.

PARTICIPANTS

Patients with newly diagnosed esophageal cancer, not candidates for potentially curative treatment, could be enrolled in the trial. The study treatment was given before other oncological treatment was introduced. Inclusion criteria were: age $\geq$ 18 years, malignant tumor in the esophagus, evaluated by a multidisciplinary team and considered unsuitable for potentially curative treatment, no other anticancer therapies were allowed before enrollment, performance status $\leq$ 2 (ECOG/WHO) 20, expected survival > three months, platelet count > 50 billion/l, International Normalized Ration <1.5, se-creatinine <150 µmole/l, willing and able to comply with the protocol, adequate contraception (if relevant), and written informed consent. Exclusion criteria were: non-correctable coagulation disorders, clinically significant cardiac arrhythmia, pregnancy or lactation/breastfeeding, concurrent treatment with another investigational medicine, contraindications for using bleomycin including a previously cumulative dose >240.000 UI/m^2, and stenosis that prevents the passage of the endoscope. Furthermore, patients with other clinical conditions that, in the investigator's opinion, would make the patient unsuitable for the study or unable to comply with the study requirements were excluded from the study.

TREATMENT PROCEDURE

Electrochemotherapy

The procedure was performed in an outpatient setting under general anesthesia. The pulses were delivered using the ePORE® generator (Mirai Medical, Galway, Ireland) with bipolar high-frequency pulses of 1000V/cm, 172 kHz (pulse burst frequency), and a total energized time of 6 ms. The EndoVE® electrode (Mirai Medical, Galway, Ireland) was used and mounted at the tip of the endoscope. The electrode has a chamber with two parallel electrodes where the tumor tissue is drawn into the treatment chamber. An ECG trigger monitor was connected to the pulse generator, synchronizing the pules with the R-wave to prevent cardiac arrhythmias. Bleomycin, Baxter A/S (15.000 IU/m^2 body surface area) was administered intravenously. Eight minutes later, the pules were delivered according to the updated European Standard Operating Procedures of Electrochemotherapy. 11 The electrode was placed on top of the tumor tissue, and pulses were applied until the whole tumor area was treated. Antibiotics (4 g Piperacillin/0.5 g Tazobactam and 1.5 g Metronidazole) and glucocorticoids (16 mg Dexamethasone) were administrated intravenously. All patients were treated with Fluconazole (100 mg daily) for two weeks to prevent and palliate possible side effects. If necessary, Ondansetron (8 mg twice daily) and Prednisolone (25-50 mg daily) were prescribed. 15

Argon Plasma Coagulation

The treatment with APC was also performed in an outpatient setting, and all patients were lightly sedated if requested. It was planned as a two-stage procedure where APC therapy was given twice, with seven days between the treatment sessions. All patients were treated with the APC2® (ERBE, Tuebingen, Germany) with a maximal electrical power of 60 W. The APC applicator used (ERBE, Tuebingen, Germany) was 2.3 mm in diameter.

OUTCOME ASSESSMENT

We followed the patients with scheduled visits in the outpatient clinic seven days, 2-4 weeks, and three months after treatment, respectively. Time to ITDD was registered for a minimum of one year for all participants. Adverse events were registered according to Common Terminology Criteria for AEs (CTCAE) scale, version 5.0 21, for 14 days after treatment. Esophageal perforation was recorded for up to 30 days. At every clinical examination, patients were asked about pain (VAS) and dysphagia (Mellow Pinkas dysphagia score 22) and were further requested to fill out a quality-of-life questionary (EORCT QLQ C-30). A CT scan and an upper endoscopic examination were performed after 2-4 weeks and again three months after treatment. Survival was registered at 90 days and a minimum of one year. An electronic Case Report Form was kept individually for all participants where only the investigators and the monitor could access the data. REDCap hosted by Capital Region of Copenhagen, was used. 23,24

STATISTICS

A sample size calculation was performed using a power of 0.8 and a significance level of 0.05 based on the primary endpoint. Mean time to ITDD (from diagnosis) was estimated to be 12 weeks in the APC group and 16 weeks in the ECT group (lasting effect for 18 weeks, 75% response rate), respectively. To demonstrate a difference, 23 patients needed to be included in each arm. To ensure complete inclusion and fulfillment of the study, we aimed to include 50 patients (approximately 10% drop-out).

Due to the premature termination of the trial, only descriptive statistics were used to present baseline characteristics, differences in time to ITDD, and results of secondary outcomes. Kaplan-Meier plots were used to illustrate survival, but statistical comparisons were not made.

ETHICS

The Danish Medicine Agency (identifier: 2020101905) and the Regional Ethics Committee (identifier: H-22068213) approved the study protocol. The trial was conducted according to the Declaration of Helsinki 25 and Good Clinical Practice and was monitored by the GCP unit at Copenhagen University Hospital. The study protocol was registered at clinicaltrialsregister.eu (EudraCT number: 2020-002878-27) before enrollment of the first patient. The randomization was performed in REDCap by one of the investigators.

Results

The enrollment of patients was prematurely terminated in June 2022 due to 1) challenges in recruitment and 2) subsequently introduced competing protocols evaluating immunotherapy for non-curable esophageal cancer (Clinicaltrials.gov Identifier: NCT05052801 and NCT 04949256, respectively).

PATIENTS

Between September 2021 and June 2022, 47 patients with non-curable esophageal cancer were initially screened for inclusion, and ten were included in the final trial. Most patients ineligible for the trial had an obstructive tumor or a performance score > 2. Nine patients were treated, five were treated with ECT, and four received treatment with APC. The last patient was randomized to APC treatment but declined treatment. Baseline characteristics are presented in Table 1.

Table 1 – Demographics

Patient ID	Gender / Age	Tumor Type / Location / cTNM-stage	Initial Dysphagia Score *	PS / ASA score	Treatment
1	Male/75 yo	Scc / Lower third / cT3N0M1	0	0 / 2	ECT
2	Male/77 yo	Adc / Lower third / cT3N1M1	2	2 / 2	ECT
3	Male/61 yo	Adc / Lower third / cT3N2M1	2	0 / 2	APC
4	Male/64 yo	Adc / Lower third / cT3N0M1	0	0 / 1	ECT
5	Male/70 yo	Adc / Lower third / cT3N3M1	2	0 / 2	APC
6	Male/69 yo	Adc / Lower third cT3N3M1	1	0 / 2	APC
7	Male/84 yo	Adc / Middle & lower third cT3N3M1	2	1 / 3	APC
8	Male/64 yo	Adc / Lower third cT3N2M1	3	1 / 2	ECT
9	Male/48 yo	Scc / Middle third cT3N3M1	1	0 / 2	N/A

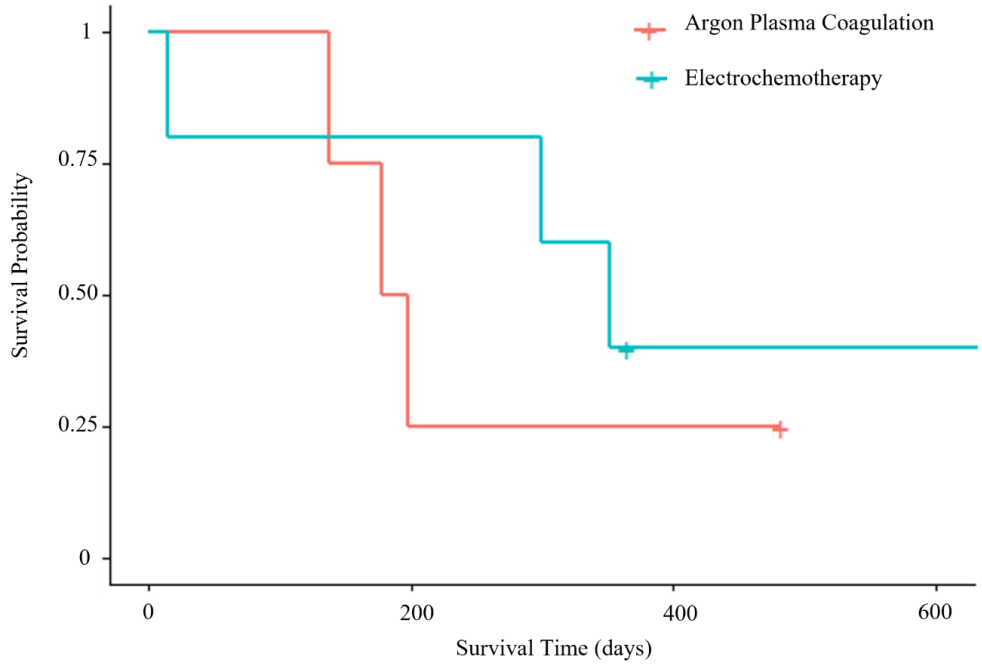
Patient ID	Gender / Age	Tumor Type / Location / cTNM-stage	Initial Dysphagia Score *	PS / ASA score	Treatment
10	Male/63 yo	Adc / Lower third cT3N3M1	1	0 / 2	ECT

General characteristics, all ten included patients. Tumor type, tumor location, and initial dysphagia are presented. Furthermore, experimental treatment type is presented. PS = Performance Score (ECOG/WHO) 20, ASA score = American Society of Anesthesiologists Score, Scc = Squamous cell carcinoma, Adc = Adenocarcinoma, ECT = Electrochemotherapy, APC = Argon Plasma Coagulation. *0 = able to swallow normal food/no dysphagia, 1 = able to swallow some solid food, 2 = able to swallow only semi-solid food, 3 = able to swallow only liquids. 22

EFFECT ON TIME TO INTERVENTIONAL TREATMENT DEMANDING DYSPHAGIA AND SURVIVAL

All patients were followed until death or were censored in June 2023 (minimum one-year follow-up for all participants). The median follow-up time was 299 days (min: 14 days, max: 652). Two patients treated with APC experienced ITDD during the follow-up period and had a stent placed at 93 days and 364 days after treatment, respectively. No patients in the ECT group developed ITDD. Survival data are presented in Figure 2. Three patients were alive at the end of the study. No statistical comparisons were made due to the low patient number.

Figure 2 – Survival



Patients (n=9) were followed until death or were censored in June 2023 (minimum 1-year follow-up). Kaplan Meier plots are provided for each treatment group separately. No statistical comparisons were made.

SAFETY

No intraoperative complications occurred. One patient was re-admitted shortly after treatment with ECT due to dehydration and hyperkalemia. The patient's condition rapidly worsened, and the patient passed away two weeks after the treatment. The CT imaging showed no changes in the treated area in the esophagus, but increased tumor burden in both pulmonary and liver metastases, compared with baseline CT. The death was considered unrelated to the study treatment. Another three patients experienced minor AEs and side effects after treatment (Table 2). Only one patient used the prescription for Ondansetron and Prednisolone, and four patients treated with ECT used the prescribed Fluconazole for preventative purposes. All seven patients initially considered eligible for systematic oncological treatment could initiate standard treatment without delays within the first month after treatment.

Table 2 – Safety assessment

Patient ID	Treatment	AEs (CTCAE Grade)
1	ECT	No AEs
2	ECT	Pain (2) Worsening of dysphagia (1) Hyperkalemia (2)* Dehydration (3)*
3	APC	Syncope (2)
4	ECT	Pain in the lower limb (2)
5	APC	No AEs
6	APC	No AEs
7	APC	No AEs
8	ECT	Nausea (1)
9	N/A	N/A
10	ECT	No AEs

All Adverse Events (AEs) occurring within the first 14 days after treatment were registered. *Condition with dehydration and hyperkalemia, which led to hospitalization and access to palliative care. ECT = Electrochemotherapy, APC = Argon Plasma Coagulation, CTCAE = Common Terminology Criteria for Adverse Events scale, version 5.0. 15

SYMPTOM PALLIATION AND QUALITY OF LIFE

Five patients (two patients treated with ECT and three patients treated with APC) reported less dysphagia one month after treatment. However, the patients initiated their chemotherapy treatment during this period. Initially, three patients suffered from local tumor pain, and one patient treated with APC reported less pain during follow-up. Only 50% of the quality-of-life questionaries were completed during the follow-up program why this data was not reported.

TUMOR RESPONSE

All nine patients were evaluated with CT. No complete response was observed. Three patients in the ECT group and one patient in the APC group had a partial response from the first CT (all patients had, however, already initiated systemic chemotherapy treatment). Six patients had an upper endoscopy performed 2-4 weeks after treatment. One patient from each group had a visual tumor response with less intraluminal tumor burden. Clinical photos from a patient before and after treatment with ECT are presented in Figure 3. In two patients, no visible changes were observed. Lastly, tumor response could not be assessed in two patients due to an obstructive tumor in one case, making it impossible to pass with the endoscope and patient discomfort in the other case.

Figure 3 – Endoscopic response evaluation

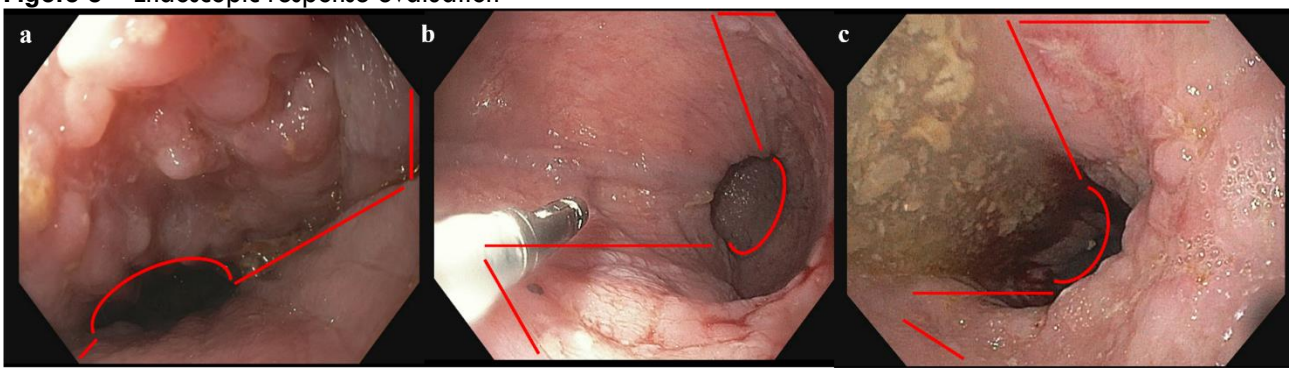


Photo of the tumor before (a), at one month (b), and at three months (c) after treatment with electrochemotherapy (Patient ID 1). The tumor area covers approximately half of the circumferential (within the outlined area, please notice that the endoscope is rotated 180 degrees on post-treatment images), and tumor length was three centimeters. At three months after treatment, scar tissue remained in the treated area. The polypous tumor tissue is much less extensive after treatment, however, the malignant tissue is still visible.

PROCEDURAL DETAILS AND FEASIBILITY

Detailed descriptions of all procedures are described in Table 3a and 3b. Overall, despite the absence of patients experiencing complete tumor obstruction, maneuvering the endoscope equipped with the EndoVE® electrode proved difficult.

Additionally, in cases of larger tumors, the limited visibility made it challenging to determine whether the entire tumor area had been adequately electroporated.

Table 3a – Endoscopic-assisted ECT – procedural details

Patient ID	Procedure time	Bleomycin administration	Electrical pulses*	Comments
1	28 min	30.000 IE IV	7	Technical issues with connecting with the heart sync system
2	35 min	28.950 IE IV	5	Balloon dilatation needed in the oral part of the tumor to pass with the endoscope
4	35 min	27.750 IE IV	16	
8	23 min	28.800 IE IV	10	
10	30 min	26.550 IE IV	8	

Table 3b – Argon Plasma Coagulation – procedural details

Patient ID	Procedure time 1st treatment	Procedure time 2nd treatment	Comments
3	15 min	15 min	
5	36 min	36 min	Balloon dilatation needed in the oral part of the tumor to pass with the endoscope (both procedures)
6	20 min	10 min	
7	20 min	15 min	
9	N/A	N/A	

Procedure-specific details are described for each procedure individually. *Pulse parameters: bipolar high-frequency pulses of 1000V/cm, 172 kHz (pulse burst frequency), and a total energized time of 6 ms.

Discussion

Ten patients were included in this trial, and nine patients were treated. This is only the second clinical study reporting results from treatment with ECT in esophageal cancer. None of the five patients treated with ECT developed ITDD during the follow-up period. Two patients from the APC group had a stent placed.

Electrochemotherapy is a well-established cancer treatment but tumor treatment in the gastrointestinal tract is still under development. Four clinical trials have reported results from endoscopic reversible electroporation within esophageal 15,17 and colorectal cancer 18,19, respectively. This current study adds to the existing evidence that endoscopic-assisted ECT is safe and feasible in the gastrointestinal tract and that the treatment induces tumor response. In the previous studies 15,17-19, obstructive tumors have caused challenges due to the electrode design when treating stenotic tumors. Offering treatment as initial therapy in the current study was an attempt to overcome this shortcoming. Nevertheless, even in the early stages of the disease, we concluded that the electrode design was suboptimal when dealing with limited luminal space. Firstly, a considerable number of patients were deemed ineligible for treatment due to tumor obstruction. Secondly, even in cases without complete obstruction, maintaining a comprehensive view and effectively treating the entire tumor area proved to be challenging. If endoscopic-assisted electroporation, either with bleomycin or with calcium 17,26, is to play a role in the future management of advanced esophageal cancer, a new electrode needs to be developed. The design would preferably contain a guidewire system or an electrode that could be deployed through the endoscope's working channel.

Four patients in this study had a partial response evaluated from CT. However, they had all received the first series of systemic therapy. Only a few side effects were seen among all treated patients, and no intraoperative complications were registered. This is further emphasized as only one patient redeemed the prescription for antiemetics and steroids. Compared with the first pilot trial 15, fewer side effects after ECT were recorded. Moreover, the experimental treatment did not prevent any patients from receiving standard oncological treatment. Argon plasma coagulation was chosen as a comparator in this trial, even if it is not a standard treatment. Argon plasma coagulation is a relatively easy treatment that does not require general anesthesia, why it could easily be implemented. However, in this trial, only one patient had a partial tumor response after APC,

and the procedure has similar limitations as ECT, as treating obstructive tumors was challenging.

The primary aim of this study was to compare ECT and APC regarding palliation, or postponement, of malignant dysphagia. Since only ten patients were included, conclusions on the primary endpoint cannot be drawn. However, none of the five patients treated with ECT had a stent placed, while two out of four patients in the APC group had a stent placed. In a previous study from our group 1, > one-third of the patients with non-curable esophageal cancer had a stent placed. Several studies have shown that placing a stent might impair survival, both among patients with non-curable disease 1,7,9,10 but also in patients who undergo surgery. 4 Similar results are found within colorectal cancer. 27,28 It has been hypothesized that the mechanical pressure from the stent on the tumor tissue might increase the risk of dissemination due to unfavorable cellular changes. 29 Moreover, placing a stent is associated with a risk of perforation and discomfort, and even afterward, the patient can only intake a semifluid or blended diet. Tumor overgrowth within the stent is a common problem, and as the tumor grows, luminal patency must be maintained regularly. Hence, we lack efficient and safe treatment tools to relieve dysphagia with long-lasting effects in this fragile group of patients.

Electrochemotherapy has also been shown to induce a systemic response outside the treated area. It is hypothesized that by further combing ECT with immunotherapeutic drugs, the cytotoxic effect of the immunotherapeutic drug can be enhanced. 30 This has been reported retrospectively in smaller case series in skin cancer 31-35 but has not been evaluated in gastrointestinal cancer. PD-1 and PDL-1 inhibitors are approved to treat advanced esophageal cancer, increasing response rates in combination with chemotherapy to 45-53% from 20-30% with chemotherapy alone and with significant improvement in overall survival. 36,37 If ECT could induce both a local symptom relief response and enhance the effectiveness of these drugs, it could potentially be of high clinical value.
The most significant limitation of both treatment modalities in this trial was that obstructive tumors could not be treated completely. Many patients screened for the study were considered not eligible due to an obstructive tumor. Even though we tried to address this by including the patients at an earlier stage based on previous experience, 15 more patients than expected were referred with an obstructive tumor. Furthermore, the trial was not designed to include a third comparative group, who received standard care, which should be considered in future similar trials evaluating palliation. Coming studies could also include examining tumor and blood samples to assess the local and systemic response. To enable multiple treatments with ECT, future studies should elaborate on using lower dosages of bleomycin. Several clinical trials have demonstrated ECT with a lower dosage of bleomycin (10.000 IE/m^2) to induce similar responses as with a standard dosage (15.000 IE/m^2). 38 The potential for multiple treatments is favorable in earlier stages when the patient has a longer expected survival time, in case of recurrence, or stepwise debulking of a stenotic tumor.

Conclusions

Endoscopic-assisted ECT can potentially play a role in managing malignant dysphagia and treating esophageal cancer in the future. Both APC and ECT treatment was offered with limited side effects and without intraoperative complications. Larger clinical studies should be performed to evaluate tumor response, palliation, and systemic effects and the results should be compared with today's standard of care in terms of both symptom relief and survival.

Conflict of Interests

The authors have no conflicts of interest to declare.

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