Laparoscopic transgastric circumferential stapler-assisted versus endoscopic esophageal mucosectomy in a porcine model

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Disclosures:	The authors declare no conflict of interest.
Grant support:	Daniel C. Steinemann is supported by the Swiss National Science Foundation (Grant P300PB-161099/1) and the Margarete and Walter Lichtenstein Foundation, Basel, Switzerland (DMS2321). All other authors have nothing to disclose.
Funding:	The Heidelberg Surgery Foundation funded the study.
Author's contribution:	GRL and AZ contributed the idea of stapler-assisted mucosectomy, DCS and GRL were responsible for conception and design of the study, DCS, PCM, FL and ACS performed the experiments and analysed the data, DCS and PCM drafted the article, GRL, AZ and BPM performed a critical revision. All authors gave their final approval.
Word count:	1569
Short title:	Stapler-assisted Mucosectomy

Abbreviations

BE	Barrett´s Esophagus
ECM	Extracellular matrix
EMR	Endoscopic Mucosal Resection
GEJ	Gastroesophageal junction
GER	Gastro-esophageal reflux
GERD	Gastro-esophageal reflux disease
HGD	High-grade Dysplasia
RFA	Radiofrequency ablation
SAM	Stapler-assisted Mucosectomy
SRER	Stepwise radical endoscopic resection

Abstract

Background and study aims: Extensive endoscopic mucosal resection (EMR) for Barrett's esophagus (BE) may lead to stenosis. Laparoscopic, transgastric, stapler-assisted mucosectomy (SAM) retrieving circumferential specimens is proposed.

Methods: SAM was evaluated in two phases. The feasibility of SAM and the quality of specimens was assessed in eight animals. The mucosal healing was evaluated in a 6-weeks survival experiment comparing SAM (n=6) and EMR (n=6). The ratio of the esophageal lumen width (REL) at the resection level measured in fluoroscopy after 6-weeks divided by the width immediately after resection was compared.

Results: In all animals a circular mucosectomy specimen was successfully obtained with an area of 492(426-573)mm^2 and 941(813-1209)mm^2 using a 21-mm and 25-mm stapler, respectively. In the survival experiments two animals developed symptomatic stenosis after EMR and none after SAM. The REL was 0.27[0.18-0.39] and 0.96[0.9-1.04] ($p<0.0001$) for EMR and SAM, respectively.

Conclusions: SAM provides a novel technique for en-bloc mucosectomy in BE. In contrast to EMR mucosal healing in SAM was not associated with stenosis up to six weeks after intervention.

Key words: mucosectomy, trangastric, Barrett's esophagus, endoscopic mucosa resection

Introduction

In patients with Barrett's esophagus (BE) and high-grade dysplasia (HGD) it is advised to remove the dysplastic epithelium and treat remaining areas of BE to minimize the risk of de novo neoplasia. Endoscopic mucosal resection (EMR) represents an established and safe method for resection of dysplastic BE. However, large lesions are resected in a "piecemeal" technique prone to incomplete resection. Moreover, if performed extensively or circularly stenosis will occur. [1, 2] Therefore stepwise radical endoscopic resection (SRER) has been proposed with extended mucosal resection performed in several sessions reducing the risk of complications. Still, stenosis develops is as much as 50% of patients.[3, 4] A different approach is the combination of EMR for dysplastic areas and of radiofrequency ablation (RFA) for the remaining BE. Here, in lesions limited to an extent in height of 2 cm and 50% of the circumference the stenosis rate is 6%.[5]

The aim of this study in a porcine model was to develop transgastric stapler-assisted mucosectomy (SAM) providing a circumferential en-bloc specimen, avoiding postoperative stenosis and representing an alternative for a minority of patients not amenable to endoscopic treatment. The novel technique was compared to the current gold standard, EMR, in a survival experiment.

Methods

Two series of experiments were performed using Landrace pigs. First the feasibility of SAM was tested in a non-survival in-vivo experiment in 8 animals. Second mucosal healing was assessed in a 6-weeks comparative survival experiment. Animals were randomly allocated to SAM (n=6) or circumferential EMR (n=6). Ethical approval was obtained.

Stapler-assisted mucosectomy

Under general anesthesia a pneumoperitoneum was established after insertion of a left subcostal 12-mm trocar. Two 12-mm and two 5-mm trocars were placed. The esophagus was mobilized by opening the hiatus. Two 12-mm trocars and a 5-mm trocar were replaced transgastrically. A 12mmHg-pneumogastrium was established. Saline solution was injected to lift the mucosa. A first purse-string suture was placed 3-cm above the Z-line including only the mucosal layer. After enlarging the left subcostal facial incision a wound protector was inserted into the stomach. The anvil of a circular stapler was introduced. In the non-survival experiments a 21-mm circular stapler (EEA-21-mm/4.8-mm,Medtronic,Ireland) was used while in the survival experiments a 25-mm stapler (CDH25A,25mm/5.5mm,Ethicon,USA) was employed. After placing the anvil into the esophagus the purse-string suture was knotted. A second purse-string suture was placed 2-cm distally from the first suture. The stapler was introduced over the wound protector, connected to the anvil and released. After removal of the trocars gastrotomies and wounds were closed by sutures (Figure 1,video).

Endoscopic mucosa resection

An esophagoscopy was performed and the mucosa was lifted by injection of saline solution. By repeated EMR using a multi-band ligation technique (Duette™-DT-6,Cook Medical,USA) a circular resection was performed.

Perioperative regime

Animals fastened 24-hours before intervention and received a yoghurt diet and pain killers for 48-hours after intervention. They were sacrificed under general anesthesia by injection of KCl intravenously.

Evaluation of feasibility

Feasibility of SAM, duration of the procedure and of the substeps (placement of intragastric trocars, purse-string suture, closure of gastrotomies), intraoperative complications, additional trocars, and occurrence of transmural stiches were assessed.

The specimen was evaluated for complete circumferential resection. The maximal and minimal length, width and area of the specimen was measured. The harvested esophagogastric junction was assessed for intactness of the anastomosis. Microscopically the mucosectomy specimens were assessed for integrity of the mucosa, presence of submucous tissue, muscle fibres or full thickness tissue.

Evaluation of mucosal healing

Animals were scaled before the procedure and before explantation. The duration of the procedure and complications were documented. Mucosal specimens by SAM or EMR were pinned on cork (Figure 2). The number of resected specimens per case was counted. Microscopic integrity of the mucosa and presence of submucous tissue, muscle fibres or full thickness tissue were assessed.

Directly after SAM and EMR and before euthanazation an esophagogram was obtained by fluoroscopy. The diameter at the resection level was measured. A ratio of the lumen width at 6 weeks divided by the lumen width after the initial intervention was calculated.

After sacrifice the presence and extent of esophageal stricture was measured in the harvested esophago-gastric specimen using a caliper ruler. Moreover, the lumen of the esophagus proximal to the resection zone was measured and the ratio of the lumen width at the level of resection and proximal to the resection level was calculated (Figure 2).

To assess the degree of fibrosis induced by SAM and EMR collagen deposition in the esophageal wall were scored according to a validated semi-quantitative assessment.[6]

Statistical analysis

Continuous variables were expressed as median and interquartile range and compared using a paired student´s-*t*-test. Categorical variables were compared using a two-sided Fisher's-exact-test. The level of significance was set at a *P*-value of ≤0.05.

Results

Evaluation of feasibility

SAM was successfully accomplished without intraoperative complications in all animals. Procedure and specimen characteristics are depicted in table 1. No additional trocars were needed.

All specimens were intact and completely circumferential (Figure 3). In the explanted esophagogastric junction an intact circular anastomosis was found in all pigs. No transmural stitches or perforations were demonstrated. No resections of the muscularis propria or full thickness tissue were found (Figure 4).

Evaluation of mucosal healing

Procedure, specimen characteristics, morbidity and degree of stenosis are depicted in table 2. In the first animal the pleura was inadvertently opened during hiatal mobilization leading to a tension pneumothorax. After drainage of the pleura the further clinical course remained uneventful.

While all animals after SAM thrived well, two pigs in the EMR-group had to be sacrificed prematurely due to symptomatic stenosis on day 34 and 39 post-EMR. At necropsy a palpable thickening of the esophageal wall was observed in all EMR animals but in none of the SAM animals.

Measured on fluoroscopy as well as in the explant at necropsy the lumen at resection level in EMR was narrowed compared to SAM (Table 2, Figure 2). EMR-specimens showed furthermore a widening of the proximal esophagus. Histological evaluation of fibrosis at resection level showed a score of 2 [0-3.3] for EMR and 0.5 [0-2.3] for SAM (P=0.437).

Discussion

SAM was feasible, reproducible and resulted in circumferentially intact en-bloc specimen. Selective mucosal resection without resection of the muscular tube and with a tight anastomosis was achieved. Mucosal healing in SAM was not associated with stenosis or fibrosis up to six weeks after intervention. These findings were clearly in contrast to the outcome in EMR. Despite the resected mucosa being significantly smaller in EMR, 2 out of 6 animals developed symptomatic stenosis and in all cases severe signs of fibrosis and at least beginning stenosis were found.

Laparoscopic mucosal resection for HGD by scissors via an anterior gastrotomy was described before.[7-9] In that technique the mucosal wound was left to open wound healing. Consequently in two out of 11 patients stenosis necessitating dilatation occurred. In a porcine study circular mucosal resection up to 5-cm in length in an open surgical technique was reported.[10] The stricture development over a 6 weeks period was compared in two groups. No or only mild fibrosis and no stenosis was observed when the defect was covered by advancement of the mucosa and hand suture. When the mucosal defect was uncovered dense fibrotic stricture occurred. In the current experiment, SAM with coverage of the submucosa was compared to EMR with uncovered mucosa. The depth of resection, which may influence the stricture development, was comparable between the groups. In SAM no strictures occurred whereas in EMR narrowing of the lumen at the resection level was observed in all animals.

EMR of HGD followed by repetitive RFA of the remaining BE is currently considered the first-line treatment.[11] The rate of complete eradication from dysplasia and from BE ranges between 86-92% and 56-87%, respectively.[5, 12, 13] In patients suffering from an extensive or even circumferential HGD beyond the limits of combined EMR and RFA, SAM may represent a safe alternative treatment to esophagectomy.

The extent of resection was limited by the capacity of the circular stapler to contain tissue. While in the first series of experiments a 21-mm stapler was used in the survival experiments a 25-mm stapler was deployed. Consequently the median area of the specimen increased largely. The used circular staplers are designed to fashion anastomosis and not for resection. The current limited resection may also explain the missing submucosal layer in 50% of the specimens thus limiting the use of SAM for adenocarcinoma infiltrating the submucosa. The risk of dysplasia increases with the length of the BE segment. As currently SAM may resect only short segments there is a need for a modified circular stapler. This modified stapler must be equipped with a larger open housing. In order to safely resection the entire BE target lesion it is intended that the upper purse-string suture is placed orally and the lower suture aborally from the lesion. Using a stapler with an open housing the mucosa to be resection can be pulled in the housing under visual control.

The advantages of SAM versus EMR are the circular en-bloc mucosectomy enabling a higher probability of complete BE eradication, the possibility for accurate microscopic evaluation of the lateral and deep resection margins, and a low probability of post-intervention stenosis. Compared to EMR these advantages should, however, be balanced against the higher invasiveness, the risk of potentially severe complications and the longer hospital stay. Moreover, stenosis in EMR might be prevented by e.g. corticosteroid injection and, if they occur, solved by endoscopic dilatation.

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Figure Legends

Figure 1: Principle of transgastric stapler-assisted mucosectomy

A) After insertion of three transabdominal, transgastric trocars in the stomach and insufflation of CO_2 two mucosal purse-string sutures are performed in the distal esophagus marking the proximal and distal indented resection borders.

B) Before tightening the pursing-sutures the anvil of the circular endostapler is inserted in the distal esophagus.

C) The two purse-string sutures are tightened around the spine of the anvil. The circular endostapler is introduced. The stapler is connected to the anvil, closed and fired.

D) A circular stapler line is obtained approximating the two resection borders.

Figure 2: Macroscopic gastro-oesophageal specimen (A) and patent lumen at the resection zone (B) as well as fluoroscopy image (C, arrow at resection zone) six weeks after stapler-assisted mucosectomy (SAM) showing no signs of stenosis. Macroscopic gastro-esophageal specimen showing hourglass-deformity (E) and stenotic lumen (F) as well as stenosis in fluoroscopy (G, arrow at resection zone) six weeks after endoscopic mucosal resection. Single, circular specimen after stapler-assisted mucosectomy (D) and piece-meal specimens after endoscopic mucosal resection (H).

The white line in the fluoroscopy marks the lumen diameter at the resection level, the red line marks the measured lumen diameter proximal to the resection.

Figure 3: Circular mucosectomy donut

Figure 4: Microscopic specimen. 1 = squamous epithelium, 2= lamina propria,

3= lamina muscularis mucosae, 4= submucous layer

Supplemental Figures and Video

Video: Transgastric stapler-assisted mucosectomy

Table 1: Animal-, procedure- and specimen characteristics of the evaluation of feasibility.

Evaluation of feasibility	SAM (n=8)
Animal characteristics	
Preoperative weight, kg, median [IQR]	44.9 [40.5-49.9]
Procedure and specimen characteristics	
Duration of surgery, minutes, median [IQR]	142 [111-158]
Duration of substeps, minutes, median [IQR]	
Placement of intragastric trocars	8.5 [7-15]
First purse-string suture	13 [8-17]
Second purse-string suture	9 [6-10]
Closure of gastrotomies	22 [16-29]
Minimal specimen length, mm, median [IQR]	8.5 [8-12]
Maximal specimen length, mm, median [IQR]	17 [15.3-18.8]
Specimen width, mm, median [IQR]	40 [40-56]
Total area of resectates, mm^2, median [IQR]	492.4 [425.7-572.9]
Muscularis mucosae preserved in specimen, n	8
Submucosa present in specimen, n	4

IQR = interquartile range

Table 2: Animal-, procedure- and specimen characteristics, post-interventional morbidity, degree of esophageal stenosis of the evaluation of mucosal healing.

Evaluation of mucosal healing	**SAM (n=6)**	**EMR (n=6)**	***P***
Animal characteristics			
Preoperative weight, kg, median [IQR]	44 [41-51.3]	45.5 [44-45.9]	0.773
Weight gain, kg, median [IQR]	8.5 [6.1-9.3]	9.1 [3.2-11.6]	0.915
Procedure and specimen characteristics			
Duration of intervention, minutes, median [IQR]	156 [150-236]	34 [26-40]	<0.0001
Number of resectates, n, median [IQR]	1 [1-1]	4 [4-5]	<0.0001
Total area of resectates, mm^2, median [IQR]	941 [813-1209]	485 [438-654]	0.0066
Area of single resectates, mm^2, median [IQR]	941 [813-1209]	117 [72-158]	<0.0001
Muscularis mucosae preserved in specimen, n	6	6	1.0
Submucosa present in specimen, n	4	6	0.450
Post-interventional morbidity			
Animals with morbidity	3	2	1.0
Symptomatic stenosis	0	2	0.455
Wound infection	3	0	0.080
Degree of esophageal stenosis			
Measured by caliper ruler			
Lumen width measured by caliper ruler at necropsy, mm, median [IQR]	16.8 [14.28-18.78]	7.45 [4.44-10.36]	0.0007
Ratio esophageal width at level of resection/proximal from resection	0.98 [0.94-0.99]	0.71 [0.69-0.81]	0.0002
Measured by fluoroscopy			
Lumen width in fluoroscopy after 6 weeeks , mm, median [IQR]	14.32 [13.03-14.95]	4.59 [2.99-6.58]	<0.0001
Ratio lumen width after 6 weeks/ immediately after intervention	0.96 [0.90-1.04]	0.27 [0.18-0.39]	<0.0001

IQR = interquartile range.