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Routine esophagram to detect early esophageal leakage after peroral endoscopic myotomy

Elise Wessels, Sara Nullens, Barbara A Bastiaansen, Paul Fockens, Gwen Masclee, Albert J. Bredenoord.

Affiliations below.

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Abstract:

Background

Peroral endoscopic myotomy (POEM) is highly successful in treating patients with achalasia. The aim of this study was to evaluate the incidence of early adverse events (AEs) following POEM and to assess whether post-procedural imaging by routine esophagram prevents serious AEs due to early detection of esophageal leakage after POEM.

Methods

Patients who underwent POEM between August 2011 and December 2022 were included in this retrospective cohort study. Post-procedural AEs were graded according to the AGREE classification. Until July 2016 routine esophagram was routinely performed one day after POEM, afterwards this was abandoned. The number and severity of post-procedural AEs were compared between patients with and without routine esophagram after POEM.

Results

In total, 352 patients were included (mean age 47 years, 48.3% female). Nineteen post-procedural AEs occurred of which ten were grade I (2.8%), three grade II (0.9%), five grade IIIa (1.4%) and one grade IVa (0.3%). No difference was found in the number and severity of post-procedural AEs between patients with and without routine esophagram . In 129 patients routine esophagram was performed one day after POEM. In two patients esophageal leakage was seen after which repeat endoscopy was performed to close the incision with additional clips. After abolishing routine esophagram from the protocol, no AEs led to severe complications related to esophageal leakage.

Conclusion

POEM is safe with relatively low number of AEs. The benefit of routine esophagram one day after POEM is limited as it does not prevent serious complications resulting from esophageal leakage.

Corresponding Author:
Elise Wessels, Amsterdam UMC, Gastroenterology & Hepatology, Meibergdreef 9, 1105AZ Amsterdam, Netherlands, e.wessels@amsterdamumc.nl

Affiliations:

Elise Wessels, Amsterdam UMC, Gastroenterology & Hepatology, Amsterdam, Netherlands
Sara Nullens, University Hospital Antwerp, Department of Gastroenterology and Hepatology, Edegem, Belgium
Sara Nullens, GZA Hospitals, Department of Gastroenterology and Hepatology, Wilrijk, Belgium
[...]
Albert J. Bredenoord, Amsterdam University Medical Centres, Department of Gastroenterology, Duivendrecht, Netherlands

INTRODUCTION

Achalasia is a rare esophageal motility disorder which is characterized by absent or uncoordinated esophageal peristalsis and insufficient relaxation of the lower esophageal sphincter (LES), resulting in impaired propulsion of food through the esophagus. The most common symptoms include dysphagia, regurgitation of undigested food, chest pain and weight loss [1]. Current treatment aims at reducing symptoms by lowering the pressure of the LES and therefore improving passage of food through the esophagus. Treatment options are pneumatic dilatation (PD), laparoscopic Heller myotomy (LHM) which is often combined with fundoplication, botulinum toxin injection and per-oral endoscopic myotomy (POEM) [2].

Since the first successful POEM was reported in 2010, this procedure is increasingly performed worldwide and is now a key element in achalasia treatment [3]. POEM is a minimally invasive procedure where muscle fibers of the distal esophagus and LES are cut endoscopically by making a submucosal tunnel towards the stomach. Previous studies have shown that POEM is non-inferior to LHM in controlling symptoms of achalasia [4, 5]. The long-term efficacy of POEM is higher compared to PD with treatment success of 81% for POEM and 40% for PD after five years [6].

POEM appeared to be safe when performed by experienced endoscopists [4, 7-12]. However, the definition and classification of adverse events (AEs) varies between studies and therefore the number of AEs are wide-ranging from 0% to 35.8% [9, 10, 12-18]. Initially, all types of mucosal injury and gas-related events such as pneumoperitoneum and pneumomediastinum were reported as AEs. These events are commonly encountered on routinely performed post-procedural imaging after POEM, are often asymptomatic and usually do not affect patient outcome, hospital stay or clinical management [19]. Therefore, routine imaging after POEM is not always recommended [20-24]. However, a clinical practice guideline for POEM states that upper gastrointestinal endoscopy has to be carried out after POEM to check for mucosal damage or hemorrhage and that routine esophagram has to be performed to exclude esophageal leakage [25]. Another study concluded that routine

postoperative CT might be helpful in the early detection of potential significant AEs, although most CT-findings did not need additional treatment [26].

Currently, there is no consensus about postoperative care after POEM and it is unknown to what extent performing routine postoperative imaging will result in the early detection and better treatment of AEs [23, 25-27]. The aim of this study is to evaluate the incidence of early AEs following POEM and to assess whether post-procedural imaging by routine esophagram prevents serious AEs due to early detection of esophageal leakage after POEM.

MATERIALS AND METHODS

Study design

This retrospective cohort study was performed at the Amsterdam University Medical Center. Data was extracted from medical records of all consecutive patients who underwent POEM between August 2011 and December 2022. Diagnosis of achalasia, hypercontractile esophagus or diffuse esophageal spasm had to be confirmed by manometry in order to be included in this study. Other inclusion criteria were a technical successful POEM procedure, at least one month of follow-up and aged eighteen years or older. The first 25 procedures after the introduction of POEM in our center were excluded, taking into account the learning curve of POEM [28]. Patients undergoing gastric-POEM were also excluded from this study.

POEM procedure

All POEM procedures were performed by two experienced interventional endoscopists (BB, PF) according to our protocol under general anesthesia and all patients received perioperative intravenous antibiotics. Carbon dioxide insufflation was routinely used in all patients. POEM started with a submucosal injection of saline and indigo carmine halfway the esophageal body followed by a two centimeter mucosal incision to entry the submucosal space. A submucosal tunnel towards the LES was created and colored saline was used to increase demarcation and to enlarge submucosal working space. The submucosal tunnel was continued to approximately three cm beyond the LES. Afterwards, myotomy of the circular muscle layer and partly the longitudinal muscle layer was performed. Once the myotomy was completed, the mucosal incision was closed with multiple endoclips.

Post-procedural care

According to the protocol, standard observation after POEM was one night admission. Until July 2016, routine esophagram was performed one day after POEM in all patients to assess signs of

esophageal leakage. Patients had to drink at least 100 mL of liquid iodized contrast (Ultravist 300) in upright position. Radiographs of the esophagus were made to rule out leakage of contrast in the submucosal tunnel and/or in the mediastinum. Patients were discharged when no significant esophageal leakage was identified on routine esophagram and liquids were well tolerated. After July 2016, routine esophagram or chest CT in the first days post-POEM was only performed in case of symptoms suggestive for post-procedural AEs (e.g. uncontrolled retrosternal pain or fever) and patients were discharged when they were able to tolerate liquids one day post-POEM. After discharge, all patients followed a liquid diet for one week and a ground diet for another week. Standard endoscopy in the first post-operative days after POEM to assess mucosal damage, the location of the clips and hemorrhage was not performed routinely. Repeat upper gastrointestinal endoscopy was only performed on indication.

Outcome measures

The primary outcome was the number of early post-procedural AEs after POEM. Early post-procedural AEs were defined as any unfavorable event within 30 days after POEM and were graded according to the Adverse events Gastrointestinal Endoscopy (AGREE) classification [29]. The occurrence of early post-procedural AEs was routinely assessed shortly after the procedure, before discharge, after two weeks and one to three months after POEM. This was documented in the medical record during follow-up. The number and grade of post-procedural AEs was compared between two cohorts of patients, with a focus on the AEs resulting from esophageal leakage. The first group included patients undergoing POEM before July 2016 with routine esophagram one day post-POEM. In the other group of patients, POEM was carried out after July 2016 and routine esophagram was not routinely performed in any of these patients. Secondary outcomes included hospital stay, signs of esophageal leakage on routine esophagram and repeat endoscopy after POEM. Intraprocedural AEs were documented in the report of the POEM procedure. Pneumoperitoneum was reported as intraprocedural AE when abdominal needle drainage was necessary or when the

procedure was temporarily stopped because of change in ventilation pressure. Bleeding was indicated as major in case of hemodynamic instability, blood transfusion or prolonged hospitalization. Mucosal injury that occurred during POEM for which extra clips were needed was also considered to be an intraprocedural AE. All AEs were discussed by the adjudication committee, consisting of the two experienced interventional endoscopists who performed the POEM procedures (BB, PF) to determine if the AEs could have been prevented or could have been less severe when early detecting esophageal leakage on routine esophagram.

Statistical analysis

SPSS statistics version 28.0 was used for statistical analysis. Comparisons were made using Chi-square test, Fisher's exact test or non-parametric testing (Mann-Whitney U test) where appropriate. Two-sided p-values below 0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

In total 425 patients underwent POEM between August 2011 and December 2022. Thirteen procedures were not successful due to submucosal fibrosis in the distal esophagus or around the LES, orientation loss, an extensive submucosal hematoma or a peptic stricture. Of the remaining 412 patients, 31 patients had an age below eighteen years, three patients underwent gastric-POEM and one patient had no esophageal motility disorder. The first 25 POEM procedures were excluded taking into account the POEM learning curve of the endoscopists. Hence, 352 patients were included in this study of which 129 underwent POEM before July 2016 and 223 after July 2016 (figure 1). All patients were routinely followed for at least one month, no patients were lost to follow-up. Patient characteristics are specified in table 1 and procedure related outcomes in table 2.

Post-procedural adverse events

Post-procedural AEs within 30 days after POEM occurred in nineteen patients (5.4%) of which ten AEs were grade I (2.8%), three were grade II (0.9%), five were grade IIIa (1.4%) and one was grade IVa (0.3%) according to the AGREE-classification [29].

Supplementary table 1 provides an overview of all post-procedural AEs. One patient had symptomatic pneumothorax, pneumoperitoneum, pneumomediastinum and subcutaneous emphysema after POEM (figure 2). In this patient the procedure was inadvertently started with room air insufflation instead of carbon dioxide. This was noticed half an hour after the introduction of the endoscope and the insufflation was at that point switched to carbon dioxide. After the procedure, no chest or abdominal drainage or other intervention was necessary and the patient was hemodynamically stable and received extra oxygen for three days. Pain was controlled with opioids for four days and the patient was discharged after seven days. Five patients underwent repeat endoscopy after POEM (grade IIIa). In two of these patients POEM was performed before July 2016 and those patients underwent repeat endoscopy because submucosal esophageal leakage was seen

on routine esophagram and was closed with extra clips (figure 3). One of these patients had deep submucosal leakage which extended through the submucosal tunnel up to the stomach, but the leakage did not enter the mediastinum. The other patient had superficial esophageal leakage which was limited to the level of the mucosal incision (figure 3). Because of persistent esophageal leakage on the esophagram the day after repeat endoscopy in both patients, another repeat endoscopy was carried out in which two extra clips were used to close the incision and a duodenal feeding tube was placed. Both patients were asymptomatic before repeat endoscopy and no opioids were necessary for retrosternal pain. One of these patients received antibiotics for two weeks because of fever measured once after repeat endoscopy. The patients were discharged after five and seven days.

One patient was readmitted to the intensive care unit (ICU) because of respiratory insufficiency three days after POEM requiring ICU-observation with oxygen support (grade IVa). CT showed significant pleural effusion and debris in the right main bronchus without signs of esophageal leakage. Upper endoscopy was performed and did not show leakage or perforation and all clips were well in place. The pleural effusion was punctured, but no bacteria were identified on culture. The patient was stable with high flow oxygen and antibiotics and could be discharged from hospital after nine days of which six days on ICU. Further recovery was unremarkable. No AEs resulted in death.

Routine esophagram

Routine esophagram was standard performed one day after POEM in 129 patients of which five had post-procedural AEs (n=5/129, 3.9%). Two were classified as grade I (n=2/129, 1.6%), one as grade II (n=1/129, 0.8%) and two as grade IIIa (n=2/129, 1.6%). Fourteen post-procedural AEs (n=14/223, 6.3%) occurred in the other group where routine esophagram was not standard performed (figure 4). Of these AEs, eight were grade I (n=8/223, 3.6%), two were grade II (n=2/223, 0.9%), three were grade IIIa (n=3/223, 1.3%) and one was grade IVa (n=1/223, 0.4%). Overall, the number and severity of the AEs was equal between patients with and without routine esophagram.

Most importantly, no severe complications due to esophageal leakage (e.g. sepsis or mediastinitis) were observed.

In five patients possible signs of esophageal leakage were reported (n=5/129, 3.9%) of which two patients underwent a subsequent endoscopy to close the potential leakage with additional clips. The esophageal leakage on routine esophagram of the other three asymptomatic patients was questionable because the leakage was very minimal and limited to the level of the mucosal incision. These patients were treated conservatively without repeat endoscopy, therefore this was not classified as AEs.

If routine esophagram would have been performed after July 2016, esophageal leakage may have been seen in one patient with retrosternal pain in whom partially dehiscence of the mucosal incision was observed during repeat endoscopy five days after POEM. However, no endoscopic intervention was needed and the patient recovered with conservative treatment approach. The adjudication committee decided that a routine esophagram would only have detected the esophageal leakage earlier, but management would not have changed since the esophageal leakage was limited to the mucosal incision and no endoscopic intervention was needed. Adjudication concluded that none of the other AEs could have been detected earlier by routine esophagram since no other AE was associated with esophageal leakage.

DISCUSSION

This study demonstrated that POEM is safe and that the number and severity of AEs is not different whether or not performing routine esophagram one day after POEM. Even more importantly, after abolishing routine esophagram from the protocol no AEs associated with esophageal leakage have led to severe complications that necessitated additional or more comprehensive interventions. Therefore, routine esophagram after POEM could not have prevented the occurrence of any AEs and would not have impacted management to a significant extent.

Post-procedural AEs within 30 days after POEM occurred in nineteen out of 352 patients (5.4%). Intraprocedural AEs occurred more frequently than post-procedural AEs. In total 41 intraprocedural AEs occurred in 38 patients (11.6%). These procedure-related events were already managed during POEM and did not influence patient outcome or hospital stay. Pneumoperitoneum for which abdominal needle drainage was necessary occurred primarily before July 2016. A possible explanation for this might be that it became common practice to increasingly widen the submucosal tunnel, allowing carbon dioxide to escape more easily.

The number of AEs in this study was slightly lower compared to the study of Haito-Chavez (2017) who reported that AEs after POEM occurred in 7.5% of the 1826 included patients. However, that percentage comprised intraprocedural AEs as well as post-procedural AEs. In total 156 AEs occurred of which 89 during the procedure and 67 post-POEM [7]. The difference in AEs rate might also be explained by the different classification that was used. For example, post-procedural medical consultation without presentation in hospital and without intervention is seen as mild AE according to the ASGE lexicon's severity grading system and as no AE when using the AGREE classification [29, 30]. In a study comparing POEM and LHM in 221 patients, serious AEs occurred in 2.7% and 7.3% of the patients undergoing POEM and LHM respectively. The number of non-serious AEs was twelve (11%) after both procedures. Intraprocedural AEs were also included in this number [4]. Another randomized controlled trial by Ponds et al. (2019) reported two serious AEs after PD and absence of AEs after POEM. Non-serious AEs occurred in 67% and 22% of the patients after POEM and PD

respectively. However, 37 out of 42 non-serious AEs after POEM were ascribed to the presence of reflux esophagitis and reflux symptoms after a follow up of more than 30 days [8].

Currently, post-procedural care varies per hospital and routine esophagram one day post-POEM is still often performed [27, 31]. Five out of 154 patients had signs of esophageal leakage on routine esophagram of which two were indicated as clinically relevant and repeat endoscopy was performed to close the leakage with additional clips. After July 2016 routine esophagram was no longer performed and no serious complication occurred due to esophageal leakage, such as mediastinitis or an abscess, which could have been prevented by performing routine esophagram one day after POEM. After July 2016, more patients were observed one day longer because of symptoms suggestive for esophageal leakage, but this did not influence hospital stay. In these patients, CT was performed which did not show esophageal leakage and symptoms improved the next day in all patients. Repeat endoscopy was carried out three times after July 2016 because of retrosternal pain four and five days after POEM in two patients and melena three weeks after POEM in one patient. For these patients, extra clips or other additional endoscopic intervention were not needed during repeat endoscopy. These patients fully recovered with conservative management. Although severe complications resulting from esophageal leakage did not occur in any of the patients in our study, these complications can be life-threating. Therefore we recommend performing CT or upper endoscopy as a valid surrogate of routine esophagram after POEM when symptoms suggestive for esophageal leakage are present.

A previous study with 78 patients evaluating the need for routine esophagram one day after POEM reported a high sensitivity of 100% and a low specificity of 45%. Abnormal findings on routine esophagram were present in 72% of the patients and it usually had no clinical significance [21]. Another study in which routine esophagram after POEM was performed in 170 patients found abnormalities with limited clinical significance in most patient. Routine esophagram correctly identified esophageal leakage in two patients, but the findings were false negative in two other patients and false positive in one patient. They concluded that routine esophagram alone was not

reliable enough to identify AEs [23]. Some studies are in favour of performing CT to detect AEs and to start prompt intervention [26, 32], but others do not recommend routine postoperative CT because of limited clinical significance [20, 22]. Abnormal findings, such as pneumoperitoneum and subcutaneous emphysema, are often seen on radiographic imaging after POEM and do not influence clinical management or patient outcome [19-21, 23, 26, 32, 33]. Therefore, these findings for which intervention is not necessary should not be regarded as AE [19, 33]. Performing routine esophagram one day post-POEM to assess delay in passage of contrast does not predict long-term efficacy of POEM and is thus not useful for that purpose either [34, 35].

This is the first study comparing AEs after POEM in patients with and without routine esophagram one day post-POEM. The year in which POEM was carried out differed between the two groups in our study, but other factors remained the same and a difference in post-procedural care will probably not have influenced the number or severity of post-procedural AEs. No changes have been made to the antibiotics prophylaxis and the post-procedural fasting protocol. It is plausible that the level of experience of the endoscopist is higher after July 2016, which might also explain the shorter procedure time after July 2016. A systematic review concluded that proficiency in performing POEM is obtained after 25 procedures. Although no post-procedural AEs occurred in the first 25 procedures, these were excluded for the above mentioned reason from further analysis. A limitation of the study is that we do not know whether the two patients in which esophageal leakage was seen on routine esophagram and subsequent repeat endoscopy was carried out, would have become symptomatic when repeat endoscopy with additional clip placement was not performed and thus, whether potentially more serious AEs may have been prevented. This study is also limited by the absence of esophageal perforations in patients undergoing POEM after July 2016. However, this illustrates that esophageal perforations after POEM are uncommon and that POEM is safe. Finally, this is a retrospective cohort study performed in one center and the best study design to assess the need for routine esophagram after POEM would be a randomized controlled trial, but this will require very large numbers of patients which seems not feasible for this rare disease. The

prospective collected data in this study and the accurate registration of AEs resulted in a high quality database with limited missing data and would seem a good alternative to the above. A relatively large number of patients were included in this study and no patients were lost to follow-up. Nevertheless, due to the small amount of AEs we could not perform multivariate logistic regression analysis to assess possible predictors of AEs occurrence.

In conclusion, the results of this study show that POEM is safe and routine esophagram one day after POEM is unlikely to be of additional value in preventing serious AEs resulting from esophageal leakage. AEs occurring after July 2016 could not have been prevented by performing routine esophagram one day after POEM and therefore we recommend to perform postoperative imaging only in case of symptoms suggestive for post-procedural AEs. This approach will reduce costs and radiation exposure and allows more rapid discharge of patients after POEM.

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FIGURE LEGENDS

Figure 1. Flow chart. POEM, peroral endoscopic myotomy.

Figure 2. Pneumothorax, pneumoperitoneum, pneumomediastinum and subcutaneous emphysema after POEM. A: chest X-ray. B: chest CT .

Figure 3. Submucosal esophageal leakage on routine esophagram. A: deep leakage into the submucosal tunnel towards the stomach. B: superficial leakage limited to the mucosal incision.

Figure 4. Percentage (number) of patients with an early AE after POEM. No difference in the number and severity of AEs between patients with and without routine esophagram. AE, adverse event. POEM, peroral endoscopic myotomy.

TABLES

Table 1: Patient characteristics

	Total (N = 352)	**Routine esophagram (N = 129)**	**No routine esophagram (N = 223)**
Age, years, mean (SD)	47 (17)	47 (16)	47 (17)
Sex			
Female	170 (48.3)	61 (47.3)	109 (48.9)
Male	182 (51.7)	68 (52.7)	114 (51.1)
BMI, kg/m^2, median (IQR)	24.0 (5.3)	23.6 (5.3)	24.2 (5.3)
ASA score			
I	126 (35.8)	65 (50.4)	61 (27.4)
II	193 (54.8)	56 (43.4)	137 (61.4)
III	33 (9.4)	8 (6.2)	25 (11.2)
Comorbidities			
Diabetes mellitus type II	23 (6.5)	6 (4.7)	17 (7.6)
Hypertension	54 (15.3)	20 (15.5)	34 (15.2)
OSAS	10 (2.8)	1 (0.8)	9 (4.0)
COPD or asthma	28 (8.0)	9 (7.0)	19 (8.5)
Thyroid disease	22 (6.3)	9 (7.0)	13 (5.8)
Malignancy (past or current)	14 (4.0)	3 (2.3)	11 (4.9)
Chronic inflammatory disease	16 (4.5)	5 (4.9)	11 (4.9)
Chronic renal failure	3 (0.9)	0 (0.0)	3 (1.3)
Barrett esophagus	1 (0.3)	1 (0.8)	0 (0.0)
Other cardiac or vascular disease	33 (9.4)	23 (10.3)	10 (7.8)

Other hematological disease	5 (1.4)	1 (0.8)	4 (1.8)
Other neurological disease	25 (7.1)	6 (4.7)	19 (8.5)
Previous surgery			
Abdominal surgery †	67 (19.0)	22 (17.1)	45 (20.2)
Thoracic surgery	4 (1.1)	1 (0.8)	3 (1.3)
Esophageal motility disorder §			
Achalasia	344 (97.7)	125 (96.9)	219 (98.2)
Type I	69 (19.6)	34 (26.4)	35 (15.7)
Type II	190 (54.0)	56 (43.4)	134 (60.1)
Type III	34 (9.7)	19 (14.7)	15 (6.7)
Non specified	51 (14.5)	16 (12.4)	35 (15.7)
Jackhammer esophagus	3 (0.9)	0 (0.0)	3 (1.3)
DES	5 (1.4)	4 (3.1)	1 (0.4)
Previous treatment	259 (73.6)	83 (64.3)	176 (78.9)
PD	228 (64.8)	70 (54.3)	158 (70.9)
BTI	41 (11.6)	17 (13.2)	24 (10.8)
LHM	85 (24.1)	28 (21.7)	57 (25.6)
POEM	9 (2.6)	0 (0.0)	9 (4.0)
TBE before POEM			
Column height, cm, median (IQR)			
0 min	8.0 (6.1)	9.0 (7.2)	7.7 (5.4)
1 min	6.4 (5.3)	7.4 (5.2)	6.0 (4.8)
2 min	5.8 (4.7)	6.0 (5.7)	5.7 (4.3)
5 min	4.9 (4.8)	5.0 (5.0)	4.9 (4.6)
Max diameter, cm, mean (SD)	3.2 (1.2)	3.2 (1.2)	3.2 (1.2)
Sigmoid esophagus	10 (2.9)	2 (1.6)	8 (3.7)

Time between diagnosis and POEM, months, median (IQR)	14.0 (45.0)	9.0 (43.5)	15.0 (45.0)

Results are presented as n (%) unless otherwise stated. † Laparoscopic Heller's myotomy not included. § Based on Chicago classification version 3.0. ASA, American Society of Anesthesiologists. BMI, body mass index. BTI, botulinum toxin injection. COPD, chronic obstructive pulmonary disease. DES, diffuse esophageal spasm. HIV, human immunodeficiency virus. LHM, laparoscopic Heller's myotomy. OSAS, obstructive sleep apnea syndrome. PD, pneumatic dilatation. POEM, peroral endoscopic myotomy. TBE, timed barium esophagram.

Table 2: procedure related outcomes

	Total (N=352)	**Routine esophagram (N=129)**	**No routine esophagram (N= 223)**
Procedure time, minutes, median (IQR)	73 (39)	90 (37)	60 (32)
Length of myotomy, cm, median (IQR)	11 (3)	13 (4)	11 (3)
Selective circular	3 (3)	4 (4)	3 (3)
Full-thickness	9 (4)	9 (4)	8 (4)
Intraprocedural adverse events, number	41 †	23	18
Pneumoperitoneum requiring abdominal needle drainage	18	15	3
Mucosal injury closed with clips	13	6	7
Second submucosal tunnel	4	0	4
Bleeding	6	2	4
Minor	4	1	3
Major	2	1	1
Number of days in hospital, days, median (IQR)	2 (0)	2 (0)	2 (0)
Routine esophagram post-POEM			
No esophageal leakage		124 (96.1)	
Signs of esophageal leakage		5 (3.9)	
Post-procedural adverse events §	19 (5.4)	5 (3.9)	14 (6.3)
Grade I	10 (2.8)	2 (1.6)	8 (3.6)
Grade II	3 (0.9)	1 (0.9)	2 (0.9)
Grade IIIa	5 (1.4)	2 (1.6)	3 (1.3)
Grade IVa	1 (0.3)	0 (0.0)	1 (0.4)

Results are presented as n (%) unless otherwise stated. † In total 41 intraprocedural adverse events occurred in 38 patients (10.8%). § Based on Classification for Adverse events Gastrointestinal Endoscopy (AGREE)[29]. POEM, peroral endoscopic myotomy.

Supplementary table 1: overview of post-procedural adverse events.

Patient	Post-procedural AE	Diagnostics	Hospital stay	AGREE-classification	Year of POEM	Days between POEM and AE
1	Retrosternal pain with opioids for pain control.	Routine barium esophagram: no esophageal leakage	Prolonged > 24 hours Total 4 days	Grade II	2013	1
2	No symptoms. Repeat endoscopy because of signs of esophageal leakage, three extra clips were placed at the incision. The next day persistent leakage for which a duodenum feeding tube was placed. Antibiotics were given because of fever measured once after repeat endoscopy.	Routine barium esophagram: submucosal leakage Second barium esophagram: persistent leakage	Prolonged > 24 hours Total 7 days	Grade IIIa	2015	1
3	No symptoms. Twice repeat endoscopy because of signs of esophageal leakage. In total five extra clips were placed at the incision. A duodenum feeding tube was placed for three days because of persistent leakage.	Routine barium esophagram: submucosal leakage Second barium esophagram: persistent leakage	Prolonged > 24 hours Total 5 days	Grade IIIa	2016	1
4	Retrosternal pain with opioids for pain control.	Routine barium esophagram: no esophageal leakage	Prolonged < 24 hours Total 3 days	Grade I	2016	1
5	Longer observation because of intraprocedural bleeding. Hemodynamically stable. No blood transfusion was needed.	Routine barium esophagram: no esophageal leakage	Prolonged < 24 hours Total 3 days	Grade I	2016	1
6	Retrosternal pain with opioids for pain control. Antibiotics were given for two days until perforation was ruled out by upper endoscopy.	CT: pneumoperitoneum, no signs of esophageal leakage, possible microperforation Upper endoscopy: no abnormalities	Re-admission 48 hours	Grade IIIa	2017	4
7	Melena three weeks after POEM due to ulcer in the cardia where previously mucosal injury was clipped during POEM. Hemodynamically stable. Recovered with conservative treatment.	Upper endoscopy: ulcer at the place of previous mucosal injury which was clipped during POEM	Not prolonged Upper endoscopy at outpatient clinic	Grade IIIa	2017	21
8	Longer observation because of low blood pressure.	None	Prolonged < 24 hours Total 3 days	Grade I	2017	0
9	Retrosternal pain with non-opioids for pain control.	Chest X-ray: no abnormalities	Prolonged < 24 hours Total 3 days	Grade I	2017	0
10	Pneumoperitoneum, pneumomediastinum, subcutaneous emphysema and pneumothorax after inadvertently using room air instead of carbon dioxide during POEM. Drainage was not needed and opioids	Chest X-ray and CT: pneumoperitoneum, pneumomediastinum, subcutaneous emphysema and pneumothorax	Prolonged > 24 hours Total 7 days	Grade II	2017	0

	were given for pain control. Hemodynamically stable.					
11	Retrosternal pain with opioids for pain control.	CT: no abnormalities	Visit emergency department without re-admission	Grade I	2018	1
12	Oral antibiotics for five days because of pneumonia.	Chest X-ray: pneumomediastinum, consolidation	Not prolonged Total 2 days	Grade II	2019	1
13	Longer observation because of intraprocedural bleeding and difficult closure of mucosal incision. Nasogastric tube was placed until esophageal leakage was ruled out by CT. No symptoms.	CT: pneumomediastinum, pneumoperitoneum, no esophageal leakage	Prolonged < 24 hours Total 3 days	Grade I	2019	0
14	Retrosternal pain with non-opioids for pain control.	CT: pneumoperitoneum, no esophageal leakage	Prolonged < 24 hours Total 3 days	Grade I	2020	1
15	Low-grade fever and retrosternal pain with non-opioids for pain control. Re-admission for observation and the patient recovered with conservative treatment.	CT: pneumoperitoneum, no esophageal leakage	Visit emergency department with re-admission for 1 night/day	Grade I	2021	2
16	Abdominal pain and respiratory insufficiency three days after POEM. Pneumonia with pleural effusion. ICU admission with high flow oxygen, ceftriaxone, metronidazole and pleural drainage (exudate, no bacteria).	CT: significant pleural effusion, no esophageal leakage, minimal pneumomediastinum, pneumoperitoneum, atelectasis, debris in right main bronchus Upper endoscopy: no perforation	Re-admission 9 days (6 days ICU)	Grade IVa	2021	3
17	Five days after POEM retrosternal pain with non-opioids for pain control. Duodenum feeding tube was placed for 25 days because of dehiscence of the mucosal incision.	Upper endoscopy: dehiscence of mucosal incision with closed tunnel after removing clip, no extra clips placed, duodenum feeding tube placed	Re-admission for 1 night	Grade IIIa	2021	5
18	Retrosternal pain after three days with non-opioids for pain control.	CT: pneumoperitoneum, no esophageal leakage	Visit emergency department without re-admission	Grade I	2022	3
19	Longer observation because of retrosternal pain one day post-POEM with non-opioids for pain control. After one week fever measured once at home and no change in retrosternal pain. Pain well controlled with non-opioids.	CT after 1 day: no esophageal leakage, little intramural contrast CT after 1 week: no esophageal leakage, lung nodule 5 mm (follow up after 6 months)	Prolonged < 24 hour Total 3 days Visit emergency department without re-admission	Grade I	2022	1 and 7

AE, adverse event. AGREE, Classification for Adverse events Gastrointestinal Endoscopy. ICU, intensive care unit. POEM, peroral endoscopic myotomy