Original article

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Outcome after iatrogenic esophageal perforation

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Outcome after iatrogenic esophageal perforation

Objectives: Iatrogenic perforations are the most common cause of esophageal perforation. We present our experience mainly based on a non-operative treatment approach as well as long-term outcome in these patients.

Materials and methods: 21 patients were treated for iatrogenic esophageal perforation at Oslo University Hospital, Ullevål from February 2007 – March 2014. The etiology of perforation was dilation of benign stricture in eight patients, either dilation, stenting or stent removal in four with malignant stenosis, during diagnostic endoscopy in four, removal of foreign body in two and by other causes in three patients, respectively. After median 82 months ten patients alive (47.6 %) were sent questionnaires about dysphagia, HRQoL and fatigue.

Results: Median age at time of treatment was 66 years. In-hospital stay and mortality was median 10.5 days and 4.8 %, respectively. Initial treatment in fifteen patients (71.4 %) was non-surgical of whom one needed delayed debridement for pleural empyema. Initial treatment in six patients (28.6 %) was surgical of whom three needed delayed stenting. Altogether 14 patients (66.7 %) were stented. Eight (57.1 %) had restenting. Number of stents used were median 1 (1 – 4). The stents were removed after median 36 days. The perforations healed after 2.5 months. After median 82 months the patients reported reduced HRQoL. There was no significant difference regarding level of dysphagia and fatigue.

Conclusion: We report satisfactorily short-term and long-term results of iatrogenic esophageal perforations. Mortality was low and HRQoL was deteriorated. Dysphagia and fatigue were comparable to a reference population.

Keywords: iatrogenic, perforation, stenting, drainage, resection, suture, dysphagia, fatigue, quality of life

Introduction

Iatrogenic injuries are the most frequent cause of esophageal perforations, accounting for 59 % of all patients [1]. The main cause for iatrogenic perforation is upper endoscopy, more frequently with a rigid then a flexible endoscope (0.11 % vs 0.03%), with a peak incidence of 2-6 % during pneumatic dilatations [2]. A meta-analysis of 75 studies including 2971 patients [3] found a pooled mortality rate of 11.9 % with a mean hospital stay of 32.9 days. The highest mortality rate was found in patients with spontaneous perforation (14.8 %), followed by iatrogenic (13.2 %) and foreign body (2.1 %) perforation. This study [3] also emphasized the need of prompt treatment since mortality rate increased from 7.4 % to 20.3 %, dependent on whether treatment started before or after 24 hours of perforation.

Traditionally the main treatment has been surgery (suture, resection, debridement). However, three major single center studies [4-6] on stent-grafting for iatrogenic perforation have demonstrated promising results with high healing rate (94 %, 94 %, 100 %), low mortality (0 %, 1.3 %, 5.8 %) and no dysphagia assessed after 3 months in a cohort of 20 patients. Moreover, we have also recently reported that self-expandable metallic stents (SEMS), for spontaneous esophageal perforation [7] as well as with accidental food bolus-induced perforation [8], is a safe treatment option with mortality rates well comparable to the traditional surgical approach.

The aim of this study, mainly based on a non-surgical treatment, was to report the results of patients treated for iatrogenic esophageal perforations at Oslo University Hospital from 2007 to 2014. The patients' long-term well-being were examined with validated scores for dysphagia, fatigue and health-related quality of life.

Materials and Methods

21 patients were treated for esophageal perforations at Oslo University Hospital Ullevål from February 2007 to March 2014. The data was retrospectively registered in an Excel-created database. The diagnosis was made by computed tomography (CT) scan with oral contrast and/or upper endoscopy. The initial treatment was non-surgical in 15 patients (71.4 %), based on sealing of the perforation by stent and percutaneous drainage of pleural and mediastinal content. Six of the patients (28.6 %) underwent surgically based treatment of the perforation by a combination of resection, suture, tegmentation, thoracic debridement as well as stenting. Both fully covered stents (UltraFlex, WallFlex) and partially covered stents (WallFlex, EndoFlex) were used for sealing the perforation. The ten patients alive in August 2016 were invited to answer a questionnaire regarding dysphagia, fatigue and Quality of Life.

Ogilvie`s dysphagia score [9] from 0 – 4 was used to determine ability to eat normal diet (score 0), swallow some solid foods (1) or only semi-solid foods (2) or liquids only (3) or unable to swallow (4 - total dysphagia).

Total fatigue score consists of 11 items of graded questions with score 0–3 per question, which is the sum of physical fatigue (7 items) and mental fatigue (4 items). This score has been validated in a Norwegian general population [10]. The respective scores for total, mental and physical fatigue are 0–33, 0–21 and 0–12, and the higher score the more fatigue. The items of physical (1–7) and mental (8–11) fatigue were: 1) Do you have problems with tiredness? 2) Do you need to rest more? 3) Do you feel sleepy or drowsy? 4) Do you have problems with starting things? 5) Are you lacking in energy? 6) Do you have less strength in your muscles? 7) Do you feel weak? 8) Do you have difficulty concentrating? 9) Do you have problems thinking clearly? 10) Do you make slips of the tongue when speaking? 11) How is your memory?

Self-reported health-related quality of life (HRQoL) was assessed with the short form 36 (SF-36) (version 2), which is a generic HRQoL questionnaire consisting of 36

items, of which 35 are grouped into the following eight health domains: (1) physical functioning (PF), (2) social functioning (SF), (3) role limitations due to physical problems (RP), (4) role limitation due to emotional problems (RE), (5) mental health (MH), (6) vitality (VT), (7) bodily pain (BP) and (8) general health perception (GH). Each domain is graded on a scale of 0-100, and the higher the score the better the HRQoL. The validity and reliability of the SF-36 form have been demonstrated for a number of countries including Norway (version 1.2) [11]. The data were compared with published data from 5396 individuals in the general population. Although there are differences in the grading of some questions in version 2 versus version 1 of the SF-36 questionnaire, for the four health dimensions 3, 4, 5 and 6, the mean values on a group level are comparable.

Student's t- test was used for comparison of fatigue and HRQoL scores between the patients and respective Norwegian population-based cohorts [10,11] and p-values below 0.05 was considered statistically significant.

The study was approved by the regional ethical committee (2012/1604/REK south-east (D) Norway).

Results

Etiology

Characteristics of the patient material and etiology of the perforations are depicted in table 1 **and table 2**. Two patients had perforation in the proximal esophagus during endoscopy for ultrasonography and biopsy of a pancreatic tumor, of whom one patient was bothered with coughing at instrumentation. Another two patients developed perforation either after failed or successful endoscopic passage of peptic strictures located in the lower esophagus. One patient experienced a perforation after initial erroneous intubation of esophagus, instead of trachea, prior to a gastric bypass operation for obesity. Perforation occurred in two patients during balloon retrieval of a piece of impacted meat and sling retrieval of a fork from the stomach, respectively. An intraabdominal esophageal perforation occurred in a young patient during a gastric sleeve operation. A middle-aged patient developed gastric retention after closure of a loop ileostomy after

low anterior resection for rectal cancer. A nasoenteral tube introduced for decompression of the stomach, caused a distal esophageal perforation in its thoracic segment.

Initial treatment

The perforations were initially diagnosed during an upper endoscopy in eight patients (38.1 %) and with a CT scan in 13 patients (61.9 %). After perforation 16 of the patients (76.2 %) were treated within less than 24 hours, two (9.5 %) during 24 – 48 hours and three (14.3 %) beyond 48 hours. The initial treatment is summarized in table 3. Most patients (71.4 %) had non-surgical treatment, of whom 11 (73.3 %) received an esophageal stent. The remaining four patients were treated solely with antibiotics in two patients and supplemented percutaneous drainage in two, respectively. After initial treatment and restenting in this group, the healing rate increased from 73.3 % to 100 %.

Six patients (28.6 %) had treatment based on surgery [Table 3]. Reasons for choosing surgery as main treatment option was pronounced and refractory stricture in two patients, considerable pleural effusion and contamination in two, and perforation of abdominal and cervical esophagus with limited contamination in two, respectively. In this group, three perforations healed after initial treatment with thoracic resection and suture of the perforation in the cervical esophagus. The remaining three patients needed stenting for ultimate healing of these perforations.

At initial treatment in 12 patients (57.1 %), seven received a fully covered stent and five a partially covered stent, respectively.

Subsequent treatment for complications

Three patients had major complications (14.3 %). A female aged 33 who underwent a gastric sleeve operation had an overlooked perforation that was sutured 10 days after initial surgery. The persisting leakage was sealed with 2 PolyFlex covered plastic stents and healed after 2.5 months. A 79-year-old male who had a covered stent for a perforated benign stricture, experienced stent migration and bleeding after 4 days from the site of perforation successfully treated by sclerotherapy and transient placement of a covered stent. Patient 3, a 61-year old male was initially stented for a delayed perforation after more than 72 hours. He developed empyema and stent migration after the initial stenting and underwent thoracotomy with debridement of the thoracic cavity, suture of the

perforation and reposition of the esophageal stent. Including stenting for complications, altogether 14 patients (66.7 %) in this patient material received a stent, of whom 8 were restented (57.1 %) for migration (n=4) or lack of sealing (n=4) of the perforation. Number of stents used were median 1 (range 1 – 4). The stents were removed after median 36 days (29-67 days).

Mortality and survival

The median stay after treatment of the 21 patients at our hospital was 10.5 days (2-51), of whom seven (33.3 %) were transferred to their local hospital for a transient stay. The overall 30-day mortality was 4.8 % and there was no in-hospital mortality. An 81-year-old female who underwent pneumatic dilation of a peptic stricture, was treated within 24 hours with stenting of the perforation, percutaneous drainage of pleural fluid and antibiotics. She refused any further treatment and died at a nursing home after 16 days. In July 2018, after a median observation time of 105 months (57 -134 months), 10 out of 21 patients (47.6 %) were alive. Estimated survival after perforation is depicted in figure 1. Six out of 11 patients (54.5 %) died from esophageal (n=4) and pancreatic cancer (n=2) after median 7.5 months (2 – 35 months). One 28 year old patient died from a psychiatric disorder after 23 months. Remaining four patients died at median age of 81 years (range 73 – 90). .

Dysphagia, HRQoL and fatigue

In August 2016 after median 82 months (range 34 – 111), the 10 patients alive (47.6 %) were sent questions concerning scores for dysphagia, HRQoL, and fatigue, with response rates of six (60 %), six and five patients (50 %), respectively. The median age of the respondents of whom 4 were men, was 42.5 years (29-61 years). The six patients that responded had perforation during gastroscopy and intubation of a passable stricture in three and one patient each by gastric sleeve operation, nasoenteral tube placement and esophageal intubation, respectively.

Dysphagia score was median 0 (range 0 -1), of whom one scored 1. The results for HRQoL for the eight different dimensions were compared with the general Norwegian

population aged 40-49, based on 543-549 men [11, Table 4]. With the exception of role limitations physical ($p=0.09$), there was a significant reduction ($p<0.05$) in seven out of the eight dimensions, compared with the general Norwegian population.

Total fatigue score (mean ± SD) was 13.8 ± 4.4, whilst physical and mental scores were 8.8 ± 4.0 and 5.0 ± 0.7, respectively. For comparison, the general Norwegian population-based values, in the age bracket 40-49 years, based on 216 males [10] were 11.7 ± 3.8 ($p=0.22$), 7.4 ± 3.0 ($p=0.31$) and 4.3 ± 1.4 ($p=0.27$). Accordingly, there was no significant difference regarding level of fatigue.

Discussion

Here we presumably report for the first time in patients with iatrogenic esophageal perforation both initial treatment and long-term outcome with regard to dysphagia, fatigue and HRQoL. Similar to other studies [1] the most common cause of perforation was endoscopic instrumentation for treatment of benign and malign esophageal strictures.

The 30-day mortality was 4.8 % which compared favorably with a pooled mortality rate of 13.2 % in a recent metaanalyisis [3] based on 26 studies of 431 patients with iatrogenic perforation.

The majority of our patients (71.4 %) received non-surgical treatment based on stenting, drainage and/or antibiotics. These patients had limited mediastinal contamination and strictures that were sufficiently opened upon dilation and insertion of a self-expandable stent. The remaining six patients underwent surgery by a combination of resection, suture and thoracic debridement. Reasons for choosing surgery was delayed start of treatment (> 72 hours), cervical perforation, high degree of stricture and development of empyema. One patient with delayed and failed suture after 10 days, should initially have been stented in order to promote healing of the abdominal perforation.

Stent migration is a common complication and patients from both treatment groups needed additional stenting for sealing of the perforation. The migration rate was 28.6 % which was similar to a literature study by Saxena et al from 2017 [12], who found a migration rate of 6-35 % based on 14 studies. In order to reduce the migration rate

anchoring of the stent by endoscopic suturing has been proposed [12], which was not used in this study. One patient who was stented and received a pleural drain after > 72 hours developed pleural empyema that was treated by delayed debridement via thoracotomy. This complication could probably have been avoided if the contaminated chest had been treated by thoracoscopic debridement at admission to hospital. Thus, degree of thoracic contamination must be carefully evaluated in terms of relevant treatment intervention.

A Swedish systematic review from 2017 [13] compared non-surgical treatment (stenting, percutaneous drainage) with a surgical exploration (suture, resection, debridement) for esophageal perforations. They reported a success rate of 88 % and an in-hospital mortality of 7.5 % in the stent-based group, whilst corresponding figures in the surgery group were 83 % and 17 %, respectively. They concluded that a "SEMS-based therapy can be successfully applied as an alternative therapeutic strategy in esophageal perforation rupture". More specifically, three large studies from 2007 [4] and 2014 [5, 6] involving more than 100 patients given a stent-based treatment, support these results with even lower mortality and higher success rate defined as healing of the perforation. The main advantage using an organ-preserving approach, by stenting of the perforation instead of surgery with resection, is probably that the functional result will be better if the perforation heals without a permanent stricture causing intractable dysphagia for the patient. Therefore, in cases of strictures resistant to dilation a resection is a better treatment option in fit patients. Generally, since the introduction of SEMS in 2008, the majority of patients with iatrogenic perforation have been successfully treated by stent-grafting.

More than 6 years after treatment only one out of six patients reported a minor degree of dysphagia for solid food, which is a satisfactorily result. The patients had a significant lower HRQoL for seven out of the eight dimensions of the SF36-score [Table 4], with the exception of physical, role limitations. We have recently reported that there was no difference neither in level of fatigue nor HRQoL in patients treated for food bolus induced esophageal perforation [8], whilst fatigue was increased in patients with spontaneous perforation [7]. The reason patients with iatrogenic perforation had lower HRQoL than patients with food bolus induced perforation may be that the percentage of

patients with esophageal disease was higher in the former group. Moreover, the reason that fatigue was normal in iatrogenic and food bolus induced perforations compared with deterioration in patients with spontaneous perforation, probably was related to increased comorbidity in the latter group of patients. However, the results on HRQoL and fatigue in iatrogenic perforations, as well as the comparisons with patients with food bolus induced and spontaneous perforations, must be interpreted with caution because of the low number of patients included.

Conclusion

Iatrogenic perforation, the most common cause of esophageal perforation, could mainly be treated non-surgically (stent, percutaneous drainage). A prerequisite for a successful outcome was that the stricture could be opened by dilation and stenting. A surgically-based approach (resection, suture, debridement) was necessary in cases with refractory strictures and considerable pleural contamination necessitating thoracic debridement. A delayed perforation should be sealed by stenting instead of an often failed closure by suture. Presumably for the first time, such patients reported reduced HRQoL, whilst scores for dysphagia and fatigue were comparable to a reference population.

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Table 2. The etiology of the perforations in 21 patients.

Etiology	No. patients	Percent
Dilation of benign stenosis	8	38.1 %
Peptic	*5*	
Achalasia	*3*	
Malignant stenosis	4	19 %
Dilation (by balloon)	*2*	
Stenting	*1*	
Stent removal	*1*	
Induced during endoscopy	*4*	19 %
Manipulation of stricture	*2*	
Instrumentation for EUS	*2*	
Removal of fork/impacted meat	*2*	9.5 %
Miscellaneous	*3*	14.3 %
Erroneous esophageal Intubation	*1*	
Surgery (gastric sleeve)	*1*	
Nasoenteral tube	*1*	

EUS= endoscopic ultrasonography

Table 1. Patient characteristics in 21 patients.

Parameter	
Males/females	12/9
Age (median, range)	66 / 26-89 years
Comobidity (number)	

GERD	*2*
Excessive alcohol consumption	*2*
Rheumatoid arthritis	*1*
Psychiatric disorder	*1*

Table 3. Initial treatment of iatrogenic perforations in 21 patients.

Treatment	No. patients	Percent
Non-surgical	15	71.4 %
Stent	*6*	
Stent and drainage	*5*	
Drainage	*2*	
Antibiotics (only)	*2*	
Surgically based	6	28.6 %
Resection	*2*	
Suture	*2*	
Debridement and Chest tube or Stent	*2*	

Table 4. SF36 Mean (standard deviation) SF-36 scale scores defining health related quality of life in six patients with iatrogenic induced esophageal perforation compared with normative data from the Norwegian male population aged 60-69.

Dimension	Patient material (n=6)	Loge JH et al [10] (n=543-549)	P-value
Physical functioning	75.0 (10)	91.7 (14.6)	0.005
Role limitations, physical	62.5 (39.1)	84.2 (31.0)	0.09
Bodily pain	51.2 (27.0)	76.6 (25.0)	0.01
General health	57.0 (15.8)	79.1 (19.7)	0.006
Vitality	42.4 (32.9)	64.3 (19.4)	0.006
Social functioning	62.5 (33.0)	88.4 (19.5)	0.001
Role limitations, emotional	69.7 (36.6)	90.4 (25.3)	0.04
Mental health	67.5 (17.5)	81.1 (15.6)	0.03

Values are given as mean and standard deviation (SD). Abbreviations: Pm; patient material, Nd; normative data

Figure 1. Estimated survival in 21 patients after treatment for iatrogenic esophageal perforation