



Postoperative Sequelae after Esophagectomy for Adenocarcinoma in the Gastroesophageal Junction; an 18 Months Nurse Specialist Outpatient Clinic Follow-Up

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Abstract

Background and Aims: Patients with Gastroesophageal Junction (GEJ) cancer have a poor prognosis with an overall 5-year survival rate of 10% to 15%. With curative surgery, survival is improved to around 40%, but esophagectomy is an extensive surgical procedure with well-documented impairments that burdens the patients. A substantial weight loss is common, and symptoms such as reflux, dumping, and fatigue are frequently observed. This study aimed to evaluate the extent of postoperative sequelae in two high-volume centers.

Methods: This study is a retrospective analysis of prospectively registered data from patients who had undergone curative esophagectomy between January 2016 and August 2017. Data were obtained from patients with an 18 months follow-up without recurrence. All of the operations were conducted at two high-volume upper gastrointestinal cancer surgical centers. A nurse specialist outpatient clinic conducted the prospective follow-up interview.

Results: 113 persons were included in the analysis. The most common postoperative problems identified were reflux (45%), fatigue (36%), dumping (31%), and dysphagia (21%). Problems with loss of appetite, activities of daily living, and pain were also reported. Most symptoms improved throughout the follow-up period, except for reflux. Six months after the operation, the weight loss leveled out at an average of 90.4% of the preoperative weight, and the patients did not regain their preoperative weight status.

Conclusion: The patients initially experienced a postoperative deterioration of all of the symptoms observed, but most improved within 12 months.

Keywords: Esophageal neoplasms; Dumping syndrome; Adverse effects; Gastroesophageal reflux; Postoperative complications

Introduction

Gastroesophageal junction cancer is the seventh most common and the sixth leading cause of cancer-related mortality, with around 400,000 deaths annually [1]. GEJ cancer prognosis is poor with a 5-year survival of 10% to 15%, but with curative surgery and perioperative chemotherapy, survival is improved to approximately 40% [2,3]. The curative treatment for cancer in the gastroesophageal junction is esophagectomy, with the surgical procedure of choice often being the transthoracic Ivor-Lewis Esophagectomy (ILE) combined with chemotherapy or chemoradiotherapy [4].

However, esophagectomy is not without significant postoperative morbidity and mortality. The major surgical reconstruction of the upper gastrointestinal tract is associated with severe complications causing more than half of the patients to develop a functional disorder [5]. The most frequently observed symptoms are reflux, dysphagia, and dumping syndrome, while general symptoms such as loss of appetite and diarrhea might also present. Eating problems are one of the worst persisting esophageal specific symptoms [6,7]. In time, some of the postoperative issues will improve and return to baseline; however, symptoms such as reflux, eating problems, nausea/vomiting, and diarrhea may persist [8]. Also, extensive surgical reconstruction carries a risk of malnutrition [9]. Weight loss is one of the most significant side effects, which might be due to altered eating behavior [9,10]. Studies have shown that most patients lose more than 10% to 15% of

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Table 1: Differences in grade scoring and data transformation.

	Department A	Department B	New scale
Irregular Intestinal Function	Obstipation: 0: Not a problem 1: Sometimes 2: Persistent problems and continued use of laxatives. Limitation of ADL 3: Obstipation with the indication of manual emptying 4: Life-threatening, immediate intervention needed.	Normal intestinal function? 1: Yes 2: No	Irregular intestinal function? 1: Yes Department A: 1-4 Department B: 1 2: No Department A: 0 Department B: 2 ^a
	Diarrhea: 0: Not a problem 1: ≤ 4 defecations a day 2: 4-6 3: ≥ 7; faecal incontinence; indication for admission; Limitations of ADL. 4: Life-threatening, indication for immediate admission.		
Dysphagia	Symptoms of stenosis? 1: Yes 2: No 5: Missing data	0: Normal funct. 1: Problems with solid foods 2: Problems with soft foods 3: Only liquid 4: Problems with liquid and saliva 5: Total inability to swallow	Symptoms of dysphagia? 1: Yes Department A: 1 Department B: 1-5 2: No Department A: 2 Department B: 0
Fatigue	0: Not a problem 1: Mild fatigue. Relieved with rest. 2: Moderate fatigue or fatigue which affects ADL. Fatigue is not relieved with rest. 3: Severe fatigue affecting ADL. Fatigue is not relieved with rest. 4: Incapacitating fatigue.	1: Nothing 2: A bit 3: A lot 4: Very much	1: Nothing Department A: 0 Department B: 1 2: A bit Department A: 1 Department B: 2 3: A lot Department A: 2 Department B: 3 4: Very much Department A: 3,4 Department B: 4 ^b
Pain	0: None 1: Pain, which requires weak analgesics (paracetamol/NSAID) 2: Pain manageable with pn. Morphine ≤ 3 times a day. 3: Pain requiring regular treatment with opioids. Either with a short-lasting or depot analgetics. 4: Pain requiring regular treatment with opioids and a need for pn. >3 tablets a day.	Problems with pain? 1: Yes 2: No Thoracic pain: 1: None 2: A bit 3: A lot 4: very much Abdominal pain: 1: None 2: A bit 3: A lot 4: very much	Department B used thoracic pain. Gratings were compared. 1: Department A: 0 Department B: 1 2: Department A: 1 Department B: 2 3: Department A: 2,3 Department B: 3 4: Department A: 4 Department B: 4
Loss of appetite	0: No problems 1: Loss of appetite without change of eating habits 2: Change in oral food intake without significant weight loss or malnutrition; indication for oral supplementation 3: Loss of appetite with significant weight loss or malnutrition (e.g., insufficient intake of calories or fluids; indication for tube feeding/Total parenteral nutrition 4: Life-threatening consequences; indications for immediate intervention	1: None 2: A bit 3: A lot 4: very much	1: Department A: 0 Department B: 1 2: Department A: 1 Department B: 2 3: Department A: 2 Department B: 3 4: Department A: 3,4 Department B: 4
Vomiting	0: No vomiting 1: 1-2 episodes within 24 hours 2: 3-5 episodes within 24 hours 3: 6 episodes within 24 hours	1: Yes 2: No	1: Department A: 1 Department B: 1 2: Department A: 0 Department B: 2

^aNo one is scoring greater than 2 at department A^bNo one from department A had a score of over 1

their preoperative weight within six months, and a fifth of the patients lose more than 20%. These weight losses continue for up to three years [10], and according to ESPEN guidelines [11], these patients are at severe nutritional risk. Furthermore, studies have found that most recurrences are diagnosed within the first two postoperative years; therefore, some of the postoperative morbidity might be related to cancer recurrence [12,13].

The aim of this study was to evaluate postoperative sequelae after curative intended surgical treatment experienced by a cohort of patients without recurrence in two high-volume centers with the follow-up conducted by a nurse specialist outpatient clinic.

Materials and Methods

A local institutional review board approved this study and the extraction of data from patients' charts.

This study was a retrospective analysis of prospectively registered data by a nurse specialist outpatient clinic in a 20 months period from 01.01.2016 to 31.8.2017. Data were obtained in an 18 months follow-up for patients who had undergone curative surgery for adenocarcinoma in the GEJ at two high-volume upper gastrointestinal cancer surgical centers. All patients who died during follow-up or had a recurrence of cancer were excluded. Patients resected with ILE were

included and all other surgical approaches (colonic interposition, transhiatal, McKeown esophagectomy, and endoscopic resections) were excluded.

Patients who had undergone curative esophagectomy were cross-referenced to a local database and patient charts. The prospective follow-up interview was conducted by a nurse specialist outpatient clinic and the patients were interviewed at discharge and 1, 6, 9, 12, and 18 months after surgery. The charts used for the nurse specialist follow-up interview had overlapping questions but were not similar in the grading systems. The differences in grade scoring and the data transformation are shown in Table 1.

The authors read the patients' charts and nurses' interviews, extracted and transformed data, and anonymized it according to general data protection regulations.

Statistics

All data registration and statistical analysis were performed in Microsoft Excel (version 16.41). Descriptive statistics were used and χ^2 - test was applied for comparison between two groups. A p-value <0.05 was considered significant.

Results

In 20 months, from January 2016 to August 2017, a total of 219 patients underwent curative ILE. At the time of analysis, 85 patients (39%) were either deceased or excluded due to recurrence. Seven patients (3%) were lost for follow-up, and 14 patients (6%) were excluded due to missing data. Thus, a total of 113 (52%) with an 18 months recurrence-free follow-up were eligible for further analysis. The population characteristics of these 113 patients are presented in Table 2.

The patients had a preoperative weight average of 83.5 kg (range 48 kg to 120 kg). After one month, the average had decreased to 94.3% of the preoperative weight, and in six months, it had been reduced to 90.4% (range 76.5% to 114.5%). A total of 49% of the patients had lost between 0% to 10% of their preoperative weight, 19% had lost 10% to 15%, and 26% lost more than 15%. Only 6% of the patients had a stable or gained weight. Weight change is displayed in Figure 1.

At the sixth month follow-up, 34 patients (55%) with a preoperative BMI ≥ 25 had lost 10% or more of their bodyweight. For those with a BMI <25, 11 patients (35%) had lost more than 10%. However, this difference was not statistically significant ($p=0.078$).

Reflux, dumping, dysphagia, irregular intestinal function



Figure 1: Weight change in percent of preoperative weight. N=107, Dsch. Day Discharge day.

Table 2: Population characteristics.

Population characteristics	% (N) ^a
Age at operation, median (range)	68 (33-84)
Preop. BMI (kg/m ²), median (range)	27.4 (19-37.17)
<20	3% (3)
20 to <25	33% (37)
≥25	64% (72)
Unknown	1% (1)
Gender	
Male	85% (96)
Female	15% (17)
ASA score	
1	15% (17)
2	71% (80)
3	13% (15)
Unknown	1% (1)
LOS, median (range)	9 (5-45)
Pathologic tumor classification	
pT0	11.5% (13)
pT1	24.8% (28)
pT2	13.3% (15)
pT3	49.6% (56)
pT4	0.9% (1)
Pathologic node classification	
pN0	67.3% (76)
pN1	20.4% (23)
pN2	9.7% (11)
pN3	2.7% (3)
Pathologic metastasis classification	
pM0	99.1% (112)
pM1	0.9% (1)
Adjuvant therapy	
Chemotherapy	61.1% (69)
Chemoradiotherapy	0.9% (1)
None	38.1% (43)

^aUnless otherwise is noted. ASA: American Society of Anesthesiologists; LOS: Length of stay (in days)

(obstipation and diarrhea combined), and vomiting are displayed in Figure 2. Symptoms of dumping, dysphagia, irregular intestinal function, and vomiting peaked within the first six months of the operation; however, these symptoms subsequently improved. During the 18 months, 31% and 21% reported dumping one or more times and dysphagia, respectively. The incidence of reflux was low in the first postoperative month but increased with time and peaked at the 18th month. During the 18 months of follow-up, 45% reported the presence of reflux at least once.

The development of Activities of Daily Living (ADL), loss of appetite, pain, and fatigue is displayed in Figures 3-6. These sequelae were reported most in the first postoperative month, but all improved in the follow-up period and stabilized after one year. In addition, the incidence of pain was high in the first six months and then improved.



Figure 2: Symptom scales. Showing different postoperative symptoms and their development. *Irr. Intest. Funct* Irregular intestinal function (diarrhea/obstipation).

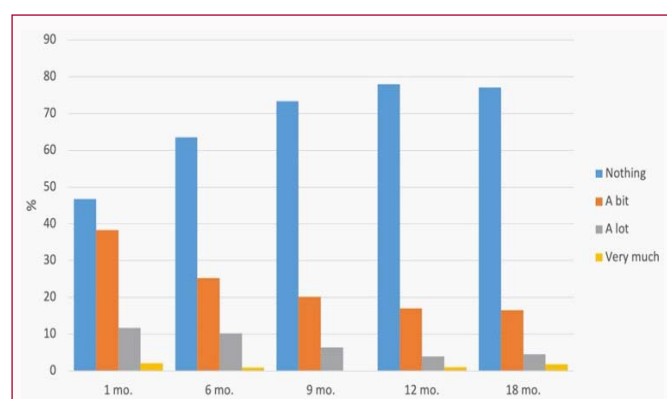


Figure 3: Problems with activities of daily living.

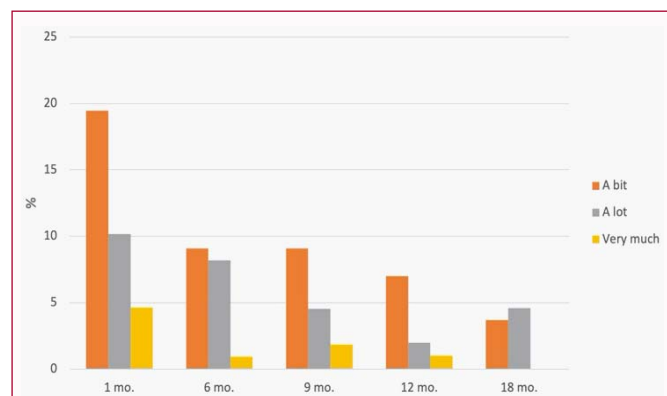


Figure 4: The development of loss of appetite after esophagectomy.

Discussion

To our knowledge, this is the first study to report routine follow-up conducted by a nurse specialist outpatient clinic. In the study, we found an extensive weight loss and a postoperative increase of all symptoms. Most symptoms improved within the first postoperative year. Dumping and fatigue sequelae were found to be most affected during the first six months but improved and stabilized within 12 months. In contrast, reflux symptoms deteriorated throughout all 18 months.

On average, patients in this study lost 9.6% of their preoperative bodyweight within the first six months, and 45% of the patients lost

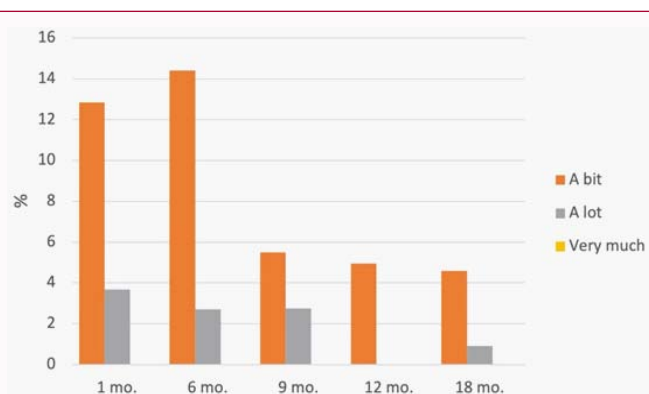


Figure 5: The development of pain experienced after esophagectomy.

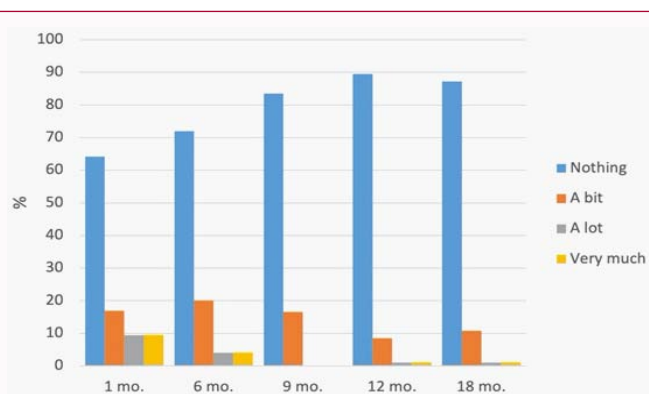


Figure 6: Postoperative fatigue.

more than 10% body weight in that same period. This underlines that patients undergoing ILE are at considerable risk of a substantial weight loss, as shown in an earlier study [9]. According to ESPEN guidelines, patients with a weight loss of $\geq 10\%$ to 15% within six months are at severe nutritional risk [11], which means that almost half of the study populations were at severe nutritional risk. However, this study found that weight change subsided after six months, in contrast with another study showing that weight loss continues for at least three years [10]. The importance of being attentive to patients' loss of weight was demonstrated in a recent study, which reported that patients with a postoperative loss of more than 20% of the bodyweight had increased mortality [14]. Almost all of the patients in our study experienced a postoperative loss of body mass, and only 6% had a stable or increased weight after six months. The excessive weight loss is most likely due to the perioperative chemotherapy and the operation method. The operation results in anatomical and physiological changes, which lead to altered eating behavior and, thus, a more significant weight loss [8]. We also found that a higher preoperative BMI correlated with a greater loss of body weight, even though this was only a tendency ($p=0.078$). However, both French and a Swedish study reported that a BMI over 25 significantly increases the risk of losing more than 15% of the bodyweight [10,15]. A reason for the increased risk might be that the overweight or obese deliberately choose to lose weight and that less attention, therefore, is paid to the postoperative weight.

On the other hand, loss of appetite might also have affected weight loss due to altered eating behavior. The highest incidence of loss of appetite was in the first postoperative month (34%). This correlates with the fact that the improvement of symptoms was

founds simultaneously as the weight loss subsided.

Another postoperative symptom that might have affected the eating behavior and, thus, the weight loss was dumping. Dumping syndrome is a combination of symptoms and a postprandial phenomenon and is a common sequela after the ILE. Symptoms include dizziness, palpitations, nausea, vomiting, abdominal cramps, and diarrhea [12,16]. We have found an overall incidence of dumping of 31%. Dumping symptoms were found to deteriorate during the first six months but improved and stabilized around the 12th month. This is conflicting with some studies, which have seen no improvement in symptoms [17,18], while other studies have reported prevalence in the range of 0% to 78% [12,19]. An extensive systematic review, which included 2,044 patients, found that >20% were troubled by symptoms of dumping [19]. The mechanism of dumping is not entirely understood and defined but might be associated with rapid gastric emptying. Surgical reconstruction is believed to influence postoperative dumping due to factors like tubularization, reduced gastric capacity, pyloric changes, and vagotomy [5,12,19]. Vomiting, which is related to dumping and potentially could influence eating behavior, was also reported in the current study. However, the patients were just slightly burdened by vomiting, with very low incidences observed.

Dysphagia, if present, might also have altered the eating behavior and, thus, the weight loss for some of the patients. During the follow-up period, 21% of patients reported problems with dysphagia at least once, with the highest prevalence being observed in the first postoperative month. In other studies, an incidence of 21% to 56% [7,20] is reported. Also, studies have found dysphagia to improve and almost return to baseline [12,21-25]. However, a previous study found no improvement between the sixth month and the third postoperative year [26]. In our study, symptoms of dysphagia improved from the first to the 12th month. We also found that symptoms of dysphagia deteriorated from the 12th to 18th month, which is in contrast to what other studies have found [12,21-25]. One explanation might be that dysphagia is associated with recurrence of cancer not diagnosed within the follow-up period or unrecognized stenosis of the anastomosis or pylorus. Studies have found that recurrence of cancer is often diagnosed within the first two postoperative years [12,13], which means that some of our patients might have experienced early symptoms of recurrence.

The most frequently reported postoperative complication after ILE is gastroesophageal reflux [7,8,27]. We found the incidence of reflux to increase with time and peak around the 18th postoperative month, where our follow-up ended. The increase is in line with other studies that reported gastroesophageal reflux as one of the few postoperative symptoms that do not improve with follow-up [12,21,25,26,28,29]. A British and a Swedish study both found an increase of symptoms with three- and five-year follow-up time, respectively [21,29]. Another study [21] reported that 75% of the patients deal with symptoms after three years. Therefore, it seems likely that our population would have continued to increase the incidence of reflux symptoms. However, even without an expected increase, reflux symptoms were a substantial burden for our patients, as 45% reported significant reflux symptoms at least once during the 18 months of follow-up. Others have reported an incidence of 20% to 80% [5,7,30,31]. One of the main reasons for developing this symptom is the removal of the GEJ, which is functioning as the normal physiological barrier. Another reason might be that the gastric conduit is submitted to the negative

intrathoracic pressure, thus creating a pressure gradient resulting in reflux [5,8,16]. Treatment advice for this postoperative complication is administering lifelong and high-dose proton-pump inhibitors as well as a recommendation to avoid the prone position and sleep with the headboard elevated [8].

For patients undergoing ILE, fatigue is very pronounced in the first six months after surgery, with the highest incidence (36%) experienced in the first month. This might be due to a lengthy recovery period followed by extensive surgical reconstruction [6]. Some of the fatigue might also be related to the use of postoperative chemotherapy. Fatigue improves markedly after the first postoperative month; however, 12.7% are still troubled by fatigue at the 18th month. This improvement is confirmed in other studies that have shown remarkable improvement in the first postoperative year, even though patients still experience long-term problems [8,21,23,26,29]. Increased fatigue might also influence ADL, as shown in two previous studies [32,33]. This may also be evident in our study as problems with ADL tended to be worst during the first six postoperative months, just as fatigue was found most pronounced during the first six postoperative months. Another sequelae that could have affected ADL is pain. Postoperative pain was worst during the first six months of follow-up but mostly improved within the 18 months, and a connection between the two thus seems likely.

One of the limitations of this study is the retrospective design that may have led to missing data or incorrect registrations. Another limitation is the relatively small sample size due to the poor prognosis of esophageal cancer. In addition, the two departments contributing with data had some differences in their follow-up questionnaires, which also could affect the results. This meant that we had to transform some of the data before the two departments' results could be compared. Finally, some patients received adjuvant therapy, which could have affected the patients' data scoring.

In conclusion, esophagectomy for adenocarcinoma results in temporary deterioration of many aspects such as dysphagia, fatigue, loss of appetite, weight loss, and dumping, but these symptoms improve with time. However, reflux, the most frequently observed complication, does not improve and thus remains a burden for the patients. This study highlights that patients operated for esophageal cancer have severe postoperative morbidity, even though it seems that most symptoms will improve with time.

Author Contributions

Andreas W. Mucha: Conceptualization, formal analysis, investigation, writing – original draft. Laser A. Bazancir: Conceptualization, formal analysis, investigation, writing – reviewing end editing. Magnus S. Joergensen: Investigation, writing – reviewing end editing. Michael H. Larsen: Investigation, writing – reviewing end editing. Michael P. Achiam: Conceptualization, formal analysis, investigation, writing – reviewing end editing, guarantor of integrity of the entire study.

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