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Original Article

The long-term effects of early oral feeding following minimal invasive esophagectomy

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SUMMARY. **A nil-by-mouth regime with enteral nutrition via an artificial route is frequently applied following esophagectomy. However, early initiation of oral feeding could potentially improve recovery and has shown to be beneficial in many types of abdominal surgery. Although short-term nutritional safety of oral intake after an esophagectomy has been documented, long-term effects of this feeding regimen are unknown. In this cohort study, data from patients undergoing minimal invasive Ivor–Lewis esophagectomy between 04–2012 and 09–2015 in three centers in Netherlands were collected. Patients in the oral feeding group were retrieved from a previous prospective study and compared with a cohort of patients with early enteral jejunostomy feeding but delayed oral intake. Body mass index (BMI) measurements, complications, and nutritional re-interventions (re- or start of artificial feeding, start of total parenteral nutrition) were gathered over the course of one year after surgery. One year after surgery the median BMI was 22.8 kg/m^2 and weight loss was 7.0 kg (9.5%) in 114 patients. Patients in the early oral feeding group lost more weight during the first postoperative month ($P = 0.004$). However, in the months thereafter this difference was not observed anymore. In the early oral feeding group, 28 patients (56%) required a nutritional re-intervention, compared to 46 patients (72%) in the delayed oral feeding group ($P = 0.078$). During admission, more re-interventions were performed in the delayed oral feeding group (17 vs. 46 patients $P < 0.001$). Esophagectomy reduces BMI in the first year after surgery regardless of the feeding regimen. Direct start of oral intake following esophagectomy has no impact on early nutritional re-interventions and long-term weight loss.**

KEY WORDS: **body mass index, esophagectomy, nutrition.**

INTRODUCTION

Enhanced recovery after surgery (ERAS) programs are being used in abdominal surgery to reduce postoperative morbidity.[1] In addition, many elements of the ERAS protocol have been successfully introduced in esophageal surgery.[2] With the introduction of these programs, morbidity rates are reduced and recovery after surgery has improved.[3–5]

An important part of ERAS protocols is early oral feeding. However, after an esophagectomy, it remains a matter of debate when oral intake should be started and which feeding route should be used if the start of oral intake is delayed.[6] Fear for increased pulmonary complications due to aspiration and aggravation of anastomotic leakage are main arguments to delay oral intake directly following esophagectomy. Furthermore, often tube feeding is given for a prolonged period to ensure adequate caloric intake.[7,8] In the postoperative period nutritional reinterventions, such as restart of enteral feeding, start of total parenteral nutrition (TPN), and replacement of feeding tubes are sometimes necessary in patients with complications or when oral intake does not meet the energy and protein requirements.[9] However, despite enteral feeding, weight loss after esophageal surgery seems to be an integral part of the procedure.[10] Weight loss is recorded in 17–82% of the patients within the first month following esophagectomy.[6] Moreover, 27–95% of the patients do not reach their baseline weight after

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esophageal surgery, losing 5–12% of their weight in the first six months postoperatively.[11] It is unclear whether early postoperative nutritional support can prevent weight loss in the long term.

Early start of oral intake has recently been shown to be safe and feasible.[12] Furthermore, short-term nutritional intake goals are reached in patients with oral intake after esophageal surgery.[12] These results contribute to the feasibility of direct start of oral intake after an esophagectomy. However, whether early start of oral intake affects long-term nutritional outcome is unknown.

The aim of this study is to investigate the effects of early versus delayed oral intake following minimal invasive esophagectomy on weight loss and nutritional reinterventions in the first year after surgery.

MATERIALS AND METHODS

Patients and design

This is a multicenter retrospective analysis of prospectively collected data that included patients undergoing minimally invasive Ivor–Lewis esophagectomy (MI-ILE) in three high volume centers in the Netherlands between April 2012 and September 2015. Patient data of 50 patients in the early oral feeding arm were retrieved from a previous prospective feasibility trial.[12] The patients in the delayed oral feeding arm were retrieved from an historical cohort in whom oral intake was delayed for 5–14 days. Patients undergoing MI-ILE and who were 18 years or older were enrolled. Patients with 3 or more measurement moments missing were not included in the study cohort.

Nutritional protocols

This retrospective analysis contains two patient groups each following a different postoperative feeding protocol. In both groups, the same postoperative protocol was used regarding analgesia, drain removal, mobilization (with physiotherapy) and nursing.

Patients in the delayed oral feeding group received enteral feeding via a jejunostomy catheter or a nasojejunal tube. Enteral tube feeding was initiated on postoperative day (POD) 1 and gradually increased until the caloric intake as calculated by the Harris–Benedict formula was reached. Oral intake was started no earlier than 5 days postoperatively and tube feeding was continued until oral intake could meet the required caloric need. Oral intake consisted of liquid nutrition and was gradually increased to a normal solid diet.

Patients in the early oral feeding group started oral intake on POD 1 and did not receive standard enteral tube feeding. The first 5 days consisted of an increasing amount of liquid oral diet. This included clear fluids and high protein energy supplementary drinks. After 5 days, the diet was increased to a normal solid diet. When patients did not reach 50% or more of their caloric need, enteral tube feeding was started via either a nasojejunal tube or jejunostomy. The postoperative nutritional protocols are displayed in the flow diagram (Fig. 1). Total parenteral nutrition was only started when enteral feeding was contraindicated (e.g. chyle leakage or intestinal ischemia).

Surgical technique

In each hospital, the surgery was performed by two specialized surgeons performing >30 MI-ILE yearly. Laparoscopic lymphadenectomy and intracorporeal gastric conduit formation was followed by a thoracoscopic lymphadenectomy and end-to-side or side-to-side intrathoracic anastomosis in prone position. The anastomosis was created using a 28 mm E/S circular stapler, a semimechanical side-to-side stapler or hand-sewn with V-loc® sutures (Medtronic, Dublin, Ireland). The anastomosis was covered with an omental wrap. A jejunostomy catheter or a nasojejunal tube was placed during surgery and was used if patient followed the enteral feeding protocol (control group) or when predefined nutritional needs were not adequately met in the early oral feeding group on POD 5. At the end of the procedure, a Jackson-Pratt drain was positioned on the dorsal side of the omental wrap and chest drains were placed.

Outcome measurements

The primary outcome parameter of this study was the body mass index (BMI) after one year. Secondary parameters were the original BMI, the BMI at diagnosis, at admission and 1, 3, 6, and 12 months postoperatively. BMI was calculated in kg/m^2. Absolute and relative weight loss in kilograms and percentage, respectively, were measured and calculated. The other outcome parameter in this study was the amount and type of nutritional interventions (prolonged tube feeding, restart of tube feeding or start of TPN) in the first year after esophagectomy. A nutritional intervention was defined as any patient that deviated from their predesignated nutritional protocol, such as when prolonged tube feeding (4 weeks or more postoperatively) was given or it had to be restarted for any reason. Additionally, the one-year survival, cancer recurrence, postoperative complications (graded according to the Clavien–Dindo[13]) in general and jejunostomy related complications specifically are presented in both groups.

Statistical analysis

Statistical analysis was performed using the SPSS 23.0. Normality of all data was evaluated using a

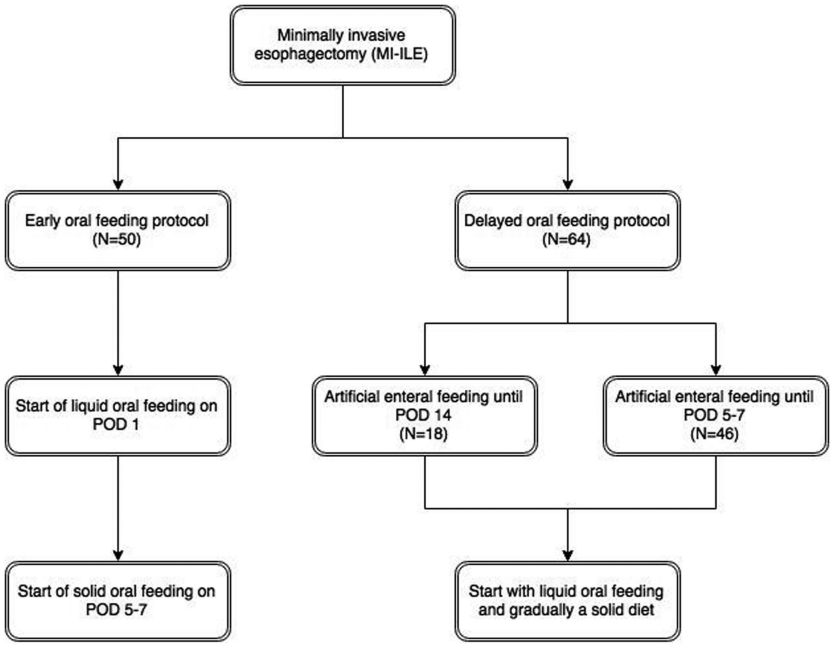

Fig. 1 Flow diagram of the postoperative nutritional protocols. POD = postoperative day.

Shapiro–Wilk test. Continuous data are presented as medians with interquartile ranges and dichotomous results are presented as frequencies with percentage of total. Chi-square and Fisher's exact tests were used to compare dichotomous data. Mann-Whitney U test was used to compare continuous data. Survival analysis was done by Kaplan–Meier analysis. A P value <0.05 was considered statistically significant.

RESULTS

One hundred and thirty six consecutive patients were screened from a prospectively collected database in the period April 2012 until September 2015. Twenty-two patients did not have 3 or more weight measurements noted in their electronic patient file and were not analyzed in this cohort, 114 patients were analyzed. Median patient age was 66 years [interquartile range IQR: 60–71] and 86% was male. Most patients received neoadjuvant chemoradiation (90%). Furthermore, no differences in baseline characteristics were observed between patients with in the two groups (Table 1).

Weight loss and body mass index

The median BMI at admission for the entire cohort was 25.6 kg/m^2 [IQR 23.6–27.4] and did not statistically differ between the early and delayed oral feeding group. At 1 month, 3 months and 6 months postoperatively the BMI was respectively 24.5 kg/m^2 [IQR 22.2–26.8], 23.6 kg/m^2 [IQR 21.9–26.5], and 23.0 kg/m^2 [IQR 21.5–25.3]. One year after surgery the median BMI was 22.8 kg/m^2 [IQR 20.8–24.8]. No statistical differences were observed for BMI or median weight at any of the time points between the two groups (Table 2).

Median weight loss one year after esophagectomy was 7.0 kg [IQR 2.0–13.0] and the percentage of weight loss was 9.5% [IQR 3.3–15.9] in the entire cohort. Patients in the early oral feeding group lost a median of 4.0 kg [IQR 3.0–6.3] within the first month after surgery compared with 2.0 kg [IQR 0.0–6.0] in the delayed oral feeding group ($P = 0.004$) (Table 3). A subanalysis was performed for patients without complications after surgery to correct for the significant difference in complications after surgery. No difference in weight loss is seen in the subanalysis compared to the entire cohort (Table 3).

Between postoperative month one and month three, median weight loss was 1.0 kg [IQR 0.0–2.0] in the early oral feeding group versus 2.3 kg [IQR 0.0–4.7] in the delayed oral feeding group ($P = 0.039$). Weight loss after the esophagectomy continued in the following 9 months but was not significantly different. The cumulative weight loss in both groups is shown in Figure 2. Patients in the early oral feeding group lost more weight in the first month, but follow the same line as patients in the delayed oral feeding group.

Nutritional reinterventions

In the early oral feeding group, 28 patients (56%) required a nutritional intervention (prolonged tube feeding, restart of tube feeding or start of TPN) during the first year after surgery, compared to 46 patients (72%) in the delayed oral feeding group ($P = 0.078$)

Table 1 Baseline characteristics

	Cohort $n = 114$	Early oral feeding $n = 50$	Delayed oral feeding $n = 64$	P-value*
Age	66 (60–71)	67 (60–71)	66 (58–71)	0.904
Sex				0.992
Male	98 (86)	43 (86)	55 (86)	
Female	16 (14)	7 (14)	9 (14)	
ASA	II (II–II)	II (II–III)	II (II–II)	0.306
Neoadjuvant therapy				0.123
None	4 (4)	1 (2)	3 (5)	
Chemotherapy	8 (7)	1(2)	7 (11)	
Chemoradiotherapy	102 (90)	48 (96)	54 (84)	
Tumor location				0.130
Proximal esophagus	1 (1)	0 (0)	1 (1)	
Mid esophagus	10 (10)	6 (12)	4 (8)	
Distal esophagus	74 (65)	36 (72)	38 (59)	
Junction	29 (25)	8 (16)	21 (33)	
Histology				0.501
Adenocarcinoma	106 (93)	45 (90)	61 (95)	
Squamous cell carcinoma	6 (5)	4 (8)	2 (3)	
High-grade dysplasia	2 (2)	1 (2)	1(2)	

Values are absolute numbers (percentage) or medians (lower quartile-upper quartile).
*$P < 0.05$.

Table 2 BMI measurements over time

	Early oral feeding $n = 50$	Delayed oral feeding $n = 64$	P-value
BMI			
Original	27.3 [24.5–30.3]	26.2 [24.4–28.5]	0.216
Diagnosis	26.3 [23.9–29.3]	25.5 [23.2–27.5]	0.164
Admission	25.9 [23.9–28.5]	25.5 [23.3–27.1]	0.178
1 month PO	24.3 [22.2–26.7]	24.5 [21.7–26.8]	0.825
3 months PO	24.3 [21.5–26.6]	23.9 [22.1–26.4]	0.678
6 months PO	22.7 [21.3–24.3]	23.2 [21.8–26.0]	0.530
1 year PO	22.9 [20.8–25.9]	22.7 [20.5–24.6]	0.568

Numbers are presented as median and [interquartile range].
BMI, body mass index (kg/m^2); PO, postoperative.
*P value < 0.05.

Table 3 Median weight loss in kilogram over time

	Early oral feeding $N = 50$	Delayed oral feeding $n = 64$	P-value
Time period			
Admission - 1 month PO	4.0 [3.0–6.3]	2.0 [0.0–6.0]	0.004*
1 month PO -3 months PO	1.0 [0.0–2.0]	2.3 (0.0–4.7]	0.039*
3 months PO - 6 months PO	2.0 [0.0–3.0]	1.7 [0.0–3.0]	0.796
6 months PO -1 year PO	0.3 [0.0–5.0]	0.0 [0.0–3.0]	0.101
Subanalysis in patients without complications			
	$N = 19$	$N = 9$	
Admission - 1 month PO	4.0 [2.0–6.0]	0.0 [0.0–2.0]	0.005*
1 month PO -3 months PO	0.5 [0.0–2.5]	2.5 [1.1–3.9]	0.191
3 months PO - 6 months PO	0.8 [0.0–4.5]	2.0 [0.3–3.9]	0.711
6 months PO -1 year PO	0.0 [0.0–3.0]	1.0 [0.0–3.0]	0.564

Numbers are presented as median and interquartile range [IQR]. PO, postoperative.
*P value < 0.05.

(Table 4). During admission, significantly more nutritional interventions were needed in the delayed oral feeding group compared with the early oral feeding group (17 vs. 46 patients, $P < 0.001$). After the initial admission, no difference in amount of nutritional interventions was observed (13 vs. 14 patients, $P = 0.607$).

Enteral tube feeding as a nutritional reintervention was used in both groups and did not significantly differ between the early oral feeding group and delayed oral feeding group (26 vs. 42 patients, $P = 0.141$). The main reason to start or prolong enteral tube feeding was a complication that prohibited oral intake. Insufficient oral intake was the other

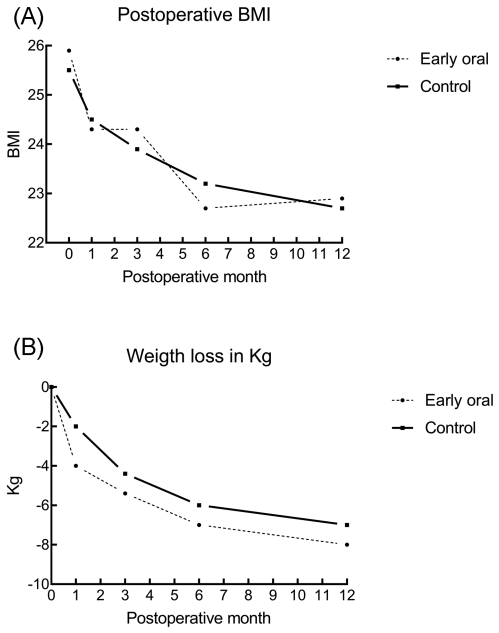

Fig. 2 (A) Body mass index measurements over time in the early oral and delayed oral feeding group. (B) Cumulative weight loss (kilograms) in patients after the esophagectomy procedure.

reason for enteral tube feeding and was necessary in 11 patients (22%) in the early oral feeding group versus 13 patients (20%) in the delayed oral feeding group ($P = 0.826$).

TPN was started in seven patients (14%) in the early oral feeding group and 18 patients (28%) in the delayed oral feeding group ($P = 0.071$). The difference in TPN interventions was also present in patients where a complication was the reason for TPN (6 vs. 17 patients, $P = 0.055$). Chyle leakage, ileus, anastomotic leakage, and intestinal ischemia were the main reasons for TPN initiation.

Complications

Thirty patients (60%) with early oral feeding after an esophagectomy developed any complication in the postoperative course, compared to 53 patients (83%) in the delayed oral feeding group ($P = 0.007$) (Table 5). The complication incidence according to the Clavien–Dindo severity score was not significantly different between both groups ($P = 0.060$). Anastomotic leakage ($P = 0.103$), pneumonia ($P = 0.103$), and chyle leakage ($P = 0.546$) were the most common complications after the esophagectomy procedure. Median length of hospital stay was significantly shorter (12 vs. 18 days, $P = 0.043$) in patients with early oral feeding. A jejunostomy tube was placed in 62 (97%) of the patients in the delayed oral feeding group compared to 14 (28%) in the early oral feeding group. In general, jejunostomy tube related complications occurred in 10 patients (13%). Most were minor, except for two patients (3%) with an abdominal abscess which required a reoperation. Jejunostomy tube malfunction (occlusion, dislocation, entry site leakage) was seen in seven patients (9%).

Survival and cancer recurrence

Mean follow-up was 35.9 months (26.5 months in the early oral feeding group and 35.8 months in the delayed oral feeding group) for patients in this cohort. Disease-free survival was not significantly different between groups ($P = 0.810$). The disease-free survival was 70% after 12 months and 60% after

Table 4 Number of patients with a postoperative nutritional reintervention

	Early oral feeding $n = 50$	Delayed oral feeding $n = 64$	P-value
Any nutritional reintervention	28 (56)	46 (72)	0.078
Complication	17 (34)	35 (55)	0.028*
Insufficient intake	11 (22)	11 (17)	0.518
Start of nutritional reintervention			
During admission	17 (34)	46 (72)	<0.001*
After admission	13 (26)	13 (20)	0.473
Enteral feeding reintervention	26 (52)	40 (63)	0.260
Complication	15 (30)	29 (45)	0.096
Anastomotic leakage	5	17	
Pneumonia	5	2	
Chyle leakage	2	6	
Stenosis	2	0	
Abscess	0	1	
Other	1	3	
Insufficient intake	11 (22)	11 (17)	0.518
Parenteral feeding reintervention	7 (14)	18 (28)	0.071
Complication	6 (12)	17 (27)	0.055
Insufficient intake	1 (2)	1(2)	1.000

Values are absolute numbers (percentage).
*$P < 0.05$.

Table 5 Surgical and tube related complications

	Early oral feeding $n = 50$	Delayed oral feeding $n = 64$	P-value
Total complications	30 (60)	53 (83)	0.007*
Surgical complications (Clavien–Dindo)			0.060
Grade 1	3 (6)	1 (2)	
Grade 2	11 (22)	17 (29)	
Grade 3a	5 (10)	8 (13)	
Grade 3b	2 (4)	8 (13)	
Grade 4a	8 (16)	18 (28)	
Grade 4b	0 (0)	1 (2)	
Grade 5	1 (2)	0 (0)	
Anastomotic leakage	7 (14)	17 (27)	0.103
Chyle leakage	4 (8)	8 (13)	0.546
Pneumonia	14 (28)	27 (43)	0.103
Length of stay	12 [8–20]	16 [10–29]	0.043*
Jejunostomy tube malfunction	1/14 (7)	6/62 (10)	1.000
Dislocation	0 (0)	4 (6)	
Occlusion	0 (0)	1 (2)	
Entry site leakage	1 (7)	1 (2)	
Jejunostomy tube related complication	1/14 (7)	9/62 (15)	0.678
Entry site infection/abscess	1 (7)	7 (11)	
Intra-abdominal abscess	0 (0)	2 (3)	

Values are absolute numbers (percentage) or medians [lower quartile -upper quartile].
*$P < 0.05$.

24 months in the early oral feeding group. In the delayed oral feeding group, the disease-free survival was 81% after 12 months, 64% after 24 months, and 53% after 36 months. The overall survival was 78% after 12 months and 70% after 24 months in the early oral feeding group and, respectively, 84%, 70%, and 58% in the delayed oral feeding group ($P = 0.933$). Cancer-specific survival was also not significantly different between the groups ($P = 0.514$). The cancer specific survival was 85% and 78% in the early oral feeding group and 85%, 73%, and 65% in the delayed oral feeding group.

DISCUSSION

This retrospective cohort study did not observe long-term differences on weight loss and BMI one year after surgery in patients with early or delayed oral feeding after minimally invasive esophagectomy.

Nonetheless, it is evident that, the impact of an esophagectomy on nutritional intake is substantial. The formation of the gastric conduit resembles the restrictive and metabolic effects of bariatric procedures and is responsible for most weight loss in the first year. Additionally, there are various additional complaints after the procedure that may contribute to weight loss, such as early satiety, postprandial dumping syndrome, inhibited easy passage, reflux, or absence of hunger.[14] Weight loss following esophagectomy has been shown to be evident in the first six months after surgery, while after this period patients reach a plateau phase.[7,11] In this cohort patients indeed lost most of their BMI and weight in the first six months (6.3 kg, 8.3%) and in the following six months only 0.7 kg.

Patients following the different postoperative feeding regimens, within this cohort, had the same amount of weight loss and loss of BMI after 3, 6, and 12 months. However, during the first postoperative month median weight loss was 4.0 kg in the early oral feeding group and 2.0 kg in the delayed oral feeding group. Patients in the delayed oral feeding group received enteral jejunostomy feeding for a longer period and some patients were transferred home with enteral feeding during the night. While these patients started with oral feeding, additional enteral feeding maintained their intake. However, as shown in Figure 2b, in the months after surgery, weight loss continued in patients where jejunostomy enteral feeding was terminated. Patients with early oral feeding lost more weight in the first month and failed to regain the excess weight loss in the first year. Nonetheless, they did not lose extra weight in comparison to the delayed oral feeding group after 3, 6, and 12 months. Some recent studies advocate prolonged enteral feeding while patients are at home.[15,16] Tomaszek *et al*. observed a reduction of postoperative recovery and morbidity and found significant changes with beneficial effects of a delay in oral intake. A recent randomized controlled trial protocol has been published and this trial will evaluate the effects of home enteral feeding after esophagectomy on quality of life, morbidity, and postoperative nutritional status.[16] However, as observed in this retrospective study, patients with enteral feeding after surgery could be subjected to an increase in nutritional interventions and long-term usage of enteral feeding tubes could be associated with an increased incidence of tube-related

complications.[6] To this day, it is unclear if early oral feeding improves recovery after surgery and quality of life as a result of fewer tube-related complications. The implementation of early oral feeding without standard enteral tube feeding is currently being explored in a large randomized controlled trial.[17] This trial will investigate the possible impact of oral feeding on faster recovery after surgery.

The total amount of nutritional reinterventions was not different between the early oral and delayed oral feeding group. Furthermore, the amount of nutritional reintervention for insufficient intake was not different and this implies that the majority of patients with early oral feeding do maintain sufficient intake. However, during admission more patients received a nutritional reintervention in the delayed oral feeding group. In the majority of these patients, enteral feeding was prolonged for more than four weeks. Patients in the delayed oral feeding group had a jejunostomy tube positioned during surgery and it is easier to start enteral feeding for these patients. However, this study shows that the effect of this prolonged feeding is not superior to oral feeding on long-term weight loss and BMI. Additionally, patients with enteral feeding tubes could be subjected to feeding tube-related complications. The complication rate as reviewed in literature is 20–40% and consists of dislocation, infection, occlusion, and leakage.[6,18] These complications are mostly minor but surgical reintervention is necessary in 2% of the patients.[6] The same amount of complications occurred in this retrospective cohort. Hence, the feeding tube could in fact hamper recovery and increase length of stay for patients after esophageal surgery.[12] In this study, patients with early oral feeding had a shorter admission time compared to the control group. This difference may be explained by the fact that patients had more surgical complications in the control group. The complication and anastomotic leakage rate in the control group was higher compared with the intervention group. We are not sure how this may be explained. The MIE procedure is complex and optimized throughout the years and a learning effect of the surgeons could be a factor. Other factors such as the prospective setting in which complications were scored in the early oral feeding group may also have played a role, however, further researched is needed to substantiate these results.

Early initiation of oral intake after esophageal surgery has been investigated in four prospective studies.[12,19–21] Short-term nutritional intake was evaluated in one prospective cohort study.[12] Most patients in this trial reached their nutritional goals on postoperative day 5. The same patient group is used in this retrospective trial. On postoperative day 5, 58% of the estimated caloric need was attained with a median caloric intake of 1205 kcal on POD5. The required minimum of 50% on POD5 is reached in the majority of patients and early oral intake could be feasible concerning short-term nutritional intake after surgery. Over the course of a year after surgery, no differences in weight loss and nutritional reinterventions were seen in patients whom received early oral feeding after esophageal surgery. Subsequently, long-term effects on weight of patients with early oral feeding after an esophagectomy are not disadvantageous.

Limitations of the study

The retrospective set-up of this study may entail bias as missing values after 6 months and 1 year postoperatively increased. The missing values in weight loss and interventions were caused by early mortality (within one year) or loss to follow-up. No data were available on long-term nutrition related complaints and nutritional intake.

CONCLUSION

Esophagectomy and reconstruction with a gastric conduit significantly reduces BMI in the first year after surgery regardless of the feeding regimen. Direct start of oral intake following esophagectomy has no impact on early nutritional reinterventions and long-term weight loss.

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