Nutritional route in esophageal resection; a single-arm feasibility trial (NUTRIENT trial)

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004557
Article Type:	Protocol
Date Submitted by the Author:	25-Nov-2013
Complete List of Authors:	Weijs, Teus; University Medical Center Utrecht, Surgery; Catharina Hospital Eindhoven, Surgery Nieuwenhuijzen, Grard; Catharina Hospital Eindhoven, Surgery Ruurda, Jelle; University Medical Centre Utrecht, Surgery Kouwenhoven, Ewout; Ziekenhuisgroep Twente, Surgery Rosman, Camiel; Canisius-Wilhelmina Hospital, Surgery Sosef, Meindert; Atrium Medisch Centrum, Surgery van Hillegersberg, Richard; University Medical Centre Utrecht, Surgery Luyer, Misha; Catharina Hospital Eindhoven, Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	Thoracic surgery < SURGERY, NUTRITION & DIETETICS, Oesophageal disease < GASTROENTEROLOGY

Study protocol

Nutritional route in esophageal resection; a single-arm feasibility trial (NUTRIENT trial)

Teus J Weijs, MD[1,2], Grard AP Nieuwenhuijzen, MD, PhD[1], Jelle P Ruurda, MD, PhD[2], Ewout A Kouwenhoven, MD, PhD[3], Camiel Rosman, MD, PhD[4], Meindert Sosef, MD, PhD[5], Richard v Hillegersberg, MD, PhD[2], Misha DP Luyer, MD, PhD[1]

Institutions and affiliations

[1]Department of Surgery, Catharina Hospital Eindhoven, Michelangelolaan 2, 5623 EJ, Eindhoven, The Netherlands

[2]Department of Surgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands

[3]Department of Surgery, Ziekenhuisgroep Twente, Zilvermeeuw 1, 7609 PP Almelo, The Netherlands

[4]Department of Surgery, Canisius-Wilhelmina Hospital, Weg door Jonkerbos 100, 6532 SZ Nijmegen, The Netherlands

[5]Department of Surgery, Atrium Medisch Centrum, Henri Dunantstraat 5, 6419 PC Heerlen, The Netherlands

Correspondence: Misha DP Luyer, Department of Surgery. Catharina Hospital, Michelangelolaan 2, 5623 EJ Eindhoven, The Netherlands. **E-mail**: misha.luyer@cze.nl. **Telephone:** +31-6-40006809 **Fax:** + 31-40-2443370

Keywords: Esophagectomy, oral nutrition, anastomotic leakage, pneumonia, enhanced recovery

Word Count: 1337

Abstract

Introduction: The best route of feeding for patients undergoing an esophagectomy is unclear. Concerns exist that early oral intake would increase the incidence and severity of both pneumonia and anastomotic leakage. However, in studies including patients after many other types of gastro-intestinal surgery and in animal experiments, early oral intake has shown to be beneficial and enhance recovery. Therefore we aim to determine the feasibility of early oral intake after esophagectomy.

Methods and analysis: This study is a feasibility trial in which 50 consecutive patients will start oral intake directly following esophagectomy. Primary outcomes will be the frequency and severity of both anastomotic leakage and (aspiration) pneumonia. Clinical parameters will be registered prospectively and nutritional requirements and intake will be assessed by a dietician. Surgical complications will be registered.

Ethics and dissemination: Approval for this study has been obtained from the Medical Ethical Committee of the Catharina Hospital Eindhoven and the study has been registered at the Dutch Trial Register, NTR4136. Results will be published and presented at international congresses.

Discussion: We hypothesize that the oral route of feeding is safe and feasible following esophagectomy as has been shown previously for other types of gastrointestinal surgery. It is expected that early oral nutrition will result in an enhanced recovery. Furthermore, complications related to artificial feeding, such as jejunostomy tube feeding, are believed to be reduced. However, (aspiration) pneumonia and anastomotic leakage are potential risks that are carefully monitored.

Strengths and Limitations

A strength of this study is the careful monitoring of safety regarding the relevant clinical outcomes pneumonia and anastomotic leakage, for safety of early oral intake after esophagectomy is a major concern of many surgeons. A limitation is its descriptive single arm design. However, due to the lack of data we consider a safety and feasibility trial more appropriate before the start of a randomized controlled trial in which standard of care is compared with early oral nutrition.

Background

For many types of gastro-intestinal surgery, early oral intake has been shown to be beneficial and enhance recovery.[1-3] However, for patients undergoing an esophagectomy it is unclear what the best route of feeding is.[4] There is a concern that early oral intake following esophagectomy would result in vomiting with subsequent aspiration pneumonia. Furthermore the sequelae of anastomotic leakage are thought to be more severe if the leaked fluids contain food besides saliva. Although these arguments are widely accepted, there is no clear scientific evidence to support this hypothesis.

On the other hand, early oral intake has been demonstrated to be feasible and can result in faster recovery of bowel function and a shorter hospitalization after partial or total gastrectomy.[2] Furthermore, a randomized controlled trial in patients after major upper abdominal surgery, including esophagectomy, demonstrated that early oral intake directly after surgery does not increase morbidity compared to a nil-by-mouth regimen with jejunostomy feeding for the first 5 postoperative days. However, only few patients undergoing esophagectomy were included in this trial.[3] Additionally, experimental evidence shows that early enteral feeding above the anastomosis improves anastomotic healing after upper abdominal surgery in rats.[5,6]

Because of paucity of evidence on this topic, we designed a feasibility trial to investigate whether starting oral intake early after esophagectomy is feasible and safe.

Methods and Design

Design

This is an exploratory single-arm multicenter trial to determine the feasibility and safety of early oral intake from the first day after esophagectomy. The trial is approved by the independent ethical committee of the Catharina Hospital in Eindhoven, The Netherlands.

Population

All patients older than 18 years that undergo minimally invasive esophagectomy are eligible for inclusion. Patients are excluded in case of > 15% weight loss at the time of surgery, a swallowing disorder, mental retardation of an inability for oral intake. Due to the paucity of evidence we designed a descriptive study, therefore no power calculation has been performed. In this study 50 patients will be included.

Study Outline

Oral intake is started from postoperative day 1 under supervision of a dietician. In this regimen the patient starts with clear liquid fluids directly following surgery. At the first postoperative day a liquid diet is started together with Nutridrink™ to ensure adequate caloric intake. After 1 week, if the clinical condition is good and inflammatory mediators decrease, the patient may progress to a solid diet. The dietician will calculate energy needs for each patient using the Harris-Benedict-formula with a surplus of 30% for energy expenditure in the postoperative phase.

Oral feeding will be terminated immediately if there is suspicion for anastomotic leakage. Artificial feeding will be started in case of complications prohibiting oral intake, or when the caloric intake is >50% of the energy needs at day 5 postoperative.

The surgeon is free to surgically place a jejunostomy during the procedure. However the jejunostomy will be sealed directly after surgery and not be used until the patient meets the criteria for artificial nutrition as mentioned above. In cases were no jejunostomy tube has been placed during surgery, a nasojejunal tube will be inserted via endoscopy by a Gastroenterologist. Total parenteral nutrition will be started only in case of chylothorax or other conditions in which enteral nutrition is not possible.

Outcomes

Primary outcomes are the incidence and severity (according to the modified Clavien Dindo classification for surgical complications) of pneumonia and anastomotic leakage.[7]

Pneumonia is defined according to the definition of the Utrecht Pneumonia Scoring System.[8] Aspiration pneumonia is defined as inflammation in the lungs following aspiration of material (solid or liquid, vomit, saliva). Anastomotic leakage is defined as clinical signs of leakage from a drain or in case of a cervical anastomosis form the cervical wound; radiological signs of anastomotic leakage (contrast leakage, or fluid/ air levels surrounding the anastomosis) or signs of anastomotic leakage during endoscopy, re-operation or post mortal investigation. When anastomotic leakage is clinically suspected, a CT-scan will be performed. Based on the individual clinical situation, an endoscopic, radiological or surgical intervention will be performed in case anastomotic leakage is present. Adequate drainage is the primary goal.

Secondary outcomes are caloric intake during the postoperative admission; need and amount of artificial nutrition (naso-jejunal tube feeding / parenteral nutrition); occurrence of vomiting; placement of a nasogastric tube; length of hospital stay; hospital re-admissions within 30 days of discharge; complications classified according to the Clavien-Dindo classification[7]; need for ICU admission and total length of ICU stay; and 30-day mortality.

All clinical data will be prospectively registered in an electronic surgical database.

Data and Safety Monitoring Board

An independent data and safety monitoring board (DSMB) will evaluate the progress of the trial and will examine safety variables. Every five patients, individualized patient data will be provided to the DSMB. The members of the DSMB will discuss the consequences of the data presented separately, and the outcome of this meeting will be discussed with the project group. If the DSMB suspects harm there will be a meeting between the DSMB, the study group and an independent statistician. During this meeting any potential causal relation between early start of postoperative oral nutrition and harm, and necessity for stopping the trial will be discussed.

Statistical analysis

The data analysis will consist of simple descriptive analyses. All analyses will be according to the intention-to-treat approach, incorporating all included patients, regardless of adherence to study protocol.

Dissemination

The results will be presented at relevant national and international congresses, and published in article format. All results will be relevant for current guidelines on postoperative care for patients undergoing esophagectomy and made known to the developers of these guidelines.

Discussion

The NUTRIENT trial investigates the feasibility of early oral intake after esophagectomy. The rationale for this trial emerges from fast-track programs in other types of gastro-intestinal surgery showing that there is no clear advantage to withhold enteral nutrition in the direct postoperative phase and that early (oral) feeding may even be beneficial compared with the traditionally applied nil-by-mouth strategy.[1,9,10]

Also for patients undergoing other upper gastrointestinal surgery it has been shown that early oral nutrition is just as safe as traditional care, consisting of a delayed oral intake.[3] Although these findings are promising, the patient group was very heterogeneous and included only a few patients undergoing an esophagectomy. Another randomized controlled trial has been started investigating early oral intake, amongst others included patients undergoing esophagectomy.[11] However, the data of this trial are not fully published yet.

A general concern regarding early start of oral intake following an esophagectomy is safety, especially regarding the sequelae of anastomotic leakage and incidence of pulmonary

complications such as aspiration pneumonia.[4] However, there are no data to support these arguments. Studies supporting a delayed oral intake following esophagectomy are scarce and retrospectively performed. In one study it was shown that anastomotic leak rates are lower when a radiographic contrast swallow was omitted postoperatively and patients were fed over a jejunostomy and kept nil-by-mouth for 4 weeks.[12] A more recent study investigated a “planned delay of oral intake”.[13] However, due to the retrospective nature of both studies, differences in definitions, selection and timing of oral intake the results are difficult to interpret.

On the contrary, existing evidence in other types of upper gastro-intestinal surgery and animal studies points towards beneficial effects of early oral nutrition.[3,5,6] Since enteral nutrition is preferred postoperatively, a jejunostomy is often placed during surgery to bridge the delayed oral intake.[14] However, a jejunostomy is associated with specific complications, sometimes leading to re-laparotomy and even death.[15]

Another concern is an insufficient caloric intake postoperatively. While this can be expected for some patients, for example those that will develop anastomotic leakage, adequate caloric intake can be secured by endoscopic placement of a nasojejunal tube in these patients.[16]

Conclusion

This trial investigates whether early oral intake after minimally invasive esophagectomy is safe and possible. Due to the paucity of evidence this will be a feasibility trial in 50 patients using anastomotic leakage and pulmonary complications as primary endpoints.

Trial status: Recruitment of patients started in August 2013

Acknowledgements: None

Competing interests: The authors declare that they have no competing interests.

Authors' contribution: TW and ML drafted the manuscript. ML authored the writing of the manuscript. All authors participated in the design of the study and read, edited, and approved the final manuscript.

References

1. Varadhan KK, Neal KR, Dejong CH, *et al*. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: A meta-analysis of randomized controlled trials. *Clin Nutr.* 2010;**29**:434-40. doi:10.1016/j.clnu.2010.01.004. [Published Online First: 29 January 2010]

2. Hur H, Kim SG, Shim JH, *et al.* Effect of early oral feeding after gastric cancer surgery: A result of randomized clinical trial. *Surgery*. 2011;**149**:561-8. doi:10.1016/j.surg.2010. [Published Online First: 13 December 2010]

3. Lassen K, Kjaeve J, Fetveit T, *et al.* Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: A randomized multicenter trial. *Ann Surg.* 2008;**247**:721-9. doi:10.1097/SLA.0b013e31815cca68.

4. Lassen K, Revhaug A. Early oral nutrition after major upper gastrointestinal surgery: Why not? *Curr Opin Clin Nutr Metab Care.* 2006;**9:**613-7. doi:10.1097/01.mco.0000241673.17300.87

5. Fukuzawa J, Terashima H, Ohkohchi N. Early postoperative oral feeding accelerates upper gastrointestinal anastomotic healing in the rat model. *World J Surg.* 2007;**31**:1234-9. doi:10.1007/s00268-007-9003-9. [Published Online First: 28 April 2007]

6. Tadano S, Terashima H, Fukuzawa J, *et al*. Early postoperative oral intake accelerates upper gastrointestinal anastomotic healing in the rat model. *J Surg Res.* 2011;**169**:202-8. doi:10.1016/j.jss.2010.01.004. [Published Online First: 4 February 2010]

7. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;**240**(2):205-13. doi:10.1097/01.sla.0000133083.54934.ae.

8. Verhage RJJ. Outcomes and perioperative course of esophageal cancer surgery. *PhD Thesis.* University Medical Centre Utrecht, Department of Surgical Oncology; 2012.

9. Maessen JM, Hoff C, Jottard K, *et al*. To eat or not to eat: Facilitating early oral intake after elective colonic surgery in the Netherlands. *Clin Nutr.* 2009;**28**:29-33. doi:10.1016/j.clnu.2008.10.014. [Published Online First: 6 December 2008]

10. Lewis SJ, Andersen HK, Thomas S. Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: A systematic review and meta-analysis. *J Gastrointest Surg.* 2009;**13**:569-75. doi: 10.1007/s11605-008-0592-x. [Published Online First: 16 July 2008]

11. Shoar S, Mahmoodzadeh H, Hosseini Araghi N, *et al*. Early postoperative oral feeding in gastresophageal tumors surgery: A randomized controlled trial [abstract]. *J Surg Res.* 2013;179(2):201.

12. Tomaszek SC, Cassivi SD, Allen MS, *et al*. An alternative postoperative pathway reduces length of hospitalisation following oesophagectomy. *Eur J Cardiothorac Surg*. 2010;**37**:807-13. doi: 10.1016/j.ejcts.2009.09.034. [Published Online First: 8 November 2009]

13. Bolton JS, Conway WC, Abbas AE. Planned Delay of Oral Intake After Esophagectomy Reduces the Cervical Anastomotic Leak Rate and Hospital Length of Stay. *J Gastrointest Surg.* Published Online First 4 September 2013. doi: 10.1007/s11605-013-2322-2

14. Fujita T, Daiko H, Nishimura M. Early enteral nutrition reduces the rate of life-threatening complications after thoracic esophagectomy in patients with esophageal cancer. *Eur Surg Res.* 2012;**48**:79-84. doi:10.1159/000336574

15. Han-Geurts IJ, Verhoef C, Tilanus HW. Relaparotomy following complications of feeding jejunostomy in esophageal surgery. *Dig Surg.* 2004;**21**:192-6. Doi:10.1159/000079345. [Published Online First: 24 June 2004]

16. Han-Geurts IJ, Hop WC, Verhoef C, *et al*. Randomized clinical trial comparing feeding jejunostomy with nasoduodenal tube placement in patients undergoing oesophagectomy. *Br J Surg*. 2007;**94**:31-5. doi: 10.1002/bjs.5283. [Published Online First: 20 November 2006]

BMJ Open

Study protocol for the nutritional route in esophageal resection trial; a single-arm feasibility trial (NUTRIENT trial)

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004557.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Apr-2014
Complete List of Authors:	Weijs, Teus; University Medical Center Utrecht, Surgery; Catharina Hospital Eindhoven, Surgery Nieuwenhuijzen, Grard; Catharina Hospital Eindhoven, Surgery Ruurda, Jelle; University Medical Centre Utrecht, Surgery Kouwenhoven, Ewout; Ziekenhuisgroep Twente, Surgery Rosman, Camiel; Canisius-Wilhelmina Hospital, Surgery Sosef, Meindert; Atrium Medisch Centrum, Surgery van Hillegersberg, Richard; University Medical Centre Utrecht, Surgery Luyer, Misha; Catharina Hospital Eindhoven, Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	Thoracic surgery < SURGERY, NUTRITION & DIETETICS, Oesophageal disease < GASTROENTEROLOGY

Study protocol for the nutritional route in esophageal resection trial; a single-arm feasibility trial (NUTRIENT trial)

Teus J Weijs, MD[1,2], Grard AP Nieuwenhuijzen, MD, PhD[1], Jelle P Ruurda, MD, PhD[2], Ewout A Kouwenhoven, MD, PhD[3], Camiel Rosman, MD, PhD[4], Meindert Sosef, MD, PhD[5], Richard v Hillegersberg, MD, PhD[2], Misha DP Luyer, MD, PhD[1]

Institutions and affiliations

[1]Department of Surgery, Catharina Hospital Eindhoven, Michelangelolaan 2, 5623 EJ, Eindhoven, The Netherlands

[2]Department of Surgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands

[3]Department of Surgery, Ziekenhuisgroep Twente, Zilvermeeuw 1, 7609 PP Almelo, The Netherlands

[4]Department of Surgery, Canisius-Wilhelmina Hospital, Weg door Jonkerbos 100, 6532 SZ Nijmegen, The Netherlands

[5]Department of Surgery, Atrium Medisch Centrum, Henri Dunantstraat 5, 6419 PC Heerlen, The Netherlands

Correspondence: Misha DP Luyer, Department of Surgery. Catharina Hospital, Michelangelolaan 2, 5623 EJ Eindhoven, The Netherlands. **E-mail**: misha.luyer@cze.nl. **Telephone:** +31-6-40006809 **Fax:** + 31-40-2443370

Keywords: Esophagectomy, oral nutrition, anastomotic leakage, pneumonia, enhanced recovery

Word Count: 1337

Abstract

Introduction: The best route of feeding for patients undergoing an esophagectomy is unclear. Concerns exist that early oral intake would increase the incidence and severity of both pneumonia and anastomotic leakage. However, in studies including patients after many other types of gastro-intestinal surgery and in animal experiments, early oral intake has shown to be beneficial and enhance recovery. Therefore we aim to determine the feasibility of early oral intake after esophagectomy.

Methods and analysis: This study is a feasibility trial in which 50 consecutive patients will start oral intake directly following esophagectomy. Primary outcomes will be the frequency and severity of both anastomotic leakage and (aspiration) pneumonia. Clinical parameters will be registered prospectively and nutritional requirements and intake will be assessed by a dietician. Surgical complications will be registered.

Ethics and dissemination: Approval for this study has been obtained from the Medical Ethical Committee of the Catharina Hospital Eindhoven and the study has been registered at the Dutch Trial Register, NTR4136. Results will be published and presented at international congresses.

Discussion: We hypothesize that the oral route of feeding is safe and feasible following esophagectomy as has been shown previously for other types of gastrointestinal surgery. It is expected that early oral nutrition will result in an enhanced recovery. Furthermore, complications related to artificial feeding, such as jejunostomy tube feeding, are believed to be reduced. However, (aspiration) pneumonia and anastomotic leakage are potential risks that are carefully monitored.

Strengths and Limitations

A strength of this study is the careful monitoring of safety regarding the relevant clinical outcomes pneumonia and anastomotic leakage, for safety of early oral intake after esophagectomy is a major concern of many surgeons. A limitation is its descriptive single arm design. However, due to the lack of data we consider a safety and feasibility trial more appropriate before the start of a randomized controlled trial in which standard of care is compared with early oral nutrition.

Background

For many types of gastro-intestinal surgery, early oral intake has been shown to be beneficial and enhance recovery.[1-3] However, for patients undergoing an esophagectomy it is unclear what the best route of feeding is.[4] There is a concern that early oral intake following esophagectomy would result in vomiting with subsequent aspiration pneumonia. Furthermore the sequelae of anastomotic leakage are thought to be more severe if the leaked fluids contain food besides saliva. Although these arguments are widely accepted, there is no clear scientific evidence to support this hypothesis.

On the other hand, early oral intake has been demonstrated to be feasible and can result in faster recovery of bowel function and a shorter hospitalization after partial or total gastrectomy.[2] Furthermore, a randomized controlled trial in patients after major upper abdominal surgery, including esophagectomy, demonstrated that early oral intake directly after surgery does not increase morbidity compared to a nil-by-mouth regimen with jejunostomy feeding for the first 5 postoperative days. However, only few patients undergoing esophagectomy were included in this trial.[3] Additionally, experimental evidence shows that early enteral feeding above the anastomosis improves anastomotic healing after upper abdominal surgery in rats.[5,6]

Because of paucity of evidence on this topic, we designed a feasibility trial to investigate whether starting oral intake early after esophagectomy is feasible and safe.

Methods and Design

Design

This is an exploratory single-arm multicenter trial to determine the feasibility and safety of early oral intake from the first day after esophagectomy. The trial is approved by the independent ethical committee of the Catharina Hospital in Eindhoven, The Netherlands.

Population

All patients older than 18 years that undergo a minimally invasive esophagectomy and intrathoracic anastomosis (Ivor Lewis) are eligible for inclusion. Patients are excluded in case of >15% weight loss at the time of surgery, a swallowing disorder, mental retardation of an inability for oral intake. Weight loss >15% at time of surgery is regarded an exclusion criterion because it is not expected that these patients will achieve sufficient intake to compensate for their weight loss. Furthermore patients undergoing conventional open surgery and cervical anastomosis are excluded in order to improve homogeneity. Due to the paucity of evidence we designed a descriptive study, therefore no power calculation has been performed. In this study 50 patients will be included.

Study Outline

The early oral intake regimen will start with clear liquid fluids directly following surgery. At the first postoperative day a liquid diet is started under supervision of a dietician. Supplementary nutrition, such as Nutridrink™, is given to ensure adequate caloric intake. Adequate caloric intake is defined as >50% of energy needs at the fifth postoperative day. The dietician will calculate energy needs for each patient using the Harris-Benedict-formula with a surplus of 30% for energy expenditure in the postoperative phase. For male patients the Harris-Benedict-formula is 88.362 + (13.397 x weight in kg) + (4.799 x height in cm) - (5.677 x age in years) and for female patients 447.593 + (9.247 x weight in kg) + (3.098 x height in cm) - (4.330 x age in years).

After 1 week, if the clinical condition is good and inflammatory mediators decrease, the patient may progress to a solid diet. A good clinical condition is defined as a decreasing CRP, good mobilisation, being independent of supplementary i.v. fluids and pain being adequately controlled with oral medication.

Oral feeding will be terminated immediately if there is suspicion for anastomotic leakage. Artificial feeding will be started in case of anastomotic leakage, ileus requiring nasogastric decompression, complications for which the patient requires treatment at he intensive care unit, or when the caloric intake is <50% of the energy needs at day 5 postoperative.

In case of an indication for artificial feeding, enteral nutrition is preferred. The surgeon is free to surgically place a jejunostomy during the procedure. However the jejunostomy will be sealed directly after surgery and not be used until the patient meets the criteria for artificial nutrition as mentioned above. In cases where no jejunostomy tube has been placed during surgery, a nasojejunal tube will be inserted via endoscopy by a Gastroenterologist. Total parenteral nutrition will be started only in case of chylothorax or other conditions prohibiting enteral nutrition.

Surgical procedures

All patients will undergo a minimally invasive Ivor Lewis esophagectomy by surgeons experienced in minimally invasive surgery. In all centres more than 30 esophagectomies yearly have been performed by two dedicated surgeons over the past three years.

The operation is started with a laparoscopic phase, and followed by the thoracoscopic phase in prone position, as described previously.[7] At the end of the laparoscopic phase a gastric conduit is created intra-corporally with endostaplers. The intrathoracic anastomosis is made at the level of the carina, depending on the height of the tumour. The anastomosis is created with staplers or V-lock^{R} sutures in an E-t-S way or S-t-S way. The remaining opening is closed with V-Lock^{R} sutures. In all patients an omental wrap is draped around the anastomosis.

Outcomes

Primary outcomes are the incidence and severity (according to the modified Clavien Dindo classification for surgical complications) of pneumonia and anastomotic leakage.[8] Pneumonia is defined according to the definition of the Utrecht Pneumonia Scoring System.[9] In this system points are assigned based on temperature, leucocyte count and radiography. Pneumonia is defined as a score of 2 points or more, with at least 1 point assigned based on radiography. Aspiration pneumonia is defined as pneumonia following a clear history of aspiration of material (solid or liquid, vomit, saliva). Cases of silent aspiration leading to pneumonia might be missed. However, by recording the overall pneumonia rate with grading of the severity we will detect if early oral intake increases the incidence and or severity of pneumonia in general. In this case major, or minor aspiration might be a cause. Anastomotic leakage is defined as clinical signs of leakage from a drain or in case of a cervical anastomosis form the cervical wound; radiological signs of anastomotic leakage (contrast leakage, or fluid/ air levels surrounding the anastomosis) or signs of anastomotic leakage during endoscopy, re-operation or post mortal investigation. When anastomotic leakage is clinically suspected, a CT-scan will be performed. Based on the individual clinical situation, an endoscopic, radiological or surgical intervention will be performed in case anastomotic leakage is present. Adequate drainage is the primary goal.

Secondary outcomes are caloric intake during the postoperative admission; need and amount of artificial nutrition (naso-jejunal tube feeding / parenteral nutrition); occurrence of vomiting; placement of a nasogastric tube; length of hospital stay; hospital re-admissions within 30 days of discharge; complications classified according to the Clavien-Dindo classification[8]; need for ICU admission and total length of ICU stay; 30-day mortality and 90-day mortality.

All clinical data will be prospectively registered in an electronic surgical database.

Data and Safety Monitoring Board

An independent data and safety monitoring board (DSMB) will evaluate the progress of the trial and will examine safety variables. Every five patients, individualized patient data will be provided to the DSMB. The members of the DSMB will discuss the consequences of the data presented separately, and the outcome of this meeting will be discussed with the project group. If the DSMB suspects harm there will be a meeting between the DSMB, the study group and an independent statistician. During this meeting any potential causal relation between early start of postoperative oral nutrition and harm, and necessity for stopping the trial will be discussed.

Statistical analysis

The data analysis will consist of simple descriptive analyses. All analyses will be according to the intention-to-treat approach, incorporating all included patients, regardless of adherence to study protocol.

Categorical data will be summarized as frequencies. Normally distributed continuous data will be summarized as means with corresponding standard deviations. Not-normally distributed continuous data will be summarized as medians with corresponding range.

Dissemination

The results will be presented at relevant national and international congresses, and published in article format. The results will be relevant for current guidelines on postoperative care for patients undergoing esophagectomy and made known to the developers of these guidelines. However, due to the explorative nature of this study it will primarily assess safety and feasibility of early oral intake and provide directions for further research.

Discussion

The NUTRIENT trial investigates the feasibility of early oral intake after esophagectomy. The rationale for this trial emerges from fast-track programs in other types of gastro-intestinal surgery showing that there is no clear advantage to withhold enteral nutrition in the direct postoperative phase and that early (oral) feeding may even be beneficial compared with the traditionally applied nil-by-mouth strategy.[1,10,11]

Also for patients undergoing other upper gastrointestinal surgery it has been shown that early oral nutrition is just as safe as traditional care, consisting of a delayed oral intake.[3] Although these findings are promising, the patient group was very heterogeneous and included only a few patients undergoing an esophagectomy. Another randomized controlled trial has been started investigating early oral intake, amongst others included patients undergoing esophagectomy.[12] Next to this study one conference abstract has been published in 2008 on a small prospective study in which patients undergoing esophagectomy with 3 field lymph node dissection started oral liquid diet on day 2 postoperative [13]. Altogether this illustrates that data on early oral intake is still scarce and more research is needed.

A general concern regarding early start of oral intake following an esophagectomy is safety, especially regarding the sequelae of anastomotic leakage and incidence of pulmonary complications such as aspiration pneumonia.[4] However, there are no data to support these arguments. Studies supporting a delayed oral intake following esophagectomy are scarce and retrospectively performed. In one study it was shown that anastomotic leak rates are lower when a radiographic contrast swallow was omitted postoperatively and patients were fed over a jejunostomy and kept nil-by-mouth for 4 weeks.[14] A more recent study investigated a “planned delay of oral intake”.[15] However, due to the retrospective nature of both studies, differences in definitions, selection and timing of oral intake the results are difficult to interpret.

On the contrary, existing evidence in other types of upper gastro-intestinal surgery and animal studies points towards beneficial effects of early oral nutrition.[3,5,6] Since enteral nutrition is preferred postoperatively, a jejunostomy is often placed during surgery to bridge the delayed oral intake.[16] However, a jejunostomy is associated with specific complications, sometimes leading to re-laparotomy and even death.[17]

Another concern is an insufficient caloric intake postoperatively. While this can be expected for some patients, for example those that will develop anastomotic leakage, adequate caloric intake can be secured by endoscopic placement of a nasojejunal tube in these patients.[18]

Conclusion

This trial investigates whether early oral intake after minimally invasive esophagectomy is safe and possible. Due to the paucity of evidence this will be a feasibility trial in 50 patients using anastomotic leakage and pulmonary complications as primary endpoints.

Trial status: Recruitment of patients started in August 2013

Acknowledgements: None

Competing interests: The authors declare that they have no competing interests.

Authors' contribution: TW and ML drafted the manuscript. ML authored the writing of the manuscript. All authors participated in the design of the study and read, edited, and approved the final manuscript.

References

1. Varadhan KK, Neal KR, Dejong CH, *et al*. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: A meta-analysis of randomized controlled trials. *Clin Nutr.* 2010;**29**:434-40. doi:10.1016/j.clnu.2010.01.004. [Published Online First: 29 January 2010]

2. Hur H, Kim SG, Shim JH, *et al.* Effect of early oral feeding after gastric cancer surgery: A result of randomized clinical trial. *Surgery*. 2011;**149**:561-8. doi:10.1016/j.surg.2010. [Published Online First: 13 December 2010]

3. Lassen K, Kjaeve J, Fetveit T, *et al.* Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: A randomized multicenter trial. *Ann Surg.* 2008;**247**:721-9. doi:10.1097/SLA.0b013e31815cca68.

4. Lassen K, Revhaug A. Early oral nutrition after major upper gastrointestinal surgery: Why not? *Curr Opin Clin Nutr Metab Care.* 2006;**9:**613-7. doi:10.1097/01.mco.0000241673.17300.87

5. Fukuzawa J, Terashima H, Ohkohchi N. Early postoperative oral feeding accelerates upper gastrointestinal anastomotic healing in the rat model. *World J Surg.* 2007;**31**:1234-9. doi:10.1007/s00268-007-9003-9. [Published Online First: 28 April 2007]

6. Tadano S, Terashima H, Fukuzawa J, *et al*. Early postoperative oral intake accelerates upper gastrointestinal anastomotic healing in the rat model. *J Surg Res.* 2011;**169**:202-8. doi:10.1016/j.jss.2010.01.004. [Published Online First: 4 February 2010]

7. Biere SS, van Berge Henegouwen MI, Maas KW, *et al.* Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet*. 2012;**19**:1887-92. doi: 10.1016/S0140-6736(12)60516-9. [Published Online First: 1 May 2012]

8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;**240**:205-13. doi:10.1097/01.sla.0000133083.54934.ae.

9. Verhage RJJ. Outcomes and perioperative course of esophageal cancer surgery. *PhD Thesis.* University Medical Centre Utrecht, Department of Surgical Oncology; 2012.

10. Maessen JM, Hoff C, Jottard K, *et al*. To eat or not to eat: Facilitating early oral intake after elective colonic surgery in the Netherlands. *Clin Nutr.* 2009;**28**:29-33. doi:10.1016/j.clnu.2008.10.014. [Published Online First: 6 December 2008]

11. Lewis SJ, Andersen HK, Thomas S. Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: A systematic review and meta-analysis. *J Gastrointest Surg.* 2009;**13**:569-75. doi: 10.1007/s11605-008-0592-x. [Published Online First: 16 July 2008]

12. Shoar S, Mahmoodzadeh H, Hosseini Araghi N, *et al*. Early postoperative oral feeding in gastresophageal tumors surgery: A randomized controlled trial [abstract]. *J Surg Res.* 2013;179:201.

13. Terashima H, Tadano S, Yamaguchi R, *et al*. Fast track program accelerates short-term recovery after transthoracic esophagectomy with extended lymphadenectomy. *Clin Nut Sup*. 2008;3:77-78

14. Tomaszek SC, Cassivi SD, Allen MS, *et al*. An alternative postoperative pathway reduces length of hospitalisation following oesophagectomy. *Eur J Cardiothorac Surg*. 2010;**37**:807-15. doi: 10.1016/j.ejcts.2009.09.034. [Published Online First: 8 November 2009]

16. Bolton JS, Conway WC, Abbas AE. Planned Delay of Oral Intake After Esophagectomy Reduces the Cervical Anastomotic Leak Rate and Hospital Length of Stay. *J Gastrointest Surg.* Published Online First 4 September 2013. doi: 10.1007/s11605-013-2322-2

17. Fujita T, Daiko H, Nishimura M. Early enteral nutrition reduces the rate of life-threatening complications after thoracic esophagectomy in patients with esophageal cancer. *Eur Surg Res.* 2012;**48**:79-84. doi:10.1159/000336574

18. Han-Geurts IJ, Verhoef C, Tilanus HW. Relaparotomy following complications of feeding jejunostomy in esophageal surgery. *Dig Surg.* 2004;**21**:192-6. Doi:10.1159/000079345. [Published Online First: 24 June 2004]

19. Han-Geurts IJ, Hop WC, Verhoef C, *et al*. Randomized clinical trial comparing feeding jejunostomy with nasoduodenal tube placement in patients undergoing oesophagectomy. *Br J Surg*. 2007;**94**:31-5. doi: 10.1002/bjs.5283. [Published Online First: 20 November 2006]

Study protocol for the nutritional route in esophageal resection trial; a single-arm feasibility trial (NUTRIENT trial)

Teus J Weijs, MD[1,2], Grard AP Nieuwenhuijzen, MD, PhD[1], Jelle P Ruurda, MD, PhD[2], Ewout A Kouwenhoven, MD, PhD[3], Camiel Rosman, MD, PhD[4], Meindert Sosef, MD, PhD[5], Richard v Hillegersberg, MD, PhD[2], Misha DP Luyer, MD, PhD[1]

Institutions and affiliations

[1]Department of Surgery, Catharina Hospital Eindhoven, Michelangelolaan 2, 5623 EJ, Eindhoven, The Netherlands

[2]Department of Surgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands

[3]Department of Surgery, Ziekenhuisgroep Twente, Zilvermeeuw 1, 7609 PP Almelo, The Netherlands

[4]Department of Surgery, Canisius-Wilhelmina Hospital, Weg door Jonkerbos 100, 6532 SZ Nijmegen, The Netherlands

[5]Department of Surgery, Atrium Medisch Centrum, Henri Dunantstraat 5, 6419 PC Heerlen, The Netherlands

Correspondence: Misha DP Luyer, Department of Surgery. Catharina Hospital, Michelangelolaan 2, 5623 EJ Eindhoven, The Netherlands. **E-mail**: misha.luyer@cze.nl. **Telephone:** +31-6-40006809 **Fax:** + 31-40-2443370

Keywords: Esophagectomy, oral nutrition, anastomotic leakage, pneumonia, enhanced recovery

Word Count: 1337

Abstract

Introduction: The best route of feeding for patients undergoing an esophagectomy is unclear. Concerns exist that early oral intake would increase the incidence and severity of both pneumonia and anastomotic leakage. However, in studies including patients after many other types of gastro-intestinal surgery and in animal experiments, early oral intake has shown to be beneficial and enhance recovery. Therefore we aim to determine the feasibility of early oral intake after esophagectomy.

Methods and analysis: This study is a feasibility trial in which 50 consecutive patients will start oral intake directly following esophagectomy. Primary outcomes will be the frequency and severity of both anastomotic leakage and (aspiration) pneumonia. Clinical parameters will be registered prospectively and nutritional requirements and intake will be assessed by a dietician. Surgical complications will be registered.

Ethics and dissemination: Approval for this study has been obtained from the Medical Ethical Committee of the Catharina Hospital Eindhoven and the study has been registered at the Dutch Trial Register, NTR4136. Results will be published and presented at international congresses.

Discussion: We hypothesize that the oral route of feeding is safe and feasible following esophagectomy as has been shown previously for other types of gastrointestinal surgery. It is expected that early oral nutrition will result in an enhanced recovery. Furthermore, complications related to artificial feeding, such as jejunostomy tube feeding, are believed to be reduced. However, (aspiration) pneumonia and anastomotic leakage are potential risks that are carefully monitored.

Strengths and Limitations

A strength of this study is the careful monitoring of safety regarding the relevant clinical outcomes pneumonia and anastomotic leakage, for safety of early oral intake after esophagectomy is a major concern of many surgeons. A limitation is its descriptive single arm design. However, due to the lack of data we consider a safety and feasibility trial more appropriate before the start of a randomized controlled trial in which standard of care is compared with early oral nutrition.

Background

For many types of gastro-intestinal surgery, early oral intake has been shown to be beneficial and enhance recovery.[1-3] However, for patients undergoing an esophagectomy it is unclear what the best route of feeding is.[4] There is a concern that early oral intake following esophagectomy would result in vomiting with subsequent aspiration pneumonia. Furthermore the sequelae of anastomotic leakage are thought to be more severe if the leaked fluids contain food besides saliva. Although these arguments are widely accepted, there is no clear scientific evidence to support this hypothesis.

On the other hand, early oral intake has been demonstrated to be feasible and can result in faster recovery of bowel function and a shorter hospitalization after partial or total gastrectomy.[2] Furthermore, a randomized controlled trial in patients after major upper abdominal surgery, including esophagectomy, demonstrated that early oral intake directly after surgery does not increase morbidity compared to a nil-by-mouth regimen with jejunostomy feeding for the first 5 postoperative days. However, only few patients undergoing esophagectomy were included in this trial.[3] Additionally, experimental evidence shows that early enteral feeding above the anastomosis improves anastomotic healing after upper abdominal surgery in rats.[5,6]

Because of paucity of evidence on this topic, we designed a feasibility trial to investigate whether starting oral intake early after esophagectomy is feasible and safe.

Methods and Design

Design

This is an exploratory single-arm multicenter trial to determine the feasibility and safety of early oral intake from the first day after esophagectomy. The trial is approved by the independent ethical committee of the Catharina Hospital in Eindhoven, The Netherlands.

Population

All patients older than 18 years that undergo a minimally invasive esophagectomy and intrathoracic anastomosis (Ivor Lewis) are eligible for inclusion. Patients are excluded in case of >15% weight loss at the time of surgery, a swallowing disorder, mental retardation of an inability for oral intake. Weight loss >15% at time of surgery is regarded an exclusion criterion because it is not expected that these patients will achieve sufficient intake to compensate for their weight loss. Furthermore patients undergoing conventional open surgery and cervical anastomosis are excluded in order to improve homogeneity. Due to the paucity of evidence we designed a descriptive study, therefore no power calculation has been performed. In this study 50 patients will be included.

Study Outline

The early oral intake regimen will start with clear liquid fluids directly following surgery. At the first postoperative day a liquid diet is started under supervision of a dietician. Supplementary nutrition, such as Nutridrink™, is given to ensure adequate caloric intake. Adequate caloric intake is defined as >50% of energy needs at the fifth postoperative day. The dietician will calculate energy needs for each patient using the Harris-Benedict-formula with a surplus of 30% for energy expenditure in the postoperative phase. For male patients the Harris-Benedict-formula is 88.362 + (13.397 x weight in kg) + (4.799 x height in cm) - (5.677 x age in years) and for female patients 447.593 + (9.247 x weight in kg) + (3.098 x height in cm) - (4.330 x age in years).

After 1 week, if the clinical condition is good and inflammatory mediators decrease, the patient may progress to a solid diet. A good clinical condition is defined as a decreasing CRP, good mobilisation, being independent of supplementary i.v. fluids and pain being adequately controlled with oral medication.

Oral feeding will be terminated immediately if there is suspicion for anastomotic leakage. Artificial feeding will be started in case of anastomotic leakage, ileus requiring nasogastric decompression, complications for which the patient requires treatment at he intensive care unit, or when the caloric intake is <50% of the energy needs at day 5 postoperative.

In case of an indication for artificial feeding, enteral nutrition is preferred. The surgeon is free to surgically place a jejunostomy during the procedure. However the jejunostomy will be sealed directly after surgery and not be used until the patient meets the criteria for artificial nutrition as mentioned above. In cases where no jejunostomy tube has been placed during surgery, a nasojejunal tube will be inserted via endoscopy by a Gastroenterologist. Total parenteral nutrition will be started only in case of chylothorax or other conditions prohibiting enteral nutrition.

Surgical procedures

All patients will undergo a minimally invasive Ivor Lewis esophagectomy by surgeons experienced in minimally invasive surgery. In all centres more than 30 esophagectomies yearly have been performed by two dedicated surgeons over the past three years.

The operation is started with a laparoscopic phase, and followed by the thoracoscopic phase in prone position, as described previously.[7] At the end of the laparoscopic phase a gastric conduit is created intra-corporally with endostaplers. The intrathoracic anastomosis is made at the level of the carina, depending on the height of the tumour. The anastomosis is created with staplers or V-lock^{R} sutures in an E-t-S way or S-t-S way. The remaining opening is closed with V-Lock^{R} sutures. In all patients an omental wrap is draped around the anastomosis.

Outcomes

Primary outcomes are the incidence and severity (according to the modified Clavien Dindo classification for surgical complications) of pneumonia and anastomotic leakage.[8] Pneumonia is defined according to the definition of the Utrecht Pneumonia Scoring System.[9] In this system points are assigned based on temperature, leucocyte count and radiography. Pneumonia is defined as a score of 2 points or more, with at least 1 point assigned based on radiography. Aspiration pneumonia is defined as pneumonia following a clear history of aspiration of material (solid or liquid, vomit, saliva). Cases of silent aspiration leading to pneumonia might be missed. However, by recording the overall pneumonia rate with grading of the severity we will detect if early oral intake increases the incidence and or severity of pneumonia in general. In this case major, or minor aspiration might be a cause. Anastomotic leakage is defined as clinical signs of leakage from a drain or in case of a cervical anastomosis form the cervical wound; radiological signs of anastomotic leakage (contrast leakage, or fluid/ air levels surrounding the anastomosis) or signs of anastomotic leakage during endoscopy, re-operation or post mortal investigation. When anastomotic leakage is clinically suspected, a CT-scan will be performed. Based on the individual clinical situation, an endoscopic, radiological or surgical intervention will be performed in case anastomotic leakage is present. Adequate drainage is the primary goal.

Secondary outcomes are caloric intake during the postoperative admission; need and amount of artificial nutrition (naso-jejunal tube feeding / parenteral nutrition); occurrence of vomiting; placement of a nasogastric tube; length of hospital stay; hospital re-admissions within 30 days of discharge; complications classified according to the Clavien-Dindo classification[8]; need for ICU admission and total length of ICU stay; 30-day mortality and 90-day mortality.

All clinical data will be prospectively registered in an electronic surgical database.

Data and Safety Monitoring Board

An independent data and safety monitoring board (DSMB) will evaluate the progress of the trial and will examine safety variables. Every five patients, individualized patient data will be provided to the DSMB. The members of the DSMB will discuss the consequences of the data presented separately, and the outcome of this meeting will be discussed with the project group. If the DSMB suspects harm there will be a meeting between the DSMB, the study group and an independent statistician. During this meeting any potential causal relation between early start of postoperative oral nutrition and harm, and necessity for stopping the trial will be discussed.

Statistical analysis

The data analysis will consist of simple descriptive analyses. All analyses will be according to the intention-to-treat approach, incorporating all included patients, regardless of adherence to study protocol.

Categorical data will be summarized as frequencies. Normally distributed continuous data will be summarized as means with corresponding standard deviations. Not-normally distributed continuous data will be summarized as medians with corresponding range.

Dissemination

The results will be presented at relevant national and international congresses, and published in article format. The results will be relevant for current guidelines on postoperative care for patients undergoing esophagectomy and made known to the developers of these guidelines. However, due to the explorative nature of this study it will primarily assess safety and feasibility of early oral intake and provide directions for further research.

Discussion

The NUTRIENT trial investigates the feasibility of early oral intake after esophagectomy. The rationale for this trial emerges from fast-track programs in other types of gastro-intestinal surgery showing that there is no clear advantage to withhold enteral nutrition in the direct postoperative phase and that early (oral) feeding may even be beneficial compared with the traditionally applied nil-by-mouth strategy.[1,10,11]

Also for patients undergoing other upper gastrointestinal surgery it has been shown that early oral nutrition is just as safe as traditional care, consisting of a delayed oral intake.[3] Although these findings are promising, the patient group was very heterogeneous and included only a few patients undergoing an esophagectomy. Another randomized controlled trial has been started investigating early oral intake, amongst others included patients undergoing esophagectomy.[12] Next to this study one conference abstract has been published in 2008 on a small prospective study in which patients undergoing esophagectomy with 3 field lymph node dissection started oral liquid diet on day 2 postoperative [13]. Altogether this illustrates that data on early oral intake is still scarce and more research is needed.

A general concern regarding early start of oral intake following an esophagectomy is safety, especially regarding the sequelae of anastomotic leakage and incidence of pulmonary complications such as aspiration pneumonia.[4] However, there are no data to support these arguments. Studies supporting a delayed oral intake following esophagectomy are scarce and retrospectively performed. In one study it was shown that anastomotic leak rates are lower when a radiographic contrast swallow was omitted postoperatively and patients were fed over a jejunostomy and kept nil-by-mouth for 4 weeks.[14] A more recent study investigated a “planned delay of oral intake”.[15] However, due to the retrospective nature of both studies, differences in definitions, selection and timing of oral intake the results are difficult to interpret.

On the contrary, existing evidence in other types of upper gastro-intestinal surgery and animal studies points towards beneficial effects of early oral nutrition.[3,5,6] Since enteral nutrition is preferred postoperatively, a jejunostomy is often placed during surgery to bridge the delayed oral intake.[16] However, a jejunostomy is associated with specific complications, sometimes leading to re-laparotomy and even death.[17]

Another concern is an insufficient caloric intake postoperatively. While this can be expected for some patients, for example those that will develop anastomotic leakage, adequate caloric intake can be secured by endoscopic placement of a nasojejunal tube in these patients.[18]

Conclusion

This trial investigates whether early oral intake after minimally invasive esophagectomy is safe and possible. Due to the paucity of evidence this will be a feasibility trial in 50 patients using anastomotic leakage and pulmonary complications as primary endpoints.

Trial status: Recruitment of patients started in August 2013

Acknowledgements: None

Competing interests: The authors declare that they have no competing interests.

Authors' contribution: TW and ML drafted the manuscript. ML authored the writing of the manuscript. All authors participated in the design of the study and read, edited, and approved the final manuscript.

References

1. Varadhan KK, Neal KR, Dejong CH, *et al*. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: A meta-analysis of randomized controlled trials. *Clin Nutr.* 2010;**29**:434-40. doi:10.1016/j.clnu.2010.01.004. [Published Online First: 29 January 2010]

2. Hur H, Kim SG, Shim JH, *et al.* Effect of early oral feeding after gastric cancer surgery: A result of randomized clinical trial. *Surgery*. 2011;**149**:561-8. doi:10.1016/j.surg.2010. [Published Online First: 13 December 2010]

3. Lassen K, Kjaeve J, Fetveit T, *et al.* Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: A randomized multicenter trial. *Ann Surg.* 2008;**247**:721-9. doi:10.1097/SLA.0b013e31815cca68.

4. Lassen K, Revhaug A. Early oral nutrition after major upper gastrointestinal surgery: Why not? *Curr Opin Clin Nutr Metab Care.* 2006;**9:**613-7. doi:10.1097/01.mco.0000241673.17300.87

5. Fukuzawa J, Terashima H, Ohkohchi N. Early postoperative oral feeding accelerates upper gastrointestinal anastomotic healing in the rat model. *World J Surg.* 2007;**31**:1234-9. doi:10.1007/s00268-007-9003-9. [Published Online First: 28 April 2007]

6. Tadano S, Terashima H, Fukuzawa J, *et al*. Early postoperative oral intake accelerates upper gastrointestinal anastomotic healing in the rat model. *J Surg Res.* 2011;**169**:202-8. doi:10.1016/j.jss.2010.01.004. [Published Online First: 4 February 2010]

7. Biere SS, van Berge Henegouwen MI, Maas KW, *et al.* Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet*. 2012;**19**:1887-92. doi: 10.1016/S0140-6736(12)60516-9. [Published Online First: 1 May 2012]

8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;**240**:205-13. doi:10.1097/01.sla.0000133083.54934.ae.

9. Verhage RJJ. Outcomes and perioperative course of esophageal cancer surgery. *PhD Thesis.* University Medical Centre Utrecht, Department of Surgical Oncology; 2012.

10. Maessen JM, Hoff C, Jottard K, *et al*. To eat or not to eat: Facilitating early oral intake after elective colonic surgery in the Netherlands. *Clin Nutr.* 2009;**28**:29-33. doi:10.1016/j.clnu.2008.10.014. [Published Online First: 6 December 2008]

11. Lewis SJ, Andersen HK, Thomas S. Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: A systematic review and meta-analysis. *J Gastrointest Surg.* 2009;**13**:569-75. doi: 10.1007/s11605-008-0592-x. [Published Online First: 16 July 2008]

12. Shoar S, Mahmoodzadeh H, Hosseini Araghi N, *et al*. Early postoperative oral feeding in gastresophageal tumors surgery: A randomized controlled trial [abstract]. *J Surg Res.* 2013;179:201.

13. Terashima H, Tadano S, Yamaguchi R, *et al*. Fast track program accelerates short-term recovery after transthoracic esophagectomy with extended lymphadenectomy. *Clin Nut Sup*. 2008;3:77-78

14. Tomaszek SC, Cassivi SD, Allen MS, *et al*. An alternative postoperative pathway reduces length of hospitalisation following oesophagectomy. *Eur J Cardiothorac Surg*. 2010;**37**:807-15. doi: 10.1016/j.ejcts.2009.09.034. [Published Online First: 8 November 2009]

16. Bolton JS, Conway WC, Abbas AE. Planned Delay of Oral Intake After Esophagectomy Reduces the Cervical Anastomotic Leak Rate and Hospital Length of Stay. *J Gastrointest Surg.* Published Online First 4 September 2013. doi: 10.1007/s11605-013-2322-2

17. Fujita T, Daiko H, Nishimura M. Early enteral nutrition reduces the rate of life-threatening complications after thoracic esophagectomy in patients with esophageal cancer. *Eur Surg Res.* 2012;**48**:79-84. doi:10.1159/000336574

18. Han-Geurts IJ, Verhoef C, Tilanus HW. Relaparotomy following complications of feeding jejunostomy in esophageal surgery. *Dig Surg.* 2004;**21**:192-6. Doi:10.1159/000079345. [Published Online First: 24 June 2004]

19. Han-Geurts IJ, Hop WC, Verhoef C, *et al*. Randomized clinical trial comparing feeding jejunostomy with nasoduodenal tube placement in patients undergoing oesophagectomy. *Br J Surg*. 2007;**94**:31-5. doi: 10.1002/bjs.5283. [Published Online First: 20 November 2006]