



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

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

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

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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 or 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 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 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]

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

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Secondary outcomes are caloric intake during the postoperative admission; need and amount of artificial nutrition (nasogastric 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

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

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

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5 **Authors' contribution:** TW and ML drafted the manuscript. ML authored the writing of the
6 manuscript. All authors participated in the design of the study and read, edited, and approved
7 the final manuscript.
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Study protocol for the nutritional route in esophageal resection trial; a single-arm feasibility trial (NUTRIENT trial)

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48 23 **Keywords:** Esophagectomy, oral nutrition, anastomotic leakage, pneumonia, enhanced
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54 26 **Word Count:** 1337
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28 Abstract

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

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

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

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

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53 **Strengths and Limitations**

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

60

61 **Background**

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

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

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

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87 **Methods and Design**

88 **Design**

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

93 **Population**

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

104 **Study Outline**

105 The early oral intake regimen will start with clear liquid fluids directly following surgery. At the
106 first postoperative day a liquid diet is started under supervision of a dietician. Supplementary
107 nutrition, such as Nutridrink™, is given to ensure adequate caloric intake. Adequate caloric
108 intake is defined as >50% of energy needs at the fifth postoperative day. The dietician will
109 calculate energy needs for each patient using the Harris-Benedict-formula with a surplus of
110 30% for energy expenditure in the postoperative phase. For male patients the Harris-
111 Benedict-formula is $88.362 + (13.397 \times \text{weight in kg}) + (4.799 \times \text{height in cm}) - (5.677 \times \text{age}$
112 $\text{in years})$ and for female patients $447.593 + (9.247 \times \text{weight in kg}) + (3.098 \times \text{height in cm}) -$
113 $(4.330 \times \text{age in years})$.

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3 114 After 1 week, if the clinical condition is good and inflammatory mediators decrease,
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5 115 the patient may progress to a solid diet. A good clinical condition is defined as a decreasing
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7 116 CRP, good mobilisation, being independent of supplementary i.v. fluids and pain being
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9 117 adequately controlled with oral medication.

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11 118 Oral feeding will be terminated immediately if there is suspicion for anastomotic
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13 119 leakage. Artificial feeding will be started in case of anastomotic leakage, ileus requiring
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15 120 nasogastric decompression, complications for which the patient requires treatment at he
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17 121 intensive care unit, or when the caloric intake is <50% of the energy needs at day 5
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19 122 postoperative.

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21 123 In case of an indication for artificial feeding, enteral nutrition is preferred. The surgeon
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23 124 is free to surgically place a jejunostomy during the procedure. However the jejunostomy will
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25 125 be sealed directly after surgery and not be used until the patient meets the criteria for
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27 126 artificial nutrition as mentioned above. In cases where no jejunostomy tube has been placed
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29 127 during surgery, a nasojejunal tube will be inserted via endoscopy by a Gastroenterologist.
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31 128 Total parenteral nutrition will be started only in case of chylothorax or other conditions
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33 129 prohibiting enteral nutrition.

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36 37 131 **Surgical procedures**

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39 132 All patients will undergo a minimally invasive Ivor Lewis esophagectomy by surgeons
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41 133 experienced in minimally invasive surgery. In all centres more than 30 esophagectomies
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43 134 yearly have been performed by two dedicated surgeons over the past three years.

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45 135 The operation is started with a laparoscopic phase, and followed by the thoracoscopic
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47 136 phase in prone position, as described previously.[7] At the end of the laparoscopic phase a
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49 137 gastric conduit is created intra-corporally with endostaplers. The intrathoracic anastomosis is
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51 138 made at the level of the carina, depending on the height of the tumour. The anastomosis is
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53 139 created with staplers or V-lock^R sutures in an E-t-S way or S-t-S way. The remaining opening
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55 140 is closed with V-Lock^R sutures. In all patients an omental wrap is draped around the
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57 141 anastomosis.
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142 **Outcomes**

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

160 Secondary outcomes are caloric intake during the postoperative admission; need and
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233 This trial investigates whether early oral intake after minimally invasive esophagectomy is
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237 **Trial status:** Recruitment of patients started in August 2013

238

239 **Acknowledgements:** None

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

242

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

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For peer review only

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

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24 recovery

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28 Abstract

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

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

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

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

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53 **Strengths and Limitations**

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

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61 **Background**

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

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

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

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87 **Methods and Design**

88 **Design**

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

93 **Population**

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

104 **Study Outline**

105 The early oral intake regimen will start with clear liquid fluids directly following surgery. At the
106 first postoperative day a liquid diet is started under supervision of a dietician. Supplementary
107 nutrition, such as Nutridrink™, is given to ensure adequate caloric intake. Adequate caloric
108 intake is defined as >50% of energy needs at the fifth postoperative day. The dietician will
109 calculate energy needs for each patient using the Harris-Benedict-formula with a surplus of
110 30% for energy expenditure in the postoperative phase. For male patients the Harris-
111 Benedict-formula is $88.362 + (13.397 \times \text{weight in kg}) + (4.799 \times \text{height in cm}) - (5.677 \times \text{age}$
112 $\text{in years})$ and for female patients $447.593 + (9.247 \times \text{weight in kg}) + (3.098 \times \text{height in cm}) -$
113 $(4.330 \times \text{age in years})$.

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3 114 After 1 week, if the clinical condition is good and inflammatory mediators decrease,
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5 115 the patient may progress to a solid diet. A good clinical condition is defined as a decreasing
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7 116 CRP, good mobilisation, being independent of supplementary i.v. fluids and pain being
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9 117 adequately controlled with oral medication.

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11 118 Oral feeding will be terminated immediately if there is suspicion for anastomotic
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13 119 leakage. Artificial feeding will be started in case of anastomotic leakage, ileus requiring
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15 120 nasogastric decompression, complications for which the patient requires treatment at he
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17 121 intensive care unit, or when the caloric intake is <50% of the energy needs at day 5
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19 122 postoperative.

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21 123 In case of an indication for artificial feeding, enteral nutrition is preferred. The surgeon
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23 124 is free to surgically place a jejunostomy during the procedure. However the jejunostomy will
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25 125 be sealed directly after surgery and not be used until the patient meets the criteria for
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27 126 artificial nutrition as mentioned above. In cases where no jejunostomy tube has been placed
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29 127 during surgery, a nasojejunal tube will be inserted via endoscopy by a Gastroenterologist.
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31 128 Total parenteral nutrition will be started only in case of chylothorax or other conditions
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33 129 prohibiting enteral nutrition.

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36 37 131 **Surgical procedures**

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39 132 All patients will undergo a minimally invasive Ivor Lewis esophagectomy by surgeons
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41 133 experienced in minimally invasive surgery. In all centres more than 30 esophagectomies
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43 134 yearly have been performed by two dedicated surgeons over the past three years.

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45 135 The operation is started with a laparoscopic phase, and followed by the thoracoscopic
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47 136 phase in prone position, as described previously.[7] At the end of the laparoscopic phase a
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49 137 gastric conduit is created intra-corporally with endostaplers. The intrathoracic anastomosis is
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51 138 made at the level of the carina, depending on the height of the tumour. The anastomosis is
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53 139 created with staplers or V-lock^R sutures in an E-t-S way or S-t-S way. The remaining opening
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55 140 is closed with V-Lock^R sutures. In all patients an omental wrap is draped around the
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57 141 anastomosis.

142 Outcomes

143 Primary outcomes are the incidence and severity (according to the modified Clavien Dindo
144 classification for surgical complications) of pneumonia and anastomotic leakage.[8]

145 Pneumonia is defined according to the definition of the Utrecht Pneumonia Scoring
146 System.[9] In this system points are assigned based on temperature, leucocyte count and
147 radiography. Pneumonia is defined as a score of 2 points or more, with at least 1 point
148 assigned based on radiography. Aspiration pneumonia is defined as pneumonia following a
149 clear history of aspiration of material (solid or liquid, vomit, saliva). Cases of silent aspiration
150 leading to pneumonia might be missed. However, by recording the overall pneumonia rate
151 with grading of the severity we will detect if early oral intake increases the incidence and or
152 severity of pneumonia in general. In this case major, or minor aspiration might be a cause.

153 Anastomotic leakage is defined as clinical signs of leakage from a drain or in case of a
154 cervical anastomosis from the cervical wound; radiological signs of anastomotic leakage
155 (contrast leakage, or fluid/ air levels surrounding the anastomosis) or signs of anastomotic
156 leakage during endoscopy, re-operation or post mortal investigation. When anastomotic
157 leakage is clinically suspected, a CT-scan will be performed. Based on the individual clinical
158 situation, an endoscopic, radiological or surgical intervention will be performed in case
159 anastomotic leakage is present. Adequate drainage is the primary goal.

160 Secondary outcomes are caloric intake during the postoperative admission; need and
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239 **Acknowledgements:** None

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

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