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Assessing timing of enteral feeding support in esophageal cancer patients on muscle function and survival

Submission date 08/11/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered
		[_] Protocol
Registration date 27/11/2018	**Overall study status** Completed	[_] Statistical analysis plan
		[_] Results
Last Edited 01/09/2022	**Condition category** Surgery	[_] Individual participant data
		[_] Record updated in last year

Plain English summary of protocol

Background and study aims

Patients with oesophageal cancer are known to suffer from significant weight loss before undergoing surgery for removal of the oesophagus (oesophagectomy) due to swallowing difficulties caused by the growing tumour. After surgery (postoperative), the challenge of maintaining weight is even more important given the new way of eating through the stomach tube that replaces the oesophagus. They often also need to tackle dysphagia (swallowing difficulties) caused by narrowing of the connection between the remaining part of the gullet and the stomach, and overcome the physiological stress of the operation. As a consequence, almost all patients experience postoperative weight loss, which is related to impaired survival. A logical reaction would therefore be to increase calorie intake in the time around and after an operation. Extra calorie intake could therefore be started as early as possible after surgery in order to improve recovery. In contrast, within the field of intensive care and nutrition, discussion has risen about timing of feeding. The focus here has shifted in the direction of postponing nutrition to a later stage in the recovery of a sick patient, rather than start feeding too soon. The concept of impaired autophagy at the muscular level in case of early feeding was put forward as the underlying mechanism which is related to worse outcome. During the process of impaired autophagy, muscle cells get swollen and their interlinking structure gets disturbed, resulting in impaired muscle function. The muscle loss itself is triggered by the initial storm of inflammation that these patients go through when their lives are at stake at admission to the intensive care unit (ICU). Early nutrition seems to aggravate this process, causing impaired recovery after critical illness. This particular finding led to postponed feeding of patients at the ICU until one week after admission, in order to minimize muscle tissue loss. As patients after surgery are also confronted with a similar inflammatory state as ICU patients, they could also be considered to suffer from similar processes that inhibit recovery as patients in the ICU. This study will test relative starvation in the early days following oesophagectomy, in comparison to the current regimen of early feeding support. The aim is to find out whether the negative impact on muscle mass and muscle function can be reduced by postponing nutrition.

Who can participate?

Patients aged over 18 with oesophageal cancer who are scheduled for oesophagectomy

What does the study involve?
Participants are randomly allocated into two groups at the end of their operation. Participants in the standard of care group receive feeding support from the first day onwards, whereas participants in the test group receive feeding support from the fifth postoperative day. Every participant takes a 6-minute walk test to assess the effect. The researchers hope to see that the participants with a delay in feeding support will be able to walk further. To get also the bigger picture on nutrition and recovery after an oesophagectomy, several side measurements are performed as well. Participants are asked to keep a nutrition diary, their daily activity is assessed using a movement sensor, their body composition is checked before and after the operation, the muscle mass is calculated from CT scan images, and their quality of life and blood sugar (glucose) levels are measured, along with several blood markers related to inflammation and nutrition. In consenting participants, a little piece of thigh muscle is taken for microscopic evaluation. Tests run until three months after the operation. Participants are followed up with questionnaires on their quality of life every three months until 1 year after the operation.

What are the possible benefits and risks of participating?
Participants in the test group should have a better recovery after their operation but the outcome will only become apparent after the study. Apart from the blood collection, the muscle sample and the glucose sensors, no tests are invasive. These tests can cause mild bruising and a small risk of bleeding. The glucose sensor might give some skin irritation in some patients.

Where is the study run from?
University Hospitals Leuven (Belgium)

When is the study starting and how long is it expected to run for?
September 2017 to December 2024

Who is funding the study?
FWO ('Fund for Scientific Research Flanders'), Kom op Tegen Kanker ('Stand Up to Cancer', a non-governmental body in Belgium) and the Catholic University of Leuven (KU Leuven) (Belgium)

Who is the main contact?
Dr Hans Van Veer

Contact information

Type(s)
Scientific

Contact name
Dr Hans Van Veer

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Contact details
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Department of Thoracic Surgery
Herestraat 49

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Belgium
3000

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT03676478

Secondary identifying numbers
S61665

Study information

Scientific Title
Assessing the influence of timing of Enteral Feeding support in Esophageal Cancer patients on muscle funcTion and Survival: a monocentric, single blinded, parallel-group, open label randomised controlled trial

Acronym
EFECTS

Study objectives
Does relative starvation (by postponing the start of postoperative enteral nutritional support) improve muscle function and recovery after esophagectomy?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Research Ethics Committee, University Hospitals Leuven campus Gasthuisberg, 09/01/2019, ref: B322201938640

Study design
Single-blinded open-label single-centre randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)

Prevention

Participant information sheet
Not available in web format nor in English (only in Dutch/French); please use contact details to request a participation information sheet

Health condition(s) or problem(s) studied
Patients after esophagectomy for cancer

Interventions
INTERVENTION:
Participants in the standard of care arm will receive feeding support from the first day onwards, whereas subjects in the test group will receive delayed enteral nutritional support of 1000 kCal after 4 days (start at postoperative day (POD) 5), in combination with oral energy intake from POD4.

ASSiGNMENT:
Subjects will be screened and informed about the study at the occasion of the preoperative clinic appointment with the surgical team. Baseline measurements start after infomed consent.

BLINDING:
Given the nature of the intervention, this study will be run in an open label fashion, as the care of patients of both arms will happen at the same ward. Logistic reasons do not permit to separate nor patients in two separate groups on the ward, nor split the caregivers on the ward. This means that patients nor caregivers will be blinded to treatment allocation.
In contrast, the outcome assessors (the physiotherapists measuring the 6mWD) will be blinded for treatment allocation. Primary analysis will be performed by a statistician off-site, after inclusion of the last subject. Subject-related results will be offered to the statistician concealing the type of intervention the participants received (e.g. entitling group A or group B rather than SoC vs INT).
By these measures a blinded outcome assessment will be obtained for the primary outcome measure at the level of the outcome assessors and the outcome adjudicators.

RANDOMIZATION AND TREATMENT ALLOCATION:
Randomisation will be performed at the end of the operation, after an esophageal resection was possible and reconstruction of the enteral route has been established, when implantation of the jejunostomy feeding tube is finished. The randomization process will take into account the stratification parameters neo-adjuvant therapy vs surgery, site of anastomosis, sex and age of the participating subjects.
By means of an electronic (computerized) system, a stratified randomization with permuted-block randomization will be performed for treatment allocation. Allocation will end up in a 1:1 distribution of participating subjects.

Every participant will take a 6-minute walk test to assess the study effect. The researchers hope to see that the participants with a delay in feeding support will be able to walk further. Treatment success is defined as an increase of 30m of the mean distance in the intervention arm, considered as a clinical relevant difference. In order to perform this analysis, a non-parametric ANCOVA will be used. To also get the bigger picture on nutrition and recovery after an oesophagectomy, several side measurements will be performed as well. Participants will be asked to keep a nutrition diary, assess their daily activity by means of a movement sensor, check their body composition before and after the operation, calculate the muscle mass on CT scan

images, obtain information on the quality of life of the participants and follow up on the sugar levels in the blood whilst receiving feeding support. The study will also evaluate several markers in the blood of the participants which are in relation to inflammation and nutrition. In consenting participants, a little piece of thigh muscle will also be taken for microscopic evaluation. Tests will run until three months after the operation. Participants will be followed up with questionnaires on their quality of life every three months until 1 year after the operation.

Intervention Type
Supplement

Primary outcome measure
Functional recovery assessed with the 6 minute walk test (6mWT) at 5 weeks postoperatively

Secondary outcome measures
1. 90-day mortality at 90 days postoperative
2. Complications following esophagectomy, defined by the Esophagectomy Complications Consensus Group (ECCG) (Low et al.), assessed up to 1 year postoperative
3. Length of hospital stay (duration of admission expressed in days) from day of operation until hospital discharge after esophagectomy, assessed up to 250 days
4. Rate of readmission following primary discharge, assessed up to 1 year postoperative
5. Reasons for readmission following primary discharge, based on the complications list as defined by the Esophagectomy Complications Consensus Group (ECCG) (Low et al.), assessed from operation up to 1 year postoperative
6. Quality of life, assessed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 - Likert Scales [range 1 to 4, lower is better] from inclusion until 1 year postoperative, every 3 months
7. Quality of life, assessed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-OES18 - Likert Scales [range 1 to 4, lower is better] from inclusion until 1 year postoperative, every 3 months
8. Overall survival from operation until 1 year postoperative
9. Activity levels and energy expenditure, monitored by means of a Dynaport® accelerometer from inclusion until 3 months postoperative
10. Bio-impedance analysis by means of Seca Body Composition Analyzer 515 from inclusion until 3 months postoperative
11. Glycaemia levels in range; effect of permissive caloric restriction in the intervention group (detection of eventual hypoglycaemia) and the effect of nocturnal enteral nutrition on glucose homeostasis in the whole patient cohort, assessed with flash glucose monitoring system. 'Level in range' defined as time with (interstitial) glycaemia level between 70mg/dl and 250mg/dl. Baseline measurement for 10 days (preoperative), from POD0 until >> 10 days postoperative, 10 days following discharge (between POD8-14 on average), 10 days after stopping nutritional support
12. Muscle mass quantity/sarcopenia assessed by CT imaging pre- and 3 months postoperative
13. Muscle mass quality, assessed by microscopic evaluation and muscle biopsy preop, immediately postintervention (POD8±2 days) and biopsy 5 weeks postop
14. Complications related to feeding catheter (recording of infections, luxations, blockages and reasons for reintervention / replacement / reinsertion) from date of randomization until the date of removal of catheter, assessed up to 12 months
15. Body Mass Index (weight and height combined to report BMI in kg/m^2) from inclusion until 3 months postoperative
16. Nutritional intake (recording of oral intake and administered caloric intake through FT) from inclusion until 3 months postoperative

Overall study start date
01/09/2017

Completion date
31/12/2024

Eligibility

Key inclusion criteria
1. Patients with cancer of the gastroesophageal junction (GEJ), distal, mid- and proximal thoracic esophagus., older than 18 years, candidates for surgical resection with a curative intent, admitted to our Department
2. All sexes
3. Able to understand the study information in Dutch or French and understand tasks related to the study measurements proposed by the researchers
4. Able to consent
5. Patients with early as well as advanced clinical stage esophageal cancer: from cT1N0 over cT2+ N+ or cT3 Nx after neo-adjuvant therapy or at the time of staging as a candidate for primary surgery
6. Histology preop: Squamous or adenocarcinoma
7. Patients must undergo at least a standard two-field lymphadenectomy; three-field lymphadenectomy if deemed necessary by the clinical team is not a contraindication for inclusion
8. All access: (robotic assisted) minimal invasive (thoracoscopy & laparoscopy) approach, left thoraco-abdominal incision, hybrid esophageal resection or R thoracotomy + laparotomy
9. Partial or subtotal esophagectomy
10. Reconstruction by gastric conduit
11. All anastomoses (intrathoracic or cervical)
12. Women of childbearing age with esophageal cancer can be included

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
300

Key exclusion criteria
1. Patients in a definitive chemoradiation protocol, or undergoing rescue resection following definitive chemoradiotherapy
2. Patients expected to die within 12 hours (=moribund patients)
3. Patients transferred from another institute after esophageal resection with an established nutritional therapy

4. Patients with a cT4b tumor after neo-adjuvant therapy
5. Patients who are at the time of surgery deemed unresectable or found to be unresectable during surgery
6. Patients with a R2-resection
7. Patients with metastasis at the time of clinical staging
8. Patients undergoing transhiatal resection of the esophagus
9. Patients undergoing total gastrectomy
10. Patients undergoing an esophageal resection or esophageal bypass as palliative treatment
11. Patients with tumors in the cervical esophagus with a distance less than 3cm from the cricopharyngeal sphincter.
12. Patients with pharyngeal cancer undergoing (laryngo-)pharyngectomy with gastric pull-up
13. Need for colonic or jejunal interposition
14. Patients with a second synchronous malignancy
15. Patients with inflammatory bowel disease (as this might interfere with caloric uptake in the small bowel)
16. Patients with contraindications for enteral nutrition
17. Patients already participating in a study with a nutritional intervention

Date of first enrolment
25/03/2019

Date of final enrolment
30/09/2024

Locations

Countries of recruitment
Belgium

Study participating centre
University Hospitals Leuven
Department of Thoracic Surgery
Herestraat 49
Leuven
Belgium
3000

Sponsor information

Organisation
University Hospitals Leuven (UZ Leuven)

Sponsor details

Herestraat 49
Leuven
Belgium
3000

Sponsor type
Hospital/treatment centre

Website
www.uzleuven.be/en/research -- www.kuleuven.be/en

ROR
https://ror.org/0424bsv16

Funder(s)

Funder type
Government

Funder Name
Fonds Wetenschappelijk Onderzoek

Alternative Name(s)
Research Foundation Flanders, Flemish Research Foundation, FWO

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Belgium

Funder Name
Kom op Tegen Kanker (Stand Up To Cancer)

Funder Name
KU Leuven

Alternative Name(s)
Katholieke Universiteit Leuven

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
Belgium

Results and Publications

Publication and dissemination plan
As soon as the study passes Ethical Board Review, the trialists plan for submission and publication of the research protocol in due course in an Open Access journal, as obliged per publication protocol of one of the funding bodies (FWO).

It is anticipated that the results of the overall study shall lead to at least one peer-reviewed article on the primary endpoint of the trial. Referring to the other secondary endpoints, more publications are expected. All investigators will be co-authoring the publications covering this trial. Other contributing parties may be added to the author list based on their involvement on proposal of a member of the research team, but only in agreement with the other investigators.

Publications will be coordinated by the Investigator or Sponsor. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal. According to FWO regulations, publications will be submitted to journals with Open Access facilities. The Open Access policy of the KU Leuven/FWO will be respected in this perspective.

Depending on requests of the financial supporters, the researchers might also be asked to spread the results of the study outcomes also to the general public in a more generalised and comprehensible language. However, a vulgarising summary will only be spread after a scientific publication of the involved data has taken place.

As a preference and to augment the quality of data reporting, a manuscript will be prepared according to a specific standard like the CONSORT criteria (Consolidated Standards of Reporting Trials) or similar at the time of writing.

Intention to publish date
01/02/2025

Individual participant data (IPD) sharing plan
Data will be stored anonymously for eventual further data mining in the perspective of further evolution of science. All data being used has been consented for by participants at the moment of inclusion.

Which data will be made available after the end of the project?
Also study protocol, statistical analysis plan and analytic code will be made available.

Where/how will the data be made available for reuse?
• In an Open Access repository
• In a restricted access repository
• Upon request by mail
A limited dataset directly related to the topic of the journal where a manuscript is submitted to, will be made available in a cvs format and/or made available in an online repository, whichever the journal requests at the time of publication. The full dataset will be stored in the University's protected data environment.
Proposals should be directed to hans.vanveer@uzleuven.be. To gain access, data requestors will need to sign a data transfer agreement.

When will the data be made available?
The limited dataset will be made available upon publication of the results.
The full dataset will stay available for a minimum of 5 years, according to the third party agreement with FWO. Given the large data accrual of this study and the prevailing legislation, data will be stored for 25 years at the UZ/KU Leuven data repository.

Who will be able to access the data and under what conditions?
1. The dataset used for the manuscript will be uploaded to an open access repository under a CC-BY license.
2. The parts of the full dataset crucial for new research will be made available after submission of a new research protocol to the study coordinator/PI and to the Ethical Committee who gave initial permission for this study. Moreover, data cannot be used for research in the future in case of refusal of usage of data for future research on the side of the subject at the time of consent for the Main Study.

IPD sharing plan summary
Stored in publicly available repository