Prophylactic pectoralis major flap to compensate for increased risk of pharyngocutaneous fistula in laryngectomy patients with low skeletal muscle mass

Published: 29-04-2020
Last updated: 30-01-2025

With this prospective randomized clinical trial, we aim to investigate if the use of prophylactic PMMF on the pharyngeal closure for reinforcement in TL patients under high risk for PCF because of low (SMM), can reduce the risk of PCF to a level of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Head and neck therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON52422

Source
ToetsingOnline

Brief title
PECTORALIS

Condition

- Head and neck therapeutic procedures

Synonym
laryngectomy, low skeletal muscle mass

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: KWF subsidie

Intervention

Keyword: Laryngectomy, Pectoralis major flap, Pharyngocutaneous fistula, Skeletal muscle mass

Outcome measures

Primary outcome

In a randomized clinical trial the addition of PMMF as onlay for reinforcement in low SMM patients will be investigated. Patients who are planned for TL without PMMC for reconstruction of the mucosal defect will be asked to participate in this study. After informed consent SMM will be measured using routinely performed CT or MRI of the head and neck. Patients with low SMM will be randomized between PMMF reconstruction at the time of TL or not. Incidence of PCF will be scored for the three groups: patients with low SMM with PMMF as onlay for reinforcement, patients with low SMM without PMMF and patients without low SMM. It is hypothesized that the use of PMMF can reduce the PCF rate to a level similar to TL patients without low SMM.

Skeletal muscle mass measurement

SMM is measured on pre-treatment CT or MRI scans of the head and neck area at the level of C3 using a previously published method. Whenever possible, CT imaging was used instead of MRI. In brief, the first slide at the level of C3 when scrolling from caudal to cranial direction to show both transverse processes and the entire vertebral arc is selected for segmentation of skeletal

muscle (SM) tissue. For CT imaging, skeletal mass (SM) area is defined as the pixel area within a radiodensity between -29 and +150 Hounsfield Units (HU), which is specific for SM tissue. For MRI, SM tissue is carefully segmented and any intramuscular fatty tissue is manually excluded. Segmentation of SM tissue was manually performed using in house or commercially available software package SliceOmatic (Tomovision, Canada). An example of SM tissue segmentation at the level of C3 is shown in Figure 1. After a learning period, the measurement of SMM requires 5 to 10 minutes per CT scan, and up to 15 minutes per MRI scan.

From SM area at C3, SM area at the level of L3 is predicted using the previously published Formula 1. The SM area at L3 is then normalized for height to calculate the lumbar skeletal muscle index (lumbar SMI), as shown in Formula 2. 12 Low SMM is defined as a lumbar SMI lower than 43.2cm2/m2. This recently published cut off value was established in a separate cohort of head and neck cancer patients.

Formula 1:

CSA at L3 (cm2)=27.304+1.363*CSA at C3 (cm2)-0.671*Age (years)+0.640 *Weight (kg)+26.442 *Sex (Sex=1 for female, 2 for male)

Formula 2:

Lumbar SMI (cm2/m2)=CSA at L3 /length (m2)

In patients who underwent FDG-PET/CT as part of the diagnostic work-up, as a control of SMM measurement at the level of C3, SMM will also be measured at the level of L3, which is the most commonly used method in medical literature as a control of SMM measurement at the level of C3. However, the use of a SMM measurement at the level of C3 is highly preferable, because of national and international differences in performing whole body FDG-PET/CT imaging in HNSCC.

Secondary outcome

All patients are asked to fill out the questionnaires, but performing function tests will be dependent on the ability in each participating center. At least in 3 centers the following function tests will be performed: patients with low SMM will be tested for shoulder and neck disability, swallowing function and voice quality. Also patients with secondary (for PCF treatment) PM flap will undergo these tests. Sub analysis will be performed to investigate if there is a difference in morbidity between prophylactic and secondary PM flap harvest.

Shoulder and neck function

Questionnaires (secondary study parameter)

The shoulder disability questionnaire (SDQ) is a validated pain-related disability questionnaire including 16 items that describe common conditions that may induce symptoms in patients with disorders of the shoulder. All items refer to the preceding 24 hours. Options are *yes*, *no* and *not applicable*. The *not applicable* category should be used when the condition referred to has not occurred during the preceding 24 hours. A final score is calculated dividing the number of *yes* scored items by the total number of items

applicable. And then multiplying the score by 100 results in a final score that ranges between 0 (no disability) and 100 (all applicable items scored *yes*). The higher the score, the greater the impairment was. All patients are asked to fill out the questionnaires for both the left and the right shoulder separately.

Shoulder function will also be measured with the Shoulder Pain and Disability Index Dutch Language Version (SPADI-DLV). This questionnaire consists of 13 items, 5 related to pain and 5 related to function.

Pain of the shoulder is rated on a visual analogue scale (VAS: 0-100 millimeter). Patients are asked to indicate the mean shoulder pain intensity over the past week.

Patients are also asked if they had experienced stiffness of the shoulder during the previous week (yes or no).

The Neck Disability Index (NDI) is a questionnaire that captures elements of neck disability such as pain, work, and headache. The NDI consist of a 10 six point Likert scale question.

Function tests (part of the main study; performance dependent on the ability in each participating center)

Active range of motion (AROM) of the shoulder is examined using an inclinometer according to a standardized protocol. Forward flexion and abduction are measured in the range of 0-180*. The mean of two sequential measurements is used for further analysis. To examine endorotation and exorotation an inclinometer cannot be used because these are combined movements. These will be

measured with a goniometer.

The AROM with the lateroflexion, rotation, extension and flexion of the neck, is examined using the digital inclinometer.

Swallowing function

Questionnaires (secondary study parameters)

The Dysphagia Severity Scale (DSS) and Dysphagia Quality of Life Scale (DQOL) are both for laryngetomized patients,non-validated, but rather simple scales to measure the degree of dysphagia. Patients can indicate on the specific visualized analogue scale in how they asses swallowing today. The scale ranges from *not being able to swallow* to * being able to swallow normally* in case of the DSS. With the DQOL patients will answer to what extend their daily lives are influenced by the swallowing disorder on the current day. Answers range from *maximum burden or limitation* to * normal/no burden or limitation.'

The swallowing function in patients after laryngectomy will be measured using the self-reported patient questionnaire, the Swallow Outcomes After Laryngectomy (SOAL).[58] This questionnaire is not yet validated for the Dutch language, but particularly specific for patients with a laryngectomy. This questionnaire consists of 17 questions about swallowing status and difficulties. Patients can answer *no*, *a little* or *a lot*. Since we want to validate the SOAL-questionnaire for the Dutch language, we will use the M.D. Anderson Dysphagia Inventory (MDADI) to compare the validity. MDADI is a self-administered questionnaire for head and neck cancer patients and validated for the Dutch language. The impact of dysphagia on the quality of life is

evaluated. Patients can answer if they *strongly agree*, *agree*, *have no opinion*, *disagree* or *strongly disagree* with statements about the swallowing ability and views of the patient.

The Functional Oral Intake Scale (FOIS) for dysphagia is the only investigator reported outcome questionnaire. It is a standardized 7 point scale to measure the level of intake (1= complete tube feeding-nothing oral, 7= all intake via oral rout without restrictions). The questionnaire is not specifically designed for laryngectomees, but still gives a good descriptive measure of the patients.

Function tests (side study; performance dependent on the ability in each participating center)

To demonstrate the type and extent of an swallowing disorder the Video Fluoroscopic Swallow Study (VFSS) is the most common used exam. The VFSS gives detailed information about the swallowing dysfunction. Recommendations regarding by what method the patient should be nourished can be given afterwards. This radiographic procedure will be performed only 6 months after TL.

Voice quality

Questionnaires (secondary study parameter)

Using the Voice Handicap Index (VHI), the psychosocial consequences of voice disorder will be quantified. This questionnaire is validated for the Dutch language and based on statements made by people to describe their voice quality

and the effect of their voice on their daily lives. TL - patients can answer if they *never* , *almost never*, *sometimes*, *almost always* or *always* experience these statements themselves. The VHI-30 will be used.

Quality index (side study; performance dependent on the ability in each participating center)

The investigator reported outcome measure will be the Acoustic Voice Quality Index (AVQI). This index is developed in 2010 and is one of the first indexes to measure the quality of the voice with a sustained vocalized and continuous speech. AVQI is a multi-parameter model in which the outcomes of six acoustic parameters are measured and combined into one objective measure of the severity of voice quality. Voices of patients will be recorded postoperatively dependent on the ability in each participating center.

Quality of Life (secondary study parameters)

The following questionnaires will be used to measure QoL: EORTC QLQ-C30, EORTC-QLQ-H&N35, specific for head and neck cancer patients and EQ-5D-5L. The EORTC-QLQ is designed to be cancer-specific, multidimensional in structure, appropriate for self-administration and applicable across a range of cultural settings. Dutch reference values are available. The EQ-5D is a standardized instrument can be used as a quantitative measure of health outcome that can be used in a wide range of health conditions and treatments, and reflects the patient*s own judgement. Questionnaires are asked to fill out before and 6 months after laryngectomy. The EQ-5D-5L will be filled out 3 months after TL

also.

Patients* experience (secondary study parameter)

Patients* experience with the needed rehabilitation of shoulder and neck function, swallowing function and voice quality related to provided information and therapy will be explored by qualitative research with semi-structures interviews based on a interview guide with a topic list. Questions will focus on patients* experience with the provided information, content of the needed therapy related to physical functioning like neck and shoulder problems, swallowing and speech quality. Semi-structured interviews will be analyzed by two researchers using thematic descriptive analyses. Data coding will be done by open, axial and selective coding and will be supported by the software package NVivo.

Cost-effectiven

Study description

Background summary

In The Netherlands about 160 patients per year undergo total laryngectomy (TL). Postoperative complications including the occurrence of a pharyngocutaneous fistula (PCF) are common and difficult to treat. In a Dutch national study with 324 TL patients the PCF rate was 25.9%. PCF may require additional surgery, prolongs feeding tube dependency, delays or interrupts oral feeding and voice rehabilitation and increases hospital stay and costs. PCF carries a high risk of postoperative infections, wound breakdown and subsequent damage to nearby tissue and structures, including potential carotid artery blowout. PCF may also cause delay of postoperative (chemo)radiotherapy, thus jeopardizing optimal oncological treatment. Surgical closure of PCF, is indicated in half of the

cases. Most often a myocutaneous pectoralis major flap (PMMC) is used to restore the mucosal defect. This surgery is associated with complications because of the poor tissue quality due to infection and saliva exposure.
A surgical strategy to minimize PCF development following TL is the transfer of a pectoralis major myofascial flap (PMMF) to the neck as onlay for reinforcement of the pharyngeal closure. Systemic reviews show that a prophylactic PMMF reduces the risk of PCF in TL patients significantly. The use of prophylactic PMMF on the pharyngeal closure for reinforcement is recommended for patients with high risk for PCF.
Low skeletal muscle mass (SMM) has been related to negative outcomes in a variety of tumour types and treatments. In oncological patients, SMM is most commonly assessed on abdominal computed tomography (CT) imaging at the level of the third lumbar vertebra (L3). Abdominal CT imaging is not routinely performed in head and neck cancer patients, and is often only available in a preselected patient group with advanced disease and high risk features for distant metastasis. Recently, a novel SMM assessment method at the level of the third cervical vertebra (C3) was published. Imaging at the level of C3 is almost always available in TL patients, allowing for the routine assessment of SMM without any extra burden for the patient or healthcare-related costs.
Two studies reported that preoperative low SMM is a significant predictor of PCF in patients undergoing TL. Recently we reported on another series of 235 patients undergoing TL either with or without reconstruction of the pharynx with PMMC/PMMF and SMM measured using CT or MRI scans at the level of C3. Low SMM was observed in 109 patients (46.4%). Patients with low SMM had more frequently PCF than patients with normal SMM (34.9% versus 20.6%, $p=0.019$) and prolonged hospital stay (median 17 versus 14 days, $p<0.001$). In multivariate logistic regression analysis low SMM remained significant predictors of PCF (OR 1.950). After exclusion of the patients who received a reconstruction of the pharynx with PMMCor PMMF from the database, the PCF rate in patients with low skeletal muscle mass was 31.0%.
Two systematic reviews of Paleri et al and Sayles et al describe a reduced risk of fistula formation in patients who underwent primary salvage surgery with the prophylactic PMMC or PMMF flap. The incidence of PCF was reduced (47/156 to 11/114), giving a relative risk of 0.32.

Study objective

With this prospective randomized clinical trial, we aim to investigate if the use of prophylactic PMMF on the pharyngeal closure for reinforcement in TL patients under high risk for PCF because of low (SMM), can reduce the risk of PCF to a level of TL patients without low SMM. We hypothesize that in patients with low SMM the use PMMF as onlay for reinforcement can reduce the PCF rate after TL from 31.0% to 9.9%.

Study design

In a multicenter randomized clinical trial patients who are planned for TL without PMMC flap for reconstruction of the mucosal defect will be asked to participate in this study. SMM is measured on pre-treatment CT or MRI scans at the level of C3 using a previously published method. One hundred twenty-eight patients with low SMM will be randomized between prophylactic PMMF flap at the time of TL or not. Incidence of PCF will be scored for the following groups: patients with low SMM with PMMF flap as onlay for reinforcement, patients with low SMM without PMMF and patients without low SMM. In patients with or without low SMM and who unexpectedly needed the PMMC for reconstruction of the pharynx PCF incidence will also be scored following the *intention-to-treat* analysis. In low SMM patients shoulder morbidity, swallowing function and perception of dysphagia and the voice quality with their psychosocial consequences will be investigated by questionnaires and shoulder function test before and 6 months after TL. Patients* experience will be explored by qualitative research with semi-structures interviews. Quality of life will be measured using EORTC questionnaires. A cost-effectiveness analysis will be performed.

Intervention

PMMF flap in TL patients with low SMM randomized for intervention arm

Study burden and risks

Burdens: Patients in the intervention arm will receive PMMF with potential shoulder morbidity. Patients with low SMM will be asked to complete questionnaires before and 6 months after TL. The EQ-5D-5L will be filled out 3 months after TL also. Shoulder function tests,voice recording and videofluoroscopic swallowing study (VFSS) will be performed dependent on the ability in each participating study. The shoulder function test will be performed before and 6 months after TL and is part of the main study. VFSS and voice recording only 6 months after TL. Radiation dose during VFSS will be < 1.5mSv, which is a lot less than a routinely performed CT thorax (4 mSv).It is estimated that it takes 50 minutes to fill out all questionnaires at one time point. Function tests will take 45 minutes. The questionnaires and function tests will be conducted during a routine consultation. Additional operation time for harvesting the PM flap will take 30 minutes. It is expected that the use of PMMF will result in less and limited (duration and extent) PCF, shorter hospital stay, less delay in adjuvant treatment, lower costs and improved quality of life. PMMC for fistula closure is probably associated with more morbidity than prophylactic PMMF. For TL patients, this study may serve as a basis for a reduction of PCF, which is a difficult problem to manage and is associated with severe complications and reduction of quality of life. Prevention of PCF is essential in the management of TL patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Planned for TL
• Eighteen years of age or older, and able to exercise their free will.
• Sufficient understanding of the Dutch language to give informed consent.

Exclusion criteria

- Planned for TL with pharyngectomy and reconstruction of the pharynx with PMMC.
- Planned TL with pharyngectomy and reconstruction with jejunal flap or gastric pull-up.
- Planned TL after treatment with chemoradiotherapy (cisplatin/carboplatin) for a previously diagnosed head and neck carcinoma

- Major (FDG-PET/)CT or MRI artefacts, impeding accurate muscle tissue identification on
imaging.
- Interval between TL and imaging > 2 months.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-09-2020
Enrollment:	246
Type:	Actual

Ethics review

Approved WMO Date:	29-04-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2021
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	03-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-01-2025
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 26043
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL72319.041.20