Organoids of Barrett*s esophagus: a feasibility study and creation of a Biobank

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Primary Objectives: - To test the feasibility of culturing patient-derived Barrett*s esophagus organoids- To test pharmacological and chemotherapeutical agents in vitro on the cultured organoidsSecondary Objectives: - To create a small Biobank (of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational invasive

Summary

ID

NL-OMON44335

Source
ToetsingOnline

Brief title
BORGANO

Condition

- Gastrointestinal inflammatory conditions

Synonym
Barrett's esophagus

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Stichting Theodora

Intervention

Keyword: Barrett, Biobank, Esophagus, Organoid

Outcome measures

Primary outcome

The main endpoint is successful growth of Barrett*s organoids and to test pharmacological and chemotherapeutical agents in vitro on the cultured organoids.

Secondary outcome

To create a small Biobank (of 10 patients) for further study

Study description

Background summary

Esophageal cancer is the eighth most prevalent cancer in the world (2) and it has been on the rise in recent decades. The incidence of esophageal cancer in the Netherlands almost doubled between 1989 and 2009, as it rose from 4.6 to 8.5 cases per 100,000 citizens. This rise is mostly explained by an increase in esophageal adenocarcinoma (EAC) in men, whereas the incidence of esophageal squamous-cell carcinoma (ESCC) has remained relatively stable. (Figure 1) (1)

The etiology of EAC is different from ESCC. While Tobacco use is a risk factor for both; obesity, reflux disease and Barrett*s esophagus are specific for EAC and increase the risk notably. (3, 4) Especially the latter two have been considered the key factors responsible for the observed increase in incidence. (5) Barrett*s esophagus will be described in more detail further on in this introduction.

The treatment of advanced esophageal cancer is traditionally surgical. This surgery, however, has a relatively high morbidity and mortality. (6) Recent discoveries have proven that neoadjuvant chemoradiotherapy (nCRT) significantly increased survival as compared to surgery alone in patients with potentially curable esophageal cancer. Moreover, in the nCRT group of the study, 49% of patients with ESCC and 23% of patients with EAC had a pathologically complete response in the resection specimen. (1, 7) This finding led to the start of the preSANO and SANO trial, of which the first started in 2013. The goal in this

study is to assess if remission after nCRT can be assessed and if so, if surgery is needed at all in patients that show remission after nCRT. (6) As of now all patients receive the same kind of chemotherapy. However, there are multiple effective pharmacological treatments known which are not equally effective in every patient. (1, 4, 8) In light of these findings, trying to improve the efficacy of chemotherapy is even more imperative.

We want to try to investigate these esophageal tissues using organoids. Organoids are defined as miniaturized and simplified versions of an organ, produced in vitro in three-dimensional culture systems, that are self-organizing and show realistic micro-anatomy. (9) This is done by placing adult stem cells, isolated from tissue, in extracellular matrix (i.e. Matrigel® containing laminin, collagen IV, heparin sulfate proteoglycans, entactin/nidogen and growth factors) and adding the correct growth factors. The stem cells will then start to build organoids through mitosis. (10, 11).

The creation of organoids has already been accomplished for healthy esophageal tissue at our facilities and for Barrett*s esophagus elsewhere. (10, 11) The purpose of this study is to create organoids of patient-derived Barrett*s esophagus tissue at our own facility. If this is successful we can use this technique for further research.

We want to use these tissue models to test different cytotoxic agents or chemotherapeutics. Hopefully this knowledge will ultimately lead to a validated model that can assess treatment-efficacy of chemotherapy. By *treating* these organoids first to see what therapy works the best, we hope that a more patient-specific and therefore possibly superior treatment can be achieved.

In conclusion, the primary aim of this pilot-study is to test the feasibility of culturing patient-derived Barrett*s esophagus organoids on a small scale at our facilities.

Secondary aims will be:
- To create a small Biobank of 10 patients for further study in the near future.
- To use organoids of Barrett*s esophagus tissue to test cytotoxic agents or chemotherapeutics in vitro.

Study objective

Primary Objectives:
- To test the feasibility of culturing patient-derived Barrett*s esophagus organoids
- To test pharmacological and chemotherapeutical agents in vitro on the cultured organoids

Secondary Objectives:

- To create a small Biobank (of 10 patients) for further study

Study design

Patients with a confirmed Barrett*s esophagus diagnosis are added to a surveillance program whereafter a surveillance endoscopy is recommended to take place every 3-5 years, dependent on absence or presence of dysplasia. During the surveillance endoscopy four quadrant-biopsies are taken at every 2 centimeters of the Barrett segment. Endoscopic biopsy of Barrett*s esophagus is considered a safe procedure; a study of 1.458 procedures found no deaths, no esophageal perforations and no gastro-intestinal bleeding that was attributable to endoscopic biopsies alone. The average number of biopsies taken during a single procedure was 35 with a maximum of 120 (12).

In addition to the standard-care biopsies, a total of 5 extra biopsies of the Barrett*s esophagus is deemed to be necessary for subsequent cell culture in the form of organoids. Members of the gastroenterology laboratory will pick the tissue up from the endoscopy ward and bring it to the laboratory for cell culture preparation.

After sufficient growth of organoids has been observed, they will be stored in a Biobank at
-80 ºC. The tissue will not leave the facilities of the Radboud University Medical Center.

Study burden and risks

Patients with a confirmed Barrett*s esophagus diagnosis are added to a surveillance program whereafter a surveillance endoscopy is recommended to take place every 3-5 years, dependent on absence or presence of dysplasia. During the surveillance endoscopy four quadrant-biopsies are taken at every 2 centimeters of the Barrett segment. Endoscopic biopsy of Barrett*s esophagus is considered a safe procedure; a study of 1.458 procedures found no deaths, no esophageal perforations and no gastro-intestinal bleeding that was attributable to endoscopic biopsies alone. The average number of biopsies taken during a single procedure was 35 with a maximum of 120 (12).
In addition to the standard-care biopsies, a total of 5 extra biopsies of the Barrett*s esophagus is deemed to be necessary for subsequent cell culture in the form of organoids.

Participation in the study does not cause any additional charge to patients. The patient does not benefit from participating in the study. On the other hand, the risk of taking an additional 5 biopsies in these patients is negligible.

The risk classification is determined as negligible based on the guideline of

the *Nederlandse Federatie van Universitair Medische Centra*. The risks associated with the participation in the study are similar to the risks of multiple biopsies in surveillance of Barrett*s esophagus.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Confirmed histological diagnosis of Barrett*s esophagus after previous endoscopy.
- Participant in the Barrett*s esophagus surveillance program.

Exclusion criteria

a) Age < 18 years
b) Previous thoracic radiotherapy.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-11-2017
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	05-09-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-12-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL61757.091.17