Stratifying Risk in Barrett*s Esophagus: A Pilot Study for Biomarker-Based Patient Management

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Primary objective:To gather information on the feasibility of a prospective, international multicenter study in which, on the basis of biomarker-based risk stratification, patients at high risk for progression are randomized to radiofrequency...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Observational invasive

Summary

ID

NL-OMON41809

Source
ToetsingOnline

Brief title
ASGE Biomarkers Study

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Barrett's esophagus, esophageal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: The American Society of Gastrointestinal Endoscopy (ASGE)

Intervention

Keyword: Barrett's Esophagus, Biomarkers, Esophageal cancer, Risk stratification

Outcome measures

Primary outcome

The endpoints for the study consist of:

1) Time taken to produce biomarker results,

2) Consistency of biomarker prevalence between the centers (Europe and the

U.S.), and,

3) Proportion of patients falling into the high risk category based on

biomarker analysis.

Secondary outcome

Not applicable

Study description

Background summary

Barrett*s esophagus (BE) is the precursor lesion of esophageal adenocarcinoma (EAC), a cancer with a >500% increase in incidence in the U.S. since the 1970*s. Effective prevention of EAC is hindered by poor risk stratification. Our only commonly used prognostic factor, dysplasia, is both poorly reproducible and inaccurate. Recently developed biomarker panels may allow for accurate risk stratification, such that subjects at higher risk may be identified early for endoscopic intervention.

EAC is increasing rapidly in incidence, and is associated with an abysmal 5-year survival rate of less than 15%. Early diagnosis has been shown to improve outcomes and should be feasible in view of the presence of the premalignant condition BE. However, because of the low conversion rate of BE to cancer, as well as inherent difficulties with sampling bias and histological assessment of specimens, the benefits of surveillance are controversial. On the basis of cost-effectiveness analyses, it has become apparent that only patients with a high risk of developing cancer should be targeted for further

intervention, such as RFA.1,2 Our inability to accurately stratify BE patients on the basis of histology has precluded this more elegant approach to patient management and as such, all BE patients, including those with low risk of progression, remain under surveillance. Current clinical practice for patients diagnosed with BE involves regular endoscopy and multiple random biopsies for the assessment of dysplasia.3 Unless there is an obvious abnormality (ulcer or nodule), then the biopsies may not sample the dysplastic area, leading to under-staging of the degree of dysplasia. Furthermore, dysplasia is a highly subjective pathological diagnosis which may miscategorize patients.4,5 The management algorithm hinges on the diagnosis of dysplasia, such that individuals with no dysplasia often undergo continued surveillance whereas those with HGD or intramucosal carcinoma (IMC) are offered a therapeutic intervention with either endoscopic therapy or surgery depending on local expertise, patient fitness, and depth of invasion. Subjects with LGD may sometimes undergo endoscopic therapy, or may be retained in an intensified surveillance program, depending on patient and physician consultation. The results of this algorithm are that many patients at very low risk are subjected to repeated endoscopy with associated risks and psychological stress, as well as financial costs. On the other hand, patients at high risk may be missed due to sampling bias, misclassification of dysplasia, or lack of surveillance due to poor compliance or inavailability of services. Our current system is thus fraught with errors and excess expense.

Determining which patients with BE have the greatest risk for progression to EAC has the potential to improve outcomes and to deliver more cost-effective care. During a retrospective validation study, Investigators have identified and validated a biomarker panel that will be used for this study to identify subjects at high risk of developing EAC. This is a pilot study to gather information on the feasibility of a prospective, international validation study, which would randomize subjects with BE and no dysplasia or low-grade dysplasia who are recognized to be at high risk for progression to either an active intervention (RFA) or to endoscopic surveillance. Subjects deemed at low risk by the biomarker panel would be retained in surveillance. Comparisons would include progression outcomes in the high risk surveillance arm to the low risk surveillance arm (to assess the accuracy of the panel at predicting risk) and progression outcomes of the high risk intervention arm (RFA) to the high risk surveillance arm (to assess if active intervention in appropriately selected individuals attenuates the risk of progression to EAC). Such an approach heralds a new paradigm, in which patients are accurately managed according to their future risk of cancer on the basis of objective, easily assayed markers. If successful, we will be able to focus resources on those at greatest risk for cancer, thus sparing low risk patients unnecessary invasive and expensive interventions, while reducing the progression to cancer in those at high risk. Technological advances in biomarker research, as well as safe and effective endoscopic therapeutic modalities (endoscopic mucosal resection and RFA) make the time ripe for such a study.

Study objective

Primary objective:
To gather information on the feasibility of a prospective, international multicenter study in which, on the basis of biomarker-based risk stratification, patients at high risk for progression are randomized to radiofrequency ablation (RFA) vs. a surveillance arm (yearly EGD), while patients in the low risk group have an attenuated EGD surveillance regimen per current standard of care.

Secondary objective:
To develop the protocols, operating procedures, and other materials necessary for application to the National Cancer Institutes for support of the multi-center trial of ablative therapy in BE.

Study design

The Investigators have previously completed a validation study in which they have identified a panel of biomarkers that can predict progression of subjects with BE and no dysplasia or low-grade dysplasia to esophageal adenocarcinoma (EAC). The biomarker panel, performed by the Fitzgerald lab, included ploidy (by image cytometry), AOL (histochemistry (IHC)), p53 (IHC), cyclin A (IHC), and dysplasia. These markers have been validated and demonstrated to be highly predictive of both progression to EAC, as well as the presence of occult malignancy elsewhere in the specimen (field effect). The final panel of validated biomarkers will be used in this study to identify patients at high risk of developing EAC.

The study will recruit 100 patients across 5 sites (University of North Carolina, UHCMC, Cambridge, Medisch Centrum Alkmaar and Amsterdam). The specific aims of this pilot study are to:
1) Demonstrate that the international, multicenter team can work together,
2) Define the logistics of assaying biomarkers in real time such that in the future interventional trial, results could influence clinical decision-making, and,
3) Provide further data to inform a power calculation for the full trial.

Subjects enrolled in the study will complete a questionnaire gathering hypothetical willingness to be randomized to receive endoscopic treatment intervention (RFA) or surveillance endoscopy. Subjects enrolled in the Dutch centers will also complete a quality of life questionnaire, focusing on general health related quality of life, as well as health perception and fear of progression, including:
- The SF-36: measures generic quality of life. Its 36 items form eight subscales: physical functioning, social functioning, physical role-functioning, emotional role-functioning, vitality, bodily pain, mental health and general

health.
- The EORTC-QLQ-C30: is a cancer specific questionnaire with 30 items, evaluating five functional scales (physical functioning, emotional functioning, cognitive functioning, social functioning and role functioning); three general cancer symptom scales (fatigue, pain, nausea and vomiting) and five separate cancer symptoms (shortness of breath, insomnia, appetite loss, constipation, and diarrhea).
- The EORTC-QLQ-OES18: measures esophageal cancer-specific quality of life. This 18 item questionnaire measures 10 esophageal cancer specific symptoms: dysphagia, reflux, pain, eating problems, trouble speaking, coughing, trouble swallowing, choking, dry mouth and taste.18
- The Hospital Anxiety and Depression Scale: measures general anxiety and depression in 14 items.
- The Fear of Progression questionnaire Short Form: measures fear of cancer progression in 12 items.
- The Brief Illness Perception Questionnaire (Brief IPQ), a nine-item scale designed to rapidly assess the cognitive and emotional representations of illness.

Biopsy samples will be obtained from all subjects and tested for all biomarkers in the panel. Results of the biomarker panel will not be communicated to sites. Subjects with low grade dysplasia will be offered the option of receiving radiofrequency ablation (RFA) as part of routine care. Subjects with low grade dysplasia who agree to RFA will receive RFA as part of routine care. Subjects with low grade dysplasia who do not want to receive RFA will receive a surveillance endoscopy in 1 year as part of routine care. Subjects with no dysplasia will undergo regular surveillance endoscopy in 3-5 years as per routine clinical care.

The goals of this pilot study are to ascertain the proportion of subjects in the high risk arm, to demonstrate the plausibility of performing the biomarker analysis efficiently in a sizable group of patients, to demonstrate the feasibility of delivering the endoscopic intervention (RFA), to obtain 1 year pilot data regarding progression in the high risk arm for use in sample size calculations, and to document collaboration among the centers.

Study burden and risks

Patients with Barrett*s esophagus undergo regular endoscopic surveillance with biopsies to assess the presence of dysplasia. This surveillance is performed as per routine clinical care, recommended by current international guidelines. Every patient that undergoes a surveillance endoscopy with biopsies stands a minute risk of bleeding as a result of these biopsies. For this study, participating patients will only undergo esophagogastroduodenoscopies as per routine clinical care. During endoscopies performed for this study, however, additional biopsies will be obtained from the Barrett*s segment (for every 2 centimeters of the Barrett*s segment 2 additional biopsies will be obtained).

However, these additional biopsies will not significantly increase the bleeding risk for participating patients, as compared to the standard amount of surveillance biopsies that would have been obtained.
The endoscopic procedure might be 10-15 minutes longer in duration compared with a regular surveillance endoscopy.
Patients will be administered a small questionnaire, consisting of a single question. This questionnaire will address the hypothetical question if patients would be willing to participate in a study that randomizes patients to prophylactic treatment or regular endoscopic surveillance. Additionally, patients will be administered a quality of life questionnaire, measuring general health related quality of life, as well as health perception and fear of malignant progression. Completing this quality of life questionnaire will take no more than 15 minutes and this questionnaire does not include questions that will threaten the personal integrity of the patient.

Taking into account the minor burden and (additional) risks for patients associated with participation in this study, we find that execution of this research study is justified.

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

1) Able to read, comprehend, and complete the consent form.
2) Aged 18 to 80.
3) Diagnosed with at least 3 centimeters (>3cm) of Barrett*s esophagus AND no dysplasia or low grade dysplasia per review by pathologist.

Exclusion criteria

1) Pregnant women.
2) Current use of blood thinners such as coumadin, warfarin, heparin and/or low molecular weight heparin (requires discontinuation of medication 5 days prior to and 6 days after EGD).
3) Known bleeding disorder.
4) Status post partial or complete esophageal resection.
5) Current or past diagnosis of invasive esophageal cancer (previous intramucosal cancer is allowable, if removed by endoscopic mucosal resection with histologically confirmed negative lateral and deep margins).
6) Prior ablative therapy of the esophagus including prior radiofrequency ablation (RFA), photodynamic therapy (PDT), spray cryotherapy, and other ablation therapies. Prior endoscopic mucosal resection (EMR) is acceptable.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-08-2014
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	16-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL48802.018.14