A multicenter prospective cohort study comparing random biopsies with Wide-Area Transepithelial brush-Sampling (WATS) for surveillance of Barrett*s esophagus.;The WATS-EURO2 study

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We aim to study the rate of developing a biopsy-based diagnosis of high-grade dysplasia (HGD) and EAC in BE patients in a prospective cohort of 204 BE patients at high risk of progression (i.e. after endoscopic removal of visible lesions containing…

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

Summary

ID

NL-OMON53667

Source
ToetsingOnline

Brief title
The WATS-EURO2 study

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Barrett's esophagus, dysplasia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Onderzoeksgroep

Intervention

Keyword: Barrett's esophagus, Random biopsies, surveillance, WATS3D brush

Outcome measures

Primary outcome

- To study the concordance/discordance between random biopsies and WATS brushing collected at the baseline endoscopy and at follow-up endoscopies for the diagnosis HGD/EAC.

Secondary outcome

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To study the rate of progression to HGD/EAC in endoscopic biopsies (targeted or random) or endoscopic resection specimens during follow-up, after any prior WATS-positive-biopsy-negative diagnosis for HGD/EAC.

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To study the rate of HGD/EAC (biopsy diagnosed) in BE patients at high risk of progression (i.e. after endoscopic removal of visible lesions containing HGD/EAC and/or a diagnosis of LGD) and in BE patients undergoing standard endoscopic surveillance.

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To study the concordance/discordance between random biopsies and WATS brushing collected at the baseline endoscopy and at follow-up endoscopies for the diagnosis intestinal metaplasia.

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To study the rate of diagnosing intestinal metaplasia in endoscopic biopsies during follow-up, after a baseline WATS-positive-biopsy-negative diagnosis for intestinal metaplasia.

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To evaluate the rate of progression to HGD/EAC in endoscopic biopsies (targeted or random) or endoscopic resection specimens during follow-up, after a baseline diagnosis WATS3D brush crypt dysplasia diagnosis.

- To assess whether a positive finding of HGD/EAC using the WATS system is reproducible on subsequent endoscopies.

Study description

Background summary

Esophageal adenocarcinoma (EAC) is a disease with a poor prognosis at advanced stages. Identifying esophageal adenocarcinoma at an early stage allows for endoscopic treatment to reduce mortality and morbidity for these treated patients. Adequate surveillance strategies with appropriate risk stratification are therefore essential.

The current endoscopic surveillance protocol relies on systemic four-quadrant biopsy at 2-cm intervals of the BE segment, with additional targeted biopsies from visible abnormalities. Obtaining random biopsies is time consuming, and it results at best in sampling less than 5% of the BE surface area (2). Thus, significant sampling error is inevitable. Sampling the BE segment with a brush has the theoretical advantage of larger field sampling and might therefore increase the detection of dysplasia. =

In the European WATS study (*Euro-WATS1*) the WATS-system was compared with random biopsies in a cohort of patients referred with low-grade dysplasia (LGD), high-grade dysplasia (HGD) or early cancer after removal of all visible abnormalities. Eligible cases underwent random biopsies and WATS brushings after randomizing the order of sampling. The study showed no significant differences in the detection rate for HGD or EAC between random biopsies and

WATS brushings. The brush detected 39/48 HGD/EAC cases versus 30/48 for random biopsies (p=0.12). The value of the WATS-3D brush as an adjunct to random forceps biopsies however, was 48/147 vs 30/147; difference 12%, with a number needed to treat of 8. Moreover, the brush had a significantly shorter procedure time than random biopsies with a larger difference in longer BE segments. Another strength of the WATS brush, compared to random biopsies, is that it paves the way towards a preferred (future) trans-oral sampling instead of endoscopic sampling. Key element in the adjunctive value of WATS is the clinical relevance of *WATS-positive-biopsy-negative*. One may argue that the morphological changes of dysplasia-positive WATS samples clearly correspond to those defining dysplasia in biopsy samples and therefore are merely different representations of the same disease which is now diagnosed at an earlier stage. Others argue that the WATS-system, by being more sensitive to detect dysplasia, simply dilutes the disease reservoir with clinically less severe cases which do not warrant the same therapeutic approach as in cases with a biopsy based diagnosis of dysplasia. The natural history of *WATS-positive-biopsy-negative* cases can, however, not be investigated in the EURO-WATS1 study because this was a transversal study with no subsequent follow-up and with the vast majority of cases having undergone ablation therapy based on their referral diagnosis and/or outcome of the endoscopic resection of visible lesions. Another limitation of the EURO-WATS1 study was the relatively high rate of WATS brushings that were deemed ineligible for assessment of the smears. In the study 23/172 (13%) of cases had suboptimal WATS samples, despite the fact that the corresponding cellblocks showed adequate cellularity.
A second European WATS study (*WATS EURO 2 study*) will be performed in which, after the baseline endoscopy with WATS brushing and random biopsies, endoscopic follow-up is continued until a biopsy-based diagnosis of HGD or cancer is made. The WATS EURO 2 study will therefore allow us to study the natural history of WATS-positive-biopsy-negative cases, will enable us to re-evaluate the role of the WATS-3D brush as a potential substitute for random sampling, after optimizing sample collection and preparation in the study. Finally, the samples collected in this study will also allow us to perform future biomarker studies on both the brush and biopsy material, to find the best sampling method for biomarker risk stratification in the future.

Study objective

We aim to study the rate of developing a biopsy-based diagnosis of high-grade dysplasia (HGD) and EAC in BE patients in a prospective cohort of 204 BE patients at high risk of progression (i.e. after endoscopic removal of visible lesions containing HGD/EAC and/or a diagnosis of low-grade dysplasia (LGD)) as well as in 204 BE patients with a non-dysplastic BE (NDBE) undergoing standard BE surveillance. In these patients we will combine biopsy sampling with WATS at baseline and all follow-up endoscopies during a 3-year follow-up period. This will allow us to study the natural history of WATS-positive-biopsy-negative-cases and of WATS-specific outcomes such as basal-crypt dysplasia. The study also allows us to collect specimens for future

biomarker studies that may help to predict progression to HGD/EAC in the absence of morphological features of dysplasia.

Study design

This is an international multicentre, prospective study in 11 European medical centres with a tertiary referral function for endoscopic detection and treatment of early Barrett*s neoplasia.

Study burden and risks

Our study population consists of patients with either a flat Barrett's esophagus (BE) with low grade dysplasia (LGD) or high grade dysplasia (HGD) or a flat BE after removal of visible lesions with LGD, HGD or early carcinoma. At baseline, an imaging endoscopy will be performed and after confirmation of absence of visible lesions, WATS brushing of the Barrett*s segment will be performed followed by random 4 quadrant mucosal biopsies every 2 cm. If the biopsies subsequently show HGD or esophagus adenocarcinoma (EAC), the patient has reached the study endpoint and will be managed according to the institution*s standard of care. If the baseline biopsies show LGD, indefinite (IND) or non dysplastic BE, patient will not undergo ablation therapy and will be scheduled for endoscopic follow-up. In case of prior endoscopic resection for a visible lesion containing HGD/EAC the follow-up schedule consists of endoscopies at 3, 6, 9, 12, 18, 24 and 36 months. For patients with a referral diagnosis of LGD, the follow-up consists of endoscopies at 6 and 12 months and annually thereafter

It is undisputed that patients referred with LGD, HGD or early cancer should have all visible lesions removed by ER techniques. In general, the endoscopic resection specimen will then show a diagnosis of HGD or early cancer. Follow-up studies have shown that the chance of the development of metachronous HGD/EAC in the remaining BE segment is about 10% per year. Therefore ablation therapy is advised for the remaining BE segment. The same 10% annual progression rate to HGD/EAC applies for patients with a confirmed diagnosis of LGD. For this category guidelines suggest that ablation therapy may be indicated for cases in which this diagnosis, apart from being confirmed by an expert pathologist, is also reproduced in subsequent endoscopies. The actual decision to ablate the remaining segment after endoscopic resection of HGD/EAC or to prophylactically ablate for LGD, is made on a per patient basis in which age and comorbidity are important factors to regard. Follow-up studies after ER of visible lesions containing HGD/EAC have found that metachronous lesions are found to be endoscopically treatable with the majority of patients not developing recurrent disease. The same holds for prophylactic ablation in cases with LGD: a significant proportion of patients will not progress or not even manifest their baseline diagnosis of LGD upon follow-up. In the SURF-study, 30% of the

LGD-patients randomized to endoscopic surveillance did not have their LGD diagnosis reproduced during 4 subsequent endoscopies in 3-years follow-up and all cases that progressed to HGD/EAC were diagnosed at an endoscopically curable stage.
Furthermore, RFA still is accompanied by complications such as esophageal stenosis and requires multiple hospital visits. Even upon complete endoscopic eradication of all Barrett*s mucosa, guidelines still dictate endoscopic surveillance after ablation virtually at the same frequency as for Barrett*s cases that are not prophylactically treated.
Therefore, keeping Barrett*s patients under strict endoscopic surveillance after ER of visible lesions or for flat LGD is a very acceptable treatment strategy that does not divert from current guidelines.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patients age: >= 18 years
- BE with a circumferential extent of >=2cm and a total maximum extent of <=18cm (in case of prior ER: BE length is measured after ER). Or a circumferential extent of 0-1 cm with a maximum extent of >=4cm.
- Cohort 1: Patients referred for work-up of IND, LGD, HGD or low-risk cancer (m1 to sm1, without lympho-vascular invasion and poor differentiation), either diagnosed in random biopsies or in prior endoscopic resection specimen within 18 months prior to baseline endoscopy
- Cohort 2: Patients with known BE without a diagnosis of dysplasia in the last 18 months, enrolled in endoscopic surveillance programs
- Ability to give written, informed consent and understand the responsibilities of participation

Exclusion criteria

- Patients with visible lesions according to the Paris classification at the time of the WATS and random biopsy testing (prior endoscopic resection is allowed)
- Patients with high-risk cancer after endoscopic resection: either sm2/3 invasion, poor differentiation, lympho-vascular invasion, or R1 vertical resection margin
- Patients within six weeks after endoscopy with biopsies and/or ER
- History of esophageal or gastric surgery other than Nissen fundoplication
- History of esophageal ablation therapy
- Presence of esophageal varices
- Subject has a known history of unresolved drug or alcohol dependency that would limit ability to comprehend or follow instructions related to informed consent, post-treatment instructions, or follow-up guidelines

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-11-2022
Enrollment:	239
Type:	Actual

Ethics review

Approved WMO Date:	01-11-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-06-2023
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	NL81868.018.22