SUrveillance of PREMalignant stomach – individualized Endoscopic follow-up

The SUPREME Project

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SUMMARY

Introduction: Gastric atrophy and intestinal metaplasia are the principal precursors for gastric cancer and, therefore, are considered gastric premalignant conditions. Although current guidelines recommend surveillance of individuals with these conditions, the best method for its identification and staging (histological vs endoscopy) and the best time schedule for follow-up are still controversial. **Aims:** To describe for the first-time patients with premalignant conditions both clinically (familial history), histologically (OLGA/OLGIM; complete/incomplete metaplasia) and endoscopically (EGGIM) using validated scales and to describe evolution of these parameters through time. To estimate prospectively the gastric cancer risk according to EGGIM stages. To define the best endoscopic surveillance follow-up for the several stages considering clinical, histological and endoscopic factors. **Methods:** Multicenter study involving different gastroenterology departments from several countries. Consecutive patients older than 45 years scheduled for upper endoscopy in each of these centers will be evaluated by High-Resolution-endoscopy with virtual chromoendoscopy and EGGIM will be calculated. Guided biopsies (if areas suspicious of IM) and/or random biopsies (if no areas suspicious of IM) in antrum and corpus will be made and OLGA/OLGIM stages calculated. Patients will be evaluated in clinical consultation and database will be fulfilled. All patients will be eradicated for *Helicobacter pylori* infection if positive. At that occasion, all the patients with EGGIM≥5 and/or OLGA III/IV and/or OLGIM III/IV will be randomized for yearly (12 to 16 months) or every three years (32-40 months) endoscopic follow-up during a period of 6 years (SUPREME I). Endoscopic observational follow-up will be scheduled for patients with EGGIM 1-4 and OLGIM I/II at 3 and 6 years (SUPREME II). For individuals with no evidence of IM (EGGIM 0 and OLGIM 0, OLGA 0-II) a follow-up endoscopy 6 years after will be proposed (SUPREME III). **Expected results:** This study will help us to define which clinical factors influence gastric cancer risk and which is the best way to determine advance gastric premalignant conditions (histology or endoscopy or both). Moreover, a precise incidence rate of dysplasia/neoplasia among patients with gastric preneoplastic conditions will be established and an individualized endoscopy follow-up for these patients may be reached. Furthermore, an improvement of the definitions and current guidelines can be expected.

INTRODUCTION

Gastric cancer (GC) is still a major problem in the world, being ranked 5th in incidence and 3rd in cancer-related mortality worldwide [1]. Intestinal-type gastric adenocarcinoma represents the final outcome of the inflammation–atrophy-metaplasia–dysplasia–carcinoma sequence, known as the Correa cascade [2-6]. *Helicobacter pylori* (Hp) is considered the initiator of this cascade, however, less than 1% of the patients infected develop cancer. Nevertheless, almost 1/3 of the infected patients will develop chronic atrophic gastritis and intestinal metaplasia (IM), that are considered precancerous conditions because they confer by themselves a risk for the development of gastric cancer and constitute the background in which dysplasia and adenocarcinoma may occur [3, 7-9].

Advanced stages of atrophic gastritis meaning significant atrophy or IM (as the best and more reliable marker of atrophy) particularly if affecting both antral and corpus mucosa are considered the main risk factors for cancer (as opposed to initial stages of gastritis). However, even though diverse efforts were made to stage or classify individuals according to the severity and/or extension of these changes the best method for risk stratification is still controversial. Endoscopic biopsies of antrum and corpus appear to be the best method for staging of gastritis. The OLGA (Operative Link for Gastritis Assessment), or OLGIM (Operative Link for Gastritis assessment based on Intestinal Metaplasia) systems have been proposed for staging of atrophy and IM, respectively, and showed to be good predictors of gastric cancer risk. Since the staging of atrophy needs the grading of the severity of gland loss and this presents a poor inter- and intra-observer agreement, OLGIM appears to be better whenever staging of mucosal changes is aimed [10-15]. The problem with these histological grading systems is that atrophic changes of the mucosa may be unevenly distributed throughout the mucosa meaning that 1) important changes may be missed by random biopsies and 2) in different time evaluations the grading may be different only because biopsies were done in different places of the mucosa.

With this in mind in theory an endoscopic evaluation will be better for a correct staging of gastritis/preneoplastic conditions by seeing all the mucosa (not depending only in small fragments of the mucosa). Nevertheless, classically the yield of conventional endoscopy to stage gastritis was suboptimal what compromised endoscopy without biopsies as a valid method for gastritis staging. Our group created a classification of endoscopic features with high-resolution and virtual chromoendoscopy that showed to be reliable and accurate for the diagnosis of IM and dysplasia/cancer [16]. Moreover, we created a scale for

Endoscopic Grading of Gastric Intestinal Metaplasia (EGGIM) that showed strong correlation with OLGIM stages and that we recently validated in multicenter study. We have also shown retrospectively that EGGIM staging was associated to gastric cancer risk and to the risk of new lesions after endoscopic resection of early gastric cancer [17, 18].

Clinical factors like family history, smoking and alcohol, may also influence gastric cancer risk but they rarely were evaluated prospectively.

Recognizing the importance of family history but more importantly of atrophic gastritis in the development of gastric cancer, current guidelines recommend endoscopic follow-up of patients with these conditions, even though the timing for endoscopic evaluation relies in scarce evidence and mostly based in expert opinion.

We believe that this project can help to improve the estimates of current guidelines and potentially redefine the "gold-standard" of ‘a at risk profile’ for gastric cancer.

AIMS

Primary aims:

1. To estimate prospectively which is the incidence rate for dysplasia/cancer among individuals with different stages of gastric precancerous conditions defined both endoscopically and histologically;
2. To define the best endoscopic follow-up for the different patients with gastric precancerous conditions considering clinical, endoscopic and histological aspects.

Secondary aims:

1. To establish prospectively for the first time the dysplasia/gastric cancer risk among the different EGGIM stages;
2. To define different groups of patients with premalignant gastric conditions based on endoscopy and histology simultaneously;
3. To evaluate the progression/regression of gastritis through time, for the first time considering both endoscopy and histology;
4. To define the need of random biopsies in patients under surveillance because of gastric premalignant conditions (based on the prevalence of dysplasia without endoscopic features suggestive of that);
5. To determine the effect of *H. pylori* eradication in endoscopic and histological staging.

METHODS

Setting and study design

- A **Prospective randomized multicenter trial**;
- Centers:
    1. International gastroenterology departments Europe and America
        - Access to HR-scopes with virtual chromoendoscopy (NBI, BLI or iscan);
        - Endoscopists must be experienced in virtual CE diagnosis (at least 100 previous virtual CE procedures/diagnosis in the stomach);
        - Participation granted if at least 100 patients per center complete the protocol, 25 of these in the randomization arm (2 authors per 50 patients, maximum of 6 authors per center);
    2. Confirmed centers (n=15) per country:
        - Portugal:
            - Portuguese Oncology Institute of Porto
            - Portuguese Oncology Institute of Coimbra
            - Porto University Hospital Centre
            - Vila Nova de Gaia and Espinho Hospital Centre
            - Braga Hospital
            - Guimarães Hospital
            - Beatriz Ângelo Loures Hospital
        - Spain:
            - Navarra Hospital
        - France:
            - University Hospital of Nantes
        - Italy
            - Sant´Andrea University Hospital
        - Romania
            - Mures Hospital
        - Poland
            - Centre of Oncology Institute Warsaw
        - England

- Nottingham University Hospitals
- Brasil
  - University Hospital of Minas Gerais
- USA
  - Los Angeles Hospital

Initial patients' selection

- Individuals **older than 45 years old** scheduled for upper GI endoscopy with indication for gastric biopsies (clinical or endoscopic findings), including those with known gastric pathology (e.g. auto-immune gastritis) or premalignant conditions (e.g patients under surveillance because of atrophic gastritis);
- **Exclusion criteria (1st phase, clinical)**: History of previous gastrectomy; History of endoscopic resection of neoplastic lesion; history of previous gastric dysplasia (even with no detectable lesion); hereditary syndromes that increase gastric cancer risk (PAF; Lynch); serious comorbidities (ASA 3 or more); medication with anticoagulants.

Endoscopic and biopsies protocol

- In all patient's complete gastroscopy first with White light and then with virtual CE will be made; all ESGE major quality parameters (including time) will be recorded;
- EGGIM will be calculated according to what previous described [17] [18];
- If EGGIM 0 (no endoscopically apparent IM) biopsies will be made in antrum, incisura and corpus according to Sydney-Houston protocol (at least two fragments antrum and corpus and one in the incisura);
- If EGGIM $\geq$ 1 guided biopsies of suspicious areas of IM should be made replacing the random biopsies in that particular area (e.g. if IM in lower curvature but not in the greater curvature of the antrum then you should do targeted biopsies in the lower curvature and random in the greater curvature; if IM in both antrum areas then you should only do targeted biopsies; in each case at least two antrum fragments should be taken and biopsies should be sent in the same antrum vial);
- Antrum, incisura and corpus fragments should be sent in 3 separate vials;

- **Exclusion criteria (2nd phase, endoscopic)**: upper GI tract neoplasia; hemorrhagic gastritis; upper GI tract varices; suspicious area of gastric superficial lesion/dysplasia; impossibility to complete biopsy protocol; ***not exclusion criteria****: benign gastric ulcer, gastric erosions, papules or polyps (in these cases gastric biopsies/resection of these areas should be sent in separate vials); esophagitis; duodenal erosions or ulcers.*

Patient inclusion in the surveillance trial and randomization

- All patients that complete the endoscopy and biopsy protocol will be evaluated 2 to 6 weeks after in a clinical consultation.
- To all patients with Hp infection, eradication will be offered and confirmed by non-invasive methods.
- Patients with EGGIM $\geq$ 5 or OLGA/OLGIM III/IV (**premalignant stomach group – SUPREME I**) will be randomized to endoscopic surveillance every one (12 to 16 months) or three years (32-40 months);
- Patients with EGGIM 1-4 (and not higher) and/or OLGIM I/II (and not higher) and OLGA stage not higher than II will be proposed for endoscopy at 3 and 6 years (**initial atrophic gastritis group – SUPREME II**);
- Patients with EGGIM 0 and OLGA 0/I/II; and patients with EGGIM 1-3 with biopsies negative for IM (OLGIM 0) and OLGA not higher than II will be proposed for endoscopy at 6 years (**non-premalignant stomach group – SUPREME III**).
- All patients will be included in the surveillance trial and clinical, endoscopic and histologic data (including type of IM) will be fulfilled on an online database (see attachment with all the variables being considered);
- Randomization to the different arms in the premalignant stomach group will be made by the computer software after all the variables have been fulfilled:

Subsequent Endoscopic and biopsies follow-up

- In all patient's complete gastroscopy first with White light and then with virtual CE will be made;
- Suspicious lesion with dysplasia/cancer will be biopsied 1-2 fragments in a different vial; if an irregular area of mucosa (pattern C) with no clearly defined lesion then 1-2 guided biopsies fragments will be taken and sent in a different vial;

- EGGIM will be calculated according to what previous described [17] [18];
- If EGGIM 0 (no endoscopically apparent IM) biopsies will be made in antrum, incisura and corpus according to Sydney-Houston protocol;
- If EGGIM 1 or more guided biopsies of suspicious areas of IM should be made replacing the random biopsies in that particular area (e.g. if IM in lower curvature but not in the greater curvature of the antrum then you should do targeted biopsies in the lower curvature and random in the greater curvature; if IM in both antrum areas then you should only do targeted biopsies; in each case at least two antrum fragments should be taken and biopsies should be sent in the same antrum vial);
- Antrum, incisura and corpus fragments should be sent in 3 separate vials;

Subsequent clinical evaluation and follow-up

- All patients that complete 2nd endoscopy and biopsy protocol will be evaluated 2 to 6 weeks after in a clinical consultation.
- Endoscopic and histologic data of the second/third procedure will be fulfilled on an online database.
- If no lesion and no irregular area were seen and random biopsies do not present dysplasia then the patient maintain the previous defined endoscopic follow-up (1 or 3 years).
- If an irregular area was seen (with no clearly defined lesion) but guided biopsies negative for atypia/dysplasia then the patient maintain the previous defined endoscopic follow-up (1 or 3 years).
- If an irregular area was seen (with no clearly defined lesion) and guided biopsies present atypia/dysplasia or if random biopsies of any gastric area present dysplasia then outcome 1 was reached and patient follow-up should respect current guidelines (endoscopy 3-6 months if high-grade and 6-12 months if low-grade dysplasia) [19].
- If a suspicious superficial lesion was seen and biopsies present atypia, dysplasia or cancer then staging and resection of the lesion will be made; Only after resection and/or complete staging, the outcome will be assumed according to the following:
    1. Outcome 1: lesion presenting only dysplasia (low or high grade)
    2. Outcome 2: lesion presenting carcinoma

- Outcome 2.1 intramucosal carcinoma with low-risk criteria ("curative" criteria)
- Outcome 2.2 submucosal, diffuse type or intramucosal carcinoma with high-risk criteria ("non-curative" criteria)
- Outcome 2.3: advanced cancer (more than previous, implying impossibility of endoscopic resection)

End of study

- The study is designed for 6 years, when all data will be analyzed and results presented;
- Patient follow-up will be completed at 6 years or when one of the outcomes is reached;
- Continuation of the study after 6 years is possible and predictable and will be decided after data analysis.

Subprojects

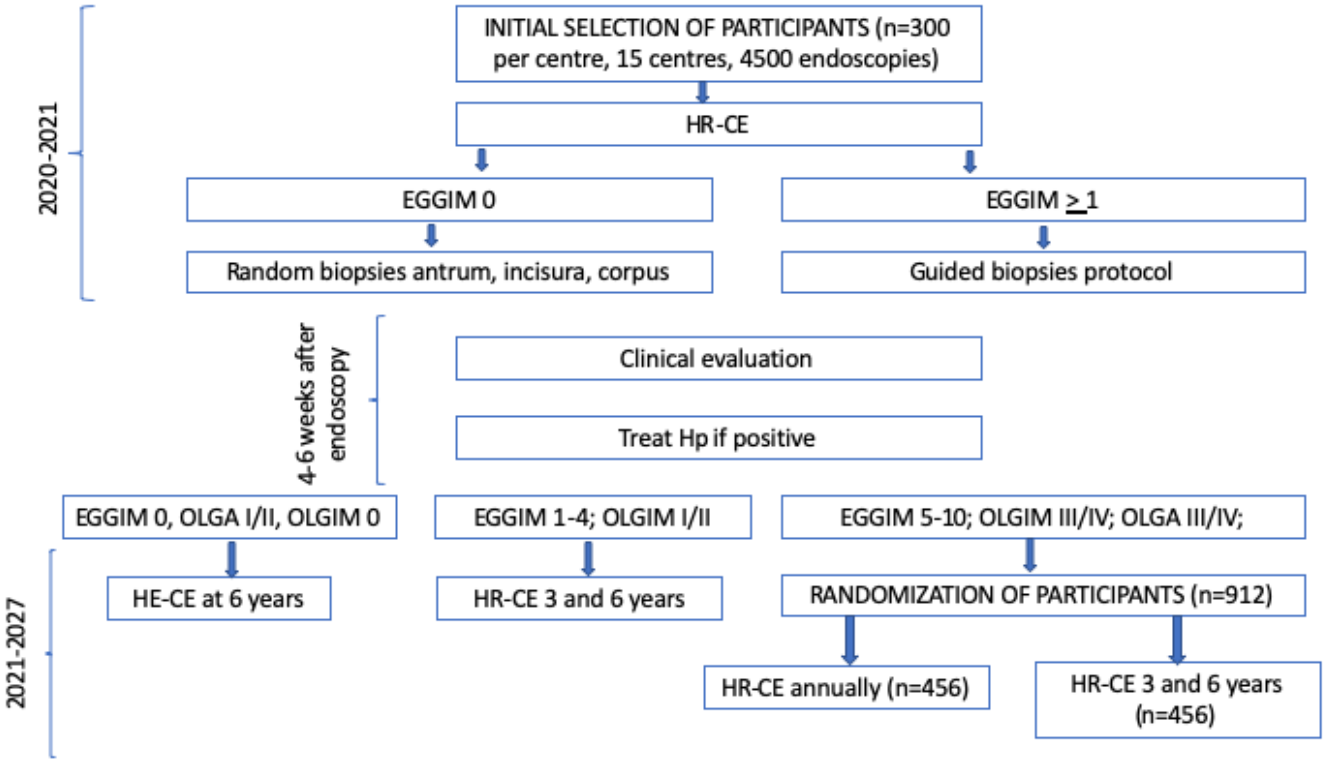
- In order to clarify the natural history of other specific situations not considered in the main project two additional groups of patients will be followed-up prospectively:
    1. Patients with persistent Hp gastritis and non-premalignant stomach (Patients with EGGIM 0 and OLGA 0/I/II; and patients with EGGIM 1-3 with biopsies negative for IM (OLGIM 0) and OLGA not higher than II);
        - We suggest endoscopic follow-up in 3 (if family history of gastric cancer) to 6 years (if no family history of gastric cancer) in these group of patients;
        - We predict 12 years follow-up of these patients (two to four follow-up endoscopies);
        - Data analysis after 12 years follow-up;
    2. Patients that in follow-up reach outcome 1 (dysplasia) but with no clearly defined lesion for resection (small irregular areas with dysplasia) or random biopsies with dysplasia; Natural history of these patients is not clearly defined since in previous studies many of them might already present a lesion at the time of diagnosis.

        - We suggest endoscopic follow-up accordingly to guidelines, 3-6 months if high-grade dysplasia and 6-12 months if low-grade dysplasia;
        - If after two negative endoscopies with no dysplasia/lesion, then we suggest endoscopy in 1 (if family history) to 3 years (if no family history).
- In both of these subprojects the endoscopic and biopsies protocol will be the same of the main project.

Sample size calculation (SUPREME I)

- We predict that the shorter interval of follow-up (1 year) will allow the diagnosis of lesions in a less advanced stage (more outcome 1 – dysplasia - and lower or inexistent outcome 2 - cancer);
- We anticipate that 1% of patients at risk per year will develop one of the outcomes (6% at the end of the 6-year follow-up) and that most of outcomes 2 (cancer) will be reached in the longer period of follow-up (3 year) for a 6-year total of 1% outcome 2 in the 1-year follow-up group (and 5% outcome 1) and 5% in the 3-year follow-up group (and 1% outcome 1);
- For showing this 4% incidence difference between the two groups (4% more incidence of outcome 2 in the 3-year follow-up group) at the end of follow-up (6 years) with an alpha level of 0.05 and a power of 90% we calculate that at least 760 patients will have to be randomized (380 per group of follow-up);
- Predicting 20% of lost to follow-up and/or necessity to anticipate endoscopy in some patients (because of symptoms/clinical reasons) we calculate that additional 152 patients will have to be randomized for a **total of 912 patients (456 per group of follow-up)**;
- We predict participation of at least 15 centers and, so, **each center must include at least 62 patients in the randomization**;
- Since inclusion of the patients in the randomization trial will only be known after an initial endoscopic and histologic evaluation, and predicting that only 20-25% of the patients will have criteria for inclusion in SUPREME I **each center must include at least 300 patients in the study (these patients will be included in SUPREME II and III)**.

Flowchart (SUPREME I, II AND III)



DISCUSSION/EXPECTED RESULTS

This prospective study will be the first study to investigate the natural history of gastric premalignant conditions in this new age of HR imaging, so based not only on random biopsies (as it was described before) but based simultaneously in HR endoscopy/chromoendoscopy and guided biopsies/histology. It has the potential to completely redefine the natural history of this disease. Moreover, it can help us to define which clinical factors influence most gastric cancer risk and which is the best way to determine and stage advance gastric premalignant conditions (histology or endoscopy or both). Moreover, a precise incidence rate of dysplasia among patients with gastric preneoplastic conditions/lesions will be established and an individualized endoscopy follow-up for these patients may be reached. Furthermore, an improvement of the definitions and current guidelines can be expected.

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