Title: Endoscopic surveillance in patients with serrated polyposis syndrome and low-risk of advanced neoplasia.

NCT:

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STUDY PROTOCOL

SCIENTIFIC BACKGROUND:

Colorectal cancer (CRC) is the most frequent neoplasm in developed countries considering both sexes and is the second in terms of cancer mortality. The incidence of the CRC is increasing in all developed countries. Detection of precancerous lesions (colon polyps) or malignant lesions (adenocarcinoma) in early stages in screening programs improves the prognosis and decreases the mortality of these patients. Serrated polyposis syndrome (SPS) is the most common colorectal polyposis syndrome and is characterized by the combination of large and/or numerous serrated lesions (SL) throughout the colorectum. There are three different types of SLs described: hyperplastic polyps (HP), sessile serrated lesions (SSL) and traditional serrated adenomas (TSA).

In 2010 the world health organization (WHO) defined the clinical criteria for the SPS diagnosis: criteria I, any patient with ≥ 5 serrated lesions proximal to the sigma, two of them> 1 cm in size; criteria II, any first degree relative of a SPS patient with at least one serrated lesion; criteria II, any patient with ≥20 serrated lesions throughout the colon. This criteria were reviewed in 2019 and criteria II was eliminated. The new criteria are: criteria 1, any patient with ≥ 5 SL proximal to the rectum, all ≥5 mm in size, with at least 2 lesions ≥10 mm in size; criteria 2, any patient with >20 SL of any size distributed throughout the colon, with ≥5 lesions proximal to the rectum.

In recent years, a new pathway in the development of colorectal adenocarcinoma have been described, the "serrated pathway". It is associated with mutations in BRAF and KRAS genes, the existence of hypermethylation in the promoter regions "CpG island" and microsatellite instability phenotype caused by methylation of the MLH-1 gene. This new pathway has a faster progression from the serrated polyp to the CRC in comparison with the classic "adenoma-carcinoma" pathway, hence the importance of detecting and removing these lesions in patients with SPS.

CRC prevalence in patients diagnosed with SPS is 15-35%, according to different studies, and the probability at 5 years of developing a CRC is around 1.3-1.9%. During surveillance, the incidence of advanced neoplasia (advanced adenoma or advanced serrated lesions) at 3 years is 13% for adenomas and 42 for serrated lesions. Risk factors for developing CRC and advanced neoplasia have been described in several studies. One of these factors is the SPS criteria 2, which has been demonstrated as a low risk of CRC and advanced neoplasia during surveillance of SPS patients. Detecting more than two sessile serrated lesions proximal to the spleenic flexure, one sessile serrated lesion with high grade of dysplasia and the detection of advanced neoplasia in

previous colonoscopies, are all risk factors of developing advanced neoplasia during surveillance. A recent multicentre prospective study established SPS patient surveillance according to lesions detected at last colonoscopy. Individuals with at least one advanced adenoma, an advanced serrated lesion or more than 5 relevant lesions (sessile serrated lesions, adenomas of any size or hyperplastic polyps more than 5 mm) were followed at one year. Patients with no lesions mentioned before were followed at 2 years with colonoscopy. Advanced neoplasia incidence in 2 years recommendation surveillance was 15.6% compared with 24.4% in the 1 year recommendation surveillance. CRC cumulative 5 years incidence was 1.3%. Regarding SPS type, the 5 years advanced neoplasia incidence was lower for patients with SPS criteria III of 2010 (26%) than for patients diagnosed with criteria I (53%) or criteria I and III (59%). In this study patients starting their surveillance with clearing phase achieved (clear colon of all polyps ≥5mm and all polyps with the optical aspect of adenoma, TSA or SSL) were at low risk of advanced neoplasia than patients without this phase achieve prior to study inclusion (HR: 0.64; $p<0.047$).

With all the above described, it can be define a SPS patient with low risk of advanced neoplasia during surveillance: those patients with SPS criteria 2, with clearing phase achieved and without any advanced lesion or less than 5 relevant lesions at last colonoscopy.

The Spanish Society of Gastroenterology (AEG) recommends surveillance with colonoscopies in 1-3 years interval for SPS patient, as it does the European Society of Digestive Oncology (ESDO). The European Society of Gastrointestinal Endoscopy (ESGE) recommends surveillance at 1 o 2 years depending on the last colonoscopy findings, annually in case of any advanced adenoma or serrated lesion or ≥5 relevant lesions (adenomas, SSL or HP≥5mm) were removed, and two surveillance in all other cases. The British Society of Gastroenterology (BSG) recommends annually surveillance for SPS patients until all serrated lesions ≥ are removed, and then 2 year-surveillance. All these Guidelines mention the limited evidence to support their recommendations and the need for prospective studies to evaluate them. As well many authors have expressed the possibility of extending the surveillance to 3 or even 5 years in low risk patients.

The aim of the study is to determine if SPS patients with SPS criteria 2, with clearing phase achieved and without any advanced lesion or less than 5 relevant lesions at last colonoscopy have the same advanced neoplasia incidence in the surveillance colonoscopy at 2 or 3 years.

OBJECTIVES:

Principal:

- Evaluate de incidence of CCR and advanced neoplasia in SPS patients with low risk factors of advanced neoplasia during surveillance.

Secondary:

- Compare the incidence of advanced neoplasia between patient surveillance with colonoscopy at 2 and 3 years.
- Describe low risk factors of advanced neoplasia in SPS patient in our environment.
- Identify a group of patients with SPS and low risk of advanced neoplasia.

METOHDS

This is a prospective, randomized (1:1) and multicenter study, in Spanish national hospitals, with SPS patients diagnosed according to the reviewed WHO criteria in 2019, in a surveillance program and who meet all the inclusion criteria and no exclusion criteria.

Inclusion criteria:

- Patients aged 18 years or older that fulfil only WHO criteria 2 of SPS and did not fulfil WHO criteria 1.
    - Criteria 1: any patient with ≥ 5 SL proximal to the rectum, all ≥5 mm in size, with at least 2 ≥10 mm in size.
    - Criteria 2: any patient with >20 SL of any size distributed throughout the colon, with ≥5 lesions proximal to the rectum.
- Patients with a previous complete colonoscopy with adequate bowel preparation and with all lesions >5mm been resected ("clearance colonoscopy), after the diagnostic of SPS.
- Nor advanced adenoma or serrated lesions at prior colonoscopy, and also either more than 5 relevant lesion (adenoma, SSL or PH>5mm) at prior colonoscopy.

Exclusion criteria:

- Patients with no inform consent or who do not agree to participate in the study.
- Patients with total or partial colectomy.

- Patients with other CCR predisposing syndromes with germinal mutation (Familial adenomatous polyposis, Lynch syndrome, Peutz-Jehgers syndrome, Cowden syndrome, Juvenile polyposis syndrome…).
- Patients with chronic inflammatory bowel disease.
- Patients with coagulation disorders.
- Fragmented lesion or submucosal invasive lesion at last colonoscopy.
- Inadequate colon preparation: any segment of the colon with <2 points in Boston Scale (BBPS).

Patients selected for the study will be randomised in two groups for the surveillance: group 1, surveillance with colonoscopy in two years; group 2, surveillance with colonoscopy in three years. Randomization will be done at the database program (RedCAP).

All colonoscopies will be performed with high definition (HD) system and it will be the choice of the endoscopist whether to use chromoendoscopy with indigo carmine o virtual chromoendoscopy. Protocol bowel preparation will be recommended by each centre. Sedation will be prescribed and decided by the endoscopist during the examination.

Data from all the resected and visualized lesions during the colonoscopy will be collected on the database. A pathologist familiarized with serrated lesions will be in charge of the sample analysis. Serrated lesions will be classified attending de WHO criteria for serrated lesions. The investigators define “advanced adenoma” as adenomas ≥10 mm with villous histology and/or with high grade of dysplasia (HGD). We define “advanced SL” as any SL ≥10mm and any SL with dysplasia. The investigators define “advanced neoplasia” as any CRC, any advanced adenoma or advanced SL.

Quality of bowel cleansing will be graded by each endoscopist following the Boston Bowel Preparation Scale. This scale evaluates each segment (ascending colon, transverse colon and descending colon) of the following form: 0 = segment of colon whose mucosa cannot be seen due to the existence of solid stools that cannot be eliminated; 1 = mucosa portion of a colonic segment that can be seen, but other areas of the colonic segment are not seen, either due to the presence of dirt, feces or opaque liquid; 2 = existence of small amount of dirt, small fragments of stool and / or opaque liquid, but the mucosa of the colonic segment can be seen well; 3 = all the mucosa of the colonic segment can be seen well without residual dirt, small traces of stool or opaque liquid. Patients with inadequate preparation (when in any segment the score is 0 or 1, or the total score is less than 6) will be excluded from the study.

During colonoscopy all complications as post-polypectomy bleeding, perforation or cardio-respiratory events will be registered. Those complications will be considered if surgery or hospital admission is required.

SAMPLE SIZE CALCULATION

This is a randomized controlled study for evaluating a non inferiority strategy in the surveillance of SPS type 2 patients, between colonoscopy in 2 years and colonoscopy in 3 years, with the incidence of advanced neoplasia as the principal aim of the study. In the study from the Netherlands, Bleijenberg and col., the incidence of advanced neoplasia in patients at 2 years surveillance was of 15%. The investigators assume an acceptable increase of advanced neoplasia at 3 years surveillance of 25%, so the margin for no inferiority is 10% between the two groups. Accepting the type I error with an unilateral contrast of 0.025, beta risk of 0.2 (power 80%) and considering a 10% of lost patients, 69 patients in each group (136 in total) are needed to detect significance differences between the two groups.

STUDY VARIABLES:

- Demographic variables: Hospital, identification number (number assigned to each hospital and consecutive number of each patient), date of birth, sex, SPS criteria (according to WHO classification and actualized in2019: 1 or 2), date of the last colonoscopy, number and type of lesions resected at the last colonoscopy, number of previous colonoscopies, number of polyps removed so far (low risk, high risk and serrated lesions), colon surgery (yes/no) and type of surgery (right colectomy, left colectomy, low anterior resection, segmental colectomy or others), smoker (yes/no/prev).

- Variables of the procedure: date of the procedure, bowel preparation according to BBPS scale [14], study arm (Colonoscopy in2 years/Colonoscopy inn3 years), number and description of lesions resected during the procedure describing its size, shape according to Paris classification[15], location of the lesions, distance to the anal margin. Inspection time in each exploration (with stopwatch and without counting the therapeutic moments). Complications during the procedure (bleeding, perforation or cardio-respiratory events).

STATISTICAL CONSIDERATIONS AND STATISTICAL ANALISIS PLAN

Numeric variables will be collected as integer number; they will be presented as mean and standard deviation in case of a normal distribution and compared with a Student´s t test. Categorical variables will be collected associated with an integer starting from cero; they will be presented as frequencies and compared with the Chi Square test. The risk of advanced neoplasia or CRC after 2 year colonoscopy surveillance will be compared with the risk of advanced neoplasia and CRC after 3 year colonoscopy surveillance using logistical regression analysis and expressed as Odds Ratio (OR).

Risk factors identified previously will be assessed in univariate and multivariate Cox Regression analysis, adjusted by age, gender and smoking status). They will be presented as Hazard Ratio (HR) with 95% of confidence interval. Statistical analysis will be performed with SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA).

NECESSARY RESOURCES:

Colonoscopies and polypectomies will be done in the usual clinical care practice. This protocol does not require additional funding. The explorations will be carried out by the researchers who are staff doctors of the Digestive Endoscopy Units. The effort, the minimum marginal expenses that may lead to the prolongation of the exploration and the collection of data will be assumed by the researchers and the Digestive Endoscopy Units.

ETHICAL CONSIDERATIONS:

This protocol follows the ethical principles of non-malfeasance, beneficence, autonomy and justice included in the Declaration of Helsinki (last update, Seoul 2008) 17, as well as in law 41/2002 on patient autonomy18 and research law 14/2007 biomedical19. The personal and clinical data of the patients will be anonymized.

INFORMED CONSENT FORM

Endoscopic surveillance in patients with serrated polyposis syndrome and low-risk of advanced neoplasia.

Colon cancer is currently the most common cancer in developed countries taking women and men together, and ranks second in cancer mortality. Detection of precancerous lesions in the colon (polyps) or malignant lesions (adenocarcinoma) in early stages of the disease improves prognosis and decreases patient mortality.*

Serrated polyposis syndrome is defined by multiple serrated or relevantly sized polyps throughout the colon. Other polyps may also be found in the colon such as adenomas and also have malignancy potential. The histological characteristics and size of these adenomas or serrated polyps make some of them considered at increased risk of malignancy (these are called advanced serrated adenomas or polyps). A recent study has shown that patients with serrated polyposis syndrome who do not have advanced serrated adenomas or serrated polyps in the last colonoscopy, have a low risk of developing advanced lesions within 2 years of follow-up (15%) and a very low incidence of colon cancer (less than 1.5%) at 5 years surveillance.

The Spanish Association of Gastroenterology (AEG) recommends monitoring patients with Serrada Polyposis Syndrome every 1 or 3 years with colonoscopy. Similarly, the European Society of Digestive Oncology (ESDO) also recommends follow-up between 1 and 3 years. Moreover, the European Society of Digestive Endoscopy (ESGE) recommends a follow-up of 1 or 2 years depending on the lesions founded in the last colonoscopy.

From of the mentioned above, we propose to participate in a randomized study in patients with serrated polyposis syndrome who are in surveillance program. If no advanced adenomas, advanced serrated polyps or less than 5 relevant lesions have been found in the last colonoscopy, follow-up randomization will be performed at 2 years or 3 years. You will be randomly assigned to perform follow-up colonoscopy at age 2 or 3 years of the last colonoscopy, provided you have not had advanced injuries (risky lesions in the last colonoscopy). Data on the lesions removed, as well as the duration of the test and various demographic variables in relation to the individual participating in the study, will be recorded during colonoscopies.

The aim of the study is to determine the incidence of advanced and non-advanced lesions in follow-up, comparing those that are performed colonoscopy at 2 years with those performed at age 3.

We look forward to your selfless collaboration in order to provide you with higher quality health care.

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&Bleijenberg AGC, IJspeertv JE , Van Herwaarden YJ et al. Personalised surveillance for serrated polyposis syndrome: results from a prospective 5-year international cohort study. Gut 2020 Jan;69:112-121.

Study title: Endoscopic surveillance in patients with serrated polyposis syndrome and low-risk of advanced neoplasia.

Study Promoter: Digestive Device Section of the University Hospital of Móstoles and Digestive Endoscopy Unit.

Researchers responsible for the study: Dr. López Vicente.

1. I..... I declare under my responsibility that I have read the study information and agree to participate in that study.

2. A copy of the Patient Information has been given to me. I have been explained the characteristics and objective of the study. I've been given time and opportunity to ask questions. All questions were answered to my satisfaction

3. I am free to withdraw from the study at any time for any reason, without having to explain and without having to negatively impact my future medical treatment.

4. I understand that the objective of the study is to assess the population under study and that the results of the study shall not be communicated to me except in the event that such findings have a significant implication for the health of the participants.

Point 1.- I give / I do not give consent to participate voluntarily in the observational study of which I have been informed

Date..... and Signature of the patient.....

I note that I have explained the characteristics and purpose of the study to the subject whose name is written above. The patient consents to participate through his signature dated in person.

Date..... and Signature..... (research physician).

Name of the Investigator or designated person to provide the information.