



UNIVERSITÉ DE NANTES

---

**UNIVERSITE DE NANTES**

---

**FACULTE DE MEDECINE**

---

Année : 2020

N° 2020-09

**THESE**

pour le

**DIPLOME D'ETAT DE DOCTEUR EN MEDECINE**

DES de Gastro-entérologie et Hépatologie

par

Orianne Valérie Anne PLANADE

née le *29 novembre 1989* à Limoges

---

Présentée et soutenue publiquement le *10 février 2020*

---

**SYSTEMATIC UPPER ENDOSCOPY CONCOMITANT WITH COLONOSCOPY  
PERFORMED WITHIN THE COLORECTAL CANCER SCREENING PROGRAM IN  
FRANCE: IMPACT ON THE PATIENTS' MANAGEMENT STRATEGY**

---

Présidente : Madame la Professeure Tamara MATYSIAK BUDNIK

Directeur de thèse : Docteur Yann TOUCHEFEU

## Remerciements

---

### Aux membres du jury :

**Madame la Professeure Tamara MATYSIAK BUDNIK,**

Merci de m'avoir fait l'honneur de présider cette thèse.

Ce travail n'aurait jamais abouti sans votre soutien, votre travail et votre persévérance. Vous avez toujours eu à cœur de transmettre vos connaissances aux internes, notamment par le biais des cours en anglais du mercredi matin, et vous nous avez également toujours encouragé et accompagné avec bienveillance dans nos travaux de recherche, de communications orales ou de publications. Vous avez toujours su vous rendre disponible pour que ce travail aboutisse malgré les autres travaux que vous dirigez. Je vous en serai toujours reconnaissante. Soyez assurée de ma gratitude et de mon plus profond respect.

**Monsieur le Docteur Yann TOUCHEFEU,**

Ce projet n'aurait pas existé sans ton implication, ta patience, ton enthousiasme, ta persévérance, et ton encadrement. Ce fut un plaisir de travailler sous ta direction, que se soit pour ce travail de thèse mais également tous les jours dans le service en oncologie digestive. Tu as toujours une solution pour régler les situations les plus difficiles, sans difficulté, avec légèreté et bonne humeur et tu t'es toujours rendu disponible pour mes multiples questions. Tes conseils avisés sont justes, et j'ai beaucoup appris à tes côtés. Sois assuré de ma gratitude et de mon plus profond respect.

**Monsieur le Professeur Emmanuel CORON,**

Vous me faites l'honneur de juger ce travail.

Merci pour votre implication dans notre formation d'interne et vos enseignements. J'ai pu appréhender des techniques d'endoscopie interventionnelle d'avant-garde grâce à vous. Merci de m'avoir formé en endoscopie et de continuer à le faire, merci de vos conseils et de votre expertise. Soyez assuré de ma gratitude et de mon plus profond respect.

**Monsieur le Professeur Jean-François MOSNIER,**

Vous me faites l'honneur de juger ce travail.

Merci d'avoir partagé vos connaissances d'expert en anatomopathologie, notamment lors des staffs anatomopathologie et hépatologie du lundi midi. Vous être toujours disponible pour nous expliquer simplement votre spécialité et je suis consciente qu'avoir collaboré avec vous pour ce travail est une opportunité. Soyez assuré de ma gratitude et de mon plus profond respect.

\*\*\*

Merci à tous celles et ceux qui ont collaboré de près ou de loin à ce projet. Je tiens à remercier particulièrement : Brigitte DESSOMME, Nicolas CHAPELLE, Marine VERDIER, Emilie DUCHALAIS, Marc Le RHUN et Nicolas MUSQUER.

\*\*\*

**A tous les médecins du service d'Hépatogastro-entérologie du CHU de Nantes**, qui m'ont tout appris pendant ces 4 ans. Merci pour votre soutien et pour votre patience lors de mes premiers pas d'interne dans cette spécialité, particulièrement le Docteur Caroline TRANG qui me forma à l'hôpital de jour, en m'initiant à la prise en charge des MICI, mais également à celle des cirrhoses décompensées lors de mon premier semestre au CHU. Merci au Docteur Isabelle ARCHAMBEAUD pour son expertise en USIMAD, merci au Docteur GOURNAY pour sa formation en hépatologie pendant un semestre d'hospitalisation conventionnelle bien rempli et pour son soutien et son aide en tant que Chef de Service. Merci à tous les médecins que j'ai côtoyés, pour votre précieux enseignement de jour comme de nuit lors des gardes.

**A l'ensemble de l'équipe d'Hépatogastro-entérologie du CHU de Nantes et à l'équipe d'endoscopie**, les infirmières et infirmiers, les aides soignantes et aides soignants, les cadres ; on arrive « piou piou » et on progresse, on apprend à voler de nos propres ailes et vous êtes présents, et vous nous accompagnez et nous soutenez du début à la fin. La médecine est un travail d'équipe, dans les moments difficiles et dans les moments joyeux, de jour comme de nuit. Je suis fière d'avoir fait partie de votre équipe pendant ces 4 années.

**A l'équipe de l'institut de cancérologie de l'ouest, à l'équipe d'Hépatogastro-entérologie du CH de Challans et du CH de Cholet** : les semestres en votre compagnie sont passés à une vitesse folle, ils furent très formateur et également très joyeux. Merci pour votre bonne humeur et vos enseignements.

\*\*\*

**A mes co-internes et anciens co-internes maintenant docteur en médecine**, Marine (la meilleure), Sarah, Matthieu, Grégoire, Annie, Ludo, Paul, Raphaël, Maeva, Marion, Catherine, Alix, Astrid, Elise, Miloud, Laure, Lucie, Hannah, Quentin, Astrid, Juliette, Pierrine, Geoffrey, Samuel, Margaux, Hugo, Victor, Pierre, Mathilde et les jeunes nouveaux Raphaëlle et Nicolas ; et tant d'autres. Nous avons beaucoup partagé, évidemment des

moments difficiles, mais aussi et surtout de la joie avec de sacré fous rires, que ce soit au travail mais aussi en dehors et c'est ce que je retiendrai. Merci pour ces années, pour votre aide et surtout, bonne continuation.

**A mes amis,** Mon Ben, maintenant professeur d'anglais (qui l'eu crut, il y a beaucoup d'avantages, cela m'a bien aidé pour la rédaction de l'article en anglais), qui a toujours été là pour me faire rire même quand j'avais l'impression que tout allait mal, qui avance dans la vie avec une apparente simplicité parfois déconcertante ; tu m'as appris que rien n'est impossible et qu'il n'est jamais nécessaire d'être désespéré. Avec toi, je peux exprimer toute ma folie, cela te fait rire, et je soupçonne que cela te manque parfois dans ton quotidien. Je reste disponible pour te briefer pour un scénario à la « scrub », et je te garde deux ou trois anecdotes médicales. En espérant pouvoir bientôt découvrir tes films. Mon Isabelle, ton amitié indéfectible m'a permis de traverser la vie, et de traverser médecine. Tu m'as appris beaucoup de choses, notamment à savoir dire je t'aime (car on ne le dit pas assez souvent, et on l'écrit encore moins souvent) aux personnes auxquelles on tient. En dehors de toutes tes qualités, toutes les discussions, tous les fous rires et toutes les soirées qu'on a partagés, merci pour ton expertise en camembert et en diagramme, en Excel et en PowerPoint, dont la présentation de ce travail a amplement bénéficié.

On est peut être un peu fou, mais la folie a du bon à plusieurs, et on peut dire que l'on s'est bien trouvé. Le monde n'aurait pas la même saveur si vous n'existiez pas, alors merci d'exister.

**A toute ma famille, et notamment à mes grands-parents,** Marie et Louis vous n'êtes plus là aujourd'hui pour voir votre petite fille prétendre au titre de médecin. J'espère que je vous aurais rendu fiers. Merci pour votre bienveillance et votre amour que je transporte précieusement avec moi. Chantale et Claude, vous m'avez toujours soutenue, je sais que vous serez toujours là pour moi et que vous m'aimez, merci. Il est illusoire de décrire tout ce que vous m'avez appris, la curiosité pour toutes les choses de ce monde, la rigueur scientifique, mais aussi la bienveillance et le courage.

**A ma sœur,** merci de ton soutien et de tes conseils, toi qui la première a réussi ce périple.

**A mes parents,** j'espère avoir raison quand je dis que vous ne m'avez pas trop « loupé ». Si j'en suis là aujourd'hui, si je suis qui je suis, le mérite vous en revient. Merci de m'avoir encouragée et soutenue pendant toutes ces années d'études, et de continuer à croire en moi.

## Sommaire

---

<b>REMERCIEMENTS.....</b>	<b>2</b>
<b>SOMMAIRE.....</b>	<b>5</b>
<b>SYSTEMATIC UPPER ENDOSCOPY CONCOMITANT WITH COLONOSCOPY PERFORMED WITHIN THE COLORECTAL CANCER SCREENING PROGRAM IN FRANCE: IMPACT ON THE PATIENTS' MANAGEMENT STRATEGY.....</b>	<b>6</b>
ABSTRACT:.....	7
KEY SUMMARY: .....	8
INTRODUCTION: .....	9
METHODS:.....	11
<i>Patients and data collection .....</i>	<i>11</i>
<i>Upper endoscopy and colonoscopy .....</i>	<i>11</i>
<i>Statistical analysis .....</i>	<i>12</i>
RESULTS: .....	13
<i>Study population.....</i>	<i>13</i>
<i>Colonoscopy findings .....</i>	<i>13</i>
<i>Upper endoscopy findings .....</i>	<i>13</i>
<i>Clinical impact of the upper endoscopy.....</i>	<i>14</i>
<i>Factors associated with a clinical impact of the upper endoscopy .....</i>	<i>14</i>
<i>Safety.....</i>	<i>14</i>
DISCUSSION: .....	15
IN CONCLUSION.....	16
FIGURE 1: FLOW CHART.....	17
TABLE 1: CLINICAL CHARACTERISTICS OF THE 100 PATIENTS WITH SYSTEMATIC UPPER ENDOSCOPY .....	18
TABLE 2: COLONOSCOPY FINDINGS IN 100 ASYMPTOMATIC PATIENTS WITH POSITIVE FIT.....	19
TABLE 3 : UPPER ENDOSCOPY FINDINGS IN 100 ASYMPTOMATIC PATIENTS WITH POSITIVE FIT .....	20
TABLE 4: RESULTS OF THE UPPER ENDOSCOPY AND THEIR CLINICAL IMPACT IN 100 ASYMPTOMATIC PATIENTS WITH POSITIVE FIT, DEPENDING ON THE RESULTS OF COLONOSCOPY .....	21
TABLE 5: RISK FACTORS OF UPPER ENDOSCOPY WITH CLINICAL IMPACT IN 100 ASYMPTOMATIC PATIENTS WITH POSITIVE FIT .....	22
ABBREVIATIONS: .....	23
DECLARATION OF CONFLICT OF INTEREST:.....	23
REFERENCES:.....	24

# **Systematic upper endoscopy concomitant with colonoscopy performed within the colorectal cancer screening program in France: impact on the patients' management strategy**

---

## **Authors :**

Oriane PLANADE (1), Brigitte DESSOMME (2), Nicolas CHAPELLE (1), Marine VERDIER (1), Emilie DUCHALAIS (1), Marc Le RHUN (1), Nicolas MUSQUER (1), Emmanuel CORON (1), Jean-Francois MOSNIER (3), Tamara MATYSIAK-BUDNIK (1), Yann TOUCHEFEU (1)

1 Institut des Maladies de l'appareil Digestif, Nantes University Hospital, 1 place Alexis Ricordeau, Nantes 44093, France

2 Service d'Evaluation Médicale et d'Epidémiologie, Nantes University Hospital, 85 rue Saint-Jacques, Nantes 44093, France

3 Service d'anatomie et cytologie pathologiques, Nantes University Hospital, 1 place Alexis Ricordeau, Nantes 44093, France

## **Corresponding Author:**

Pr Tamara MATYSIAK-BUDNIK,  
IMAD, Hépatogastroentérologie & Oncologie Digestive  
Hôtel Dieu, CHU de Nantes  
1, Place Alexis Ricordeau  
44093 Nantes, France  
Tel: +33240083152  
Fax: +3324008154  
Email: tamara.matysiakbudnik@chu-nantes.fr

**Keywords:** upper digestive endoscopy, fecal immunochemical test (FIT), colorectal screening program

## **Abstract:**

**Background:** The French screening program for colorectal cancer is based on a fecal immunochemical test (FIT), followed by colonoscopy in case of positivity. The benefit of adding a concomitant upper endoscopy to detect upper digestive lesions (precancerous or others) is still debated.

**Objective:** Our aim was to evaluate the frequency of upper digestive lesions detected by upper endoscopy performed concomitantly with colonoscopy for positive FIT, and their impact on the management of patients (i.e., surveillance, medical treatment, endoscopic or surgical procedure)

**Methods:** Data of all the patients who consulted for a positive FIT between May 2016 and May 2019 in our center, and for whom concomitant upper endoscopy and colonoscopy were performed, were analyzed retrospectively. Patients with significant history of upper gastrointestinal diseases or with current gastrointestinal symptoms were excluded.

**Results:** One hundred patients were included [median age (min-max): 62 (50-75), men 64%]. Macroscopic and/or microscopic upper digestive lesions were found in 58 of them (58%): *Helicobacter pylori* infection in 17 patients, gastric precancerous lesions in 9 patients (chronic atrophic gastritis with intestinal metaplasia, n=8, low grade dysplasia, n = 1), and Barrett's esophagus requiring surveillance in 4 patients. In 44 patients (44%), the upper endoscopy findings had an impact on patients' management, with no significant difference between the groups with positive (CRC or advanced adenoma)- or negative (any other lesions or normal) colonoscopy.

**Conclusion:** A systematic upper endoscopy combined with colonoscopy for positive FIT could represent an efficient strategy for upper digestive lesions screening in France as it reveals macroscopic and/or microscopic lesions requiring specific management in 44% of patients, including 10% with precancerous lesions. Further studies are necessary to confirm these results and to evaluate cost-effectiveness of this approach.

## **Key Summary:**

1) The value of adding a concomitant upper endoscopy to a colonoscopy for a positive fecal immunochemical test is debated.

2) Upper digestive symptoms poorly correlate with the presence of upper digestive lesions, in particular precancerous, and no general screening strategies are validated in European countries.

3) In our study, a systematic upper endoscopy revealed macroscopic and/or microscopic lesions changing the patients' management in 44% of cases, including more than 10% of precancerous lesions.

4) A systematic upper endoscopy combined with colonoscopy for positive FIT could represent an interesting strategy for upper digestive lesions screening in France.



## Introduction:

Colorectal cancer (CRC) is the second cause of death by cancer in France. However, the CRC-related mortality has been steadily decreasing since 1980 [1], certainly in part due to the introduction of a nation-wide screening program based on realization of a faecal occult blood test (FOBT) followed by colonoscopy in case of positivity [2]. This program targets the asymptomatic, moderate risk population (men and women aged between 50 and 74 years, with no family history of CRC and no other specific risk factors) [2]. Since 2015 in France, the guaiac FOBT has been replaced by the Immunochemical test (FIT) (OC sensor®), which shows a better positive predictive value for the detection of colonic advanced adenomas and cancers [2, 3].

France belongs to the countries of low incidence of gastric cancer (GC), but the prognosis of this cancer remains very poor, with the 5-year overall survival inferior to 30% [1, 4]. GC is considered a preventable disease, especially by the means of eradicating *Helicobacter pylori* (*H. pylori*) and healing of the associated gastritis. Indeed, it is estimated that over 90% of GC are due to this infection inducing chronic gastritis which may evolve toward precancerous lesions, i.e, successively, chronic atrophic gastritis, intestinal metaplasia, and dysplasia [4, 5, 6]. Surveillance of gastric precancerous lesions appears as a logical approach to decrease the risk of advanced GC, and has been implemented in several countries, although the recommendations in this respect differ among different countries [5, 7, 8, 9]. The early detection, at the stage of superficial lesions, gives the best chance to cure and has been shown to decrease the GC-related mortality in high-incidence countries in Asia [7, 10, 11]. However, there are no validated strategies for general GC screening in low- and intermediate-incidence countries, like Western European countries. [4, 5, 6, 8, 12].

In addition to the detection of potential precancerous lesions, a systematic upper endoscopy may allow to discover other oeso-gastro-duodenal lesions requiring surveillance or treatment. Indeed, in several studies, upper endoscopy combined with colonoscopy for positive FIT, allowed to diagnose gastro-duodenal ulcer, Barrett's oesophagus and oesophageal varices [13, 14, 15, 16, 17]. Accordingly, some authors suggested a strategy of combining the gastric screening with CRC screening [8, 12, 17, 18].

The potential benefit of performing an upper endoscopy in case of negative colonoscopy realized because of a positive FOBT, was already discussed at the time when the guaiac-based FOBT was used, but no clear recommendation could be proposed [19]. The same question remains after the introduction of FIT: despite a positive test, an advanced adenoma or CRC is found in less than 50% of cases [20]. Different studies have given conflicted results [14, 15, 21, 22], and no firm recommendations could be proposed [23].

To propose an upper endoscopy in addition to colonoscopy to search for potential upper digestive lesions, is a technically easy approach since both examinations may be performed during the same general anesthesia, commonly used in France for colonoscopy.

Therefore, our aim was to evaluate the diagnostic yield of systematically performed upper endoscopy in patients addressed for colonoscopy because of positive FIT, and to assess its impact on patients' management.

## **Methods:**

### ***Patients and data collection***

In May 2016, in our center, a fast track specifically dedicated to the patients with a positive FIT was opened within the outpatient clinic. It comprised a rapid (<7 days after patient's call) appointment with gastroenterologist, immediately followed by an appointment with anesthesiologist in view of general anesthesia, followed by an endoscopic examination scheduled within the two weeks following the patient's visit (or later if asked by the patient).

The present study included the asymptomatic patients who were included in this fast track because of a positive FIT between May 2016 and May 2019, and in whom an upper endoscopy was combined with colonoscopy as a routine screening procedure. Patients with upper gastrointestinal symptoms, under proton pump inhibitor (PPI) treatment, or with any other indication for upper endoscopy, were excluded.

For all the patients, the following data were retrospectively collected from the electronic patients' records: demographic data, body mass index (BMI), medical and surgical history, family history of colonic adenomas and CRC, alcohol consumption, smoking status, current treatments, indications and results of endoscopy, results of histological analysis of the biopsies, follow-up recommendations, and complications.

A complete oral and written information about the potential benefits and risk of endoscopy was given to the patients during the initial visit, and all the patients signed a written informed consent in accordance with the SFED (Société Française d'Endoscopie Digestive) recommendations [24]. The study protocol was conform to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of the Nantes University Hospital (GNEDS) in July 2019. Informed consent is not required by the French legislation for the studies using anonymized, retrospective data.

### ***Upper endoscopy and colonoscopy***

All endoscopies were performed according to the international standards of quality by certified gastroenterologists trained in endoscopic procedures. The endoscopy standardized reports contained information on the aspect, location, and size of the visible lesions, resection or biopsy procedures, completeness of the examination, and additionally for colonoscopy, the quality of bowel preparation. During the upper endoscopy, systematic gastric biopsies could be obtained from the antrum and from the corpus. Histological analysis was performed by pathologists experienced in digestive pathology in accordance with the current standards.

Significant findings at colonoscopy were defined as follows:

- colorectal cancer (adenocarcinoma or other histology),
- advanced adenoma (adenomatous lesion measuring  $\geq 10$  mm in diameter, and/or high-grade dysplasia, sessile serrated adenoma  $\geq 10$  mm in diameter and/or with dysplasia) [25],
- other and unknown types of polyps (including benign adenoma: adenomatous lesions or sessile serrated adenomas which do not correspond to the criteria for advanced lesions, and hyperplastic polyps if they were  $\geq 10$  mm or localized before the rectum and the sigmoid, as they need an endoscopic monitoring [25]),
- other lesions (e.g. inflammatory lesions, angiodysplasia, diverticula),
- non-contributive (incomplete colonoscopy or insufficient bowel preparation with a BOSTON score  $< 7$  requiring early endoscopic control).

Significant findings at upper endoscopy were defined as follows:

- H. pylori infection diagnosed by histology
- Gastric precancerous lesions diagnosed by histology: chronic atrophic gastritis, intestinal metaplasia, dysplasia.
- Chronic non-atrophic gastritis diagnosed by histology
- Reactive gastritis diagnosed by histology,
- Barrett's oesophagus, confirmed histologically or not if the endoscopic aspect was typical,
- Esophagitis, graded according to the Los Angeles classification, confirmed histologically, or not if the endoscopic aspect was typical,
- Portal hypertension: oesophageal, gastric or ectopic varices,
- Other lesions (e.g.: adenoma, hyperplastic polyp).

Endoscopy was considered to have a clinical impact if the diagnosis changed the management of the patients, i.e., led to a medical treatment, immediate or postponed endoscopic treatment, endoscopic surveillance, surgical procedure or any other procedure. The discovery of hiatus hernia was considered as coincidental finding.

**Statistical analysis**

Statistical analysis was performed using XLStat2019 and SPSS software. Differences among the groups were evaluated using the  $\chi^2$ -test or Fisher exact test statistic, with a significance level of  $P < 0.05$ . Risk factors of an upper endoscopy having an impact on the management were analyzed using logistic regression. Variables with a P-value  $< 0.05$  or clinically relevant with a  $P \leq 0.20$  in univariate analysis were included in the multivariate analysis.

## **Results:**

### ***Study population***

Between May 2016 and May 2019, 221 patients visited the outpatient clinic for positive FIT. Of these 221 patients, 143 had at the same day both, the upper endoscopy and colonoscopy. In 43 of these 143 patients, the upper endoscopy was performed because of upper digestive symptoms or other indications. In the remaining 100 patients included in the study, the upper endoscopy was performed as systematic screening (Figure 1). The clinical characteristics of these 100 patients are presented in table 1.

### ***Colonoscopy findings***

The colonoscopy success rate was 86% (6 incomplete colonoscopies and 8 colonoscopies realized in the conditions of insufficient bowel preparation). Nevertheless, some lesions were found in 2 of 6 incomplete colonoscopies, and in 7 of 8 colonoscopies realized in the conditions of insufficient bowel preparation.

In total, 15 colonoscopies (15%) were normal and during the remaining 85 colonoscopies (85%) some lesions were found: adenocarcinoma in 8 patients, advanced adenoma in 29 patients, benign adenoma in 30 patients, and other lesions in the remaining patients (Table 2).

### ***Upper endoscopy findings***

The upper endoscopy was successful in 99% of cases. It was incomplete in one patient because of a desaturation during procedure related to a bronchial spasm. Nevertheless, a grade A esophagitis could be diagnosed in this patient.

Biopsies were performed in 79 patients (79%): gastric biopsies only in 64 patients, oesophageal biopsies only in 3 patients, gastric and oesophageal biopsies in 4 patients, gastric and duodenal biopsies in 8 patients.

In 26 patients (26%), the upper endoscopy was macroscopically and microscopically normal; in 16 patients (16%) the upper endoscopy was macroscopically normal but with unknown microscopic result because no biopsies were performed. In total, 42 upper endoscopies (42%) were normal while in 58 patients (58%), some macroscopic and/or microscopic lesions were found. In 17 of the total of 100 patients (17%), but out of 76 patients (22%) in whom gastric biopsies were performed, *H. pylori* infection was diagnosed by histology. In 9 of the total of 100 patients (9%), but out of 76 patients (12%) with gastric biopsies, some gastric precancerous lesions were found. The detailed results of upper endoscopy in these 100 asymptomatic patients are presented in Table 3.

### ***Clinical impact of the upper endoscopy***

The overall potential impact of the upper endoscopy was of 44% (n=44/100). The clinical impact of the upper endoscopy when the colonoscopy did not show an advanced adenoma or an adenocarcinoma (negative colonoscopy with respect to CCR screening) was of 48% (n=30/63), as compared to 38% (n=14/37) if colonoscopy was positive (p=0.341) (Table 4).

### ***Factors associated with a clinical impact of the upper endoscopy***

The explanatory variables initially selected were the following: sex, age $\geq$ 60 years old, BMI $>$ 24,9kg/m<sup>2</sup>, presence of diabetes, smoking status, current anti-platelet treatment, absence of oral anticoagulant treatment. Adjusted for the other variables, the factors most strongly associated, with the clinical impact, but not significant, were: smoking status, presence of diabetes, BMI and absence of oral anticoagulant treatment. Only smoking status current was significant in the multivariable analysis with OR: 4,69, IC95% [1,24-17,17], p=0,023 (Table 5).

### ***Safety***

Four complications were described. There was one bronchial spasm likely related to anesthesia and upper endoscopy. There were two complications related to colonoscopy: one case of rectal bleeding in a hemophilic patient, with a spontaneously favorable evolution but requiring a prolonged hospitalization, and one case of rectal bleeding after patient's discharge from the hospital, with a favorable evolution not requiring new hospitalization. One episode of bradycardia was likely related to anesthesia and colonoscopy, requiring an oro-tracheal intubation during the procedure but no further specific management.

## Discussion:

Our study shows that screening upper endoscopy performed independently of the results of colonoscopy, is a safe procedure, as already reported [26], and allows to detect significant macroscopic or microscopic upper digestive lesions in 58% of patients, with a clinical impact in 44% of patients.

We did not find any upper digestive cancer but this is not surprising since France is a country of a low incidence of gastric and esophageal cancer [1]. However, we found gastric precancerous lesions in 12% of the patients with gastric biopsies performed, and these patients, according to the current European guidelines [5], should undergo surveillance. Interestingly, the 12% rate of gastric precancerous lesions is much higher than the 3% rate observed in our previous study, which concerned the patients undergoing endoscopy with gastric biopsies for any reason [27], indicating that individuals with a positive FIT may have a higher risk of gastric precancerous lesions and thus of GC. Furthermore, we found 4 patients with previously unknown Barrett's oesophagus requiring surveillance, and 22% of the patients with gastric biopsies performed were *H. pylori* positive, requiring *H. pylori* eradication treatment (), which is consistent with the expected *H. pylori* prevalence in France (15-30%). It could be argued, however, that the number of *H. pylori* positive patients may be underestimated due to sampling error, especially in patients with atrophic changes of the gastric mucosa where the bacterial load is known to be decreased [27, 28].

The studies evaluating the diagnostic yield of systematic upper endoscopy in patients with positive FIT have given conflicted results, with heterogeneous study population and outcomes. Currently, no firm recommendations can be proposed.

The risk of upper digestive cancer differs according to the geographic region, and in case of gastric cancer, to the prevalence of *H. pylori* infection. In Korea, a country with a high incidence of *H. pylori* infection and of GC, in a retrospective study by Choi et al, a systematic upper endoscopy performed in 243 patients with positive FIT and without advanced colorectal neoplasia, ulcerator colitis at colonoscopy, allowed to detect 3 GC (1%) [15]. In another retrospective study from Singapore, a country of an intermediate GC-incidence, 202 patients, of whom 65% were asymptomatic, underwent a systematic upper endoscopy for a positive FIT. Fifty two percent of these patients had a positive examination with different findings, including gastritis, duodenitis requiring treatment, *H. pylori* infection, and peptic ulcer. No upper digestive cancer was detected [14].

There are also some studies performed in Europe. In a retrospective Dutch study including individuals undergoing screening for CRC without systematic upper endoscopy, less than 1% of patients were diagnosed with an upper digestive (i.e. oral/throat,

oesophageal, gastric or small bowel) cancer within 3 years after the colonoscopy. No significant differences were found in the cumulative incidence of upper digestive cancer between FIT-positive patients with a negative colonoscopy, FIT-positive patients with a positive colonoscopy, and FIT-negative patients, suggesting that upper endoscopy may not be recommended in individuals with positive FIT and negative findings at colonoscopy [22]. On the contrary, in an Italian study, the incidence of GC was increased in patients with positive FOBT or FIT and negative colonoscopy from the CRC screening, when compared to the expected GC standardized incidence rates, with a four-fold excess incidence during the first year [21].

The rate of upper digestive lesions found during systematic upper endoscopy in our study did not differ between the patients with positive and negative results of CRC screening colonoscopy, suggesting that the screening of upper digestive lesions may be indicated in all the patients with positive FIT. There is also no clear evidence that upper digestive lesions can lead to the FIT positivity [13, 16, 29, 30]. In fact, some studies suggested that a combined approach, based on a serological test (i.e. measurement of serum pepsinogen I and II level) followed by the upper endoscopy combined with colonoscopy in case of its positive result (decreased pepsinogen I level or pepsinogen I/II ratio), could be the best strategy in Europe [8, 12, 17, 18].

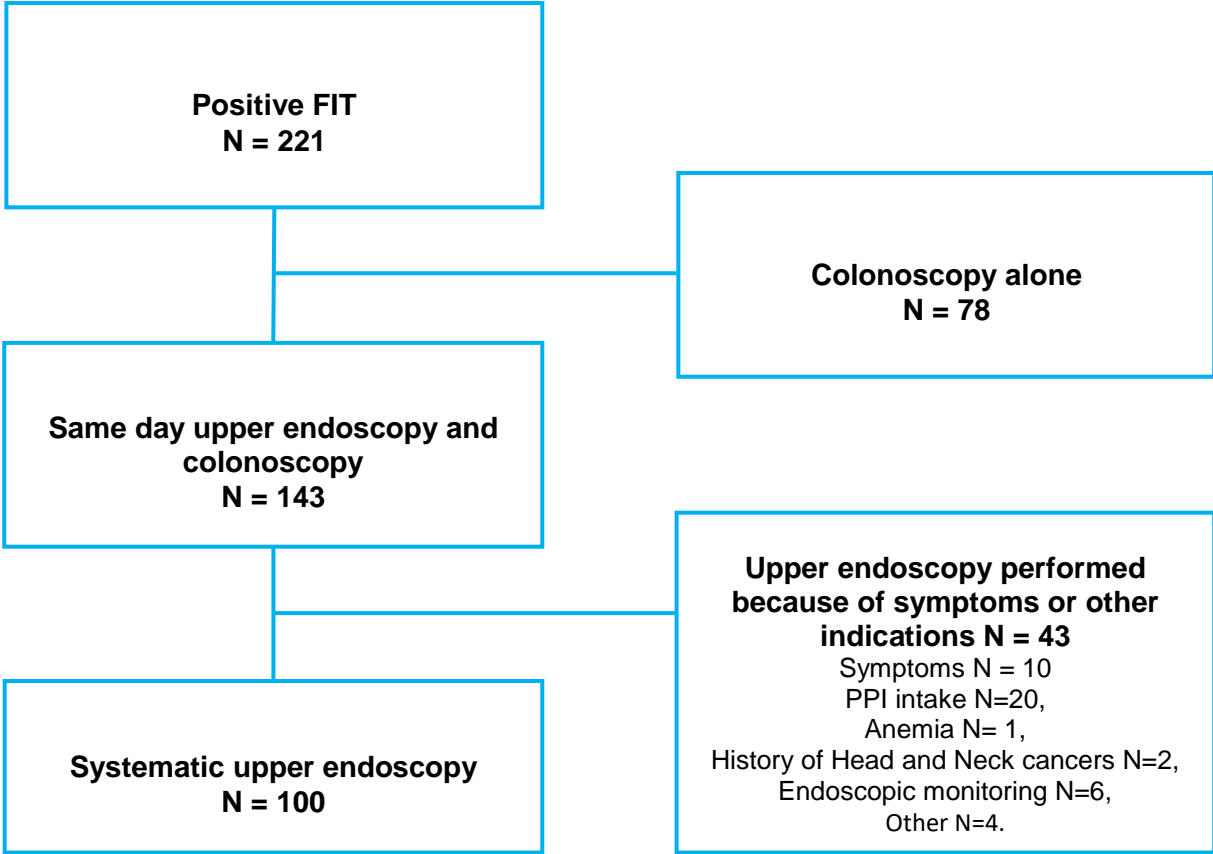
Our study has some limitations. It is a retrospective study with a relatively limited sample size. There are some missing data that could have been interesting, especially concerning alcohol consumption and smoking status. In our study, only current smoking status was significantly associated with the impact on management in multivariate analysis, which is consistent with the data from the literature [5, 9, 31]. However, our study has also some strengths. We report here the data from a homogeneous asymptomatic population, with no significant history of gastro-intestinal disease and no PPI treatment. We investigated all the lesions that could have an impact on the management, not only cancers or lesions likely to bleed.

There was no medico-economic evaluation in our study. When an upper endoscopy is conducted with a colonoscopy under the same anesthesia in French state hospitals, there is no added reimbursement cost, which could make this a cost-efficient strategy. Some studies from the United States or Portugal suggested that upper endoscopy could be cost-effective in selected populations [32, 33, 34].

**In conclusion**, systematic upper endoscopy combined with colonoscopy for positive FIT could represent a valuable strategy for upper digestive lesions screening in France. Further prospective studies are necessary to evaluate the efficacy and cost-effectiveness of this approach, and to better identify the individuals the most susceptible to benefit from it.



**Figure 1: Flow chart**



Note:

PPI intake: long-term proton-pump inhibitor treatment

Endoscopic monitoring: chronic gastritis (n=1), Barret’s oesophagus (n=2), portal hypertension in case of cirrhosis (n=3).

Other: giardiasis (n=1), oesophageal motor disorder (n=2), coeliac disease (n=1).

**Table 1: Clinical characteristics of the 100 patients with systematic upper endoscopy**

Age, year, Median (min-max)	62 (50-75)
Men, n (%)	64 (64)
BMI*, kg/m <sup>2</sup> , Median (min-max)	25.4 (17,6-44,5)
Medical history of CRC or polyps, n (%)	14 (18)
Unknown, n (%)	21 (21)
Smoking status	
Current, n (%)	15 (16)
Past, n (%)	40 (42)
Unknown, n (%)	5 (5)
Chronic alcohol consumption	
Current, n (%)	13 (18)
Past n (%)	7 (10)
Unknown, n (%)	29 (29)
Diabetes	
Type 1, n (%)	2 (2)
Type 2, n (%)	7 (7)
Anti-platelet treatment, n (%)	19 (19)
Oral anticoagulant treatment, n (%)	8 (8)
Genetic haemostasis disorder**, n (%)	4 (4)

\*BMI: Body Mass Index

\*\*Genetic haemostasis disorder: haemophilia A (n=1), Willebrand disease (n=3)

**Table 2: Colonoscopy findings in 100 asymptomatic patients with positive FIT (number = %)**

Normal colonoscopy	15
Adenocarcinoma	8
Advanced adenoma*	29
Other types of polyps	33
Benign adenoma**	30
Hyperplastic polyps***	1
Other types of polyps §	1
Unknown types of polyps	1
Other lesions	40
Inflammatory lesions†	5
Angiodysplasia	1
Diverticulosis	20
Non contributory‡	14

In some patients, several different lesions were found

\*Advanced adenoma: adenomatous lesion  $\geq$  10 mm and/or high-grade dysplasia, sessile serrated adenoma  $\geq$ 10 mm and/or with dysplasia.

\*\*Benign adenoma : adenomatous lesions or sessile serrated adenomas which do not correspond to the criteria for advanced lesions

\*\*\*Hyperplastic polyps : if  $\geq$ 10 mm or localised before the rectum and the sigmoid

§Other types of polyps: Peutz-Jeghers' hamartomatous polyp

†Inflammatory lesions: Ulcerative colitis (n=1), acute colitis (n=2), non-specific chronic colitis (n=11), pinworm (n=1)

‡Noncontributory : incomplete examination (n=6), insufficient bowel preparation (n=8)

**Table 3 : Upper endoscopy findings in 100 asymptomatic patients with positive FIT (number = %)**

Lesions (macroscopic and/or microscopic)	58
<i>H. pylori</i> infection*	17
Gastric precancerous lesions**	9
Atrophy	0
Intestinal metaplasia	8
Intestinal metaplasia limited to the antrum	6
Intestinal metaplasia in the antrum and the corpus	1
Intestinal metaplasia limited to the corpus	1
Low grade dysplasia	1
Chronic gastritis***	20
Reactive gastritis	8
Gastric or duodenal ulcer	4
Barrett's oesophagus	4
Length < 1 cm	0
Length ≥1 cm and < 3 cm	2
Length ≥3 cm and < 10 cm	2
Length ≥ 10 cm	0
Esophagitis§	6
Grade A/B	6
Grade C/D	0
Portal hypertension	3
Other†	4
Normal upper endoscopy	42

\**Helicobacter pylori* infection : histology diagnosed, with or without induced lesion

\*\*Gastric precancerous lesions: with or without *Helicobacter pylori* infection, atrophy without intestinal metaplasia associated, intestinal metaplasia with or without atrophy associated

\*\*\*Chronic gastritis: without atrophy nor intestinal metaplasia, with or without *Helicobacter pylori* infection.

§Grade according to the Los Angeles classification.

†Other: foveolar gastric metaplasia, classified as "undefined for neoplasia/dysplasia" (n=1), duodenal tubulovillous adenoma with low-grade dysplasia (n=1), foveolar fundal adenoma (n=1), hyperplastic antral polyp (n=1)

**Table 4: Results of the upper endoscopy and their clinical impact in 100 asymptomatic patients with positive FIT, depending on the results of colonoscopy**

	Total : n=100 (number =%)	Positive* colonoscopy n=37 (%)	Negative* colonoscopy n=63 (%)
Lesions (macroscopic and/or microscopic) with clinical impact:	44	14 (38)	30 (48)
<i>H. pylori</i> infection**	17	5 (14)	12 (19)
Gastric precancerous lesions***	9	3 (8)	6 (10)
Gastric or duodenal ulcer	4	1 (3)	3 (5)
Barrett's oesophagus	4	1 (3)	3 (5)
Esophagitis	6	1 (3)	5 (8)
Portal hypertension	3	1 (3)	2 (3)
Other§	4	2 (5)	2 (3)
No Clinical impact :	56	23 (62)	33 (52)
Chronic gastritis without <i>H. pylori</i> infection †	6	1 (3)	5 (14)
Reactive gastritis	8	4 (11)	4 (11)
Normal upper endoscopy	42	18 (49)	24 (65)

\*Positive colonoscopy: advanced adenoma or adenocarcinoma; Negative colonoscopy: any other lesion or normal

\*\**H. pylori* infection : histology diagnosed, with or without induced lesion

\*\*\*Gastric precancerous lesions with clinical impact: severe atrophic changes (OLGA III/IV) and/or intestinal metaplasia (OLGIM $\geq$ 1) and/or dysplasia, with or without *H. pylori* infection

§Other: foveolar gastric metaplasia, classified as "undefined for neoplasia/dysplasia" (n=1), duodenal tubulovillous adenoma with low-grade dysplasia (n=1), foveolar fundal adenoma (n=1), hyperplastic antral polyp (n=1)

†Chronic gastritis : without atrophy nor intestinal metaplasia

**Table 5: Risk factors of upper endoscopy with clinical impact in 100 asymptomatic patients with positive FIT \***

	Univariate		Multivariate	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Sex (N=100), Male	1,662 (0,719-3,843)	0,233		
Age (N=100), ≥60years	1,313 (0,583-2,953)	0,511		
BMI (N=100), >24,9kg/m2**	2,109 (0,900-4,531)	0,087	2,091 (0,830-5,268)	0,118
Diabetes (N=100), Presence	5,108 (1,005-25,972)	<b>0,041</b>	3,882 (0,714-21,116)	0,117
Smoking status (N=95),	Current	4,154 (1,177-14,659)	<b>4,699 (1,242-17,179) §</b>	0,074
	Past	1,535 (0,617-3 819)		
Chronic alcohol consumption (N=71),***	Current	2,333 (0,678-8,032)	<b>0,094</b>	
	Past	5 (0,878-28,490)		
Anti-platelet treatment (N=100), Presence	1,536 (0,563-4,187)	0,4		
Oral anticoagulant treatment (N=100), Absence	6,143 (0,726-51,947)	0,075	4,057 (0,461-35,740)	0,207

\*Observations with missing data have been deleted for statistical analysis.

\*\*BMI: Body Mass Index

\*\*\*Chronic alcohol consumption was not taking into account in multivariate analysis as it was closely related with smoking status

§The subgroups smoking status current is significantly associated,  $p=0.023$

**Abbreviations:**

BMI: Body Mass Index

CRC: Colo-rectal cancer

FIT: Faecal Immunochemical Test

FOBT: Fecal Occult Blood Test

GC: Gastric cancer

*H. pylori* : *Helicobacter pylori*

PPI: proton-pump-inhibitor

**Declaration of conflict of interest:**

The Author(s) declare(s) that there is no conflict of interest'.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## References:

1. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *European Journal of Cancer* 2018; 103: 356–387.
2. Haute Autorité de Santé - Cancer colorectal : modalités de dépistage et de prévention chez les sujets à risque élevé et très élevé, [https://www.has-sante.fr/portail/jcms/c\\_2772744/fr/cancer-colorectal-modalites-de-depistage-et-de-prevention-chez-les-sujets-a-risque-eleve-et-tres-eleve](https://www.has-sante.fr/portail/jcms/c_2772744/fr/cancer-colorectal-modalites-de-depistage-et-de-prevention-chez-les-sujets-a-risque-eleve-et-tres-eleve) (accessed 9 April 2018).
3. Tinmouth J, Lansdorp-Vogelaar I, Allison JE. Faecal immunochemical tests versus guaiac faecal occult blood tests: what clinicians and colorectal cancer screening programme organisers need to know. *Gut* 2015; 64: 1327–1337.
4. Ruge M, Genta RM, Di Mario F, et al. Gastric Cancer as Preventable Disease. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2017; 15: 1833–1843.
5. Pimentel-Nunes P, Libânio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. *Endoscopy* 2019; 51: 365–388.
6. Bornschein J, Bird-Lieberman EL, Malfertheiner P. The Rationale and Efficacy of Primary and Secondary Prevention in Adenocarcinomas of the Upper Gastrointestinal Tract. *Dig Dis Basel Switz* 2019; 37: 381–393.
7. Hamashima C, Systematic Review Group and Guideline Development Group for Gastric Cancer Screening Guidelines. Update version of the Japanese Guidelines for Gastric Cancer Screening. *Jpn J Clin Oncol* 2018; 48: 673–683.
8. Li S, Chung DC, Mullen JT. Screening high-risk populations for esophageal and gastric cancer. *J Surg Oncol*. Epub ahead of print 1 August 2019. DOI: 10.1002/jso.25656.
9. Banks M, Graham D, Jansen M, et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. *Gut* 2019; 68: 1545–1575.
10. Zhang X, Li M, Chen S, et al. Endoscopic Screening in Asian Countries Is Associated With Reduced Gastric Cancer Mortality: A Meta-analysis and Systematic Review. *Gastroenterology* 2018; 155: 347-354.e9.
11. Zhou L, Guan P, Sun L, et al. Health Economic Assessment for Screening of Gastric Cancer in A High Risk Population in Northeastern China. *Chin J Cancer Res* 2011; 23: 21–24.
12. Quach DT, Hiyama T, Gotoda T. Identifying high-risk individuals for gastric cancer surveillance from western and eastern perspectives: Lessons to learn and possibility to develop an integrated approach for daily practice. *World J Gastroenterol* 2019; 25: 3546–3562.
13. Chiang T-H, Lee Y-C, Tu C-H, et al. Performance of the immunochemical fecal occult blood test in predicting lesions in the lower gastrointestinal tract. *Can Med Assoc J* 2011; 183: 1474–1481.



14. Ng JY, Chan DKH, Tan KK. Is gastroscopy for fecal immunochemical test positive patients worthwhile? *Int J Colorectal Dis* 2017; 32: 95–98.
15. Choi JS, Choi JY, Cho HG, et al. Is esophagogastroduodenoscopy necessary in patients with positive fecal occult blood tests and negative colonoscopy? *Scand J Gastroenterol* 2013; 48: 657–662.
16. Levi Z, Vilkin A, Niv Y. Esophago-gastro-duodenoscopy is not indicated in patients with positive immunochemical test and nonexplanatory colonoscopy. *Eur J Gastroenterol Hepatol* 2010; 22: 1431–1434.
17. Tepes B, Seruga M, Vujasinovic M, et al. Premalignant Gastric Lesions in Patients Included in National Colorectal Cancer Screening. *Radiol Oncol* 2017; 52: 7–13.
18. Selgrad M, Bornschein J, Kandulski A, et al. Combined Gastric and Colorectal Cancer Screening—A New Strategy. *Int J Mol Sci*; 19. Epub ahead of print 3 December 2018. DOI: 10.3390/ijms19123854.
19. Allard J, Cosby R, Del Giudice ME, et al. Gastroscopy following a positive fecal occult blood test and negative colonoscopy: Systematic review and guideline. *Can J Gastroenterol* 2010; 24: 113–120.
20. Pellat A, Deyra J, Coriat R, et al. Results of the national organised colorectal cancer screening program with FIT in Paris. *Sci Rep* 2018; 8: 4162.
21. Zappa M, Visioli CB, Ciatto S, et al. Gastric cancer after positive screening faecal occult blood testing and negative assessment. *Dig Liver Dis* 2007; 39: 321–326.
22. van der Vlugt M, Grobbee EJ, Bossuyt PM, et al. Risk of Oral and Upper Gastrointestinal Cancers in Persons With Positive Results From a Fecal Immunochemical Test in a Colorectal Cancer Screening Program. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2018; 16: 1237-1243.e2.
23. Robertson DJ, Lee JK, Boland CR, et al. Recommendations on Fecal Immunochemical Testing to Screen for Colorectal Neoplasia: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2017; 152: 1217-1237.e3.
24. Fiches info patients. *SFED*, <http://www.sfed.org/professionnels/recommandations-et-autres-fiches/informations-patients/fiches-info-patients> (2015, accessed 4 June 2019).
25. Haute Autorité de Santé - Quand faut-il faire une coloscopie de contrôle après une polypectomie ?, [https://www.has-sante.fr/portail/jcms/c\\_1695396/fr/quand-faut-il-faire-une-coloscopie-de-contrôle-après-une-polypectomie](https://www.has-sante.fr/portail/jcms/c_1695396/fr/quand-faut-il-faire-une-coloscopie-de-contrôle-après-une-polypectomie) (accessed 4 June 2019).
26. Levy I, Gralnek IM. Complications of diagnostic colonoscopy, upper endoscopy, and enteroscopy. *Best Pract Res Clin Gastroenterol* 2016; 30: 705–718.
27. Chapelle N, Péron M, Mosnier J-F, et al. Prevalence, Characteristics and Endoscopic Management of Gastric Premalignant Lesions in France. *Dig Dis* 2019; 1–7.
28. Malfertheiner P, Megraud F, O’Morain CA, et al. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; 66: 6–30.
29. Nakama H, Kamijo N, Fujimori K, et al. Diagnostic accuracy of immunochemical faecal occult blood test for gastric cancer. *J Med Screen* 1996; 3: 113–114.
30. Nakama H, Zhang B. Immunochemical fecal occult blood test is inadequate for screening test of stomach cancer. *Dig Dis Sci* 2000; 45: 2195–2198.

31. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy* 2017; 49: 191–198.
32. Gupta N, Bansal A, Wani SB, et al. Endoscopy for upper GI cancer screening in the general population: a cost-utility analysis. *Gastrointest Endosc* 2011; 74: 610-624.e2.
33. Areia M, Spaander MC, Kuipers EJ, et al. Endoscopic screening for gastric cancer: A cost-utility analysis for countries with an intermediate gastric cancer risk. *United Eur Gastroenterol J* 2018; 6: 192–202.
34. Saumoy M, Schneider Y, Shen N, et al. Cost Effectiveness of Gastric Cancer Screening According to Race and Ethnicity. *Gastroenterology* 2018; 155: 648–660.

**Vu, le Président du Jury,**



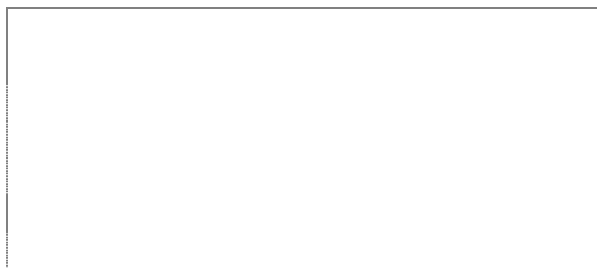
Professeure Tamara MATYSIAK BUDNIK

**Vu, le Directeur de Thèse,**



Docteur Yann TOUCHEFEU

**Vu, le Doyen de la Faculté,**



Professeur Pascale JOLLIET

## **Endoscopie oeso-gastro-duodénale systématique associée à une coloscopie pour test immunologique de dépistage du cancer colorectal positif : Impact sur la prise en charge du patient**

---

**Introduction :** En France, le programme de dépistage organisé du cancer colorectal repose sur la réalisation d'un test immunologique fécal (TIF) tous les 2 ans, suivi d'une coloscopie en cas de test positif. L'intérêt d'une endoscopie oeso-gastro-duodénale (EOGD) concomitante à la coloscopie de dépistage, pour détecter des lésions digestives hautes (précancéreuses ou autres) est toujours débattu. Notre objectif était d'évaluer la fréquence des lésions digestives détectées par l'EOGD et leur l'impact sur la prise en charge des patients, chez des sujets consultant pour TIF positif en France.

**Patients et Méthodes :** Les données de tous les patients ayant consulté pour un TIF positif entre mai 2016 et mai 2019 dans notre centre, et chez qui une EOGD concomitante d'une coloscopie a été réalisée, ont été analysées rétrospectivement. Les patients présentant des symptômes digestifs hauts, ou ayant un antécédent de pathologie gastro-intestinale significatif, ont été exclus. Une EOGD a été considérée comme ayant un impact thérapeutique si le diagnostic modifiait la prise en charge des patients (surveillance, traitement médical, endoscopique ou chirurgical). Les facteurs de risque d'impact thérapeutique ont été évalués par régression logistique.

**Résultats :** Parmi 100 patients inclus (64 hommes, âge médian de 62 ans, [50-75]), la coloscopie a révélé dans 37% des cas ( $n = 37/100$ ) un cancer colorectal ou un adénome avancé. L'EOGD systématique a révélée dans 58% des cas ( $n = 58/100$ ) des lésions macroscopiques et/ou microscopiques, dont 17 infections à *Helicobacter pylori* diagnostiquées par l'histologie, 9 lésions précancéreuses gastriques (gastrite chronique atrophique avec métaplasie intestinale  $n=8$ , dysplasie de bas grade  $n=1$ ), et 4 endobrachyoesophages. Quarante-quatre pourcents de ces examens ( $n = 44/100$ ) avaient un impact thérapeutique, sans différence significative selon que la coloscopie ait révélée ou non un cancer colorectal ou un adénome avancé. En analyse multivariée, seul le statut tabagique actif était associé de manière significative à l'impact thérapeutique (OR 4.699, IC95% [1.242-17.1786],  $p = 0,023$ ).

**Conclusion:** Une EOGD systématique met en évidence des lésions macroscopiques et/ou microscopiques chez plus de 50% des patients consultant pour un TIF positif. Il existe un impact sur la prise en charge des patients dans plus de 40% des cas, avec plus de 10% de lésions précancéreuse digestives hautes détectées. Ces résultats ne semblent pas liés aux résultats de la coloscopie. Une EOGD systématique couplée à la coloscopie pour TIF positif pourrait représenter une stratégie de dépistage de lésions digestives haute en France, les deux examens étant réalisés durant la même anesthésie, sans tarification supplémentaire du séjour hospitalier.

---

### **MOTS-CLES**

Endoscopie oeso-gastro-duodénale, Test immunologique fecal, cancer colo-rectal, dépistage.