

## Screening by Chromo Endoscopy for Colorectal Cancer and Dysplasia in Ulcerative Colitis: An Algerian Prospective Cohort

Houria Saoula, Amira Fatima Boutaleb, Zine Charaf Amir, Saadi Berkane, Abdelmalek Balamane, Tadjedine Boucekkine, Mhamed Nakmouche

Houria Saoula, Amira Fatima Boutaleb, Mhamed Nakmouche, Department of Gastroenterology, University Hospital Bab El Oued, bd Said Touati, Bab El Oued, Algiers, Algeria

Houria Saoula, Amira Fatima Boutaleb, Zine Charaf Amir, Saadi Berkane, Abdelmalek Balamane, Tadjedine Boucekkine, Mhamed Nakmouche, Algiers University, Algiers, Algeria

Zine Charaf Amir, Department of Histology, Mustapha bacha University Hospital, Algiers, Algeria

Saadi Berkane, Tadjedine Boucekkine, Department of gastroenterology, Mustapha Bacha University Hospital, Algiers, Algeria

Abdelmalek Balamane, Department of Gastroenterology, BeniMessous University Hospital, Algiers, Algeria

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**Correspondence to:** Houria Saoula, Department of Gastroenterology, University Hospital Bab El Oued, bd Said Touati, Bab El Oued, Algiers, Algeria.

Email: [houriasaoula@yahoo.fr](mailto:houriasaoula@yahoo.fr)

Telephone: +213-555-243-328

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### ABSTRACT

Patients with longstanding extensive ulcerative colitis have an increased risk of colorectal cancer.

**AIMS:** To determine the incidence of dysplasia and colorectal cancer, in patients with longstanding ulcerative colitis. To evaluate prospectively, the proportion of dysplastic lesions detected by chromoendoscopy from targeted biopsies of macroscopically visible abnormalities, as opposed to random biopsies of colonic mucosa.

**PATIENTS AND METHODS:** In this prospective study, consecutive patients with clinically inactive, longstanding UC (more than 8 years) were recruited from 4 centers; colonoscopy with chromoendoscopy using 0.1% methylene blue was performed for each patient. Four mucosal biopsy specimens were taken every 10 cm between the cecum and the rectum, with additional biopsies or removal of any mucosal abnormality. All the endoscopies were performed by a single specialist in gastroenterology. All the biopsies have been reviewed by a pathologist experienced in gastroenterology.

**RESULTS:** Two hundred and twenty four chromoendoscopies were performed in 106 patients. We diagnosed 49 neoplastic lesions in 31 patients; there were six adenocarcinomas, eight high grade dysplasia, 24 low grade dysplasia, and 11 lesions indefinite for dysplasia. We took 8035 random biopsies and found seven dysplastic lesions in six patients: one high grade dysplasia, two low grade dysplasia and four lesions indefinite for dysplasia. Random biopsies alone diagnosed dysplasia in two patients (1.8%), and had clinical impact only in one patient (0.9%).

**CONCLUSION:** In our cohort, we experienced a high diagnostic yield of chromoendoscopy in the detection of neoplasia in high risk IBD patients. Random biopsies don't have clinical impact and should be abandoned.

**Key words:** Ulcerative colitis; Dysplasia; Colorectal cancer

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## INTRODUCTION

The first case of colorectal cancer (CRC) occurring in ulcerative colitis (UC) was published by Crohn and Rosenberg in 1925<sup>[1]</sup>. Today, it is widely accepted that the risk of CRC is higher in UC colitis compared to the background population. The magnitude is variable in the literature, depending on population or hospital-based studies, earlier or recent studies: the risk appears to be lower in population-based and recent studies<sup>[2-13]</sup>. The incidence of CRC in UC appears to have decreased worldwide over the last 30 years, incidence rates have changed from 4.29 / 1000 in studies published in the 1950s to 1.21 / 1000 patient years in publications of the last decade<sup>[11-12]</sup>.

The cause of this risk reduction is not clear, but could be related to a recruitment bias, a better control of inflammation, or endoscopic surveillance of patients. International guidelines recommend submitting patients with UC to a screening program involving a full colonoscopy with random and targeted biopsies in order to detect pre-cancerous lesions (dysplasia) or colorectal cancer at an early stage<sup>[14-19]</sup>. This screening should lead to therapeutic consequences: endoscopic resection or surgery. Chromo endoscopy with methylene blue or indigo carmine significantly improves the rate of dysplastic lesions detected compared to standard endoscopy<sup>[20-22]</sup>, some authors have suggest abandoning random biopsies and perform only targeted biopsies (assisted by chromo endoscopy) on visible lesions since the majority of dysplasia lesions are visible at endoscopy<sup>[23-25]</sup>.

To our knowledge, there is no published data on this subject in Algeria, and throughout the African continent.

### Aims

To determine the incidence of dysplasia and CRC, in a hospital based cohort of patients with longstanding UC. To evaluate prospectively, the proportion of dysplastic lesions detected by chromoendoscopy from targeted biopsies of macroscopically visible abnormalities, as opposed to random biopsies of colonic mucosa.

## PATIENTS AND METHODS

In this observational prospective study from June 2005 to January 2015, 4 centers in Algiers recruited consecutively patients with clinically inactive, longstanding UC, who are being seen on a regular basis by their hospital physicians. All patients regardless of extent of disease were offered to join a surveillance study with regular colonoscopies and biopsies and after giving informed consent, they were referred to Bab el Oued hospital for surveillance endoscopy. The study was accepted by the scientific and ethical committee of the faculty of medicine of Algiers University.

**Inclusion criteria:** Patients with endoscopic and histologic proven UC, Longstanding UC >8 years (in case of primary sclerosing cholangitis (PSC) surveillance was started at diagnosis of PSC), clinically inactive UC.

**Exclusion criteria:** Pregnancy, Clinical active disease, thrombopenia < 50000/mm, inadequate bowel preparation.

Baseline characteristics and clinical data were reported for each patient including: age, gender, family history of IBD or CRC (first degree siblings), onset of symptoms (as documented in hospital charts) and diagnosis of UC, duration of disease (from diagnosis), smoking status, diagnosis of PSC, extent (defined by the most proximal location of either histological or endoscopical inflammation, classified as pancolitis, left colonic or rectal) and severity of the first flare, number of the flares since diagnosis as well as medications.

Colonoscopy with chromoendoscopy using 0.1% methylene blue

was performed in each patient. Four mucosal biopsy specimens were taken every 10 cm from the cecum to the rectum, with additional biopsies or removal of any abnormal mucosa. All the samples were forwarded to histological evaluation.

Any abnormality leading to targeted biopsies was classified according to Paris morphological classification<sup>[26]</sup>. Lesions were also defined as endoscopically resectable or not according to their endoscopic appearance: type IIc, III (according to Paris classification), large lesions with irregular margin and non lifting lesions were considered as unresectable. Resectable lesions were endoscopically removed and send to histological evaluation.

Histological grading of lesions was categorized based on the Vienna classification for intraepithelial gastrointestinal neoplasia<sup>[27]</sup> and dysplasia was categorized as negative for dysplasia, indefinite for dysplasia (IND), low-grade dysplasia (LGD), and high-grade dysplasia (HGD). All the endoscopies were performed by a single gastroenterologist (H.S). All the biopsies have been reviewed by two pathologists and in case of dysplasia a third pathologist experienced in gastroenterology (Z.C.A).

In the case of CRC, or high grade dysplasia (HGD), the patients were referred to surgery. In the case of resected low grade dysplasia (LGD) or indefinite for dysplasia (IND) an endoscopic control was done at 6 months and thereafter every year. The patients with no neoplastic lesions were scheduled for biannual controls. Patients were followed up from the date of the first surveillance colonoscopy in this study (index chromoendoscopy) after June 1, 2005, until the last surveillance colonoscopy before January 10, 2015.

### Statistical analysis

Baseline characteristics were summarized with means  $\pm$  standard deviations (SD), ranges, and percentages. Mann-Whitney *U*-test was used to analyze the variance between groups for continuous variables, and chi-square or Fisher's exact test was used for comparison of categorical variables. A *p*-value < 0.05 was considered statistically significant. The Epi info software (version 6.0) was used for data entry, descriptive study and uni-varied analysis.

## RESULTS

One hundred and fourteen patients with UC were referred to our endoscopy unity for surveillance endoscopy. We exclude eight patients: five because of inadequate bowel preparation at several times and three patients who were diagnosed with Crohn's disease after screening colonoscopy. We included 106 patients, 48 men (45.3%), and clinical characteristic are summarized in table 1.

Eighty patients (76%) had not been examined by any surveillance endoscopic earlier, among them 80% with extensive colitis. Colonoscopy was performed during disease's remission in all patients. In average, the last flare was  $23.49 \pm 24.47$  months before surveillance colonoscopy (range: one and 96 months). We performed 224 chromoendoscopies (average per patient: 2.11, range: 1 to 5). Seventy nine patients (74.5%) were followed up, with a mean interval of 31 months (range 4.2 - 46 months), the shortest time corresponding to patients who had a dysplastic lesion on first colonoscopy. Twenty-seven (26.4%) patients did not have a follow-up colonoscopy for various reasons: two patients died, one of a cardiovascular pathology, the other in the postoperative course of a total colectomy for rectal adenocarcinoma. One patient had severe respiratory failure with orthopnea, and a patient with HGD had a total colectomy with final ileostomy. One patient has been postponed several times for poor colonic preparation. Eleven patients (10.37%) refused

control, 11 (10.37%) patients were lost to follow-up.

**Findings at index chromoendoscopy**

The cecum was reached in 102 patients (96.2%). A tubular colon was found in 29 patients (27.4%), a shortened colon in 13 patients (12.3%), inflammatory polyps in 48 patients (45.3%), and a sigmoid stenosis in one patient (0.9%). Although all included patients were in clinical remission, only 61 (57.5%) were in endoscopic remission (Mayo score 0) and only 30 patients in histological remission (quiescent colitis). Seventy four patients (69.8%) had pancolitis, 23 left sided-colitis (21.7%) and nine (8.5%) proctitis at time of endoscopy. Between the diagnosis and the first screening colonoscopy, colonic disease had progressed in 16.98%, decreased in 14.15% and remained unchanged in 67.92% of patients.

**Neoplastic lesions**

**At first index chromoendoscopy:** thirty four neoplastic lesions were identified in 25 patients: five adenocarcinomas and 29 dysplasia (six HGD, 15 LGD and eight IND).

**On follow up chromoendoscopy:** Fourteen dysplastic lesions were found in 13 patients: two HGD, nine LGD, and two IND. One adenocarcinoma was recognized on colectomy performed for HGD

**Neoplastic lesions identified during the complete study:** forty nine neoplastic lesions were found in 31 patients (29.2%): 43 dysplasia and six CRC. 87.5% of neoplastic lesions were within colitic mucosa, the others (12.7%) were therefore considered to be of sporadic origin. Table 2 shows the proportion of neoplastic lesions detected at index chromoendoscopy, on follow-up and the complete study.

**Contribution of random biopsies:** We harboured 8035 randomized biopsies (4216 on index colonoscopy and 3819 during follow-up) with an average of 75.80 ± 31.99 biopsies per patient (minimum 28 - maximum 200); 550 targeted biopsies with an average of 5.18 ± 5.45 (minimum 0- maximum 29). We identified 49 neoplastic lesions: seven (14.2%) by random biopsies and 42 (85.7%) by targeted biopsies. Table 3 shows proportion of neoplastic lesions identified by random or target biopsies.

One thousand one hundred and forty seven random biopsies were needed to detect one dysplasia. The seven dysplastic lesions were found in six patients: in two patients (1.8%), dysplasia was found only on random biopsies; in four patients, dysplastic lesions were also found on targeted biopsies. These six patients had all an endoscopic inflammation, for the 100 patients who had no dysplasia on systematic biopsies, active endoscopic involvement was found in 41 (40.6%). Patients with dysplasia diagnosed on random biopsies had significantly more extensive lesions at endoscopy ( $p = 0.006$ ), these lesions were pancolitic ( $p = 0.001$ ). The presence of dysplasia on systematic biopsies was not related to the presence of histological inflammation nor to its extent ( $p = 0.38$ ).

**Outcome of dysplastic lesions diagnosed on randomized biopsies:** one patient with HGD found on random biopsies had also two HGD on visible lesion during the same examination. He had a total colectomy with ileo rectal anastomosis. The other five patients were followed, and the various control endoscopies did not confirm neoplastic lesions with a mean follow-up of 30.8 months (range 23 - 45 months). Dysplasia diagnosed on systematic biopsies had therapeutic sanction only in a single patient who also had dysplasia on targeted biopsies.

**DISCUSSION**

This study is the first Algerian screening program for CRC in a risk

**Table 1** Baseline characteristic of patients.

Number of patients	106 patients
Median age at onset of symptoms*	33.83 ± 11.69 years (range 10 - 66)
Median age at diagnosis of IBD	32 ± 11.01 years (range 10 - 66)
Median age at first surveillance	50.67 ± 10.39 years (range 22 - 78 )
Median time from onset of symptoms to diagnosis of UC*	11.43 months (range 1 - 60)
Median time from diagnosis to first surveillance	16.05 ± 7.09 years (1 - 43 years).
Family history of CRC (first degree sibilings)	6 (5.7%)
Primary sclerosing cholangitis	7 (6.6%)
<b>Extension of UC at diagnosis</b>	
Pancolitis	47 (44.3%)
Left sided	46 (43.4%)
Proctitis	13 (12.3%)
<b>Most proximal extension (histological or endoscopic) during course of disease</b>	
Pancolitis	74 (69.8%)
Left sided	23 (21.7%)
Proctitis	9 (8.5%)

\*in 34/106 patient's data about onset of symptoms was missing

**Table 2** Neoplastic lesions identified on first surveillance, follow-up, and complete study.

Neoplastic lesion	First surveillance	Follow-up	Complete study	Patients n (%)
Adenocarcinoma*	5*	1	6*	6* (5.6%)
Dysplasia	29	14	43	27 (25.4%)
HGD	6	2	8	5 (4.7%)
LGD	15	9	24	19 (17.9%)
IND	8	3	11	8 (29.2%)
Total number of lésions	35	14	49	31 (29.2%)

\*One adenocarcinoma was recognized on colectomy performed for HGD.

**Table 3** Neoplastic lesions identified by random or target biopsies.

Target Biopsies (n = 550)	
6 adenocarcinomas in 6 patients (5.6%)	
36 dysplasia	7 high grade dysplasia
	22 low grade dysplasia
	7 lesions indefinite for dysplasia
Random Biopsies (n = 8035)	
7 dysplasia in 6 patients (5.6%)	1 high grade dysplasia
	2 low grade dysplasia.
	4 lesions indefinite for dysplasia

population of UC patients. We diagnosed six CRC in 106 patients (5.6%) and 43 dysplasia in 27 patients (25.5%). This is higher than reported in recent studies<sup>[2-13]</sup>, especially in Scandinavian studies<sup>[2,3,5,8,12]</sup>. However, our results are consistent with those reported by Lindberg: 143 patients were followed for twenty years, CRC was found in 4.9%<sup>[31]</sup>. In a Dutch screening programs<sup>[28]</sup> cancer rate was 5.1%, and in that of St Marks Hospital<sup>[6]</sup>: 600 patients were followed for 30 years, CRC were observed during 30 cases (5%)<sup>[5]</sup>.

The incidence of dysplasia is variable, and this can be explained by the absence until recent years of consensual definition of dysplasia<sup>[27]</sup>, and the interobserver variability especially for LGD. In Connell's series, the concordance was only 17%, In addition, underlying inflammation can seriously influence the results, leading to false positives<sup>[29]</sup>. Lindberg shows a low agreement in classifying LGD

versus IND<sup>[31]</sup>. In our study, all the IND had been initially graded as LGD, and it is the third reading that made it possible to correct the diagnosis.

Only 13.5% of dysplasia were found in the St Mark Hospital program<sup>[6]</sup>, however, this screening program was performed by conventional colonoscopy. In 2015, the same team published the results after 40 years of follow-up<sup>[30]</sup>. If the rate of CRC remained stable at 5.2%, the rate of identified dysplastic lesions was, for its part, 23.6%. The authors explained this increase in the number of dysplasia by the introduction of chromoendoscopy in their center during the last decade<sup>[30]</sup>. In Stolwijk's study, 72/293 patients (24.5%) showed dysplasia<sup>[28]</sup>; authors explained these results by the high percentage of pancolitis (61%) in their studies<sup>[28]</sup>. In prospective studies based on chromoendoscopy, the rate of dysplasia varies from 7 to 21%<sup>[20-22]</sup>.

The high rates of neoplastic lesions found in our study could be explained by many hypotheses: It is likely that the incidence of UC has plateaued in Western countries, so CRC rates on UC tend to stabilize or decrease. In countries where the incidence of UC has increased in recent years, however, the incidence of CRC is likely to increase proportionally. In Algiers, epidemiological studies carried out between 1980 and 2006 show that the incidence and prevalence of IBD has increased significantly between 1980 and 1998, with an increase of 46% for all IBD and 24% for UC<sup>[32,33]</sup>. It is likely that the problem of CRC in UC will become more important in our country in the years to come. Second, there is certainly a selection bias, as our data are from a reference hospital, selecting patients with a more extensive or more severe disease. Patients with low-degree of symptoms are not being followed by hospitals. Thus, our hospital based cohort harbors more patients with higher risk of CRC in UC.

In our patients, extent of disease progressed over time to pancolitis in 69.8% (taking into account histological data), and in 81.2% of patients with dysplasia. Between the diagnosis and the first screening colonoscopy, colonic disease had progressed in 16.98%, decreased in 14.15% and remained unchanged in 67.92% of patients. In the IBSEN cohort, 69/288 or one fifth of patients with left colitis or proctitis had progressed during the course of the disease<sup>[34]</sup>. This predominant pancolitis involvement may be the explanation for the high rate of cancers and dysplasias found in our study, since it is today a recognized risk factor for the occurrence of neoplasia in UC with a risk of between 5.9 and 14.8<sup>[35]</sup>.

Seventy six percent of our patients never had endoscopic surveillance, among them 80% had pancolitis, which had been evolving for over ten years in 86% of cases. This lack of adherence of doctors to the recommendations of guidelines has already been reported by numerous studies<sup>[36-38]</sup>. If these patients had undergone endoscopic surveillance, dysplastic lesions would have been diagnosed and resected at an early stage.

85.7% of the neoplastic lesions were visible, 14.2% were not. 100% of the cancers were perfectly visible even before staining with methylene blue. When visible, 100% of dysplastic lesions were also detected before staining. Our results are consistent with other studies that show that most neoplastic lesions are perfectly visible at endoscopy<sup>[23-25]</sup>.

We performed 8035 systematic biopsies to identify seven dysplasia, so 1147 biopsies were needed to detect a single dysplasia. There was less dysplasia diagnosed on random biopsies during follow-up colonoscopies compared to index chromoendoscopy. This could be related to the learning curve of the gastroenterologist performing the procedure. In all cases, the presence of dysplasia on random biopsies was accompanied by an active endoscopic inflammation, which

underlines the importance of performing this screening colonoscopy in endoscopic remission.

In our study, random biopsies alone identified dysplasia only in two patients (1.8%). In other studies, this rate is 1.2% by chromoendoscopy and 2.6% by standard colonoscopy<sup>[43]</sup>. Dysplasia detected by randomized biopsies had clinical significance in our study only in one case (0.9%), Van den Broek found similar results<sup>[40]</sup>.

Over the last decade, therapeutic goals in IBD have become ambitious and include now achieving endoscopic healing. As we have shown in our study, only 56.6% of patients in clinical remission had also endoscopic remission with a Mayo score = 0, among them only 44.4% were in histological remission. Baars found similar results: 152 patients in clinical remission had a surveillance colonoscopy, 50% of these patients had a normal endoscopy, and 75% had histological lesions<sup>[41]</sup>. Our study have some limitations, it was conducted on a population at a tertiary referral center with higher proportion of patients with more severe disease, thus limiting generalizability of the results. Because the number of patients is limited, the risk of neoplasia in UC may be under- or overestimated. The strengths of study is that one gastroenterologist performing all endoscopies minimizes interobserver variation. Including all patients with longstanding UC (both with limited extent of disease as well as pancolitis) and a considerable observation time (10 years) ensures a good evaluation of the performance of surveillance chromoendoscopy in UC patients in Algeria.

## CONCLUSION

This is the first Algerian screening program for CRC in a risk population of UC. The risk of CRC on UC is prominent: six CRC (5.6%) and 43 dysplasia in 27 patients (25.5%) were identified. In our cohort, we experienced a high diagnostic yield of chromoendoscopy in the detection of neoplasia in high risk IBD patients. Patients with UC should have a regular endoscopic surveillance to identify early neoplastic lesions and prevent the development of invasive cancer. Random biopsies are not critical for the management of patients; these biopsies unnecessarily lengthen the duration of the surveillance colonoscopy without providing a definite benefit. Their usefulness should be limited to determine the severity and extent of colitis.

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