ORIGINAL ARTICLE

Are random biopsies still useful for the detection of neoplasia in patients with IBD undergoing surveillance colonoscopy with chromoendoscopy?

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ABSTRACT

Background Colonoscopy with pan-chromoendoscopy (CE) is superior to standard colonoscopy in detecting neoplasia in patients with IBD. Performing random biopsies in unsuspicious mucosa after CE remains controversial.

Methods Consecutive patients with IBD who underwent surveillance colonoscopy using CE were prospectively included. The standardised procedure used CE, performed targeted biopsies or endoscopic resection on suspicious lesions and then quadrant random biopsies every 10 cm. A panel of five expert pathologists reviewed histological slides with dysplasia. Logistic regression model was used to evidence the factors associated with neoplasia in any or in random biopsies.

Results 1000 colonoscopes were performed in 1000 patients (495 UC, 505 Crohn's colitis). In 82 patients, neoplasia was detected from targeted biopsies or removed lesions, and among them dysplasia was detected also by random biopsies in 7 patients. Importantly, in 12 additional patients dysplasia was only detected by random biopsies. Overall, 140 neoplastic sites were found in 94 patients, 112 (80%) from targeted biopsies or removed lesions and 28 (20%) by random biopsies. The yield of neoplasia by random biopsies only was 0.2% per-biopsy (68/31 865), 1.2% per-colonoscopy (12/1000) but 12.8% per-patient with neoplasia (12/94). Dysplasia detected by random biopsies was associated with a personal history of neoplasia, a tubular appearing colon and the presence of primary sclerosing cholangitis (PSC).

Conclusions Despite their low yield, random biopsies should be performed in association with CE in patients with IBD with a personal history of neoplasia, concomitant PSC or a tubular colon during colonoscopy.

Trial registration number IRB 001508, Paris 7 University.

Significance of this study

What is already known on this subject?

- Guidelines recommend surveillance colonoscopy to detect neoplasia in patients with IBD and long-standing colonic involvement.
- Chromoendoscopy with targeted biopsies is increasingly recommended for surveillance, and the need for additional random biopsies is debated.

What are the new findings?

- In a large series of patients with IBD at risk of neoplasia, chromoendoscopy with targeted biopsies and endoscopic removal of resectable lesions detects most of the patients with neoplasia.
- The additional percentage of patients with neoplasia detected only by random biopsies performed in unsuspicious appearing mucosa is around 15%.
- Detection of neoplasia by random biopsies is associated with a personal history of neoplasia, concomitant primary sclerosing cholangitis (PSC) and a tubular appearing colon.
- The likelihood to find neoplasia by random biopsies is nearly nil in patients in whom these three risk factors are lacking, which accounts for the majority of patients.

How might it impact on clinical practice in the foreseeable future?

- This prospective study shows that a personal history of neoplasia, concomitant PSC or a tubular appearing colon may still warrant taking random biopsies during surveillance colonoscopy with chromoendoscopy.
- This study will help to stratify patients with IBD in whom random biopsies warrant to be or not to be performed during surveillance colonoscopy using chromoendoscopy.

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INTRODUCTION

Patients with a long-standing UC have an increased risk of colorectal cancer (CRC). Growing evidence suggests a similar risk in patients with Crohn's

disease (CD), with an extensive colonic involvement. In both diseases, clinical factors and several endoscopic features resulting from chronic or severe inflammation (ie, postinflammatory polyps, strictures, tubular or shortened colon) have been shown to predict an increased risk of neoplasia.[1–6]

In patients with IBD, CRC develops through a chronic inflammation-dysplasia-carcinoma sequence and dysplasia may appear in flat mucosa. Protocols for CRC surveillance recommended classically to take random biopsies (2–4 every 10 cm) with additional biopsies on suspicious areas if conventional colonoscopy was used. Chromoendoscopy (CE) of the entire colon with targeted biopsies and endoscopic removal of resectable lesions is now being increasingly recommended for surveillance.[1–3] Compared with conventional endoscopy with random biopsy, the likelihood to detect any dysplasia is 8.9 times higher (95% CI 3.4% to 23%) when using CE.[7]

The dysplasia yield of random biopsies is very low when using CE;[8] therefore, it has been suggested that random colonic biopsies should be abandoned if CE is undertaken.[1 2 9–11] This would decrease duration of the colonoscopic procedure and costs related to pathology analysis. However, abandoning random biopsies when using CE means that, when no lesion is detected with CE, no biopsy has to be performed. Yet, it is currently recommended to take random biopsies to assess histological disease extent and mucosal healing, and to determine if there is histological inflammation that will require enhanced surveillance.[2 3] Abandoning random biopsies when using CE in case of treating dysplastic lesion by endoscopic resection may also reduce the likelihood to find associated dysplasia elsewhere in the colon, a finding that should initiate referral for colectomy.[1 2] Likewise, abandoning random biopsies risks to reduce the likelihood to find dysplasia in multiple areas, which has not the same prognostic value as dysplasia located in a single area.[1 12] Finally, in the three prospective studies using dye-enhanced methods of the entire colon (pancolonic CE and not in a targeted fashion) and performing targeted biopsies and subsequently random biopsies, although the yield of random biopsies is very low (0.1%–0.4%), the additional percentage of patients diagnosed with neoplasia by only random biopsies may be notable (8.3%–30.8%).[13–15] As a result, panellists did not reach consensus regarding random biopsies when using CE in the recent Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) consensus statement.[8]

The aims of this prospective study were (1) to determine the number of patients in whom neoplasia was detected by random biopsies in relation to that in whom neoplasia was detected as a whole (by either targeted biopsies and resection of CE-visible lesions or random biopsies), (2) to assess the impact of neoplasia found in random biopsies and (3) to re-evaluate the risk factors for neoplasia in general or found in random biopsies in a large series of patients with IBD.

PATIENTS AND METHODS

Patients

It was a prospective multicentre cohort study conducted in 14 French academic departments of gastroenterology from the Groupe d'Etudes et de Thérapeutiques des Affections Inflammatoires du tube Digestif (GETAID). Consecutive patients were recruited according to the following criteria: (1) an extensive (proximal to the splenic flexure) or pancolitis UC or a colonic CD (involving at least one-third of the colon) with a duration of >8 years, (2) or a left colitis UC with a duration of >15 years, (3) or at the time of diagnosis of associated primary sclerosing cholangitis (PSC), (4) and an indication for colonoscopy to detect neoplasia. Patients could have had bowel resection excepted subtotal colectomy. They had to present, as far as possible, a clinically quiescent IBD defined as an abbreviated Colitis Activity Index (CAI) without endoscopy <3 for UC and a Harvey-Bradshaw Index (HBI) <5 for patients with CD. Finally, patients were not included in the study when the endoscopy revealed poor bowel preparation preventing from doing CE or was incomplete. All participants had colonoscopy according to clinical need and gave informed consent to the protocol, which was approved by the Institutional Review Board of the GETAID.

Colonoscopy protocol

Patients received a standard bowel preparation (low-fibre diet and oral intake of 4 L of polyethylene glycol). In all examinations, a high-definition video endoscope without optical magnification was used under sedation. All the endoscopists, members of the GETAID group, had a specific expertise in colitis surveillance and CE with at least 5 years of experience after full graduate training. The CE was performed only when the quality of the preparation was rated excellent (clean and empty), good (clear fluid) or fair (brown fluid but no residue after aspiration). The endoscopist had to qualify the aspect of the colon as normal, tubular or reduced in length, and recorded the presence of backwash ileitis. On withdrawal from the caecum to the rectum, the endoscopist reported in each 10 cm colonic segment the presence of postinflammatory polyps or colonic stricture. Endoscopic severity was scored as no inflammation, mild (erythema, decreased vascular pattern, mild friability, aphthous lesion), moderate (marked erythema, absent vascular pattern, superficial ulceration) or severe inflammation (spontaneous bleeding, ulceration). Each 10 cm segment was then sprayed by using a catheter with 0.25% indigo carmine; when suspicious lesions were evidenced, their location and size were recorded and they were classified according to Paris criteria.[16] The duration of the colonoscopy was not recorded.

Biopsy protocol

All lesions identified as suspect by the endoscopist were biopsied or resected endoscopically. As recommended,[1 8 17] the flat mucosa surrounding suspicious lesion was biopsied to assess whether there was any dysplasia in the surrounding mucosa. We distinguished in two separate jars the targeted biopsies or the resected lesion and the biopsies around the lesion. Finally, according to standard guidelines, two (on current or previous non-affected area) to four quadrant random biopsies (on current or previous affected area) were performed every 10 cm from normal appearing mucosa without a visible lesion and put in individual jars. The number of biopsies was calculated from the pathology report.

Pathological evaluation

Biopsies were analysed by the pathologist of each centre for the presence of inflammation and of neoplasia. All biopsy slides, on which the diagnosis of dysplasia was made by the local GI pathologist, were sent to be reviewed jointly by a panel of five expert GI pathologists (DC-H, PB, AL-S, J-FF and FB) with extensive experience in the field of IBD in order to obtain a consensual diagnosis and to refrain from using the indefinite dysplasia category. Neoplasia was graded according to the revised Vienna classification[18] as low-grade dysplasia (LGD), high-grade dysplasia (HGD) and cancer; those graded as 'indefinite for dysplasia' were not considered neoplastic. Neoplasia

was classified to be in random biopsies if a histological diagnosis of neoplasia was made in the absence of documentation by the endoscopists and pathologists of a lesion.

Statistics

Statistical analysis was performed with SPSS V.17 (SPSS, Chicago, Illinois, USA). Descriptive statistics were presented with n (%), means±SD or median values with their IQR. The quantitative and qualitative data were compared by using the Mann-Whitney U test and χ^2 test, respectively ($p<0.05$). A multivariable logistic regression model was used to detect an association between neoplasia and risk factors as type of IBD, age, extension and duration of disease, presence of familial or personal history of colonic neoplasia (previous neoplasia detected on lesions and/or by random biopsies, a distinctive finding not collected), concomitant PSC, moderate or severe endoscopic inflammation and histological inflammation (in at least one colonic segment), colonic appearance, that is, normal without postinflammatory polyps, tubular or shortened, presence of postinflammatory polyps, colonic strictures, backwash ileitis and current IBD treatment. A second multivariable logistic regression model was used to detect an association between dysplasia evidenced by random biopsies and the same risk factors. As the management of dysplastic lesions depends on the presence of dysplasia in random biopsies elsewhere in the colon,[1 2] patients included in this second analysis had either dysplasia in random biopsies only or in both random biopsies and targeted specimens. Variables associated with neoplasia (any or in random biopsies) on univariable analysis ($p<0.30$) were introduced in the multivariable model. Final multivariable model was obtained through backward selection using the likelihood ratio test. In addition, a simplified model was derived by combining the number of risk factors. ORs with 95% CI were used to express the strength of the association.

RESULTS

Clinical characteristics of the patients

From March 2009 to December 2011, 1058 patients with IBD were recruited. Fifty-eight patients were not included because of poor bowel preparation (57) or incomplete endoscopy due to anaesthetic problem (1). Finally, 1000 patients (495 UC and 505 CD) were included in the study (table 1). The number of previous colonoscopes averaged 1.1±1.5 (mean±SD, range 0–10).

Endoscopic features

The quality of bowel preparation was excellent, good or fair in 362, 399 or 239 patients, respectively. Neoplastic lesions were found in 32 patients out of 362 (8.8%), 27 patients out of 399 (6.8%) and 23 patients out of 239 (9.6%), when the preparation was excellent, good and fair, respectively ($p=0.28$ excellent vs good, $p=0.74$ excellent vs fair and $p=0.19$ good vs fair).

Inflammation was detected endoscopically in at least one 10 cm colonic segment in 408 patients (41%) (205 UC and 203 CD). The worst endoscopic inflammation in at least one 10 cm colonic segment was qualified as mild in 211 patients, moderate in 174 patients and severe in 23 patients. Among the 197 patients with moderate-to-severe inflammation, 131 (66%), 57 (29%) and 9 (5%) had 1, 2 and 3 inflamed colonic segments, respectively. Inflammation was noted histologically in at least one 10 cm colonic segment in 467 patients (47%) (213 UC and 254 CD). Terminal ileal intubation was performed in 338 out of 495 patients with UC and backwash ileitis was documented in 16 of them (5%). Stenosis was documented in 50 patients (12 UC and 38 CD) and postinflammatory polyps in 286 patients (161 UC and 125 CD). The colon appeared normal and without postinflammatory polyps in 356 patients (36%) (200 UC and 156 CD), tubular in 52 (5%) and reduced in length in 55 (6%).

Table 1 Patient characteristics at inclusion (n=1000 unless otherwise indicated)

	IBD	UC (n=495)	CD (n=505)	p Value*
Age (year)				
Median (IQR)	45 (37–56)	48 (39–58)	43 (35–53)	<0.001
Sex, male, n (%)	470 (47)	281 (57)	189 (37)	<0.001
Clinical activity (abbreviated CAI for UC or HBI for CD) at inclusion, n (%)				
CAI<3		480 (97)		
HBI<5			470 (93)	
Duration of disease (year)†				
Median (IQR)	16 (11–22)	16 (11–22)	16 (11–22)	0.81
Extension: extensive/pancolitis for UC or ≥4 segments for CD, n (%)‡§	769 (78)	375 (77)	394 (78)	0.39
Primary sclerosing cholangitis, n (%)	85 (9)	48 (10)	37 (7)	0.21
Familial history of colonic neoplasia, n (%)¶	106 (12)	59 (14)	47 (10)	0.18
Personal history of colonic neoplasia, n (%)	103 (10)	73 (15)	30 (6)	
Number of previous surveillance colonoscopes per-patient median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	0.001
Maintenance therapy**				
Mesalamine, n (%)	613 (61)	338 (68)	275 (54)	<0.001
Immunosuppressants, n (%)††	249 (25)	66 (13)	183 (36)	<0.001

*UC versus CD.
†n=943.
‡n=990.
§Pancolitis/extensive UC and Crohn's colitis ≥4 segments.
¶n=890; referred to first-degree family members.
**Therapy was considered when patients used the medication for at least 6 months before the colonoscopy whatever the dose. Only few patients were under treatment by anti-TNF antibodies.
††Thiopurines or methotrexate.
CAI, Colitis Activity Index without endoscopy; CD, Crohn's disease; HBI, Harvey-Bradshaw index; TNF, tumour necrosis factor.

Table 2 Total and median number of biopsies, random biopsies and targeted specimens

	IBD (n=1000)	UC (n=495)	CD (n=505)	p Value*
Total number of biopsies	35 630	17 967	17 663	
Median (IQR)	34 (29–40)	35 (30–41)	33 (28–40)	0.02
Total number of random biopsies	31 865	15 781	16 084	
Median (IQR)	30 (27–37)	31 (26–37)	30 (26–36)	0.82
Total number of targeted specimens†	3801	2 184	1 617	
Median (IQR)	0 (0–5)	2 (0–6)	0 (0–4)	<0.001

*UC versus CD.
†Targeted biopsies, resected lesions and from the mucosa surrounding the lesions.
CD, Crohn's disease.

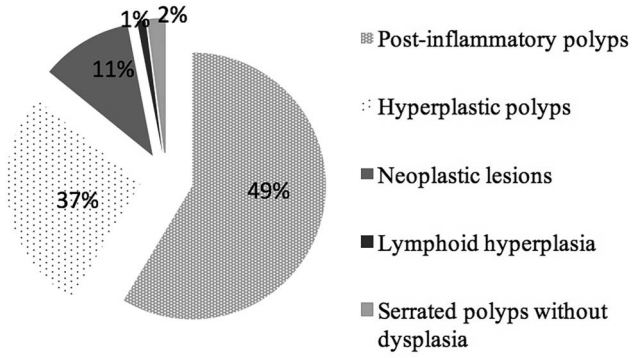

Figure 1 Pathological characteristics of lesions (n=1044) assessed as suspicious during colonoscopy.

Per-biopsy analysis

During the 1000 colonoscopes, a total of 35 630 biopsies were performed (14–93 per-patient), corresponding to a mean of 35.6±11.2 biopsies per-surveillance colonoscopy (table 2).

A total of 3801 targeted specimens (ie, targeted biopsies and resected lesions) were performed on 1044 suspicious lesions and from the mucosa surrounding the lesions. The number of targeted specimens was significantly higher in patients with UC (p<0.001) than in patients with CD. The mean number of lesions was 1.1±1.6 per-colonoscopy, and among them there were 112 (11%) neoplastic lesions (figure 1 and table 3). Among 112 neoplastic lesions, 94 were treated endoscopically, 8 removed by polypectomy, 32 by mucosal resection, 1 by submucosal dissection and the remainder—n=53—was small (<5 mm) and removed by cold biopsy forceps. Eighteen neoplastic lesions detected on biopsy analysis in 16 patients were referred for surgery. In addition to five macroscopic cancers and six dysplastic lesions (5 0-IIa and 1 0-Is, wide with no clear margins and adjuvant flat dysplasia), seven dysplastic lesions (3 0-Is, 2 0-IIb, 1 0-IIa and 1 0-IIa/0-IIc, size 4–6 cm) were not amenable to endoscopic resection because of non-lifting at submucosal injection.

The total number of random biopsies was 31 865, with a mean number per-patient of 31.9±9.1 (table 2). This latter was not higher in patients known to have history of dysplasia (31.2 ±10.6 vs 32.1±8.9, p=0.36) or PSC (32.4±11.1 vs 31.8±8.8, p=0.29) and when the bowel preparation was fair or excellent/good (31.5±8.5 vs 32.4±9.5, p=0.20). Among 31 865 random biopsies, only 68 demonstrated dysplasia (59 LGD and 9 HGD) and dysplasia was detected in random biopsies in a total of 28 sites (24 LGD and 4 HGD) (table 4). The dysplasia yield of random biopsies was 0.2% (68/31 865).

Overall, 140 neoplastic sites were found, 112 (80%) from targeted biopsies or removed lesions and 28 (20%) by random biopsies only.

Per-patient analysis

A total of 470 patients presented at least one suspicious lesion (range 1–12): 262 patients with UC (53%) and 208 patients with CD (41%). Ninety-four patients (9.4%) presented at least one neoplastic site: 75 patients (7.5%) presented at least one neoplastic lesion evidenced from targeted biopsies or removed lesions, 7 patients (0.7%) presented at the same time at least one dysplastic lesion with also dysplasia in random biopsies and 12 patients (1.2%) presented dysplasia only in random biopsies (figure 2 and table 4). The per-patient dysplasia yield of random biopsies only was 12.8% (12/94).

Among the seven patients with dysplastic lesions and also dysplasia in random biopsies, dysplasia in random biopsies was multifocal in two of them (table 4). Among the 12 patients with dysplasia in random biopsies only, dysplasia was multifocal in 4 patients (table 4). In two out of three patients in whom HGD was found in random biopsies, dysplasia was also detected by targeted biopsies on neoplastic lesions. Cancer was detected by targeted biopsies in five patients, but was never detected by random biopsies (table 3).

Table 3 Characteristics of the 112 neoplastic lesions found in 82 patients

	Grade of neoplastic lesions, n (%)					Location		Patients with neoplastic lesions, n	
Neoplastic lesions, n	LGD	HGD	Cancer	Paris class	Size, mm mean±SD	RCP	LCP	UC	CD
112*	97 (87)	10 (9)	5 (4)†	50 0-IIa, 39 0-Is, 13 0-IIb, 8 0-Ip, 2 0-Iia/0-IIc	10±12	64	48	47	35

*Sixteen neoplastic lesions were located in current or previous non-affected areas.
†Two patients with UC underwent restorative proctocolectomy with ileal pouch anal anastomosis (pT2N0 and pT2N0 adenocarcinomas); one old patient with UC underwent rectal anterior resection (pT2N0 adenocarcinoma). Two patients with CD underwent colectomy with ileorectal anastomosis (pT3N0 and pT3N+ adenocarcinomas).
CD, Crohn's disease; HGD, high-grade dysplasia; LCP, left colonic part (descending/sigmoid colon and rectum); LGD, low-grade dysplasia; RCP, right colonic part (ascending/transverse colon).

Table 4 Characteristics of random biopsies with dysplasia (IEN) in patients with either dysplasia in random biopsies only (n=12) or in random biopsies and associated dysplastic lesions (n=7)

	Random biopsies with IEN, n	Grade of IEN in random biopsies, n		Dysplastic sites in random biopsies, n	Grade of IEN sites, n		Patients with IEN in random biopsies, n			Grade of IEN in patients, n		Patients with multifocal IEN in random biopsies, n
		LGD	HGD		LGD	HGD	UC	CD	IBD	LGD	HGD	
IEN in random biopsies only	48	42	6	18	16	2	7	5	12	11	1	4/12
IEN in random biopsies and also dysplastic lesions	20	17	3	10	8	2	5	2	7	5	2	2/7
Total	68	59	9	28	24	4	12	7	19	16	3	6/19

CD, Crohn's disease; HGD, high-grade dysplasia; IEN, intraepithelial neoplasia, that is, dysplasia; LGD, low-grade dysplasia.

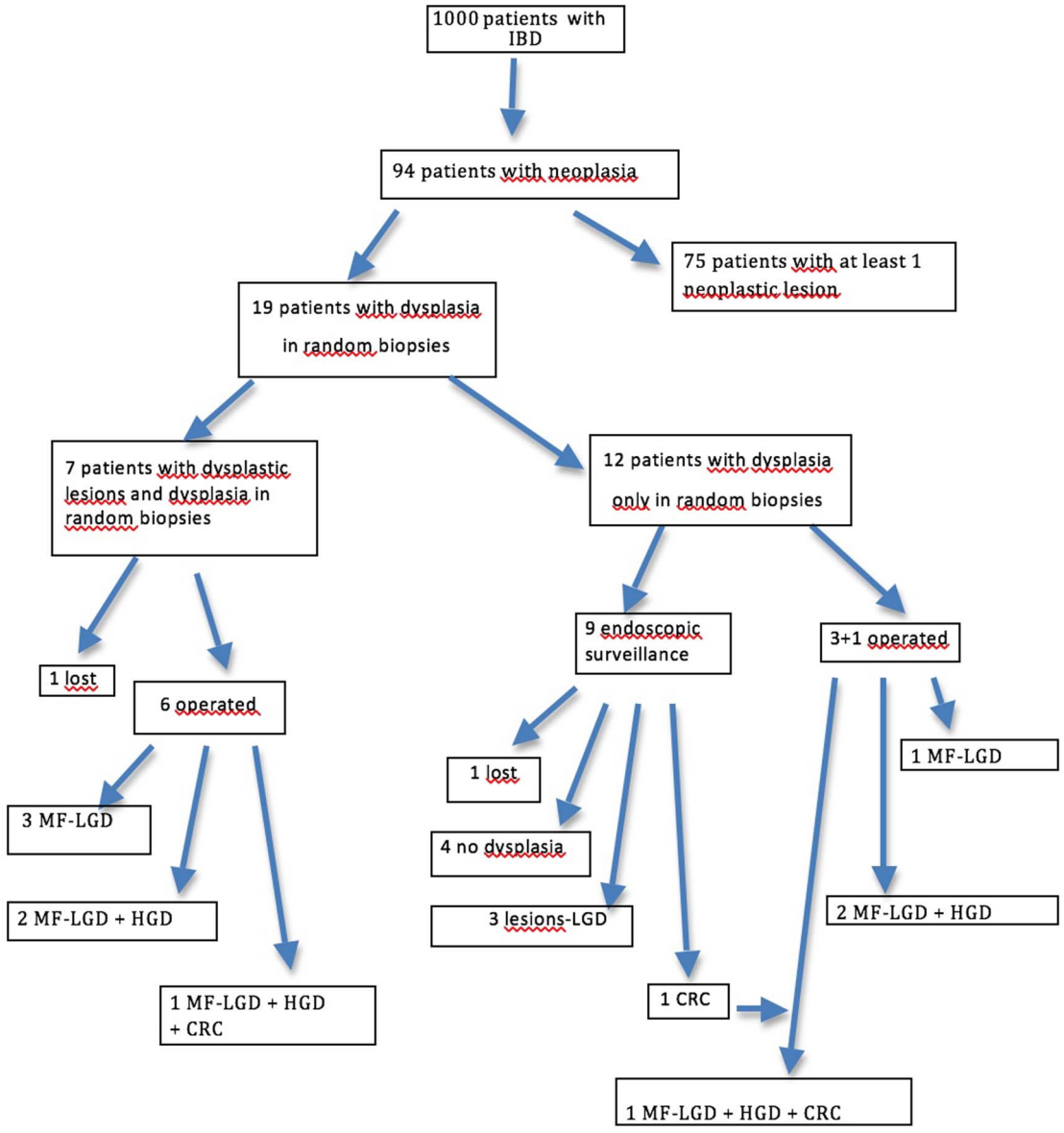

Figure 2 Outcome of patients with dysplasia in random biopsies. MF, multifocal; LGD, low-grade dysplasia; HGD, high-grade dysplasia; CRC, colorectal cancer.

The mean number of random biopsies performed per-patient with dysplasia detected by random biopsies was very close to that of patients without dysplasia in random biopsies (31.8±9.9 and 32.0±8.8, respectively). In addition, the mean number of neoplastic lesions per-patient with dysplasia detected by random biopsies was not smaller than that in patients without dysplasia in random biopsies (1.7±0.8 and 1.3±0.7 neoplastic lesions per-patient, respectively).

Follow-up of patients with dysplasia in random biopsies

Among the seven patients with dysplastic lesions and dysplasia in random biopsies, one patient was lost from follow-up and three patients were operated because lesions were not amenable to complete endoscopic resection (pts 17, 18, 19 in online supplementary table). Postoperative histopathology revealed multifocal LGD in two patients and multifocal LGD and HGD in one patient. Three other patients had raised lesions, which were resected endoscopically, but were operated because they had LGD in random biopsies during earlier colonoscopes (pts 13, 14, 15). The surgical specimen revealed multifocal LGD in one patient, multifocal LGD and HGD in one patient and multifocal LGD and HGD associated with two adenocarcinomas (pT1N0) in the last one (see figure 2).

Among the 12 patients who presented dysplasia detected by only random biopsies, 8 patients had unifocal LGD and underwent subsequent colonoscopes (median follow-up 24 months, range 14–40). In four patients subsequent colonoscopes did not confirm neoplasia, one patient was lost of follow-up and three patients showed LGD on lesions, which were endoscopically resected and located in a different site from initial dysplasia. Three patients had multifocal LGD and one multifocal HGD, three of them underwent subsequent colectomy (pts 10, 11, 12). Postoperative histopathology revealed multifocal LGD in one patient and multifocal LGD and HGD in two patients at the same site as previously noted in colonoscopy and elsewhere along the colon. The last patient with multifocal LGD in the rectum and sigmoid colon declined surgery and elected for endoscopy surveillance (pt 9). Subsequent colonoscopes showed rectal LGD in one random biopsy 7 months later and finally a rectal cancer 30 months later (pT2N1 associated with multifocal LGD and HGD in the rectum and sigmoid colon in the surgical specimen after restorative proctocolectomy with ileal pouch anal anastomosis). Adjuvant chemotherapy was performed and the patient was still alive without recurrence at the last visit 44 months after surgery.

Risk factors of neoplasia

On multivariable regression analysis, age >45 years, personal history of neoplasia, concomitant PSC and strictly normal appearing colon without postinflammatory polyps were independently associated with neoplasia detected by targeted specimens and random biopsies (table 5). There was no significant association between location of neoplastic sites and one of these four risk factors. The likelihood to find neoplasia was 2.8% in 358 patients, 7.8% in 410 patients, 19.2% in 182 or 34.0% in 50 patients, respectively when 0, 1, 2 or 3–4 factors were present.

A further multivariable regression analysis was performed to evaluate associations between risk factors of neoplasia and the detection of dysplasia by random biopsies in 19 patients. Personal history of neoplasia, concomitant PSC and tubular colon were the only significant independent risk factors of neoplasia detected by random biopsies (table 6). The presence of suspicious lesions was associated with an increased risk of dysplasia on univariable but not after multivariable analysis. The likelihood to find neoplasia was 0.5% in 782 patients, 5.1% in 197 patients or 23.8% in 21 patients, respectively when 0, 1 or 2–3 factors were present.

Table 5 Univariable and multivariable analysis evaluating associations between risk factors and the detection of neoplasia during colonoscopy* (n=1000 unless otherwise indicated)

Risk factors of neoplasia	Univariable analysis OR (95% CI)	p Value	Multivariable analysis OR (95% CI)	p Value
Diagnosis CD UC	1.4 (0.9 to 2.1)	0.110		
Age ≤45 years >45 years	3.6 (2.3 to 5.6)	<0.001	3.0 (1.9 to 4.8)	<0.001
Duration† ≤22 years >22 years	1.8 (1.1 to 2.8)	0.018		
Extensive colonic disease‡§	1.0 (0.6 to 1.6)	0.903		
Familial history of neoplasia¶	0.9 (0.4 to 2.0)	0.803		
Personal history of neoplasia**	5.3 (3.3 to 8.8)	<0.001	4.1 (2.5 to 6.9)	<0.001
Primary sclerosing cholangitis	2.3 (1.2 to 4.2)	0.006	2.5 (1.3 to 4.7)	0.008
Endoscopic inflammation††	1.0 (0.6 to 1.6)	0.888		
Histological inflammation‡‡	0.7 (0.4 to 1.1)	0.133		
Normal appearing colon	1.8 (1.2 to 2.8)	0.005	1.6 (1.0 to 2.6)	0.035
Tubular colon	1.5 (0.7 to 3.5)	0.303		
Shortened colon	1.7 (0.8 to 3.7)	0.180		
Postinflammatory polyps	1.3 (0.8 to 2.0)	0.324		
Colonic strictures	1.1 (0.4 to 2.8)	0.881		
Backwash ileitis§§	1.9 (0.5 to 7.2)	0.314		
Using mesalamine	0.7 (0.5 to 1.1)	0.090		
Using immunosuppressants	0.9 (0.6 to 1.6)	0.919		

*Neoplasia was present in 94 patients and absent in 906 patients.
†n=943.
‡n=990.
§Pancolitis/extensive UC and Crohn's colitis ≥4 segments.
¶n=890.
**Previous neoplasia on lesions and/or random biopsies.
††Moderate or severe inflammation in at least one colonic segment.
‡‡In at least one colonic segment.
§§In 338 patients with UC with ileal intubation.
CD, Crohn's disease.

Table 6 Univariable and multivariable analysis evaluating associations between risk factors and the detection of neoplasia by random biopsies* (n=1000 unless otherwise indicated)

Risk factors of neoplasia	Univariable analysis OR (95% CI)	p Value	Multivariable analysis OR (95% CI)	p Value
Diagnosis CD UC	1.8 (0.7 to 4.5)	0.229		
Age ≤45 years >45 years	0.9 (0.4 to 2.4)	0.914		
Duration† ≤22 years >22 years	1.8 (0.7 to 4.7)	0.200		
Extensive colonic disease‡§	2.5 (0.6 to 10.8)	0.209		
Familial history of neoplasia¶	0.4 (0.1 to 3.2)	0.400	12.7 (4.9 to 33.3)	<0.001
Personal history of neoplasia**	13.3 (5.2 to 33.9)	<0.001		
Primary sclerosing cholangitis	4.0 (1.4 to 11.5)	0.005	4.1 (1.3 to 12.9)	0.026
Endoscopic inflammation††	1.5 (0.5 to 4.1)	0.464		
Histological inflammation‡‡	1.7 (0.6 to 4.4)	0.278		
Normal appearing colon	1.3 (0.5 to 3.3)	0.550	7.0 (2.2 to 22.5)	0.004
Tubular colon	7.1 (2.5 to 20.5)	<0.001		
Shortened colon	2.1 (0.5 to 9.2)	0.332		
Postinflammatory polyps	1.5 (0.6 to 3.8)	0.422		
Colonic strictures	1.1 (0.1 to 8.1)	0.958		
Backwash ileitis§§	3.0 (0.3 to 26.0)	0.300		
Suspicious lesions	3.2 (1.2 to 9.0)	0.019		
Using mesalamine	1.4 (0.5 to 3.7)	0.520		
Using immunosuppressants	1.8 (0.7 to 4.6)	0.224		

*Neoplasia was detected by random biopsies in 19 patients and absent in 981 patients.
†n=943.
‡n=990.
§Pancolitis/extensive UC and Crohn's colitis ≥4 segments.
¶n=890.
**Previous neoplasia on lesions and/or random biopsies.
††Moderate or severe inflammation in at least one colonic segment.
‡‡In at least one colonic segment.
§§In 338 patients with UC with ileal intubation.
CD, Crohn's disease.

DISCUSSION

In this study, 1000 colonoscopes were performed in 1000 patients, including as many patients with UC as with Crohn's colitis. We used prospectively a protocolised surveillance examination, which follows classic (with the large number of biopsies required to detect dysplasia with a high confidence)[19] and recent guidelines (CE) applied to a large number of patients. Overall, the mean number of biopsies per-colonoscopy was 35.6 ±11.2 and a special care was paid to confirm neoplasia by an expert group of GI pathologists. Neoplasia was detected in 94 patients, that is, 9.4%, which is in the range of what is reported using CE by most series (between 6% and 21%).[5 11 13 20–22] In 82 patients, neoplasia was detected from targeted biopsies or removed lesions, and among them dysplasia was detected also by random biopsies in 7 patients. In 12 additional patients, dysplasia was only detected by random biopsies. Overall, 140 neoplastic sites were found in 94 patients of which 20% by random biopsies. The yield of neoplasia by random biopsies only was 0.2% per-biopsy, 1.2% per-colonoscopy (12/1000) but 12.8% per-patient with neoplasia (12/94). In 10 patients, in whom several neoplastic sites were detected either by random biopsies only or by both random and targeted specimens, the surgical specimens confirmed the presence of multifocal neoplasia with cancer in two patients.

Some authors consider that dysplasia found on random biopsies is only due to a default of CE quality. First, we performed CE only when the global assessment of bowel cleanliness was excellent/good or fair and, although preparation was not totally satisfactory in 24% of the study subjects, this did not affect the detection rate of neoplastic lesions. We did not use the Boston Bowel Preparation Score, which was not fully validated at the time of designing our study. Instead, we used a home-made score, which assessed colonic cleanliness taken as a whole without the ability to capture colonic segment differences. With this score, fair bowel preparation was defined as brown fluid but no residue after aspiration and represented the worst colonic segment. Our fair preparation corresponded to a Boston score of 2 and did not mean that individual colonic segments had all this score or a Boston score of 3, this latter corresponding to our excellent/good preparation. Second, the proportion of neoplastic lesions (11%) among suspicious detected lesions was in the range of other series using CE (6%–16%).[5 11 23 24] Third, the number of neoplastic lesions per-patient was not smaller in patients with dysplasia evidenced by random biopsies and the mean number of random biopsies performed per-patient with or without dysplasia in random biopsies was very close. Finally and above all, the histological diagnosis of dysplasia in random biopsies was made in the absence of documentation by the expert pathologists of a lesion at the biopsy site. Altogether, these data show that in our study the endoscopist's skill and expertise with CE, which may be lower than in highly specialised endoscopy centres, should not explain the rate of patients with dysplasia found by random biopsies only. Moreover, this rate (1.2%) is close to that found in similar studies using CE (1.2%–6.2%).[8 13–15 20] As a result, the additional percentage of patients detected with neoplasia by random biopsies only was

around 15% in our study, which is in the range of that reported previously using CE (8%–31%).[8 13–15 20]

Our results confirm that in some cases dysplasia cannot be seen by CE but could be detected by the random biopsies.[13 15] They are in line with previous data showing that dysplasia in patients with IBD may begin in the crypt bases and progress with time to involve the full length of the crypt and the surface epithelium (bottom-to-up growth pattern), which explain why CE can fail in detecting dysplasia.[25–29] As in other studies,[6 15] dysplasia detected by random biopsies was frequently unifocal with low grade (12 out 19 patients, table 4 and online supplementary table). It remains a controversy to the significance of detectable dysplasia in apparently normal mucosa and to its clinical impact. In the 10 patients with several neoplastic sites detected either by random biopsies only or by both random and targeted specimens, multifocal neoplasia with cancer in one patient was confirmed in the surgical specimen of nine operated patients (figure 2 and online supplementary table). In addition, a rectal cancer was diagnosed during the follow-up in one patient who elected for intensified endoscopic surveillance. Omitting random biopsies would have changed clinical management in seven patients since three patients required surgery because they had neoplastic lesions not amenable to endoscopic resection.

Several independent risk factors of neoplasia have been reported in patients with IBD[1–6 30 31] that we found in our study on multivariable analysis, such as age, personal history of neoplasia and PSC, duration being associated with neoplasia only on univariable analysis (table 5). A strictly normal colonic appearance was also associated with a slightly increased risk of neoplasia, suggesting that neoplastic lesions could be better detected in an otherwise normal colon. This finding contrasts with some previous studies performed in patients with UC without CE,[6 32] but it is in line with a recent work.[33] The difference in risk factors of neoplasia among different cohorts of patients could be due to variation in patient characteristics in terms of neoplastic risk. In our study, half of the patients had CD, whereas previous studies have included exclusively or mainly patients with UC. Although dysplasia was found in a smaller number of patients with CD than with UC, the diagnosis (UC vs CD) was not associated with a higher risk of neoplasia (table 5), supporting the same surveillance strategies for patients with UC and CD.

In this work, personal history of neoplasia, concomitant PSC and the presence of tubular colon were independently associated with the detection of dysplasia by random biopsies, whereas the presence of suspicious lesions was associated with an increased risk on univariable but not after multivariable analysis (table 6). Two recent retrospective studies aimed to evaluate the yield and clinical impact of random biopsies during surveillance colonoscopy.[6 34] van den Broek *et al*[6] studied 167 patients with UC who underwent several colonoscopes without CE (n=466). Although they showed a lack of clinical impact of random biopsies, they recommended taking random biopsies only in case of the presence of PSC, tubular colon and visible neoplastic lesions. Navaneethan *et al*[34] studied 71 patients with UC with PSC who underwent several colonoscopes without CE (n=267). Patients with prior diagnosis of neoplasia were excluded. They concluded that random biopsies significantly increased the yield of neoplasia in patients with PSC-UC even in the absence of endoscopic features of prior inflammation and significantly impact clinical outcomes. Taking into account these retrospective data with our prospective results, instead of abandoning random biopsies, their selective use during colonic surveillance using CE may be a realistic option in patients with a personal history of neoplasia, concomitant PSC or a tubular colon. Conversely, as the risk of dysplasia detected by random biopsies is nearly nil when these three factors are lacking, it may be considered omitting random biopsies in such clinical states, that is, in the majority of patients from this study (n=782). However, one may argue that this proposition would result in reducing the subsequent rate of personal history of neoplasia; this cannot be evaluated in our study since we did not assess whether neoplasia found during previous colonoscopes were from random or targeted biopsies, and most of previous colonoscopes were done in our patients without CE and high-definition endoscopes.

Our study has some limitations. We used endoscopes from different companies, which may vary in resolution, and we did not assess the duration of the procedure, two factors that may affect the detection of dysplasia. As in other studies, endoscopic features of suspicious lesions, backwash ileitis or indicative of chronic or severe previous inflammation were based on the endoscopist's subjective assessment. In addition, validated scoring systems were not used to assess the endoscopic inflammation in a mixed cohort of patients with IBD and the histological inflammation. A special care was paid to confirm dysplasia by an expert group of GI pathologists, and we can consider that the pathological results are conclusive enough to validate the dysplasia frequency. However, our study was not designed to evaluate the role of an expert pathologist review in relation to the diagnosis of dysplasia made by GI pathologists from academic centres. In addition, we did not perform cost-effectiveness analysis taking into account expenses and time taken for additional random biopsies and pathologist working load in one hand and clinical benefit in the other hand.

In conclusion, this prospective study, specifically designed to evaluate the yield of neoplasia from random biopsies during surveillance colonoscopy with CE, confirms its low yield, but demonstrates the interest of performing random biopsies in patients with IBD, who present a personal history of neoplasia, concomitant PSC or a tubular colon during colonoscopy.

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Contributors DM, MA, DL, J-MR, PM, J-FC, A-LC, SN, YB, FB designed and performed the study, analysed the data and wrote the manuscript. XT, AB, HB, J-MG, CS, JM, A-LP, FC, PS, MS performed the study and were involved in the critical revision of the manuscript. DC-H, PB, A-LV, J-FF, FB reviewed slides with neoplasia and revised the manuscript critically for important intellectual content.

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