**APPENDIX 1**

**Danish Society for Gastroenterology and Hepatology’s clinical recommendations (English translation)**

**Colonoscopic surveillance of patients with chronic inflammatory bowel disease (IBD) for dysplasia and colorectal cancer in patients with inflammatory bowel diseases.**

**Is the risk of dysplasia and CRC increased in patients with ulcerative colitis?**

Multiple studies have shown that the incidence of CRC is increased in patients with ulcerative colitis. The relative risk (RR) varies among countries, and is less than originally assumed in a comprehensive meta-analysis from 2001, which included studies of varying quality, from surgical case series to population-based cohort studies (1). The meta-analysis found a cumulative risk of CRC after 30 years at 18%.

In a meta-analysis from 2012 based on population-based studies in Denmark, Sweden, and Canada amongst others, there was a significantly increased risk of developing CRC (standardised incidence ratio [SIR] 2.4, 95% CI 2.1 to 2.7). The risk in patients with extensive ulcerative colitis (inflammation proximal to the left colic flexure) increased almost five-fold (SIR 4.8, 95% CI 3.9 to 5.9) (2).

In a meta-analysis by Lütgens et al in 2013, the risk of CRC increased in patients with ulcerative colitis, both in population-based studies (SIR 1.7, 95% CI 1.03 to 2.4). However, the risk of CRC was not increased in patients with left-sided ulcerative colitis in population-based studies (SIR 1.7, 95% CI 0.6 to 4.5) (3).

In the French CESAME study, almost 20 000 thiopurine-treated IBD patients participated, 30% with ulcerative colitis. Among patients with both a long duration and extensive ulcerative colitis, there was a five-fold increased risk of CRC (SIR 5.22, 95% CI 2.39 to 9.91). The CESAME study was not population-based, so may be affected by selection bias, because patients were included in varying numbers from numerous clinics including tertiary centres (4).

**Danish studies**

A number of smaller regional Danish population-based studies have been performed. In a capital region study, the risk of CRC was not increased (SIR 1.05, 95% CI 0.56-1.79) (5), while an Odense based study found a numerically increased risk of CRC (SIR 1.67, 95% CI, 0.61 to 3.62) that did not reach statistical significance (6). In an IBD cohort in Northern Jutland, the risk of CRC was not increased (SIR 0.85, 95% CI 0.48 to 1.41), and in a subgroup of patients with extensive ulcerative colitis there was a non-significant increased risk of CRC (1.85, 95% CI 0.60 to 4.32) (7). The non-significant results cannot exclude a type 2 error. The patients in these regional Danish population-based studies are also present in the nationwide studies below.

A large Danish population-based study by Jess et al, with data from the Danish National Patient Register and the Danish Cancer Register covering a 30-year period (1977-2008), showed that the risk of developing CRC was not increased in IBD patients (8). Nonetheless, a number of risk factors were identified:

* In patients with early IBD debut (<19 years old) the risk was significantly increased (RR 43.8, 95% CI 27.2 to 70.7). Early debut of IBD was identified as a risk factor for development of CRC but could be confounded by long symptom duration. A Swedish population-based study of children found a correspondingly increased relative risk (9). The absolute risk is low as cancer is rare in childhood, therefore few cases can result in high relative risk estimates.
* The risk of CRC was low in the first years following IBD diagnosis, but rose to the same level as the background population after 8 years. After 13 years, there was a significantly increased risk of developing CRC at 50% greater than the background population.
* In patients with UC and PSC, the risk of CRC was significantly increased (RR 9.13, 95% CI 4.54 to 18.5).

The extent of the disease was not investigated, therefore it was not possible to estimate the risk in the subgroup of patients who had both long-duration and extensive ulcerative colitis, and which are seen to have the greatest risk of developing CRC (10).

In 2020, Olén et al published a Scandinavian population-based cohort study with 32 919 Danish and 63 528 Swedish patients with ulcerative colitis in the period 1977-2017, with 949 207 matched controls, who were followed to the primary endpoint of death due to CRC, and a secondary endpoint of CRC diagnosis (11).

The Danish data was collected in the period 1977-2011. In agreement with other studies (12), a fall in the absolute risk of CRC over time compared to the background population was observed. However, in the overall analysis, both a significantly increased risk of death due to CRC at 59%, and a 66% increased risk of CRC. In Denmark, patients with ulcerative colitis had both an increased relative risk of dying of CRC (HR 1.32, 95% CI 1.12 to 1.56) and of CRC diagnosis (HR 1.3, 95% CI 1.17 to 1.45).

In agreement with the meta-analysis by Lütgens et al (3), only patients with extensive ulcerative colitis (both Danish and Swedish) had an increased risk of both CRC (HR 1.88, 95% CI 1.72 to 2.07), and of dying of CRC (HR 1.93, 95% CU 1.68 to 2.21) (11). However, this disease classification should be taken with caution, as it is not made based on patient case note review.

The increase in absolute risk in the last 5 years of the follow up period (Swedish data only) was estimated to be one extra death due to CRC for every 3041 UC patients and one new CRC case for every 1058 UC patients. The absolute risk is therefore very modest for the patient population with ulcerative colitis as a whole, which supports the decision to offer endoscopic surveillance to well-defined risk groups only.

**Risk factors in ulcerative colitis patients >8 years disease duration or in the first year of PSC debut**

In most guidelines, patients are first offered colonoscopic surveillance when the disease duration is more than 8 years, or one year after PSC is diagnosed (13-17). In a subanalysis of the Scandinavian IBD patients. The risk of death was significantly increased (HR 1.87, 95% CI 1.66-2.10), as the risk of CRC (HR 1.81, 95% CI 1.67-1.96).

There was not a subanalysis of the group of patients who had both a disease duration of more than 8 years and extensive ulcerative colitis, which is the type of IBD offered colonoscopic surveillance in the majority of guidelines including Danish guidelines (18).

**Is the risk of dysplasia and CRC increased in patients with Crohn’s disease?**

In the meta-analysis by Lütgens et al, the risk of CRC was significantly increased in patients with Crohn’s disease in both population-based studies SIR 1.7 95% CI 1.01-2.05) and the studies from the tertiary centres SIR 4.4 (1.5-7.2) (3). Among patients with extensive Crohn’s disease in the colon, the risk of CRC was not increased in the populations studies (SIR 1.7, 95% CI 0.9-2.6).

In the CESAME study, 60% of the patients had extensive Crohn’s disease (4). In patients with both long-duration and extensive colonic Crohn’s disease, there was an increased risk (SIR 9.04, 95% 4.81-15.5) for developing CRC. Again, it must be emphasised that the study can be affected by significant selection bias.

**Danish studies**

In the North Jutland cohort, there was a significantlyincreased risk of CRC in men with colonic Crohn’s disease (SIR 1.96, 95% CI 0.72-4.28) (7). Again, this result could be affected by type 2 error.

Jess et al found in the Danish population-based study (8):

* No significantly increased risk in patients with early debut of Crohn’s disease (<19 years of age) RR 2.35 (95% CI 0.33-16.7).
* In the Swedish children’s population-based study, the risk of CRC was significantly increased 6-fold.
* In contrast to patients with UC, the disease duration was not a factor in Crohn’s disease, nor after 20 years disease duration.
* There was only one patients with PSC and Crohn’s disease, so a meaningful risk estimate could not be calculated.

In 2020, Olén et al published a Scandinavian population-based cohort study of Crohn’s patients (19). All 47 035 CD patients in the period 1969-2017 were included, whereof 13 056 Danish and 33 9979 Swedish patients were compared to 463 187 matched controls. In the overall analysis, there was a 74% and 40% significantly increased risk of death due to CRC and of developing CRC, respectively. The Danish Crohn’s patients had both an increased relative risk of dying of CRC (HR 1.42, 95% CI 1.08-1.86) and of getting CRC (HR 1.39, 95% CI 1.16-1.67).

The absolute risk increase was estimated in the last 5 years of the follow-up period (Swedish data) with one extra death due to CRC for every 2275 patients, and one newly diagnosed RC case for every 9593 CD patients. The absolute risk was therefore very modest for the whole group of Crohn’s patients, which supports offering colonoscopic surveillance only to the specified risk groups (19).

**Risk factor in Crohn’s patients >8 years disease duration or in the first year of PSC**

To study the risk factors in the Scandinavian Crohn’s patients who can be offered colonoscopic surveillance according to guidelines (13-17), a subanalysis of patients with at least eight years disease duration or one year after PSC diagnosis was performed (19). This showed:

* A significantly increased relative risk of death due to CRC (HR 1.4 95% CI 1.16-1.68).
* A non-significantly increased relative risk of death due to CRC (HR 1.12, 95% CI 0.98-1.28).
* Heredity (CRC in first-degree relatives) was not a risk factor in Crohn’s patients.

In agreement with the Scandinavian cohort study of UC patients, there was not a subanalysis of groups of patients, who had both disease duration longer than 8 years, and extensive Crohn’s disease (11).

**Other risk factors for developing colorectal cancer**

**Endoscopic inflammation**

Histological inflammation is associated with increased risk of developing CRC. Gupta et al found a 3-fold increase in the risk of CRC among patients with extensive UC (20). In a case-control study, mucosal healing decreased the risk of developing neoplasia (21), furthermore a macroscopically normal mucosa is thought to decrease the risk down to corresponding levels in the background population.

**Post-inflammatory polyps (PIP)**

PIP occur in the healing phase following severe inflammation (24), and have previously been thought to be as a risk factor for developing CRC (21,23). New data indicates that PIP does not increase the risk of CRC (24), likewise, in the St. Marks cohort, PIP was not a significant risk factor for developing CRC, as opposed to the so called cumulative inflammatory burden (25), therefore, routine biopsy of removal of post-inflammatory polyps is not recommended.

**Primary sclerosing cholangitis (PSC)**

PSC is an independent risk factor for CRC (2,26). In a meta-analysis by Soetikno et al, the risk was increased 4-fold in patients with UC and PSC compared to patients without PSC (OR 4.09, 95% CI 2.89-5.76) (26). The clinical course is often characterised by subclinical inflammation in the right ride of the colon, which may have been present for years before diagnosis, and can be a contributing cause for the apparent development of CRC earlier in the disease course than in UC patients without PSC.

A Danish register study compared 257 IBD patients with PSC to 8231 IBD patients without PSC (27). At the time of diagnosis (since 1976), 72% had UC, and the median age was 23 years. The risk of developing CRC was more than 20 times increased (HR 21.4, 95% CI 9.6-47.6). The cumulative risk was 7% and 9% after 10 and 20 years disease duration respectively, compared with 0.9& in the control group. In the Swedish children’s registers-based study with 9404 IBD patients with disease debut <18 years of age, the risk of CRC as increased 6-fold in patients with concurrent PSC.

**Familial disposition**

In the population-based study by Askling et al, with 19 876 Swedish IBD patients, the risk of CRC was doubled in patients with first degree relatives with CRC (RR 2.5, 95% CI 1.4-4.4), but was 9 times greater if the first degree relative was under 50 years old at CRC diagnosis (28). The increase risk was present regardless of IBD type and disease extent.

In the Swedish population-based children’s study, only patients with UC with a first degree relative under 50 years old with cancer had an increased risk of cancer (9). In the Scandinavian register studies, first-degree relatives with CRC were a risk factor only in patients with UC (9,19).

**Classification and incidence of dysplasia and colorectal cancer in IBD patients**

Lesions are classified as indefinite for dysplasia, low-grade dysplasia (LGD) or high-grade dysplasia (HGD) (29). The prevalence of neoplasia detected by chromoendoscopy in IBD patients is thought to lie between 6% and 21% (30-32). There is great inter-observer variation in diagnosing dysplasia. If dysplasia is detected—including indefinite dysplasia—a second opinion from another pathologist with expertise in gastroenterology can be requested in cases of uncertainty. In a Dutch study, less experienced IBD pathologists had a tendency to overestimate the grade of dysplasia (33).

**Risk assessment for development of dysplasia and CRC in the patients with UC**

The incidence of dysplasia and CRC was investigated in the largest prospective cohort through 40 years of patients with extensive UC from St. Marks Hospital, London (34). Up until 2013, 1375 patients underwent 8650 colonoscopies, whereof 1098 were chromoendoscopies.

**Prevalence of dysplasia and CRC in patients with long-duration extensive ulcerative colitis.**

**Sporadic adenomas**

Sporadic adenomas developed in 6.2% of patients, both within and beyond the inflamed part of the colon. The risk of CRC was independent of the localisation of the adenoma.

**Indefinite dysplasia**

Lesions indefinite for dysplasia developed in 3.7% of patients. Half of these progressed to more advanced neoplasia.

**Low-grade dysplasia (LGD)**

Low grade dysplasia developed in 10.5% of patients, and around 1 in 5 patients underwent colectomy for this diagnosis, of which a third of patients were found to have unrecognised synchronous CRC.

Among the patients with LGD who did not undergo colectomy, 15.9% developed CRC during surveillance.

**High-grade dysplasia**

High-grade dysplasia developed in 3.5% without previously identified LGD.

Patients who underwent colectomy for HGD, unrecognised synchronous CRC was found in half of patients.

Of patients with HGD who did not undergo colectomy, 21.2% developed CRC.

**CRC**

CRC developed in 5% of patients and among these, 40% had a synchronous cancer or dysplasia in another site in the colon.

Patients under colonoscopic surveillance had significantly fewer CRC cases in UICC stage ≥3 (Duke 3) than patients who developed an interval cancer.

The CRC incidence was significantly lower in patients who had undergone at least one chromoendoscopy compared to non-surveilled patients.

**Cumulative risk of CRC in IBD patients.**

**Table 1**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **St. Marks cohort (34)** | **Lütgens et al meta-analysis (5)** | |  |
| UC patients | IBD patients | |  |
| Tertiary centre | Population-based studies | One tertiary center (35) | All studies |
| ***Disease duration*** | **Cumulative risk of CRC** | | |  |
| < 10 years | 0.1 % | 0.8 % | 0.6 % | 0.7 % |
| 10-20 years | 2.9 % | 2.2 % | 11.4 % | 2.6 % |
| 20-30 years | 6.7 % | 4.5 % | 43.3 % | 6.6 % |
| 30-40 years | 10 % | NA | NA | NA |
| 40-50 years | 13.6 % | NA | NA | NA |

In the St. Mark’s cohort, there was no significant change in the yearly hazard rate of CRC at around 0.37% after the first decade; therefore, surveillance was not intensified with longer disease duration. These risk estimates are in concordance with the meta-analysis by Lütgens et al (3). In the Danish data, the risk of CRC was low in patients with UC during the first year after diagnosis, but it increased after 8 years disease duration to the same level as in IBD-free controls (8). After 13 years disease duration, the risk of CRC increased to 50% greater than the background population; however, the absolute number of patients was very low.

**Sessile serrated lesions**

Sessile serrated lesions (SSL) are defined as a lesion with serrated dilated crypts, including dilatation of the base of the crypts and is indicated to be responsible for up to 20% of all sporadic colon cancers (35,37).

SSL is associated with long lasting IBD (38), and often occurs in the right side of the colon, is often more than 10mm in size, and presents with Kudo’s pit-pattern II (39).

SSL is diagnoses with chromoendoscopy or virtual chromoendoscopy in around 6% of colonoscopy surveilled IBD patients, but is detected in up to 11% of IBD patients (40). The lesions can easily be overlooked because of their flat morphology, and because the lesions have the same colour as the surrounding mucosa, and has morphological characteristics in common with hyperplastic polyps (HP) (41). Furthermore, the lesion sis often covered with mucus, which can be difficult to wash away.

**Management of SSL in IBD patients**

SSL with dysplasia follows the same management as other dysplastic lesions.

Patients with SSL larger than 10 mm without dysplasia should be offered repeat colonoscopy after 3 years.

**Image-enhanced endoscopy modalities for detection of dysplasia and CRC in IBD patients (42)**

Dye-spray chromoendoscopy (DCE), henceforth referred to as ‘chromoendoscopy’ was first described 15 years ago (30). The use of dyes that enhance the mucosal topography clarifies the border of the lesion, emphasises the surface relief and increases the contrast in relation to the background. A detailed review of the conduct of chromoendoscopy is presented in Appendix 2 (43, 44). Subsequently a number of virtual chromoendoscopy modalities have been developed, such as narrow-band imaging (NBI), iSCAN and autofluorescence imaging (AFI).

Bisschops et al performed in 2018 the first prospective randomised controlled trial of direct comparison between HD-NBI (n=65) versus HD chromoendoscopy (n=66) (47). No significant difference was proven in the neoplasia detection rate by NBI (21,5%) compared to chromoendoscopy (21.2% The withdrawal time was significantly shorter with NBI, at seven minutes.

A meta-analysis by Imperatore et al in 2019 included 27 studies with 6167 IBD patients who underwent image-enhanced endoscopy (DCE, NBI, I-SCAN, AFI) to reveal 2,024 dysplastic lesions (45). The meta-analysis found that:

* Chromoendoscopy was significantly better at revealing dysplasia than either HD-WLE (five studies) or SD-WLE (12 studies)
* NBI (four studies) didn´t detect more dysplastic lesions than HD-WLE. (46). Iacucci et al found that HD-WLE was not inferior to chromoendoscopy or I-SCAN, in a single centre study conducted by a single investigator (46).

Imperatore et al concluded that HD-chromoendoscopy is superior to WLE but no other single technique was better that all others in dysplasia detection.

However, a direct comparison between HD-chromoendoscopy and HD-NBI was performed in a subanalysis including 3 studies, which found a numerically higher, though not significantly increased detection rate, using HD-chromoendoscopy (37%) compared to HD-NBI (28.4%). In the per-patient analysis the numerical difference vanished (21.2% vs 21.3%, odds ratio 0.992).

Bisschops et al (47) concluded that HD-NBI is not inferior to chromoendoscopy, however more and larger studies should be performed before the role of virtual chromoendoscopy in clinical practice can be confirmed. If NBI is implemented for colonoscopic surveillance, the endoscopist should undergo a supervised training course, as with chromoendoscopy (see appendix 2), with a focus on diagnosing non-polypoid lesions.

**Endoscopic classification**

Current endoscopic classification systems used for the morphology and characterisation of IBD lesions comprise the Paris classification (Appendix 3) and SCENIC classification (Appendix 4) (50, 51).

In 2019 a new endoscopic classification of colitis associated neoplasia was published (42,52). Frankfurt Advanced Chromoendoscopic IBD lesions (FACILE) (Appendix 5) is a validated and reproducible, and is considered easier to use than the SCENIC nomenclature. FACILE consist of four endoscopic characteristics:

1. Type of lesion according to Paris classification (50)
2. Superficial appearance
3. Vascular pattern
4. Inflammation of the lesion

Classification can predict whether the lesion is:

1. A sessile serrated lesion
2. Post-inflammatory polyp
3. Dysplastic lesion
4. Cancer

The goal of the development and validation of FACILE is to better distinguish colitis-associated neoplasia from non-neoplastic lesions without use of Kudo’s pit-pattern (39), which optimally requires image-augmentation. In addition, staining may obscure the Kudo pit-pattern, In connection with the development of FACILE, a number of gastroenterologists went through a training programme, through which the accuracy increased from 79% to 86%. In comparison, a validation study of NBI International Colorectal Endoscopic (NICE) classification found an accuracy of over 90% (53).

**Targeted and/or random biopsies for the diagnosis of visible and invisible colorectal dysplasia**

Imperatore et al found that significantly more dysplastic lesions were detected by targeted biopsies than by random biopsies (17.3% and 0.33% respectively) (45). The “number needed to scope” with targeted random biopsies were 6 and 300 patients, respectively. In contrast, Watanabe et al found no difference in the detection rate of dysplasia with targeted compared to random biopsies in patients with long-duration ulcerative colitis (11.4% and 9.3% respectively, p=0.67) (54). However, the time spent as substantially less with colonoscopy with targeted than with random biopsies (26.6 and 41.7 minutes respectively).

In a prospective study, Moussata et al took targeted and random biopsies during chromoendoscopy of 1000 patients, and detected neoplasia in 94 (31).

* 89% of patients with colorectal dysplasia were diagnosed either by targeted biopsies or from resected lesions. 8.5% of cases were diagnosed from random biopsy samples.
* 13% of patients had invisible dysplasia, which were detected by random biopsies. This corresponds to the prevalence of invisible dysplasia of 1.2% when a biopsy protocol of 32 biopsies is used, The investigation found three risk factors invisible dysplasia detected by random biopsies:
  + Previous colorectal neoplasia
  + Concurrent PSC
  + Tubular colon

This finding is supported by to retrospective studies (55,56). The experienced and trained endoscopist will find approximately 85% of dysplastic lesions by the use of chromoendoscopy, while the remaining 15% are invisible and can only be detected by random biopsies. As the probability of finding neoplasia by random patients approaches nil in patients who have not had previous dysplasia, concurrent PSC, or tubular colon, the biopsy protocol is appropriate.

The use of random biopsies alone in these patients groups is not implemented in current guidelines including the first Danish guidelines (13-18).

In the latest guidelines from 2019, ESGE recommends taking random biopsies in patients with the aforementioned risk factors, and in patients with UC who have strictures (57).

**Invisible dysplasia**

* The prevalence of invisible dysplasia is greater in older studies, likely because of underdiagnosis of discrete flat/depressed lesions by the use of older colonoscopies.
* ECCO recommends that in case of finding invisible dysplasia, follow-up with an expert HD chromoendoscopy is conducted to investigate for a well-defined visible lesion that can be resected, and additional investigation for synchronous dysplasia (13).
* If a visible lesion cannot be detected by follow-up chromoendoscopy:
  + Patients with invisible HGD or multifocal LGD can be offered colectomy (58).
  + Patients with invisible LGD can be offered follow-up chromoendoscopy after 6-12 months.

**The effectiveness of colonoscopic surveillance**

There are no—and will likely never be—randomised studies to finally clarify whether colonoscopic surveillance of IBD patients results in lower CRC-related morbidity and mortality. In the latest Cochrane meta-analysis from 2017, including five observational studies and 7,199 patients reduced, there was a reduced risk of CRC and CRC-mortality associated with surveillance colonoscopy (not chromoendoscopy) (59). The evidence level is moderately low. Findings of CRC at earlier stages can be one of the explanations for improved survival in chromoendoscopic surveillance.

* In three of five studies, there was a significantly lower prevalence of CRC (1.83% in colonoscopy-surveilled patients versus 3.17% in non-surveilled patients).
* In four studies, there was a significantly lower CRC-related mortality in colonoscopy surveilled versus non-surveilled patients. (8% and 22% respectively).
* In two studies there were significantly more UICC stage ≤2 (Duke A and B) cancers in colonoscopy surveilled patients compared to non-surveilled patients (16% and 8% respectively).

The number needed to scope to find a cancer in IBD patients under colonoscopic surveillance

This was summarised in the first report from St. Mark’s, which over the course of 30 years with 2,627 colonoscopies of 600 patients found 30 cases of CRC, of which 14 were count by colonoscopic surveillance (60). The “number needed to scope” was 88 to find one cancer, while the number which school be performed to find a resectable cancer was 188. This can be compared to the “Fyn investigation”—a screening of 31,000 healthy persons aged 45-75 years with Haemoccult and, if positive, subsequent colonoscopy (61). In that study the number needed to scope was eight to find 1 cancer, and 10 to find a resectable cancer.

**Special patient populations**

**Patients with UC, colectomy and retained rectal stump**

After colectomy for UC, there continues to be a risk of development of cancer in the rectal stump (62-65). The risk for cancer is thought to rise with disease duration (64).

* Patients with a rectal stump should be informed of the presumed cancer risk, as well as that surveillance does not ensure against cancer development (62).
* After risk stratification, patients with a rectal stump can be offered chromoendoscopic surveillance following the same guidelines as presented in Figure 1 for patients with UC with a preserved colon
  + Patients with concurrent PSC can be offered yearly chromoendoscopy.
  + Other patients should be individually risk assessed to determine how often the patients can be offered chromoendoscopy.
  + Consider rectal excision in patients who do not wish to have an ileoanal reservoir.

**Patients with ulcerative colitis and ileoanal reservoir (pouch)**

Relatively few cases of cancer in the pouch and anal canal after siting of an ileoanal reservoir are described (67, 68). Preoperative occurrence of cancer or dysplasia are risk factors for subsequence malignancy in the pouch (69). The rear incidence of malignant changes do not justify routine surveillance in patients with an ileoanal reservoir.

**Screening of 50-75 year old IBD patients for bowel cancer**

In Denmark, people aged 50-75 years are offered screening every two years for CRC with immunochemical faecal occult blood tests (iFOBT), and if positive, are offered colonoscopy. Healthy individuals with no polyps or bowel cancer detected on colonoscopy are given an eight-year waiting period corresponding to the skipping the next three screening rounds (70). IBD patients are also invited to partake in the national bowel cancer screening programme.

**Recommendations for 50-75 year old IBD patients regarding participation in the national bowel cancer screening programme**

In the participant information leaflet that IBD patients must contact their medical gastroenterology clinic and discuss whether they can participate.

IBD patients who partake in the chromoendoscopy surveillance programme are recommended to decline bowel cancer screening to avoid unnecessary colonoscopies (via [www.sundhed.dk](http://www.sundhed.dk)).

Patients with active IBD frequently have blood in the stool, and the test will therefore often be false positive for bowel cancer. These patients are advised to decline bowel cancer screening until the bowel disease is in remission.

IBD patients who have undergone a full colonoscopy within the last year because of disease activity are also advised to decline the next round of bowel cancer screening. This means that if the iFOBT is positive then the patient will undergo colonoscopy maximum three years after the last colonoscopy, corresponding to a waiting period of only three years for IBD patients compared to the usual 8 years waiting period.

**Patient information leaflet**

After being supported by gastroenterologists in becoming informed that the effectiveness of colonoscopic surveillance for dysplasia and CRC is not completely clarified, IBD patients themselves must decide whether to participate in the chromoendoscopy surveillance programme.

International studies indicate that patients overestimate both the risk of CRC and the effectiveness of surveillance (71, 72). A patient information leaflet can be provided to patients offered colonoscopic surveillance (Appendix 6).

**Appendix 2**

**Practical execution of chromoendoscopy (42, 43):**

* Chromoendoscopy should be performed when the disease is in clinical remission (73).
* The colon must be optimally emptied. Repeat colonoscopy is advised if a complete overview is not achieved after washing.
* Before the colonoscopy, a weak and a strong solution of indigo carmine should be prepared:
* 0.03% indigo carmine solution: 4 ampules of 5 ml indigo carmine 8 mg/ml diluted in 500 ml water.
* 0.13% indigo carmine solution: 1 ampule of 5 ml indigo carmine 8 mg/ml diluted in 25 ml water.
* Indigo carmine solution can be distributed via the water jet channel. Alternatively, a spray catheter via the biopsy channel can be used, but this procedure is more time-consuming. In addition, the biopsy channel is occupied by the spray catheter when biopsies are needed.
* The disadvantage of using a pump with a foot pedal is that more indigo carmine solution is used, which must be aspirated before one can inspect the mucosa.
* During the procedure, the endoscope is washed and aspirated thoroughly with water.
* The endoscope is proceeded to the caecum and into terminal ileum. Photo-documentation of complete colonoscopic visualisation is performed.
* The wash fluid is changed to 0.03% indigo carmine solution.
* CO2 is insufflated so that the caecum is dilated and a complete visualisation is acheived.
* Indigo carmine solution is sprayed on to the opposite side of where the fluid settles (i.e. against gravity).
* The colon is deflated completely, so that the indigo carmine solution makes contact with the mucosa all the way round.
* Subsequently, CO2 is insufflated again, so that complete visualisation is achieved. Any excess fluid is aspirated and the mucosa is inspected closely.
* Then systematic staining of the colon segments at approximately 10 cm intervals is performed. It is important to take sufficient time during withdrawal.
* Further doses of hyoscine butylbromide (Buscopan) 5 mg IV can be used to improve visualisation.
* If a suspect lesion is identified, change to 0.13% indigo carmine solution.

**Training in chromoendoscopy should comprise (74):**

* Knowledge of the use of high-defiiniton colonoscopes.
* Knowledge of which stains are used (indigo carmine or methylene blue)
* Knowledge of the two types of stain applications, either with a spray catheter or the use of a pump.
* Knowledge of the biopsy protocol with use of targeted biopsies and the use of random biopsies, four biopsies for each segment in selected patient groups, and the use of 4-quadrant biopsies with resection.
* Knowledge of the Paris, FACILE, and SCENIC classifications.
* Thorough training in the endoscopy technique (online resources, websites, video, and photo).
* Performance of the first five chromoendoscopies under the supervision of an experienced chromoendoscopist.
* Polyp removal with endoscopic mucosal resection/endoscopic submucosal dissection requires significant training and is conducted in specialised centres.

**E-learning for chromoendoscopy**

* The practical execution of chromoendoscopy can be seen in the 2014 ASGE presentation:

*Chromoendoscopy with targeted biopsy to detect nonpolypoid colorectal neoplasms in inflammatory bowel disease:* <https://www.youtube.com/watch?v=OARkbgwlObI>

* Atlas of nonpolypoid colorectal neoplasms by Soetikno et al [(75).](#_ENREF_78)

**Appendix 3**

**Schematic representation of type 0 superficial neoplastic lesions of the digestive tract.**



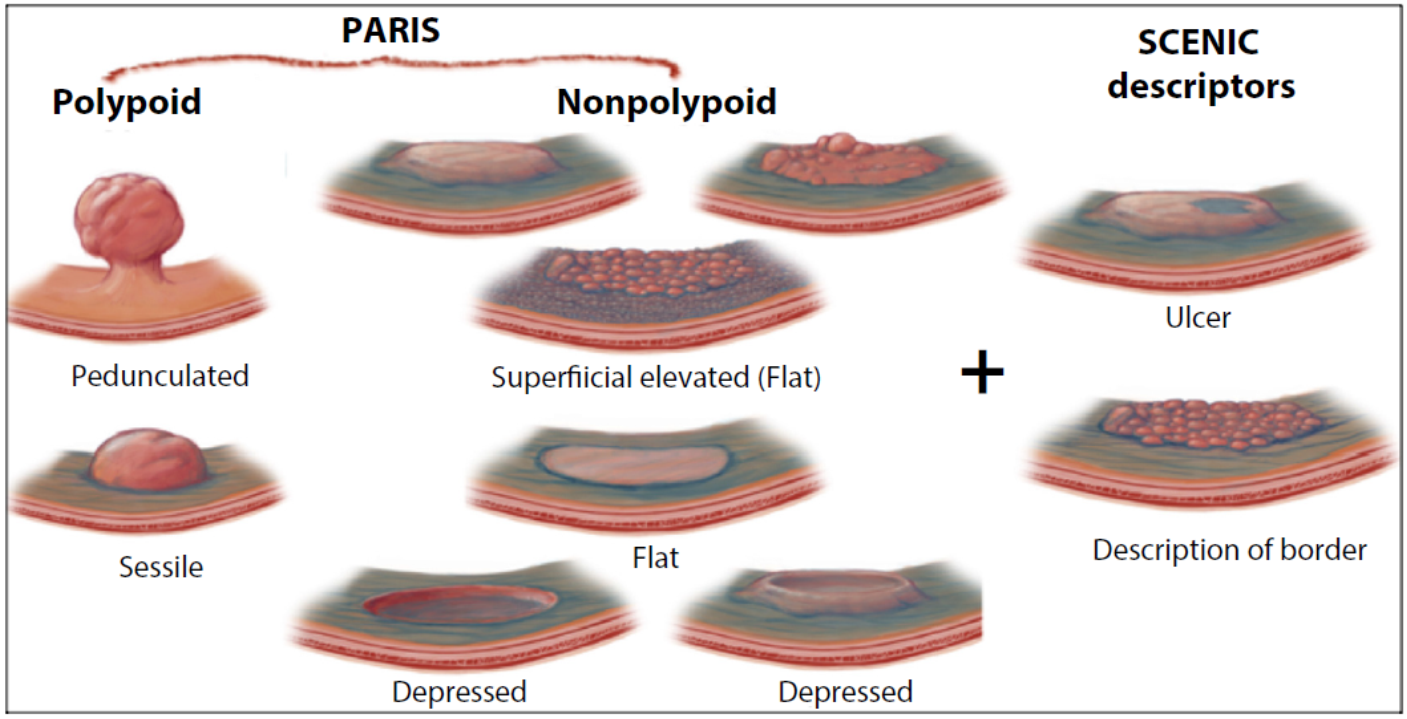


Reprinted with permission from *The Paris classification of neoplastic colonic lesions with superficial morphology* (50).

* A polypoid lesion, sessile (Is) or pedunculated (Ip), is defined as >2.5 mm.
* Anon-polypoid lesioncan be superficial (1-2.5 mm) **IIa,** flat **IIb**, slightly depressed **IIc**, or deep and excavated III.

**Appendix 4**

**SCENIC classification of colorectal lesions (44, 51)**

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The SCENIC classification uses the Paris classification, in which visible lesion are characterised as either:

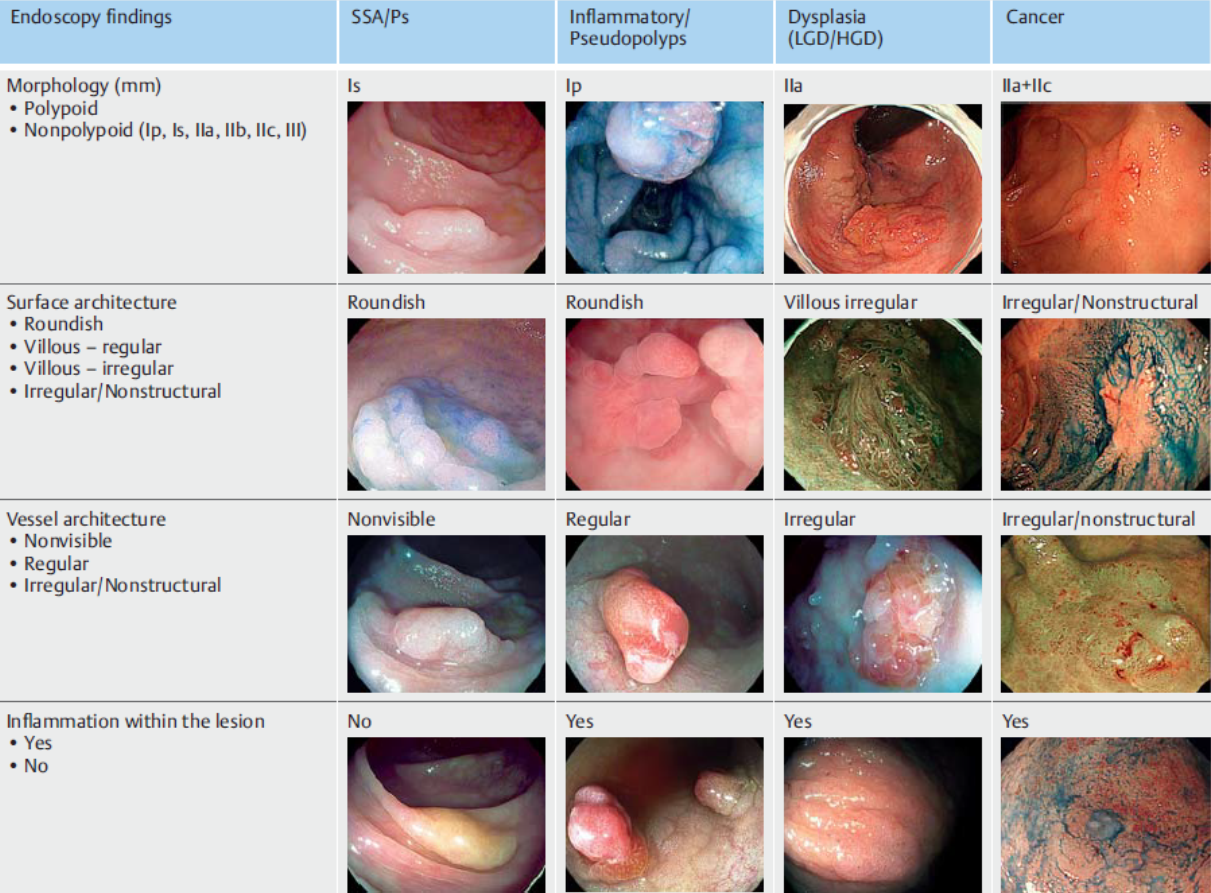
* Polypoid (sessile or pedunculated) lesions which reach more than 2.5 mm into the lumen, or
* Nonpoylpoid lesions which are slightly elevated lesions (<2.5 mm), flat, or depressed.

The SCENIC classification adds two parameters to the Paris classification: 1) is the border of the lesion significant? 2) is the the lesion itself inflammmed?

Reprinted with permission from Kaltenbach et al. (44).

**Appendix 5**

**Frankfurt Advanced Chromoendoscopy IBD lesions (FACILE) (52)**

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Abbreviations: SSA/Ps (sessile serrated adenoma/polyp), LGD (low grade dysplasia), HGD (high grade dysplasia).

Reprinted with permission from Iacucci et al (52).

**Appendix 6**

**patient information leaflet**

**Screening for bowel cancer in patients with inflammatory bowel diseases (IBD): ulcerative colitis and Crohn’s disease in the colon.**

You are invited to participate in a preventative surveillance programme using an optical investigation of the large bowel (colonoscopy), because we expect that you have a slightly increased risk of developing bowel cancer. With colonoscopy it is possible to discover discrete pre-stages of cancer, which can be removed during the procedure or by a subsequent colonoscopy or operation. It should be emphasised that the effectiveness of this surveillance is not completely clear.

The procedure will typically be a so-called chromoendoscopy, where a harmless blue dye (indigo carmine) is sprayed on the inner lining of the bowel (mucosa), or a virtual chromoendoscopy, where the images are coloured happens electronically. With these methods it is possible to see discrete changes to the mucosa that can contain cell changes. This procedure requires that the bowel disease is in remission and that your bowel is optimally emptied.

**Which patients with IBD are offered screening for bowel cancer?**

Cancer in the large bowel is one of the most common forms of cancer, which every year affects around 1 in 1000 in Denmark. If you belong to one of the groups below, your risk for bowel cancer is slightly increase in relation to people without IBD:

**Patients with a minimum 8-10 years duration of extensive ulcerative colitis or extensive Crohn’s disease**

Patients with ulcerative colitis or Crohn’s disease who also have been diagnosed with the rare biliary disease primary sclerosing cholangitis (PSC) are offered their first colonoscopy in the same year that PSC is detected.

**Detection of cell changes**

If the colonoscopy detects cell changes either as polyps, which are outgrowths form the mucosa, or certain discrete flat or depressed changes, they are removed during the same procedure if possible. If it is not possible, then you will be offered a repeat colonoscopy by an expert in polyp removal. Subsequently, the removed tissue is investigated for cell changes, and their degree of severity.

**When will I be offered the next chromoendoscopy?**

For most patients, the next investigation will usually be after five years, but if there are cell changes, we will offer you the next investigation sooner.

**The effect of screening for cancer in the large bowel**

Whether regular chromoendoscopy of patients with IBD leads to fewer cancer of cancer in the large bowel is not completely clear. Research indicates that bowel cancer is likely discovered earlier and therefore the chance of it being treatable is increased.

**The national screening programme for bowel cancer**

All citizens aged 50-75 are invited to take part in the national screening for bowel cancer by returning a stool test every two years.

If you choose to take part in the colonoscopy surveillance programme described in this leaflet, then we ask you to decline participation in the national screening programme, via [www.sundhed.dk](http://www.sundhed.dk)

If you will not participate in the described colonoscopy surveillance programme, then you are asked to return the stool test as requested, and if you are tested positive, we recommended that you contact us to discuss who will perform the investigation.

If you have undergone colonoscopy in the last year because of a flare-up of IBD, then you should not take part in the next round of the national screening programme, and can wait two years before returning the next test.

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