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Value of green sign and chicken skin aspects for detecting malignancy of colorectal neoplasia in a prospective characterization study

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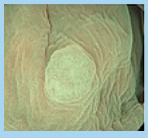
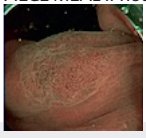
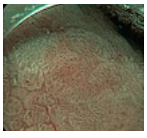
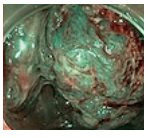
ABSTRACT

Background and study aims Accurate endoscopic characterization of colorectal lesions is essential for predicting histology but is difficult even for experts. Simple criteria could help endoscopists to detect and predict malignancy. The aim of this study was to evaluate the value of the green sign and chicken skin aspects in detection of malignant colorectal neoplasia.

Patients and methods We prospectively characterized and evaluated the histology of all consecutive colorectal lesions detected during screening or referred for endoscopic resection (Pro-CONECCT study). We evaluated the diagnostic accuracy of the green sign and chicken skin aspects for detection of superficial and deep invasive lesions.

Results 461 patients with 803 colorectal lesions were included. The green sign had a negative predictive value of 89.6% (95% confidence interval [CI] 87.1%–91.8%) and 98.1% (95% CI 96.7%-99.0%) for superficial and deep invasive lesions, respectively. In contrast to chicken skin, the green sign showed additional value for detection of both lesion types compared with the CONECCT classification and chicken skin (adjusted odds ratio [OR] for superficial lesions 5.9; 95% CI 3.4–10.2; $P<0.001$), adjusted OR for deep lesions 9.0; 95% CI 3.9–21.1; $P<0.001$).

Conclusions The green sign may be associated with malignant colorectal neoplasia. Targeting these areas before precise analysis of the lesion could be a way of improving detection of focal malignancies and prediction of the most severe histology.

	OE Neuro-endocrine tumor	IH Hyperplastic polyp	IS Sessile serrated lesion (without dysplasia)	IIA Low-risk adenoma	IIC High-risk adenoma or superficial ade-nocarcinoma	IIC+ Borderline invasive adeno-carcinoma	III Deeply invasive adeno-carcinoma
Location	Rectum	Rectum or sigmoid	Colorectal	Colorectal	Colorectal	Colorectal	Colorectal
Macroscopic aspect	Subepithelial lesion	Often <10 mm Paris IIa	Paris IIa or IIb Cloud aspect Unclear margins	Paris Ip or Is or IIa or "Valley sign"	Often IIc or nongranular LST or macronocule (>10 mm) on a granular LST	Demarcated or depressed area	Often IIIor IIc with a nodule in the depressed area Spontaneous bleeding
Color (virtual staining)	Yellowish	Light Color or equivalent to the background	Variable yellow mucus (red in VCE)	Darker than the background	Often dark	Dark area	Heterogeneous lighter and darker in an amorphous area
Vessels (virtual staining)	Normal	None or thin vessels across the lesion, not following the pits	Round shape Dark spots at the bottom of the pits	Elongated or bran-ched crypts, cerebriform aspect	Irregular but persistent No amorphous area	Absent, amorphous, destroyed area <10 mm (clear demarcation)	Absent, amorphous, destroyed area >10 mm (clear demarcation)
Pits (virtual staining)	Normal (sometimes minimal mucosal lesion)	Round shape, withish pits	Round shape Dark spots at the bottom of the pits	Elongated or branched crypts, cerebriform aspect	Irregular but persistent No maorphous area	Absent, amorphous, destroyed area <10 mm (clear demarcation)	Absent, amorphous, destroyed area >10 mm (clear demarcation)
Resection method	R0 (ESD, EID, EFTR)	No resection if <5 mm	EN BLOC R0 if possible (Cold snare then discard if <10 mm) PIECE MEAL if not		En bloc R0 (EMR or ESD)	Diagnostic resection (ESD, EID, EFTR)	Staging SURGERY
							

▶ **Fig. 1** The CONECCT Classification (version 3.1). EID, endoscopic intermuscular dissection; EMR, endoscopic mucosal resection; ESd, endoscopic submucosal dissection; LST, laterally spreading tumor; VCE, virtual chromoendoscopy.

Introduction

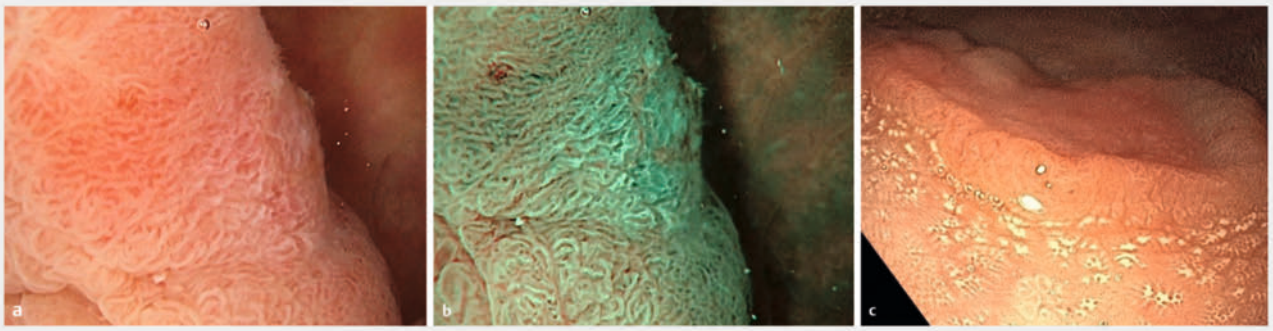
Accurate endoscopic characterization of colorectal lesions is essential to predict histology, but remains very difficult [1]. Lesions are characterized on the basis of real-time assessment of their macroscopic appearance and vascular and pit pattern with magnification, both in white light and with virtual chromoendoscopy. All validated criteria have been previously grouped into a single table: the CONECCT (COlorectal Neoplasia Endoscopic Classification to Choose the Treatment) classification (▶ **Fig. 1**). This table significantly improves the histological prediction and therapeutic choice of French gastroenterologists on still images produced by experts [1, 2, 3], but detection of the interest area needs to be improved. Indeed, characterization reveals considerable histological heterogeneity within the lesion, with malignancy often appearing in a focal zone within dysplastic lesions with completely different prognoses. This crucial zone must be detected to predict the most unfavorable histology and, therefore, to choose the right treatment [3]. Detection of these zones of interest is not easy, but they have the particularity of potentially having a different color, as previously described, with a green zone in virtual chromoendoscopy, creating a contrast with the color of the rest of the lesion [4] or with yellow-speckled mucosa in white light surrounding the lesion, called chicken skin. Although chicken skin mucosa has been associated with advanced colorectal adenoma in previous studies, its histopathological mechanism remains unclear [5, 6].

We conducted this study to assess the diagnostic accuracy of presence of green sign [4] or chicken skin aspects [5, 6] for histological evaluation of consecutive colorectal lesions included in the prospective Pro-CONECCT trial characterizing all colorectal lesions detected or referred for endoscopic resection.

Patients and methods

Study design

We conducted a prospective observational cohort study (Pro-CONECCT, NCT05983315) at our tertiary referral center in France, including patients who came for colonoscopy between September 2021 and February 2023, either for screening or for endoscopic resection of neoplastic lesions. During this period, all colorectal lesions detected during colonoscopies were characterized by experienced endoscopists and the CONECCT clas-



▶ **Fig. 2** Endoscopic visualization of green sign in **a** white light imaging and **b** virtual chromoendoscopy. **c** Endoscopic visualization of chicken skin in white light imaging.

sification (▶ **Fig. 1**) was determined. All lesions were then completely resected to obtain their final histology. Our ethics committee approved this study, and all patients gave informed consent prior to the procedures.

Patients aged ≥18 years who required diagnostic colonoscopy due to digestive symptoms, medical or family history of colorectal cancer or polyps, positive screening test, acromegaly, or referred to our center for colorectal lesion resection were included. We did not include patients with no colorectal lesions or no available histology, a metastatic lesion diagnosed prior to colonoscopy, a colorectal lesion previously resected by endoscopy, or presenting with adenomatous or sessile serrated polyposis syndrome, or who had inflammatory bowel disease. Patients with submucosal lesions were excluded from the study.

Procedures

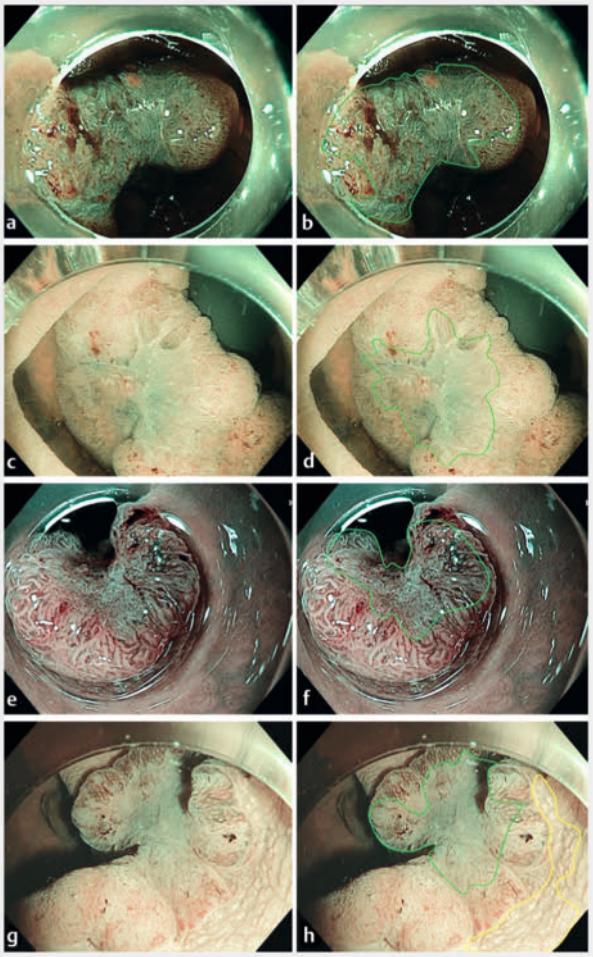
All colonoscopies were performed by eight senior endoscopists, with the patient under general anesthesia and using CO_2 insufflation. Optical characterization of lesions was performed using high-definition white light endoscopy followed by close-up examination assisted by virtual chromoendoscopy, with or without magnification, using Olympus CF-HQ190 L/I colonoscopes (Olympus, Tokyo, Japan).

Histopathological examination was carried out by expert digestive pathologists according to the Vienna and TNM classifications [7, 8].

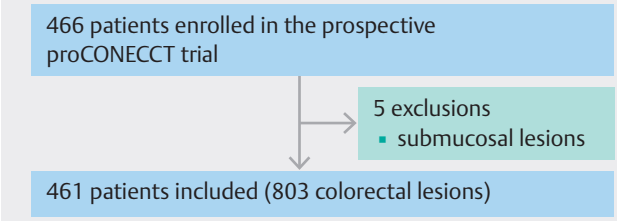
Study objectives

The primary objective was evaluation of diagnostic accuracy of the green sign and chicken skin aspects for detection of superficial lesions accessible to curative endoscopic treatment (low- and high-grade dysplastic adenoma, intramucosal adenocarcinoma, superficial submucosal adenocarcinoma with <1000 µm submucosal invasion) and deep invasive lesions requiring surgery (deep submucosal adenocarcinoma with >1000 µm submucosal invasion, intramuscular or deeper T2-T3 cancer).

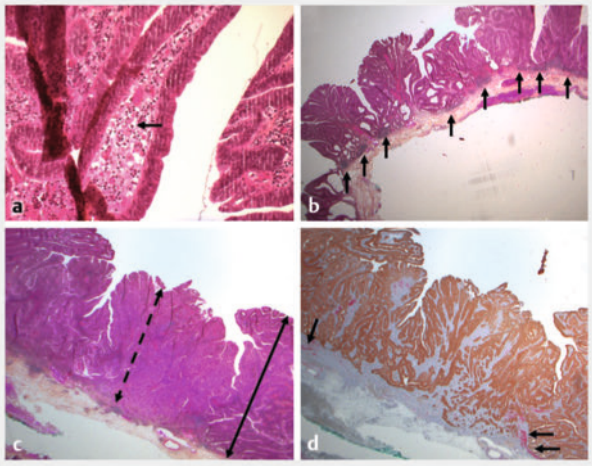
The green sign was defined in virtual chromoendoscopy by a clearly delimited area of green color creating a spontaneous contrast with the color of other parts of the lesion, whatever its size (▶ **Fig. 2**, ▶ **Fig. 3**).



▶ **Fig. 3** Examples of endoscopic visualization of green sign (bounded by green line) and chicken skin (bounded by yellow line). **a, b** CONECCT IIC + lesion in the valvula, deep submucosal adenocarcinoma. **c, d** CONECCT III lesion in the transverse colon, T3 cancer. **e, f** CONECCT III lesion in the left colon, superficial submucosal adenocarcinoma. **g, h** CONECCT IIC + lesion in the sigmoid, deep submucosal adenocarcinoma.



▶ **Fig. 4** Flow chart of the study.



▶ **Fig. 5** Microscopic examination of the resection specimen containing **a, b** chicken skin and **c, d** green sign. Macrophagic infiltration with xanthomatous morphology (black arrow in **a**), as previously described in other studies. Increased number of lymphoid nodules at the periphery of invasive carcinoma (black arrow in **b**) corresponding to a hyperplastic reaction of the gut associated lymphoid tissue, which could at least partially explain the chicken skin with regularly scattered small nodules lifting the mucosa. Thinning of the mucosa (dotted double arrow in **c**) compared with the adenomatous mucosa (double arrow in **c**) as invasive glands destroy the mucosa. Destruction of the muscularis mucosae (black arrow in **d**, in red) by invasive glands which may contribute to the increase in the hemoglobin detection signal, resulting in the green sign.

Chicken skin was defined in white light as an appearance of yellow-speckled mucosa surrounding the lesion (▶ **Fig. 2**, ▶ **Fig. 3**).

Secondary endpoints were evaluation of the overall severity of the histology of colorectal lesions with green sign or chicken skin compared with those without, with adjustment for class of CONECCT classification. A cross-assessment between green sign, chicken skin, and the CONECCT classification was carried out.

Data collection

Data collected were patient demographics including sex and age at the time of colonoscopy; endoscopy indication and lesion characteristics: location, size, morphology, demarcation line, green sign, chicken skin mucosa and classification according to Paris, Kudo, Sano and CONECCT classifications.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or as median with the first and the third quartile. Categorical variables were presented as numbers and percentages. Diagnostic accuracy was assessed by sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV), with the associated 95% confidence interval (95% CI). Analysis of the association between green sign/chicken sign on the severity of histology was performed by ordinal logistic regression and quantified by an odds ratio with associated 95% confidence interval (95% CI). Multivariable analyses were performed with adjustment for CONECCT classification. Some patients had multiple lesions, but for diagnostic accuracy, lesions from the same patient can be considered independent. P <0.05 was considered significant. The analyses were performed using R software (version 4.1.2).

Results

Characteristics of patients and colorectal lesions

We prospectively included 461 patients with 803 colorectal lesions, median age 70 years (range, 63–76); 252 men and 209 women (▶ **Fig. 4**). Patients and colorectal lesions characteristics are presented in ▶ **Table 1** and ▶ **Table 2**, respectively.

The green sign

In our cohort, 15.8% of colorectal lesions (127/803) presented with a green sign described by the endoscopists. After histological assessment, the green sign was described in none of the 56 hyperplastic lesions, in 1.0% of the sessile serrated lesions (1/96), in 8.6% of low- or high-grade dysplastic adenomas (43/498), in 31.3% of intramucosal adenocarcinomas (26/83), in 80% of superficial submucosal adenocarcinomas (8/10 < 1000 um), in 75.6% of deep submucosal adenocarcinomas (31/41) > 1000 um) and in 94.7% of intramuscular or deeper cancers (18/19) (▶ **Table 3**). Lesions with the green sign were larger than those without the sign, with large and small mean diameters of 45.02 mm (SD 25.82) and 39.00 mm (22.18), respectively, for lesions with the green sign and 22.33 mm (25.62) and 20.05 mm (22.73) for lesions without the sign. Pseudodepressed nongranular laterally spreading tumors were diagnosed in 33.3% of lesions (41/127) with the green sign and 3.2% of lesions (21/676) without the green sign. A demarcation line was seen in 77.2% of lesions (98/127) with the green sign and 5% of lesions (34/676) without the green sign. Of the lesions with the green sign, 45.7% of lesions with the green sign (58/127) and 0.7% of lesions without the green sign (5/676) were classified as Kudo Vn and 44.9% of the lesions with the green sign (57/127) and 0.7% of the lesions without the green sign (5/676) were classified as Sano IIIb.

Diagnostic accuracy of the green sign

The green sign had a negative predictive value of 89.6% [95% CI: 87.1–91.8%] and 98.1% [95% CI: 96.7–99.0%] for superficial and deep invasive lesions, respectively. The diagnostic accuracy, sensitivity, specificity, PPV and NPV of the green sign for

▶ **Table 1** Patient characteristics.

Characteristic	
Patients, n	461
▪ **Gender, n (%)**	
– Male	252 (54.7)
– Female	209 (45.3)
▪ **Age at diagnosis, y**	
– Median (range)	70 (63–76)
▪ **Indication for colonoscopy**	
– Positive screening test	91 (19.7)
– Digestive symptoms	131 (28.4)
– Hematochezia	74 (16.1)
– Individual screening	163 (35.4)
– PET-CT colonic fixation	26 (5.6)
– Acromegaly	1 (0.2)
– Other	23 (5.0)

PET-CT, positron emission tomography-computed tomography.

▶ **Table 2** Colorectal lesion characteristics.

Characteristic	
Lesions, n	803
▪ **Lesion size, large diameter, mean (SD), mm**	25.92 (26.94)
▪ **Lesion size, small diameter, mean (SD), mm**	23.05 (23.66)
▪ **Location, n (%)**	
– Cecum	138 (17.2)
– Valvula	49 (6.1)
– Right colon	171 (21.3)
– Right angle	83 (10.3)
– Transverse colon	77 (9.6)
– Left angle	21 (2.6)
– Left colon	57 (7.1)
– Sigmoid	105 (13.1)
– Rectum	101 (12.6)
▪ **Macroscopic type, n (%)**	
– Polypoid	290 (37.5)
– Granular homogeneous LST	85 (11.0)
– Granular mixed LST	150 (19.4)
– Nodular LST	42 (5.4)
– Flat nongranular LST	51 (6.6)
– Pseudodepressed nongranular LST	62 (8.0)

▶ **Table 2** (Continuation)

Characteristic	
▪ **Macronodule > 1 cm, n (%)**	
– Yes/No	211 (26.3)/592 (73.7)
▪ **Demarcation line, n (%)**	
– Yes/No	132 (16.4)/671 (83.6)
▪ **Green sign, n (%)**	
– Yes/No	127 (15.8)/676 (84.2)
▪ **Chicken skin, n (%)**	
– Yes/No	101 (12.6)/702 (87.4)
▪ **Green sign and chicken skin, n (%)**	
– Yes/No	54 (6.7)/749 (93.3)
▪ **Paris classification, n (%)**	
– Ip	26 (3.2)
– Is	90 (11.2)
– Is-IIa	115 (14.3)
– Is-IIa-IIc	4 (0.5)
– Is-IIa-Is	1 (0.1)
– Is-IIc	8 (1.0)
– IIa	481 (59.9)
– IIa-IIc	69 (8.6)
– IIc	2 (0.2)
– IIc-Is	2 (0.2)
– III	5 (0.6)
▪ **CONECCT classification, n (%)**	
– IH	45 (5.6)
– IS	104 (13.0)
– IIA	312 (38.9)
– IIC	279 (34.7)
– IIC +	34 (4.2)
– III	29 (3.6)
▪ **JNET classification, n (%)**	
– I	145 (18.1)
– IIA	445 (55.4)
– IIB	150 (18.7)
– III	63 (7.8)
▪ **NICE classification, n (%)**	
– I	152 (18.9)
– II	589 (73.3)
– III	62 (7.7)

CONECCT, COlorectal Neoplasia Endoscopic Classification to Choose the Treatment; JNET, Japan NBI Expert Team; LST, laterally spreading tumor; NICE, NBI International Colorectal Endoscopic; SD, standard deviation.

▶ **Table 3** Final histology of lesions according to green sign.

Characteristic	All lesions	Green sign	
		Yes	No
Lesions, n	803	127	676
Histology, n (%)			
▪ hyperplastic polyp	56 (7.0)	0	56 (8.3)
▪ Sessile serrated lesion	96 (12.0)	1 (0.8)	95 (14.1)
▪ Low-grade or high-grade dysplastic adenoma (Vienna 4.1)	498 (62.0)	43 (33.9)	455 (67.3)
▪ Intramucosal adenocarcinoma (Vienna 4.4)	83 (10.3)	26 (20.5)	57 (8.4)
▪ Superficial submucosal adenocarcinoma (<1000 µm)	10 (1.2)	8 (6.3)	2 (0.3)
▪ Deep submucosal adenocarcinoma (>1000 µm)	41 (5.1)	31 (24.4)	10 (1.5)
▪ Intramuscular or deeper cancer	19 (2.4)	18 (14.2)	1 (0.1)

▶ **Table 4** Diagnostic accuracy of green sign and chicken skin aspects for detection of superficial and deep invasive lesions.

	Sensitivity 95% CI	Specificity 95% CI	Positive predictive value 95% CI	Negative predictive value 95% CI
Superficial lesions				
Green sign	54.2 (46.0–62.3)	93.2 (91.0–95.0)	65.4 (56.4–73.6)	89.6 (87.1–91.8)
Chicken skin	31.4 (24.1–39.4)	91.8 (89.5–93.8)	47.5 (37.5–57.7)	85.0 (82.2–87.6)
Green sign and chicken skin	44.3 (32.4–56.7)	90.5 (88.1–92.5)	30.7 (21.9–40.7)	94.4 (92.5–96.0)
Green sign or chicken skin	62.1 (53.9–69.8)	87.8 (85.1–90.3)	54.6 (46.9–62.1)	90.8 (88.2–92.9)
Deep invasive lesions				
Green sign	81.4 (70.3–89.7)	90.5 (88.1–92.5)	44.9 (36.1–54.0)	98.1 (96.7–99.0)
Chicken skin	31.4 (24.1–39.4)	91.8 (89.5–93.8)	47.5 (37.5–57.7)	85.0 (82.2–87.6)
Green sign and chicken skin	42.9 (31.1–55.3)	96.7 (95.2–97.9)	55.6 (41.4–69.1)	94.7 (92.8–96.2)
Green sign or chicken skin	82.9 (72.0–90.8)	84.2 (81.3–86.7)	33.3 (26.4–40.9)	98.1 (96.7–99.0)

the detection of superficial and deep invasive lesions are presented in ▶ **Table 4**.

Association with colorectal lesion histology

The green sign had additional value for detecting superficial or deep lesions compared with CONECCT classification alone (adjusted odds ratio [OR] for superficial lesions 7.1; 95% CI 4.2–12.0; *P* <0.001, adjusted OR for deep lesions 11.6; 95% CI 5.3–26.0; *P* <0.001) as well as CONECCT classification and chicken skin (adjusted OR for superficial lesions 5.9; 95% CI 3.4–10.2; *P* <0.001, adjusted OR for deep lesions 9.0; 95% CI 3.9–21.1; *P* <0.001).

Chicken skin

In our study, 12.6% of colorectal lesions (101/803) presented with a chicken skin aspect. After histological assessment, chicken skin was reported in none of the 56 hyperplastic lesions, in 2.1% of sessile serrated lesions (2/96), in 10.2% of low- or high-grade dysplastic adenomas (51/498), in 20.5% of intramucosal adenocarcinomas (17/83), in 40.0% of superficial submucosal adenocarcinomas (4/10 <1000 um), in 39.0% of deep submucosal adenocarcinomas (16/41 > 1000 um), and in 57.9% of intramuscular or deeper cancers (11/19) (▶ **Table 5**). Lesions with chicken skin were larger than those without the sign, with large and small mean diameters of 36.03 mm (SD 20.41) and 32.46 mm (SD 19.16), respectively, for lesions with chicken skin and 24.47 mm (27.46) and 21.70 mm (23.95) for lesions without it.

Diagnostic accuracy of chicken skin

Chicken skin had a negative predictive value of 85.0% (95% CI 82.2–87.6%) for superficial and deep invasive lesions. Diagnostic accuracy, sensitivity, specificity, PPV, and NPV of the chicken skin for detection of superficial and deep invasive lesions are presented in ▶ **Table 4**.

▶ **Table 5** Final histology of lesions according to chicken skin.

Characteristic	All lesions	Chicken skin	
		Yes	No
Lesions, n	803	101	702
Histology, n (%)			
▪ Hyperplastic polyp	56 (7.0)	0	56 (8.0)
▪ Sessile serrated lesion	96 (12.0)	2 (2.0)	94 (13.4)
▪ Low-grade or high-grade dysplastic adenoma (Vienna 4.1)	498 (62.0)	51 (50.5)	447 (63.7)
▪ Intramucosal adenocarcinoma (Vienna 4.4)	83 (10.3)	17 (16.8)	66 (9.4)
▪ Superficial submucosal adenocarcinoma (<1000 µm)	10 (1.2)	4 (4.0)	6 (0.9)
▪ Deep submucosal adenocarcinoma (>1000 µm)	41 (5.1)	16 (15.9)	25 (3.6)
▪ Intramuscular or deeper cancer	19 (2.4)	11 (10.9)	8 (1.1)

Association with colorectal lesion histology

Chicken skin had additional value for detection of superficial or deep lesions compared with CONECCT classification alone (adjusted OR 5.2; 95% CI 3.3–8.0; P <0.001, and 7.5; 95% CI 4.4–12.8; P <0.001, respectively). It also had additional value compared with CONECCT classification and the green sign for detection of superficial lesions (adjusted OR 1.9; 95% CI 1.0–3.4; P = 0.036), but it was not possible to show additional value for deep lesions (adjusted OR 2.1; 95% CI 0.9–4.7; P = 0.063).

Discussion

To our knowledge, this is the first systematic description of presence or absence of the green sign and chicken skin aspects, reporting that a green-colored area on virtual chromoendoscopy, or green sign, could be associated with a more pejorative histology of colorectal lesions, including after adjustment on the CONECCT classification and the chicken skin aspect. In contrast, although chicken skin was associated with neoplastic polyps in a recent study [5, 6], it could not be associated with a more pejorative histology independent of CONECCT classification and the green sign. Although the green sign alone is not sufficiently reliable for affirming presence of superficial lesions that can be treated endoscopically and deep invasive lesions requiring surgical treatment, absence of the green sign could be used to exclude the diagnosis of these lesions.

Accurate real-time characterization of colorectal lesions during endoscopy is crucial for histological prediction. After analyzing the macroscopic shape of a lesion with white light imaging, the endoscopist should look for an existing area of degeneration and then analyze these areas of interest in terms of vascular and mucosal relief. However, the malignant components can sometimes represent a small area of the whole lesion, and hence be relatively difficult to detect, especially for unexperienced endoscopists. Some aspects of a lesion, clearly identifiable during analysis of the lesion, can help the endoscopist identify these pejorative areas suspected of deep invasion. These are areas with demarcation, depression, or even ulcerations or spontaneous bleeding, and the green sign could be part of these warning signs or a red flag an endoscopist should look for. Furthermore, the green sign appears to be more easily detected on a distant view of the lesion, without the need to analyze the entire surface with magnification, which can be time-consuming. A further study of green sign detection in a population of gastroenterologists is needed to assess whether this sign could be detected by general gastroenterologists.

Although artificial intelligence (AI) is now very effective at detecting lesions [9], human intervention is still required to detect colorectal lesions and AI can sometimes be less effective at detecting flat lesions [10]. Furthermore, current development of computer-aided detection systems focuses on assessment of neoplastic versus nonneoplastic lesions and is not geared toward predicting invasion depth [9]. The development of systems dedicated to detection of the green sign would be a valuable aid and would encourage gastroenterologists to examine this focal area.

Although chicken skin was described in 1998 as being due to macrophagic infiltration with xanthomatous morphology [5], we found this infiltration only very rarely (▶ **Fig. 5**). An increased number of lymphoid nodules visualized at the periphery of the invasive carcinoma and corresponding to a hyperplastic reaction of the gut-associated lymphoid tissue could at least partially explain the chicken skin with regularly scattered small nodules lifting the mucosa. The green sign in chromoendoscopy is related to an increased hemoglobin signal in the invasive zone [11]. The increased signal may be due to the increased visibility of submucosal blood flow, which may be explained, on the one hand, by thinning of the mucosa compared with the adenomatous mucosa, as invasive glands destroy the mucosa. On the other hand, destruction of the muscularis mucosae by invasive glands may also contribute to the increase in the hemoglobin detection signal, resulting in the green sign.

The main limitation of this study is the use of a single endoscope brand and tertiary center, which may not exactly reflect

practice with lesions found in other centers. Green sign detection may be less effective in less experienced centers.

Conclusions

In conclusion, the green sign is associated with a more pejorative histology of colorectal lesions, irrespective of CONECCT classification and the chicken skin aspect. Targeting these areas before precisely analyzing a lesion could be a way to improve detection for inexperienced endoscopists and avoid missing malignancies in colorectal neoplasia.

Conflict of Interest

The authors declare that they have no conflict of interest.

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