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In vivo Optical Diagnosis of Polyp Histology: Can We Omit Pathological Examination of Diminutive Polyps?

Marco Bustamante-Balén

Additional information is available at the end of the chapter

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1. Introduction

In the United States colorectal cancer (CRC) is the third more commonly diagnosed cancer in both sexes and it is also the third leading cause of cancer death among men and women [1]. In Europe CRC is the second leading cause of cancer death in both sexes [2]. These figures mean a heavy economic burden for any health system. The national cost of a year of CRC care in the United States has been estimated to be between \$4.5 and \$9.6 billion [3]. In Spain €180.6 million of annual losses in work productivity because of CRC have been reported [4].

Adenomatous polyps are the precursors of CRC in most of the cases. Through a progressive accumulation of mutations and following some of the described carcinogenetic pathways [5], a benign adenomatous polyp develops into an advanced adenoma with high-grade dysplasia (HGD) and then progresses to invasive cancer (Figure 1). Invasive cancers confined to the wall of the colon (TNM stages I and II) are curable by surgery while more advanced cancers are treated by a combination of surgery and chemotherapy.

Detecting cancer at an early stage or, even better, diagnosing and resecting adenomas before a carcinoma has developed improves outcomes. This was first confirmed in the initial report of the National Polyp Study [6] which showed a reduction in the incidence of colorectal cancer of around 76% in patients in which a polypectomy had been performed. Recently, the same group has described in the same cohort of patients a reduction in mortality of 53% in the long term [7]. This is the rationale for population-based screening programs, designed to detect advanced adenomas and CRC at an early and curable stage. For instance, recently the results of a nationwide screening colonoscopy program in Germany have been reported of a nationwide screening colonoscopy program in Germany, showing that 69.6% of diagnosed CRC were stages I and II [8]. Therefore, screening for CRC with removal of adenomas and surveillance colonoscopy of patients who have been treated for adenomas or CCR is recom-

mended by Professional Societies and authorities [9-11]. Surveillance intervals after resection of one or more adenomas are planned based primarily in the number, size and presence of advanced histological features [12]. Polyps larger than 10 mm, with villous component (> 25%) or with high-grade dysplasia are considered advanced adenomas and have a greater tendency to malignancy [13]. Detection and resection of these advanced adenomas is the main objective of the surveillance programs [14,15]. Therefore, submitting all resected polyps to pathologic evaluation is the standard of care.

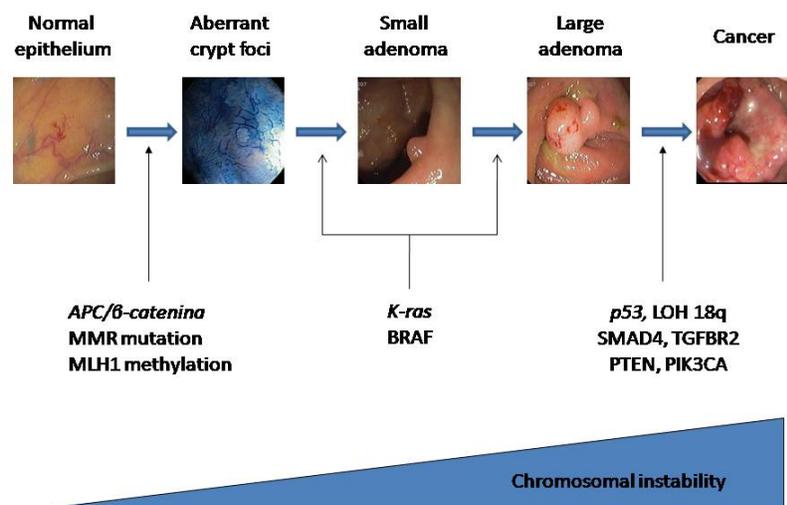


Figure 1. Development of CRC from normal tissue to adenocarcinoma

However, most of the adenomas diagnosed in colonoscopies are 5 mm or less (diminutive polyps). In symptomatic patients the proportion of adenomas larger than 10 mm is between 5 and 15% [16-18]. A report from our group using chromoendoscopy to improve the adenoma detection rate showed that 73% of adenomas were < 5 mm [19]. This is also the situation in screening colonoscopy, with reported proportions of adenomas < 5 mm of around 80% [20]. A significant proportion of diminutive polyps, between 23% and 40%, are not even adenomas [21-24]. Overall, the prevalence of advanced histology in diminutive polyps seems low, although there is some heterogeneity in the literature due to different inclusion criteria (screening versus symptomatic patients; patients only with polyps less than a specific size, etc.), differences in the performed analysis (per-patient, per-polyp) and probably also due to the variability in the pathologic interpretation of dysplasia and proportion of villous component (table 1).

A recent systematic review with stringent inclusion criteria (average-risk asymptomatic population, clear definition of advanced adenoma, definition of the method adopted to assess polyp size, reported prevalence of advanced adenomas according to polyp size, and at least 500 subjects included) showed that the prevalence of advanced lesions among patients

whose largest polyp was diminutive (≤ 5 mm), small (6-9 mm) and large (≥ 10 mm) was 0.9%, 4.9% and 73.5% respectively [27]. The most recent study on this topic, a retrospective review of data from three prospective clinical trials has shown that the prevalence of advanced histological features in diminutive polyps is 0.5%.

Study (n patients)	AA ≤ 5 mm	AA 6-9 mm	AA ≥ 10 mm	HGD ≤ 5 mm	HGD 6-9 mm	HGD ≥ 10 mm
Unal [22] (n = 5087)	32 (0.6%)	12 (0.2%)	NA	-	-	-
Tsai [21] (n = 5087)	105 (2.1%)	67 (1.3%)	76 (1.5%)	2 (0.04%)	1 (0.02%)	0
Bretagne [25] (n = 2294)	-	-	-	6 (0.26%)	19 (0.82%)	227 (9.9%)
Lieberman [26] (n = 13992)	45 (0.3%)	62 (0.4%)	737 (5.3%)	1 (0.007%)	9 (0.06%)	45 (0.3%)
Gupta [23] (n = 1150)	3 (0.26%)	3 (0.26%)	6 (0.5%)	1 (0.08%)	0	1 (0.08%)

Table 1. Absolute prevalence of advanced adenomas according to the largest polyp size. AA: advanced adenoma; HGD: high-grade dysplasia; NA: non-applicable

Moreover, it remains unclear the practical role of advanced histological features in assessing the individual risk of CRC and in planning the management of patients with colonic polyps. First, there is a substantial interobserver variability in the diagnosis of the villous component and even HGD, with kappa index ranging from 0.35 to 0.48 and 0.38 to 0.69 respectively [28,29]. This problem may be even greater in polyps less than 10 mm [30]. Second, it is not clear that villous component or HGD are independent predictors of the subsequent development of advanced adenomas during follow-up. In the case of villous component the published studies do not separately identify patients whose most advanced polyp is a tubulovillous or villous adenoma < 10 mm in size, therefore the risk of this subgroup of polyps cannot be accurately assessed [31]. High grade dysplasia has not been shown to be an independent risk factor for metachronous advanced neoplasm in the NCI Pooling Project after adjustments for size and histology [32].

Taking all these data as a whole it appears clear that the standard practice of submitting all diminutive polyps found in colonoscopy to pathological assessment may have little clinical impact on the management of patients, and may result in substantial costs. Waiting for the pathological report may induce a delay in informing the patient and in recommending the next colonoscopy surveillance interval. In this context, some authors are recommending a “resect and discard” strategy to be applied to diminutive polyps found anywhere in the colorectum. Following this strategy the histology of a diminutive polyp would be assessed by an appropriate endoscopic method, the assessment would be recorded by means of a high-

resolution photograph and the polyp then would be resected and discarded. The endoscopic assessment of histology would be used to make an immediate recommendation regarding the next colonoscopy surveillance interval. Finally, when multiple diminutive rectosigmoid hyperplastic polyps are suspected endoscopically, histology can be established by real-time endoscopic assessment and documented by photography without the need of resection and pathological evaluation [33].

2. Endoscopic assessment of polyp histology

The key factor in adopting the “resect and discard” strategy is the endoscopic evaluation of polyp histology, since this information is necessary to plan the next surveillance interval. Moreover, the presence of suspicious endoscopic features may prompt a polyp to be submitted to pathologic assessment. Therefore, a reliable endoscopic method of evaluating histology is needed.

In recent years several imaging-enhancing technologies have emerged as an adjuvant for diagnosing and evaluating colorectal lesions [34]. High-resolution and magnification endoscopes allow enlarging the image and discriminating details. These endoscopes are often used in combination with chromoendoscopy, which involves the topical application of dyes at the time of endoscopy to enhance tissue characterization. Narrow-band imaging (NBI) is a technology that applies narrow-bandwidth filters to white light endoscopy allowing discrimination of mucosal vascular net. Fuji Intelligent Color Enhancement (FICE) and i-Scan are based on the same physical principles as NBI but are not depending on optical filters but on a postprocessing image system. All these technologies have been evaluated in the prediction of histology of colon polyps.

2.1. High-resolution/magnification endoscopy and chromoendoscopy

The usefulness of this technology in assessing histology is based on the pit-pattern classification proposed by Kudo which is intended to differentiate between non-neoplastic, neoplastic and malignant polyps. Following this classification patterns I and II correspond to non-neoplastic lesions and patterns III to V to neoplastic ones. Type V suggests malignant transformation [35].

Several large case series evaluate the utility of pit-pattern analysis to differentiate neoplastic from non-neoplastic lesions. Generally speaking, positive predictive values (PPV) for neoplastic lesion range between 70 to 100% and negative predictive values (NPV) between 70 and 99%. Studies with the largest number of lesions show an overall accuracy of 80-95% [36-38]. One study focused in diminutive lesions, reported an overall accuracy of 95% [39]. There are also some randomized controlled trials comparing magnification plus chromoendoscopy to conventional chromoendoscopy. Konishi et al. [40] showed an accuracy of magnification colonoscopy in distinguishing non-neoplastic from neoplastic lesions < 10 mm in size of 92% vs 68% for conventional chromoendoscopy. Emura et al. [41] using a similar design showing an overall accuracy of 95% vs 84%. These figures were similar when the sub-

group of lesions ≤ 5 mm was analyzed. Conventional colonoscopy, chromoendoscopy and magnification chromoendoscopy were compared in the study by Fu et al. [42], and the latter was found to have the highest accuracy (95.6%).

Magnification chromoendoscopy has also been evaluated in the prediction of malignant histology and invasive depth of cancer with variable results. Overall, it seems that its sensitivity and accuracy are lower. For instance, Bianco et al. [43] showed that endoscopic differentiation between invasive and noninvasive neoplasm had a PPV of 79% and a NPV of 95%. Hurlstone et al. reported an accuracy of 78% and a specificity of 50% [44]. Some authors use a modification of the Kudo classification with different subtypes of the type V pattern that may be quite cumbersome to use [45].

In conclusion, high-magnification chromoendoscopy allows the prediction of histology even in small and diminutive lesions, but is better differentiating nonneoplastic from neoplastic lesions than differentiating invasive from noninvasive neoplasms. Moreover, it must be kept in mind that overall accuracy is not 100%, despite the fact that a technology with a NPV of 95% for adenomatous histology fulfils the PIVI criteria for leaving suspected rectosigmoid hyperplastic polyps ≤ 5 mm in size in place [33].

2.2. Narrow-band imaging

2.2.1. Predicting histology by means of vascular features

Angiogenesis is a main step in the progression of neoplasms; therefore the diagnosis based on vascular morphological changes seems ideal for early detection and diagnosis of colon neoplasms. NBI enhances the visibility of the capillary network on the surface layer of the mucosa.

Normal mucosa displays a regular hexagonal or honeycomb-like pattern of capillary vessels around the crypt of the gland. This capillary meshwork, named meshed capillary (MC), is invisible or faintly visible (Figure 2a). In the neoplastic lesion, vessels grow thicker, with increasing diameter size, disruption and rise of vessel density as the lesion progresses. Therefore, recognizing the lesion becomes easier because it appears as a brownish area (Figure 2b).

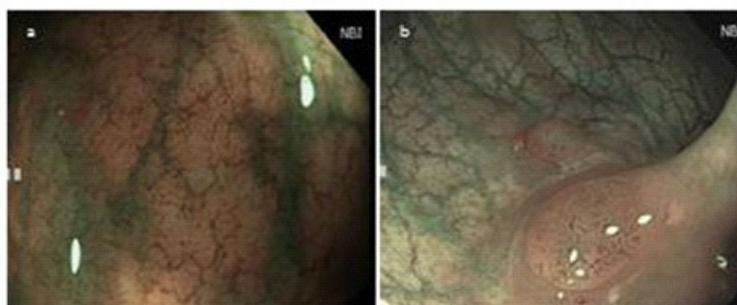


Figure 2. NBI image of normal mucosa (a) and a diminutive adenoma (b)

Several studies have evaluated the performance of NBI in characterizing colorectal lesions, focusing in the characteristics of the vascular capillary network. Generally speaking, NBI sensitivity and specificity for diagnosing neoplastic lesions ranges between 77% and 99% and 59 – 100% respectively (table 2). This heterogeneity may be explained by the use of different descriptions of vascular networks. Examples are, brown blob or dense vascular network to predict neoplasia [46-48]; fine capillary network, dark dots, light rounds, tubular or gyrus like [49]; microvessel thickness (invisible, thin, thick) and microvessel irregularity (invisible, regular, mildly irregular, severely irregular) [50]; vascular patten intensity (weaker, the same or darker than the surrounding mucosa) [51]; fine vascular network or dilated corkscrew type vessels and abnormal branching patterns [52]; and finally, capillary pattern (CP type I: invisible or faintly visible, CP type II: capillaries elongated and thicker and CP type III: capillaries of irregular sizes, thicker and branched) [53-55]. Other causes of heterogeneity are the use of magnification or high-resolution endoscopes since the results with the latter are not as encouraging (see section 2.2.5) [46,49,56], and finally, better results are reported by experts.

2.2.2. Predicting histology by means of pit pattern evaluation

Most of the published studies, mainly from Japan, use optical magnification in combination with NBI, and the performance of pit pattern analysis with NBI has also been assessed (table 3). Sensitivity for neoplastic lesion ranges between 86 and 100%, while specificity ranges between 84 and 100%. Some studies have compared NBI with chromoendoscopy showing similar diagnostic accuracy, suggesting that NBI could replace chromoendoscopy in the diagnostic evaluation of colon lesions [46, 47, 52]. However, the original pit pattern classification was not designed for NBI, and has not been validated for this purpose. NBI fundamentals are different than those of chromoendoscopy. The latter uses dyes that lie inside the pits or stain their edges depending on the stain used while NBI highlights the capillary plexus that surrounds the opening of each pit. Machida et al. [57] described the use of NBI with magnification for pit pattern classification, showing that NBI was superior to conventional colonoscopy for pit pattern delineation but inferior to chromoendoscopy. The correlation between pit pattern analysis using chromoendoscopy and NBI is far from perfect especially for the pattern with the utmost clinical importance, type V. A study compared the pit pattern analysis obtained by NBI with stereoscopic examination and showed that the correlation was only 57% for type V_N [58]. East et al. [51] found a kappa score of only 0.23 between both types of pit pattern evaluation. Better results were obtained by Hirata et al. [48] (78% of agreement for pit pattern V_I and 100% for V_N).

Author	Mag	Patients/ Lesions	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
Su [47]	Yes	78/110	96	87	93	92	92
Tischendorf [52]	Yes	99/200	94	89	94	89	92
East [51] ^a	Yes	30/33	77-91	50-60	-	-	69-81

Author	Mag	Patients/ Lesions	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
Chiu [46] ^a	Yes/No	133/180	87-95	88-72	96-92	67-80	87-90
Sano [53]	Yes	92/150	96	92	97	90	95
Hirata [50]	Yes	163/189	99	90	99	90	98
Hirata [48]	Yes	99/148	99	94	99	94	99
Rastogi [49]	No	40/123	96	86	90	95	92
Kanao [55]	Yes	223/289	95	100	100	20	99
Henry [54]	No	42/126	93	88	909	91	91
Ignjatovic [56]	Yes/No	48/80	93-74	59-56	-	-	76-85

Table 2. Vascular pattern analysis with NBI for prediction of adenomatous histology. Mag: use of optical magnification; PPV: positive predictive value; NPV: negative predictive value; DA: diagnostic accuracy. ^aTwo observers. Values for each observer are shown.

Author	Mag	Patients/ Lesions	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
Machida [57]	Yes	34/43	100	75	91	100	93
East [51] ^a	Yes	20/33	86-77	80-60	-	-	84-72
Tischendorf [52]	Yes	99/200	90	89	93	84	90
Van den Broek [59]	Yes	100/208	90	70	69	90	78

Table 3. Pit pattern analysis with NBI for prediction of adenomatous histology ^aTwo observers. Values for each observer are shown. Mag: use of optical magnification; PPV: positive predictive value; NPV: negative predictive value; AC: diagnostic accuracy.

A systematic review which included 6 reports published until 2008 comparing NBI (pit pattern and vascular assessment) and chromoendoscopy showed a pooled sensitivity, specificity and overall accuracy of 92%, 86% and 89% respectively [60].

2.2.3. Predicting submucosal invasion

NBI has also been evaluated to diagnose early colorectal neoplasia and submucosal invasion. Katagiri et al. [61] used the capillary pattern classification in colon adenomas. Those showing CP type III harbored HGD or invasive cancer. In a recent report this group further developed this classification expanding CP type III in group IIIA (visible microvascular architecture and high microvessel density with lack of uniformity, branching and curtailed irregularity) and group IIIB (nearly avascular or loose microvascular area). This detailed classification allowed differentiation between lesions with Sm1 submucosal invasion from Sm2-Sm3 with a sensitivity, specificity and diagnostic accuracy of 84.8%, 88.7% and 87.7% respectively [62]. Hirata et al.[50] found that the accuracy of diagnosis of submucosal mas-

sive invasion on the basis of thick and severely irregular vascular pattern was 100%. Kanao et al. [55] used a combination of capillary pattern and pit pattern and showed that lesions with irregular microvessels with variable sizes and distribution, and pit absence with avascular areas harbored more often massive submucosal invasion.

2.2.4. NBI compared with other diagnostic modalities

NBI has been compared with other image enhancing technologies, most frequently with chromoendoscopy. Overall, the diagnostic accuracy of NBI is better than that of conventional colonoscopy and equivalent to that of chromoendoscopy (figure 3) [46,47,52], especially if vascular assessment rather than pit pattern is used [51].



Figure 3. Invasive carcinoma in a depressed lesion observed with white light (a), NBI (b), and chromoendoscopy (c)

Four recent studies perform an evaluation of endoscopic trimodal imaging (high-resolution endoscopy, autofluorescence imaging and NBI) for colonic polyp characterization. Three studies from the same group show a poor diagnostic accuracy for NBI without magnification and autofluorescence with similar sensitivity but worse specificity [59,63,64]. Ignjatovic et al. [56] reported that NBI with magnification appeared to have the best accuracy, albeit modest and not adequate for in vivo diagnosis.

2.2.5. NBI without optical magnification

Most of the studies on prediction of histology using NBI have been carried out in Japan using Olympus equipments with optical magnification (Lucera), a feature not included in high-resolution systems (Exera) available in the USA and in continental Europe. Most of the capillary pattern descriptions or classifications have been designed using optical magnification, therefore are not directly applicable to high-resolution examinations. That is also the case for the Kudo's pit pattern classification.

The results of NBI without optical magnification in predicting histology are variable with authors showing an accuracy similar to that of optical magnification NBI and authors obtaining worse results [56]. Again, different definitions for a vascular pattern typical of adenoma (table 4) may account for these discrepancies. None of these classifications have been appropriately validated and its reproducibility in different clinical settings is unknown.

Author	Predictive of adenoma	Predictive of hyperplastic
Rastogi [49, 65, 66]	Round/oval pattern (dark outer and a lighter central area) Tubulogyrus pattern	Fine capillary network alone but absent mucosal pattern Circular pattern with dots (central dark area surrounded by a lighter area)
Rex [67]	Overall brown color Short thick blood vessels Tubular or oval pits, variable size pits Central brown depression Straight blood vessels around pits forming rectangles, pentagons, etc.	Bland, featureless appearance Pattern of black dots surrounded by white Thin blood vessels coursing across polyp surface, and not surrounding pits
Rogart [68]	Modified Kudo's classification	Vascular color intensity (light, medium, dark)
Sikka [69]	Neoplastic pit pattern (elongation of crypts, cerebriform pattern) Increased vascular markins	Non-neoplastic pit pattern (circular pit pattern) No vascular markins

Table 4. Prediction of histology using NBI without magnification

The group of the Indiana University has very recently designed a simple classification for determination of polyp histology (NICE classification) and has validated it for its use by experienced and non-experienced examiners (table 5) [70]. Further studies are needed to evaluate the reproducibility of this classification in real-time endoscopy.

2.2.6. Prediction of histology of diminutive polyps

Some authors have evaluated the diagnostic accuracy of NBI on diminutive polyps showing similar results to those on polyps of any size. In a study by Rex [67] the sensitivity of NBI in diagnosing adenomas was 92%, specificity 87%, PPV was 88%, NPV 91% and accuracy 89%. Grading the confidence on the endoscopic diagnosis in high and low, high confidence predictions of adenomas were correct in 92% of polyps and in 91% of ≤ 5 mm polyps. The equivalent figures for hyperplastic prediction were 95%. The same group evaluated the performance of NBI in real time for distal colorectal polyps, and showed a sensitivity of 96%, a specificity of 99.4%, and NPV and PPV of 99.4% and 96% respectively [71]. The authors concluded that NBI is sufficiently accurate to allow distal hyperplastic polyps to be left in place without resection and small, distal adenomas to be discarded without pathologic assessment. In the study of Henry et al. [54] the sensitivity for predicting histology was 87%, specificity was 93%, PPV was 89%, NPV was 91% and overall accuracy was 90%. Paggy et al. [72] found similar results both in the whole group of < 10 mm polyps and in diminutive polyps. Other authors have not showed as good results [56,73]. The most recent report using the NICE classification found an accuracy of 89%, sensitivity of 98% and a NPV of 95%. In conclusion, diagnostic accuracy of endoscopic prediction of histology of diminutive polyps seems equivalent to that of larger polyps, at least in expert hands.

NICE criterion	Type 1	Type 2
Color	Same or lighter than background	Browner relative to background
Vessels	None, or isolated lacy vessels coursing across the lesion	Brown vessels surrounding white structures
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular, or branched white structures surrounded by brown vessels
Most likely pathology	Hyperplastic	Adenoma

Table 5. The NBI International colorectal endoscopic (NICE) classification

2.2.7. Learning NBI. Does expertise matters?

Most of the published studies have been performed by experts endoscopists, both in Japan and in Western countries. Reliable information about reproducibility of this results is lacking. Moreover, the overall accuracy in prediction of histology es markedly influenced by expertise in NBI interpretation, as has been shown in a study performed in a non academic setting in which sensitivity for high-confidence prediction was 77% and specificity 78% [73]. Experts have been shown to perform better than non-experts and with a higher interobserver agreement [74]. Fortunately, NBI interpretation of histology can be easily learned. Several studies have shown significant improvements in diagnostic accuracy and in interobserver agreement after following a computer-based training module [75] or a short teaching session [76].

2.3. Fujinon intelligent color enhancement system (FICE) and i-Scan

FICE also narrows the bandwidth of light components using a computed spectral estimation technology that arithmetically processes the reflected photons to reconstitute virtual images for a choice of different wavelengths [77]. Therefore, it no depends on optical filters to modify the image. There are less studies using FICE or i-Scan than NBI but its accuracy seems broadly similar.

In the study by Pohl et al. [77] FICE (with set 4 activated) was used to identify the pit pattern and the vascular pattern intensity in a similar way to NBI. The sensitivity and specificity of FICE for the prediction of adenoma was 93.2% and 61.2%, figures similar to those of chromoendoscopy. Parra et al. [78] showed that FICE performance in predicting histology was inferior to that of chromoendoscopy with magnification. Kim et al. [80] reported that FICE with magnification was better than without magnification especially for diminutive polyps [79]. Regarding i-Scan, a study compared this technology with NBI for histology prediction of diminutive polyps and showed a similar performance with good agreement between the two modalities (kappa index > 0.7).

3. Conclusion

New image-enhancing technologies may allow in vivo histological assessment of colorectal polyps, avoiding the need to pathological evaluation of all resected polyps. This would represent substantial savings and a more direct planning of surveillance intervals [81]. However, there are several steps to achieve before the resect and discard strategy is widely implemented. First a more simple, reproducible and validated way of characterize colon lesions is needed, especially in community practice. Learning the technique is also crucial because when learning curve is achieved NBI performs significantly better [68]. Moreover, implementing PIVI guidelines [33] implies accepting a 10% rate of false negative when in vivo assessing histology of rectal polyps. Endoscopists may feel more comfortable with a much lower rate before leaving polyps behind. Finally, if in vivo histology is applied in daily practice this represents a turning point in the management of colon polyps, which must be supported by Professional Societies.

In vivo histology seems here to stay, but we are still at the beginning of the way. Improvement in equipments and development of new technologies will help the medical community to take this step forward.

Author details

Marco Bustamante-Balén*

Address all correspondence to: mbustamantebalen@gmail.com

EndoscopyUnit. University Hospital La Fe.Valencia, Spain

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