6. Flat and depressed colorectal neoplasia in the Western hemisphere

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Synopsis

Knowledge about colon cancer prevention has evolved in the last century. There is a substantial body of literature that supports the concept that colorectal cancers arise slowly, as a result of incremental genetic alterations (adenoma–carcinoma sequence). Cancer therefore should typically develop from grossly visible polyps, with the size of the latter correlating with its malignant potential. This paradigm forms the basis of current clinical recommendations for colon cancer screening and prevention. On a practical note, it has also allowed most American gastroenterologists to feel comfortable ignoring small (less than 0.5–1 cm) lesions. However, even though the majority of clinically significant cancers may develop in the classic manner, a growing body of evidence suggests the existence of an alternative, albeit less common, pathway originating from so-called nonpolypoid (flat and depressed, or F & D) lesions.

As far back as 1974, Morson estimated that although two-thirds of colorectal cancers arise from polypoid lesions the origin of the remainder remained unexplained [1]. Although nonpolypoid dysplasia has typically been noted in the setting of other colorectal diseases such as inflammatory bowel disease or familial adenomatous polyposis [2–7], it may also occur sporadically in the average risk population. These lesions are difficult to detect, a problem that is compounded by the general lack of familiarity with this lesion amongst most Western gastroenterologists. This chapter will review the literature on this subject and attempt to address some of the clinical controversies and questions surrounding it.

Definitions

The spectrum of nonpolypoid lesions and their morphogenesis

Muto and colleagues are credited with the first recognition of the small flat adenoma as a distinct entity in 1985 [8]. Indeed much of what is known today about these lesions comes from Japan, where their existence and significance has since become well established and free of the controversy surrounding these lesions in the West. The Japanese Research Society for Cancer of Colon and Rectum has classified colorectal neoplasms as either protruded (polypoid) or superficial (nonpolypoid) lesions, with the latter further categorized as flat, flat elevated, depressed, or some combination thereof (Figs 1 and 2) [9]. Occasionally, an additional term, laterally spreading tumor (LST), has also been used to describe what can probably be considered a large flat adenoma [10]. According to one hypothesis, both polypoid and nonpolypoid tumors arise from a small dysplastic lesion that either grows exophytically (to form a protuberant lesion), endophytically (to form a depressed lesion), or laterally (small and large flat lesions) [10] (Fig. 3).

Endoscopic criteria

F & D tumors can be defined endoscopically as well as histologically. Although strict criteria for endoscopic recognition have not been agreed, a useful working definition is that of an endoscopically
visible flat and/or depressed mucosal lesion with a height that is less than half of the diameter of the lesion [11]. Typically, most such lesions are less than 2 mm high [12]. Small flat adenomas are thus minimally elevated lesions less than 10 mm in diameter; lesions with larger diameters but still relatively flat may be called laterally spreading tumors although the term large flat adenoma may be preferred. Flat adenomas are typically more erythematous than the surrounding mucosa (hyperplastic polyps can also appear ‘flat’ but typically are of the same color as the surrounding normal mucosa); however, small lesions are easy to misdiagnose or miss altogether and may require special techniques for detection (see later).

Depressed lesions are flat lesions with a definite central depression (not to be confused with simple grooves or pseudodepressions); their size may vary. They may be very difficult to find and a strong index of suspicion needs to be maintained for small areas of color change (relatively pale or erythematous compared to the surrounding mucosa). A useful technique to accentuate these lesions during routine endoscopy is repetitive air inflation and deflation, when the surrounding mucosa moves more quickly than the lesion and elevates around the depression. Representative pictures of these lesions are shown in Figs 4 and 5. Specialized techniques to detect these lesions endoscopically will be discussed later.

**Pathological criteria ▲▼**

Histologically, flat adenomas are characterized by slightly elevated dysplastic mucosal plaques, never greater than two times the thickness of adjacent nondysplastic mucosa (with the height being measured from the muscularis mucosa to the top of the lesion) [13] and by the lack of exophytic polypoid configuration. The Japanese also follow a pathological classification of colorectal neoplasms that is somewhat similar to their gross appearance (Fig. 5). The degree of correlation between endoscopic and pathological criteria has not been well studied, and most studies rely on one or the other method to classify these lesions.

**The epidemiology of flat and depressed lesions in the West ▲▼**

Originally considered a Japanese ‘anomaly’, F & D lesions are increasingly being recognized in the occidental population in diverse regions of the world including Australia [14], Europe, and North America (Fig. 6). Some of the larger studies will now be described in detail.

**Sweden ▲▼**

Jaramillo *et al.* studied 232 patients in Stockholm between 1992 and 1993 after excluding inflammatory bowel disease and hereditary colorectal polyposis syndromes [17]. Using high-resolution video endoscopy and indigocarmine chemoendoscopy, these investigators found 109 colorectal flat neoplastic lesions in 55 of 232 patients (about 24%). These lesions were generally seen in patients over 60 years of age (78%) but not in patients under 40 years of age and were twice as common in men as in women. Most (71%) were 0.5 cm or less, 21% were between 0.6 and 1.0 cm, and 8% were more than 1.0 cm. Low-grade dysplasia was seen in 86% and high-grade dysplasia in 12% of flat lesions. Adenocarcinoma was diagnosed in 3% of flat lesions. Flat lesions with a central depression showed high-grade dysplasia more often than those without central depression (43% vs. 7%).

**Germany ▲▼**

Kiesslich *et al.* [21] studied 100 consecutive patients during routine colonoscopy using vital staining
with indigocarmine solution (0.4%, 1–10 ml) on all visible lesions as well as in the rectum if macroscopic examination was unremarkable. A total of 52 patients had 105 visible lesions (89 polypoid, 14 flat, and 2 depressed). The mean size of the lesions was 1.4 cm. Among the 48 patients with mucosa of normal appearance, 27 showed 178 lesions after staining (176 flat, 2 depressed) with a mean size of 3 mm. On histological investigation, 210 lesions showed hyperplastic or inflammatory changes, 67 were adenomas and 6 were cancers.

**United Kingdom ▲▼**

The incidence of flat adenomas in an asymptomatic population (3000 subjects, aged 55–64 years) participating in a large randomized controlled trial of flexible sigmoidoscopy screening was investigated in Leicester General Hospital, UK [19]. Three subjects had a total of four flat lesions, i.e. one per 1000 people screened. Three contained severely dysplastic lesions, and one with a focus of adenocarcinoma. Three of the four lesions were less than 5 mm in size and the fourth was 15 mm in diameter.

In a prospective study of 210 consecutive patients attending for routine colonoscopy in Leeds by an experienced Japanese endoscopist [18] using a standard Olympus 200 L colonoscope and the 200Z magnifying colonoscope and indigocarmine chromoendoscopy, 68 adenomas were found: 40 (59%) were polypoid, 26 (38%) were flat, and 2 (3%) appeared depressed. The majority of adenomas contained mild to moderate dysplasia. Four were severely dysplastic, three were in protruding lesions and one in a 6-mm depressed lesion. Two of the three Dukes A cancers were either flat or depressed lesions.

In another prospective study by the Leeds group of investigators [12] of 1000 consecutive patients attending for routine colonoscopy, this time by a single European colonoscopist, between June 1995 and March 1999, using a standard Olympus 200 L colonoscope and the 200Z magnifying colonoscope using indigocarmine chromoendoscopy, 321 adenomas were found; 202 (63%) were polypoid, 117 (36%) were flat and 2 (0.6%) were depressed. Most adenomas contained areas of mild to moderate dysplasia, 31 (10%) were severely dysplastic. The likelihood of Dukes'A cancer or severe dysplasia increased from 4% (3/70) in small flat lesions, to 6% (9/154) in small polyps, 16% (8/50) in larger polyps, 29% (14/49) in large flat lesions, and 75% (3/4) in depressed lesions. Slightly over half (54%) lesions containing severe dysplasia or Dukes' A cancer were flat or depressed.

**North America ▲▼**

**Vancouver ▲▼**

In a review of surgical pathology data of 340 adenomas examined between 1988 and 1989 at the Vancouver General Hospital, Canada, 29 (8.5%) adenomas were classified as flat adenomas. Flat adenomas were found in 18 (8.6%) of the 210 patients. Multiple adenomas were found in 12 of the 18 patients (40 adenomas total) and multiple flat adenomas were identified in nine patients. Two patients had concurrent flat, ulcerated colonic carcinomas without identifiable polypoid precursor adenoma. At colonoscopy, all the adenomas were sessile, flat, plaque-like or an abnormal fold, and less than 1 cm in diameter. All 29 flat lesions were tubular adenomas. However, there was a 10-fold greater frequency of lesions containing high-grade dysplasia than for an analogous polypoid adenoma with an equivalent spherical diameter [15].
In an often-cited ‘negative’ study of 184 patients referred for colonoscopy to Creighton University Medical Center, Nebraska from September 1989 to September 1990 (excluded patients with hereditary colon cancer family syndrome), 157 polyps were found in 57 patients. Thirty-five patients had adenomas, of which 12 patients had only flat adenomas while 6 had both flat and other adenomas. The flat adenomas have the same prevalence and associated risk factors as other adenomas, except for younger age of onset [16].

A prospective study of the prevalence of flat and depressed colorectal adenomas was performed on American patients in Galveston, Texas, using dye-assisted colonoscopy by a Japanese investigator between 1 June 1998 and 28 February 1999 [20].

Patients with inflammatory bowel disease and polyposis syndrome were excluded. A total of 298 polypoid lesions were detected: after excluding 110 lesions that were hyperplastic polyps, in the remaining 188 lesions (from 102 patients) excised, 66 lesions were of the flat and depressed type and 122 had a polypoid appearance.

Flat and depressed lesions were seen in 48 of the 211 patients (22.7%). Flat and depressed lesions were difficult to detect with conventional colonoscopy and required dye spray; 62% of the flat and depressed lesions were found only after the use of indigocarmine dye. Histologically, 82% of the flat and depressed lesions were adenomatous in nature, compared with 67% of polypoid lesions ($P = 0.03$). The incidence of adenomas tends to be higher in IIc (slightly depressed) and IIa + IIc (flat elevated with depression) than in IIa (flat elevated) type of lesions.

Flat and depressed lesions contained invasive cancer more often than did polypoid lesions (4.5% vs. 0%; $P = 0.04$). The average size of these advanced flat and depressed lesions was smaller than for the polypoid lesions (10.75 ± 2.7 mm vs. 20 ± 2.9 mm; $P < 0.05$). The Dukes stage of the flat and advanced cancers was more advanced despite the small size of these tumors, with subserosal extension in one case and lymph node metastasis in another. Flat and depressed adenomas showed significantly stronger fragile histidine triad (FHIT) expression and lower p53 reactivity than similarly sized polypoid adenomas, whereas proliferative and apoptotic indices were similar in both groups.

This is an area of considerable ongoing controversy, but one that is potentially of great clinical importance. Several of the studies discussed above seem to reinforce the view that Japanese gastroenterologists have held for some time, namely that nonpolypoid colorectal lesions behave differently than their more common polypoid counterparts, with the adenoma–carcinoma progression being accelerated, and in some instances, bypassed altogether, giving rise to the concept of a ‘de novo’ cancer. This issue will now be examined in some detail.

Despite what has been described above, it has been argued that F & D tumors do not represent a distinct category of colorectal lesions and should simply be regarded as very small polypoid adenomas [22–24]. Evidence cited for this belief includes a study in patients with familial adenomatous polyposis which
showed that adenomas typically grow horizontally to a diameter of 0.5 cm before beginning vertical growth [25]. Thus, according to one school, all colorectal neoplasia begins as a flat lesion. This would be a purely semantic issue were it not for the sinister implication of a greater likelihood of finding advanced pathology in F & D lesions.

However, some experts in the USA have vociferously denied this, based on several plausible arguments.

**Nomenclature issue ▲▼**

First, it has been claimed that the high-grade dysplasia reported to be associated with these lesions is simply a reflection of differences in diagnostic criteria used by American and Japanese pathologists [26,27]. Indeed the concept of cancer itself may be quite different, with Western pathologists requiring invasion of the submucosa or beyond. Japanese pathologists, on the other hand, are willing to label as cancerous those lesions showing severe cytological atypia, even though the epithelial cells remain confined to the mucosa (a finding that would be called high-grade dysplasia within an adenoma by their Western counterparts). These differences can have dramatic effects on histopathological interpretation, as was shown by Schlemper *et al.* [26].

In this study, eight expert pathologists from Japan, North America, and Europe individually reviewed slides of 20 colorectal lesions from Japanese patients. Western pathologists diagnosed suspected or definite carcinoma in only 20% of these as compared with the 64% incidence reported by Japanese pathologists. In fact agreement between the two groups was only seen in 9 of 20 cases.

Whereas some of these discrepancies were due to differences in nomenclature (such as intraepithelial cancer vs. high-grade dysplasia), what was more surprising was that some of the cancers diagnosed by the Japanese were reported simply as adenomas with low-grade dysplasia by the Western pathologists. Other reports have suggested that even within Japan, the interpretation of F & D lesions may vary from institution to institution, in part perhaps due to the extent of familiarity with these lesions [28].

This suggests that apart from differences in nomenclature, differences in the criteria used for histopathological classification and their importance may also contribute to the discrepancies in the results of studies on flat lesions between the various regions of the world.

**USA national polyp study ▲▼**

A second argument is based on the marked reduction in colorectal cancer incidence demonstrated by the National Polyp Study, in which all visible lesions by standard colonoscopy were removed [29]. During a follow-up of 8400 person-years, which was 97% complete, only five new cancers were detected. And according to one of the authors of that study ‘if small flat adenomas with appreciable malignant potential had been missed during colonoscopy, flat small cancers without associated benign adenomatous tissue should have been detected during this careful follow-up surveillance [24].

The National Polyp Study results also form the basis of a third argument. Although it did not prospectively classify lesions as flat or polypoid, a recent retrospective analysis of histologically resected specimens collected during that trial suggested an incidence of flat adenomas in 27% of all adenomas removed at the index examination [30]. The incidence of high-grade dysplasia in flat adenomas was low (around 1%) and not higher (and perhaps even lower) than that in polypoid
adenomas. Multivariate analysis of the follow-up data showed no evidence of a greater tendency for advanced adenomas to be found at surveillance colonoscopy.

**Flat lesions are different ▲▼**

Despite the plausibility of the above arguments, evidence is accumulating that supports the hypothesis that these lesions are truly a separate clinical and biological entity. Several recent studies both from Japan (using internationally accepted nomenclature) as well as studies from the West using local pathologists and standards have confirmed that flat and depressed lesions may well have a real risk of advanced pathology (see below).

Further, the results of the National Polyp Study are not necessarily reassuring. Despite a very rigorous protocol of careful examination of the entire colon with removal of all identified polyps, five cancers were still discovered in later follow-up. This may simply reflect the limitation of human skills; however, more disturbing is that cancer was seen in lesions as small as 6 mm (with the others being 8, 15, 15, and 25 mm); three of these cancers were detected within 3 years of the index colonoscopy. Although the morphology of these lesions is not specifically commented upon, these findings emphasize the fact that small aggressive cancers do exist in the Western world. Similarly, the retrospective histological analysis of resected polyps cited above does not differentiate between simple flat lesions and those with a predominant depressive component, a distinction that is now being recognized as being critically important (see below).

**Association of flat lesions with advanced pathology ▲▼**

When small F & D lesions are compared as a group with their polypoid counterparts, a striking difference in the incidence of high-grade dysplasia and cancer has been observed as was first reported by Muto. This observation is not confined to the Japanese population, as shown by Wolber and Owen from Canada [15] who found high-grade dysplasia in 41% of flat adenomas but in only 4% of polypoid lesions. Similarly F & D lesions are more often associated with invasive cancer, a finding that has also been confirmed in the USA by our group who reported an overall incidence of invasive cancer in 4.5% of these lesions [20].

We also found that the average size of all F & D advanced lesions (severe atypia and cancer) was significantly smaller than polypoid advanced lesions (about 11 vs. 20 mm) and that the stage of the F & D cancers was disproportionate to their size, with extension to the subserosa in one case and lymph node metastases in another. These findings are consistent with most Japanese reports [31–33].

The risk of high-grade dysplasia and cancer with F & D lesions may display some regional variations. A previous report employing similar diagnostic criteria found a higher incidence of advanced pathology in flat lesions from a Japanese population as compared with a Swedish one [34]. Of the 141 flat neoplasms seen in Tokyo, 24.8% had high-grade dysplasia, 7.0% intramucosal carcinoma, and 9.9% invasive carcinoma. On the other hand, of the 90 flat mucosal neoplasms seen in Stockholm, 13.3% had high-grade dysplasia, 1.1% intramucosal carcinoma, and 1.1% invasive carcinoma.

**Depressed lesions are more important than simple flat lesions ▲▼**

In recent years it is also becoming increasingly clear that not all nonpolypoid lesions have equivalent relevance. The greatest risk of advanced pathology is associated with lesions with a prominent depressed morphology, rather than the ‘pure’ flat polyp. This has been seen in Japanese [10,35] and Western [13] populations (Fig. 7). Top: from Sakashita et al. Bottom: adapted from Rembacken).
Depressed lesions also are increasingly being reported as more likely to be rapidly growing and invasive [36,37]. When cancer develops in such lesions, it is less likely to be associated with an adenomatous component [36] and k-RAS mutations are distinctly uncommon or absent altogether [35]. The distinction between simple flat lesions and those with depressive features was not always made in the older literature but clearly has very important implications for screening and treatment (see later). It is therefore critical that future studies classify these lesions more carefully.

‘De novo’ colorectal cancer and the relationship between early cancer and F & D lesions

According to the Japanese literature, many nonpolypoid early colorectal carcinomas (ECC, confined to the submucosa) [38] are not associated with an adenomatous component [10,35]. This has led investigators to hypothesize an alternative to the classic adenoma–carcinoma sequence for carcinogenesis, at least in a smaller proportion of cases [39,40]. Early colorectal cancer is clearly not confined to Japan: Stolte and Bethke have reported the largest series from the Western world, consisting of 155 patients seen over a seven year period [41]. About 60% of these lesions, defined as submucosally invasive cancers without evidence of precursor adenomatous tissue, were of the polypoid type, with the rest being of the F & D type.

If ECC is defined as superficially invasive cancer only, then it appears that the vast majority of ECC of the flat type is not accompanied by adenoma [42,43]. This may be explained in at least two ways. First, flat adenomas are not precursors to flat carcinomas, and the latter arise ‘de novo’ [43]. Alternatively, flat cancers may quickly replace the small cluster of adenomatous cells from which they arise [44].

Again, it appears important to distinguish depressed lesions from other flat lesions as this morphological pattern is least associated with adenomatous tissue and is most likely to invade the submucosa (Fig. 8).

Differences in genetic and biological markers between flat and polypoid lesions

The classic adenoma–carcinoma sequence in polypoid colorectal lesions involves a series of genetic ‘hits’ whose nature and sequence have been reasonably well defined. If nonpolypoid lesions deviate significantly from this paradigm, a powerful case can be made for a distinctive identity. Although these studies are only just beginning to emerge, several important differences have indeed been found (Fig. 9).

Colorectal carcinogenesis and F & D lesions

The significance of these observations, and how they relate to the putative differences in biological and clinical behavior, remains to be resolved. However, based on the findings discussed above, a hypothesis supporting a distinct pathway to carcinogenesis has begun to take shape. The classic multistep genetic model for colorectal carcinogenesis proposed by Vogelstein et al. proposes mutations in the APC gene (and associated loss of heterozygosity or LOH of chromosome 5q) as a very early, if not initial, step in this sequence, being found in the majority of tumors, even those of very small size [60]. This is followed by changes in the ras gene, allowing progress to larger more dysplastic tumors. Later, p53 mutations may be important in the transformation to cancer.
A different genetic pathway? ▲▼

It is now clear that K-ras mutations are distinctly uncommon and indeed may be absent altogether in F & D lesions, particularly in those with a predominant depressive feature (see above discussion). APC mutations have also been examined [53] in at least one large study of 47 adenomas with high-grade dysplasia (intramucosal cancer by the Japanese approach), about half of which were polypoidal and the others F & D lesions. Overall, APC mutations were nearly twice as common (44% vs. 25%) in the former. Further, when the F & D group was analyzed, this difference appeared to be contributed entirely by the depressed lesions, only 13% of which showed an APC mutation, as compared with 45% of the flat lesions. By contrast, several studies have shown that p53 mutations are similar in polypoid and nonpolypoid tumors [54,56,57] or lower in the latter [20,55].

These findings have led Watanabe et al. [39] to speculate a genetic model for colorectal tumorigenesis that varies according to the ultimate morphology of the tumors (Fig. 10). According to this, simple flat lesions closely follow the genetic pathway of their polypoid counterparts, with the exception perhaps of a low frequency of ras mutations.

Depressed lesions on the other hand may follow a distinct route that involves as yet uncharacterized genetic mutations, leading to accelerated cancerogenesis or in some cases de novo cancer. In this setting, the absence of ras mutation may be the limiting factor in terms of tumor size: without such mutations, flat lesions do not grow larger but nonetheless may progress to malignancy. It is also conceivable that the lesser degree of collagenosis and angiogenesis [59] induced by flat lesions may contribute to the restriction on their growth; alternatively, this may simply reflect different growth requirements of these neoplastic cells.

Finally, based on both rodent [61] and human [62] data, flat lesions are more likely to be associated with subjacent lymphoid nodules than their polypoid counterparts. This curious finding has led some to speculate that M cells (epithelial cells that cover colonic lymphatic tissue) may represent the precursors of the dysplastic cells found in flat lesions.

Clearly, these studies are in their infancy and much needs to be learned about the molecular and biological basis of nonpolypoid adenoma development and carcinogenesis.

The challenge of endoscopic detection of F & D lesions ▲▼

It is clear from the above discussion that the final role of F & D lesions in the overall morbidity and mortality from colorectal cancer, particularly in the West, has not yet been established. While there may be genuine differences in the behavior of these lesions in different ethnic populations, it is equally obvious that these lesions can no longer be dismissed casually in people of European descent.

An unfortunate and perhaps unintended consequence of the validation of the adenoma–carcinoma sequence in the majority of cases has been the readiness of gastroenterologists to ignore small lesions encountered during colonoscopy. Ironically, the remarkable reduction in colorectal cancer incidence demonstrated by the National Polyp Study may largely have been due to the rigor with which any identifiable polyp was pursued and removed (in other words, distinguishing between morphological types of small lesions is a purely academic exercise if all of them are resected).

Since then, however, we have moved in the opposite direction, because of a formidable combination of expediency and complacency. The Galveston study compared the findings in the study group (using dye
spray and the assistance of a skilled Japanese gastroenterologist) to a control group of patients undergoing colonoscopy by an experienced American endoscopist alone [20]. These results provided a ‘current practice’ perspective that may be generalizable to the wider gastroenterology community in this country. Overall, nearly twice as many polyps and nearly four times as many small (< 5 mm) adenomas were found in the study group. Therefore, many small polyps are either routinely missed or ignored under current methods of colonoscopy.

Although there is no current evidence to suggest that detection and removal of all F & D lesions during the initial colonoscopy will provide greater prophylaxis against the development of colorectal cancer over subsequent years, the opposite has not been proven either. Recent studies showing an unexpectedly high rate of second colorectal cancer during surveillance colonoscopies (with some cancers being detected despite several colonoscopic examinations within the preceding few years) have raised the alarming possibility that some cancers do indeed follow an aggressive and accelerated pathway and their precursor lesions may not be readily detectable [63]. Clearly, larger studies with long periods of follow-up will be required to address this issue and provide a definitive argument for changing the current endoscopic approach to small polyps. In the meantime, it is clear that gastroenterologists owe it to their patients to try and remain vigilant with a high index of suspicion for any peculiarities of the colonic mucosa.

In this regard, the Japanese have long ago routinely adopted chromoendoscopy as an aid to detection of these tumors and recently, have also developed optical zoom endoscopy. The utility of these techniques has also developed in the Western population [13,20,21]. The details of both these techniques are covered elsewhere. However, it is important to emphasize that these procedures not only involve additional time but also require training and orientation for their proper utilization. In particular, surface characteristics of tumors, based on the pit pattern, need to be learned as they provide the basis for an accurate prediction of their true histological nature (Figs 11 and 12).

Kiesselich et al. have also shown that such an approach can be useful in the Western population [21]. They used the pit pattern system (with indigocarmine) to classify lesions with a sensitivity of 92% and a specificity of 93%. Lesions with pit patterns III–V showed higher rates of dysplasia.

In the future, other forms of ‘bioendoscopy’[64] including Optical Coherence Tomography will undoubtedly be used to help unravel the enigma of the flat and depressed lesion. Once these lesions are found, endoscopic mucosal resection techniques can be used successfully to remove these lesions; further therapeutic decisions will depend upon the results of the histological interpretation of the depth of invasion, if any.

**Conclusion and clinical approach**

It is clear that no consensus yet exists on what to do with F & D lesions. We have made the argument that these lesions have the potential of being clinically quite significant and therefore gastroenterologists should remain alert to their existence. It is of utmost importance that ‘colonoscopic’ investigators in the West abandon the position of denial and move on to plan definitive studies that can either disprove or prove this hypothesis. At the same time, further translational studies will be invaluable in providing insight into alternative pathways of colorectal carcinogenesis.

While the results of these studies are awaited, we believe a strong case can be made for an aggressive policy of detection for at least one subtype of nonpolypoid lesions, that with a prominent component of depression.
This is based on the substantial evidence that depressed lesions have clear differences in terms of their invasive potential, coupled with differences in the frequency of ras mutations and accompanying adenomatous components.

In order to detect these F & D lesions, gastroenterologists in the West have to acquire the tools of their Japanese counterparts such as chromoendoscopy and magnification endoscopy, so they can be in a position to truly assure their patients that all lesions with malignant potential will be diligently looked for and removed. At the same time, it is quite possible that most simple flat lesions; less than 5 mm in size and without a depressive component may not be any more threatening than their polypoid counterparts. Final validation of these approaches needs further studies, and until then they can at best be regarded as speculative.

**References**


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