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## CLINICAL REVIEWS

# Flat and Depressed Neoplasms of the Colon in Western Populations

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Flat and depressed neoplasms of the colon are defined endoscopically as visible non-exophytic, flat and/or depressed mucosal lesions with a height less than half the diameter of the lesion. These neoplasms are typically smaller than their polypoid counterparts, and might be associated with a more aggressive biological behavior. While these lesions have been described in cohorts of Japanese patients for over two decades, their existence in Western populations has been less well described. This review focuses on the epidemiology and biological behavior of flat and depressed neoplasms in Western populations as well as the strategies for their identification, endoscopic staging, and therapy.

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## INTRODUCTION

Flat and depressed lesions of the colon have been described for over 20 yr by Japanese investigators (1, 2). Their existence in Western countries and more aggressive biological behavior remain points of controversy (3). Flat and depressed colonic neoplasms are typically smaller than their polypoid counterparts and can be more difficult to identify using standard colonoscopes, especially with an untrained eye (4, 5). However, the emergence and validation of advanced imaging technologies (6–11) have led to an increased rate of detection of these lesions, and several studies describing a significant prevalence of flat and depressed colorectal neoplasms in Western populations have now been published (3, 5, 9, 11–16). As these neoplasms might be associated with advanced histopathology (2, 9, 13, 15, 17–19) and an increased likelihood of submucosal invasion with the development of cancer (5, 20, 21), their identification and treatment becomes of great clinical importance.

## DEFINITION AND PATHOLOGY

Endoscopically, flat and depressed lesions are defined as visible non-exophytic, flat and/or depressed mucosal lesions with a height less than half the diameter of the lesion (2, 5, 19). These lesions are typically smaller in size than their polypoid counterparts, and are usually located on the right side of the colon (5, 9, 13, 15, 18). Flat and depressed colonic neoplasms can be further classified according to macroscopic criteria (Fig. 1) (22–24). This subclassification has clinical implications as slightly depressed type (IIc) and flat elevated with depression type (IIa/IIc) lesions have been shown to have a

higher likelihood of harboring a carcinoma with submucosal invasion than type IIa lesions (9, 13–15, 18, 25–27).

Laterally spreading tumors (LST) represent an important subtype of flat and depressed colonic neoplasms, and are distinguished from other flat and depressed lesions by their size. By definition, LST are greater than 10 mm in diameter with a low vertical axis and extend laterally along the luminal wall (28, 29). Two distinct subtypes of LST have been described (Fig. 2)—granular-type (G-type) and flat-type (F-type) (30). G-type lesions (Figs. 2 and 3) are composed of superficial spreading nodular aggregates forming a flat, broad-based lesion (carpet-like lesions); F-type lesions (Fig. 2) typically have a flat, smooth surface with an absence of granularity. Aside from the phenotypic differences which have been described, these two subtypes of LST have been found to have different clinicopathologic behaviors. F-type LST are typically located in the right colon and are smaller than G-type LST (22, 28, 30, 31). In addition, F-type LST have also been found to have a higher incidence of carcinoma with submucosal invasion as compared to G-type LST (1, 28).

Serrated adenomas represent another important colonic neoplasm that might present endoscopically as flat lesions varying in size from a few millimeters to several centimeters, which are located throughout the colon (32). These lesions can be difficult to distinguish endoscopically from other flat colorectal neoplasms, although depressed, or type IIc, serrated adenomas have not been described. Histopathologic examination of resected lesions reveals the presence of adenomatous glands containing a serrated epithelium similar to that found in hyperplastic polyps (33) (Fig. 4). The identification of these lesions has clinical importance, as several reports have now described invasive adenocarcinoma arising from serrated colorectal adenomas (34, 35).

Endoscopic appearance	JRSC class		Description
Protruded lesions	Ip		Pedunculated polyps
	Ips		Subpedunculated polyps
	Is		Sessile polyps
Flat elevated lesions	Ila		Flat elevation of mucosa
	Ila / Ile		Flat elevation with central depression
Flat lesions	Ilb		Flat mucosal change
	Ile		Mucosal depression
	Ile / Ila		Mucosal depression with raised edge

**Figure 1.** The Japanese Research Society classification of colorectal lesions. Reprinted with permission from Hurlstone *et al.* *Am J Gastroenterol* 2005;100:1283–9.

**PREVALENCE AND BIOLOGICAL BEHAVIOR IN WESTERN POPULATIONS**

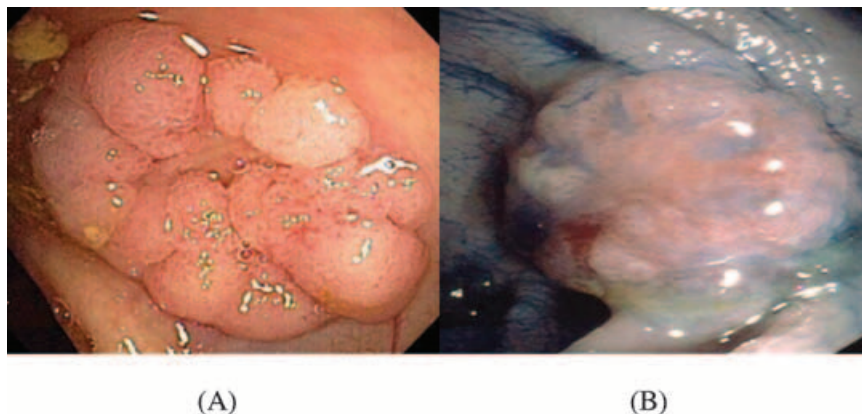
Although flat and depressed colorectal neoplasms have been well described in Japanese populations (1, 2), a decreased awareness of their existence, lack of training in endoscopic recognition, and differences in nomenclature and diagnostic criteria diagnose carcinoma between Japanese and Western pathologists (25, 36–40) may account for the decreased prevalence of these lesions reported in the Western hemisphere (37) over the past two decades. When experienced Japanese endoscopists were paired with their North American counterparts for the performance of colonoscopies at a single American center, flat and depressed lesions were identified in 22.7% of 211 patients that were studied (5). A control group, who only underwent colonoscopy by an American gastroenterol-

ogist, found significantly fewer lesions of any kind. Further analysis revealed that this difference was attributed entirely to a higher rate of detection of adenomas less than 5 mm in size in the study population, suggesting that operator experience and awareness of the existence of these smaller, flat and depressed lesions are important in their detection. Similar findings were described in a study from the United Kingdom (14). The results of several studies have now documented the existence of flat and depressed colonic neoplasms in Western populations (Table 1).

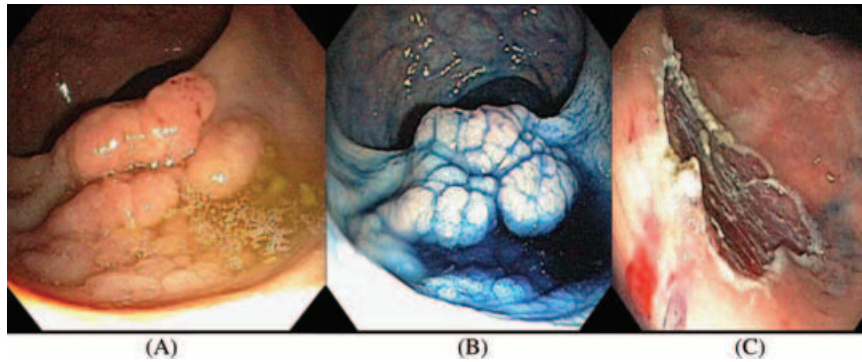
Multiple reports from the Japanese literature (1, 16, 25–27, 38, 41, 42) suggest that flat and depressed adenomas are associated with a higher incidence of advanced histopathology, which includes high-grade dysplasia and intramucosal adenocarcinoma. In a Korean study, 23.7% of the flat and depressed lesions which were identified contained “advanced” histopathology (19). Studies in Western countries have found high-grade dysplasia to be present in between 12% and 41% of flat adenomas (5, 9, 13, 15, 17, 39, 43, 44), where this number has been reported to be between 8% and 61% in Japan (2, 17, 18).

Not all studies have found an increased risk for advanced histopathology in flat and depressed adenomas. Recently, investigators for the American National Polyp Study reclassified the 933 sessile adenomas removed over a 10-yr period (3). After reclassification, 27% of the sessile adenomas met the study criteria for flat adenomas. No statistically significant difference was observed between flat and polypoid lesions with respect to the presence of high-grade dysplasia or early carcinoma. Moreover, these same findings held true when flat adenomas were compared to pedunculated adenomas.

This study has several limitations. First, this was a retrospective analysis which was based primarily on a histologic reclassification of sessile lesions into flat and polypoid adenomas, and was without an endoscopic correlation. Furthermore, the investigators were not trained in the identification of flat or depressed colorectal lesions; a factor which has been found to be important in the detection of these neoplasms which are small and often difficult to identify (5).



**Figure 2.** Endoscopic appearance of a G-type, type Ila (A) and F-type, type Ila/c (B) flat and depressed colorectal neoplasm.



**Figure 3.** Granular-type laterally spreading tumor of the colon prior to (A) and after (B) the application of a 0.4% indigo carmine solution. A mucosal defect (C) is seen following endoscopic mucosal resection of the identified lesion.

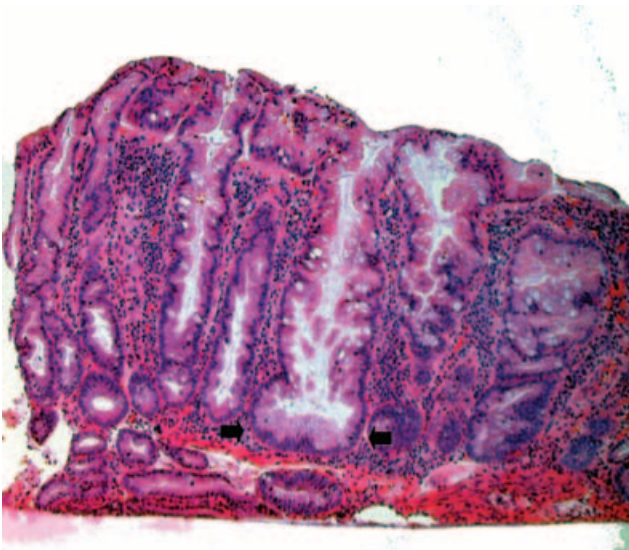
Finally, the American National Polyp Study was performed using older generation colonoscopes. Several studies have demonstrated that the use of advanced techniques such as high-magnification chromoendoscopy increases the detection rate of flat or depressed colorectal lesions (4, 5, 9, 10, 24, 45, 46).

In addition to an increased risk for advanced histopathology, flat and depressed adenomas are thought to be associated with a higher incidence of carcinoma, with rapid submucosal invasion than their exophytic counterparts (25, 38, 43). Studies performed in Japan have suggested that the incidence of early cancers in flat lesions is between 32% and 41%, and that flat lesions with central depression are at highest risk for submucosal invasion (20, 47). Teixeira *et al.* (21) classified excised colonic lesions >1 cm in size into three categories: flat elevation (22 lesions), laterally spreading (26 le-

sions), and polypoid (82 lesions). Following classification, all lesions underwent histopathologic examination. Carcinoma was identified in 77% of the flat elevation lesions but only 45% of polypoid lesions and 42% of LST. Interestingly, none of the cancers identified within the LST and 3% of the cancers identified within the polypoid lesions invaded the submucosal layer. However, submucosal invasion was identified in 24% of the carcinomas arising from flat lesions, thus suggesting that submucosal invasion occurs with increased frequency in carcinomas arising from flat neoplasms.

Given the more aggressive biological behavior associated with flat and depressed colonic adenomas, some have suggested an alternative pathway for cancer development in flat colorectal adenomas as compared to polypoid adenomas (37, 48, 49). One theory suggests that flat neoplasms might begin as flat adenomas which never progress to adenomatous polyps, but still have the potential to progress to larger, non-polypoid adenomas, which then progress through dysplasia to become flat cancers (50). A second theory suggests that flat colorectal cancers in some cases develop *de novo* without evidence of initial adenomatous tissue, suggesting that these lesions might not progress through the adenoma to carcinoma sequence (41, 50).

Evidence supporting the possibility of an alternative pathway for carcinogenesis in flat lesions comes from studies which found a lower incidence of K-ras and APC mutations in flat adenomas or carcinomas as compared to polypoid adenomas or carcinomas, respectively (37, 51–55). Almost half of all cancers arising from polypoid adenomas demonstrated a loss of chromosome 17P and 18Q. On the other hand, carcinomas arising from flat adenomas have been demonstrated to be associated with significantly more frequent loss of heterozygosity at chromosome 3P as compared to polypoid cancers. These findings support the notion that malignant transformation in exophytic neoplasms is associated with K-ras and APC gene mutations, while malignancies arising from flat adenomas are more likely to be associated with the loss of chromosome 3P (37). Although the importance of microsatellite instability (MSI) in the pathogenesis and prognosis of polypoid colorectal cancers is well established (56), the role which



**Figure 4.** Histopathologic example of a sessile serrated colon polyp. Note the lateral extension of the crypt base along the basement membrane (arrows) which is a characteristic histopathologic feature of these lesions. Image courtesy of Dr. John Hart, The University of Chicago Hospitals.

**Table 1.** Summary of Findings from Studies Describing the Prevalence of Flat and Depressed Colorectal Neoplasms in Western Populations

Source	Study Type	HMC	CE	Number of Patients (% Flat Neoplasm)	Number of Flat Adenomas Identified	Number of Flat Adenomas with Advanced Histopathology* (% All Flat Lesions)
Wolber and Owen (44)	Retrospective PR	No	No	210 (8.6)	27	2 (6.8)
Jaramillo <i>et al.</i> (9)	Prospective NR	No	Yes	232 (23.7)	94	15 (13.7)
Fujii <i>et al.</i> (14)	Prospective NR	No	Yes	210 (N/A)	26	2 (7.1)
Rembacken <i>et al.</i> (15)	Prospective NR	No	Yes	1,000 (N/A)	99	20 (16.8)
Lanspa <i>et al.</i> (16)	Prospective NR	No	No	148 (12)	66	0 (0)
Saitoh <i>et al.</i> (5)	Prospective NR	No	Yes	211 (22.7)	54	3 (5.2)
Kiesslich <i>et al.</i> (11)	Prospective NR	No	Yes	100 (N/A)	5	1 (16.7)
Tsuda <i>et al.</i> (13)	Prospective NR	No	Yes	371 (N/A)	50	16 (24.2)
Hurlstone <i>et al.</i> (47)	Prospective NR	Yes	Yes	1,000 (N/A)	195	59 (23.2)
O'Brien <i>et al.</i> (3)	Retrospective PR	No	No	938 (35.7)	420	14 (3.3)
Park <i>et al.</i> (43)	Retrospective PR	No	Yes	1,758 (15.4)	259	10 (3.7)

CE = chromoendoscopy; HMC = high-magnification colonoscopy; PR = pathology review; NR = nonrandomized.

\*Advanced histopathology: high-grade dysplasia or beyond.

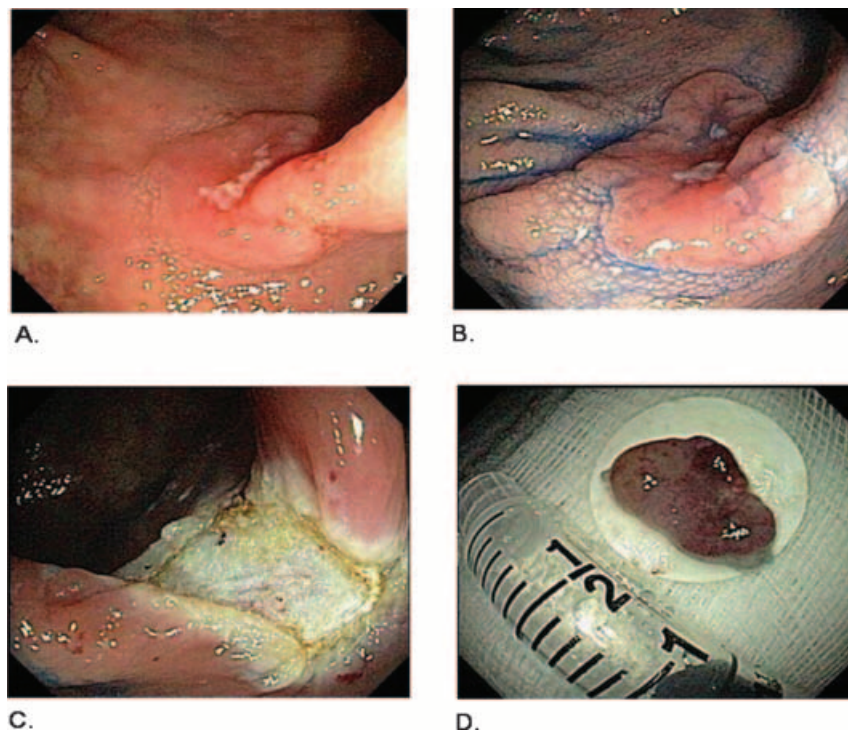
Adapted from Tsuda *et al.* (13), with permission.

MSI plays in cancers arising from flat colonic neoplasms is still being elucidated (51, 57).

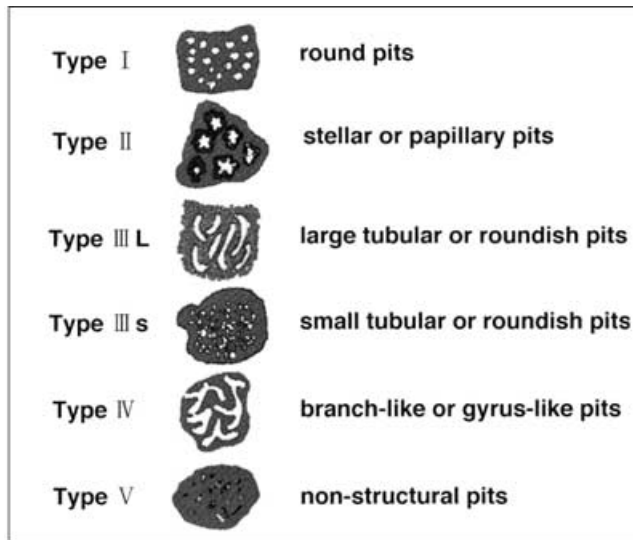
#### ENDOSCOPIC DETECTION STRATEGIES AND STAGING

Although colonic neoplasms, both flat and polypoid, may be detected using older generation, conventional colonoscopes, the implementation into clinical practice of chromoendoscopy coupled with (Figs. 3 and 5) high-resolution

and -magnification colonoscopes has allowed for higher rates of detection and more detailed endoscopic characterization of identified flat lesions (4–6, 9, 10, 24, 45, 46, 58). Chromoendoscopy involves the application of a 0.2% or 0.5% solution of indigo carmine to the colonic mucosa. This allows for superior evaluation of the mucosal surface, thus enhancing the detection and endoscopic staging of identified lesions (6, 58). Other technologies such as the use of high-frequency (20 MHz) ultrasound probes, have also been studied and have



**Figure 5.** A type IIa/IIc flat and depressed colonic neoplasm is identified (A). The surface characteristics as well as lesion borders are better defined using indigo carmine (B). Post-EMR appearance (C). The specimen is resected intact and sent for pathologic evaluation (D). Reprinted from Kinney *et al.* (57), with permission.



**Figure 6.** Kudo classification of mucosal surface patterns as observed on magnifying colonoscopy. Reprinted from Kudo *et al.* (8), with permission from the American College of Gastroenterology.

been found to be useful in the endoscopic staging of flat and depressed colorectal neoplasms (23, 59, 60).

In 1991, Kato reported the results of a retrospective study using chromoendoscopy and high-magnification colonoscopes in an attempt to predict histologic findings (10). The investigators used Kudo's classification of the mucosal surface pattern (61) in an attempt to predict the underlying histopathology of the identified lesions (Fig. 6). Non-neoplastic lesions, or those with a type I or II mucosal surface pattern, were diagnosed with 75% accuracy and a corresponding sensitivity and specificity of 42% and 99%, respectively. Colorectal adenomas, or those lesions with a type III or IV mucosal surface pattern, were diagnosed with an accuracy of 94%, and a sensitivity and specificity of 98% and 52%, respectively. Finally, invasive carcinomas (type V mucosal surface pattern) were diagnosed with an accuracy of 85%, a sensitivity of 82%, and a specificity of 99%. Although far from a replacement for microscopic examination, especially with regard to non-neoplastic lesions, this suggested that chromoendoscopy using high-magnification colonoscopes could potentially be useful in predicting histopathology, and thus, could help direct the appropriate resection technique, *i.e.*, surgical or endoscopic. These findings have been replicated by other studies (62).

While high-magnification colonoscopes and chromoendoscopic techniques have proven to be useful in predicting the histology of colorectal lesions, these technologies add cost and time to the examination (62). As later-generation colonoscopes with higher resolution have the ability to determine the mucosal surface pattern of polyps, some investigators have asked the question as to whether or not magnification endoscopes are needed at all. Konishi *et al.* (4) randomized 660 patients to colonoscopy using either a conventional colonoscope or magnifying colonoscope. All identified lesions <10 mm

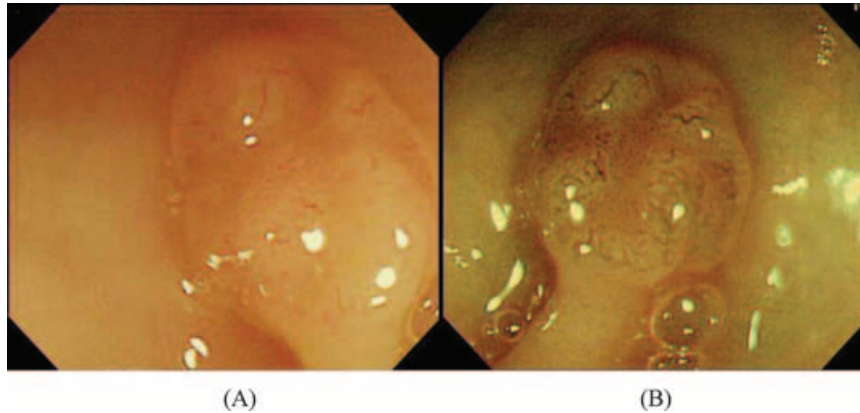
were sprayed with 0.2% indigo carmine dye, and histopathologic examination was performed. The diagnostic accuracy of the high-magnification endoscope in determining neoplastic versus non-neoplastic lesions was 92%, while that associated with the conventional colonoscope was 68%. The difference was statistically significant, suggesting that the addition of the high-magnification colonoscope had additional utility in predicting the histopathology of identified colorectal lesions.

The data from a study by Saitoh *et al.* (24) would argue to the contrary. Using the combination of non-magnifying chromoendoscopy and four endoscopic criteria—expansion appearance, convergence of folds toward the tumor, depth and irregularity of the depression surface—the investigators were able to correctly identify 90% of mucosal and superficial submucosal tumors, and 91% of tumors which penetrated into the deep submucosa or beyond. In a similar study, Hurlstone *et al.* (28) concluded that although there was a 100% staging accuracy utilizing sophisticated endoscopic techniques, the combination of basic chromoendoscopy using standard colonoscopes with the lack of a “lifting sign” following saline injection at the base of the lesion would have correctly staged 86% of the lesions identified.

Novel endoscopic techniques for staging of flat and depressed colorectal neoplasms are currently under investigation. A group of Japanese investigators (63) is currently studying narrow band imaging (NBI) (Olympus Medical, Japan) in the diagnosis and prediction of histopathology of flat and depressed colonic lesions. NBI employs a filter system corresponding to the wavelength of blue light (400–430 nm). These shorter wavelengths have been found to be absorbed by hemoglobin *in vivo*, thus allowing enhancement of submucosal capillaries and definition of the mucosal surface pattern without the need for dye application (Fig. 7). A preliminary investigation (63) in patients undergoing colonoscopy for suspected colonic neoplasms found that the NBI system, when used in combination with a magnifying colonoscope, detected a significantly higher number of colonic lesions than did standard colonoscopes alone. Furthermore, histopathology of the identified lesions could be accurately predicted in 94% of the cases, using the NBI system. This technique remains investigational; however, if it is proven to be useful, NBI might obviate the need for chromoendoscopy.

## ENDOSCOPIC THERAPY

Proper endoscopic staging of flat and depressed colorectal lesions is important, as it helps the endoscopist select the appropriate method for resection: endoscopic or surgical. EMR allows for endoscopic resection of flat and colonic lesions by longitudinal section through the submucosal wall in the horizontal plane (47) (Figs. 3 and 5). Because EMR allows for complete resection of the lesion down to the level of the submucosa, resection margins can be established by histological examination of the resected specimen.



**Figure 7.** A type IIc flat and depressed colonic neoplasm as visualized with a conventional colonoscope (A) and using the narrow banded imaging system (B). Note that with the use of the narrow banded imaging system, the mucosal surface pattern can be determined without the use of dye. Images courtesy of Dr. Yusuke Saitoh, Asahikawa City Hospital, Japan.

While cancers arising from flat and depressed lesions may have a propensity for submucosal invasion, the risk of regional lymph node involvement is low and is dependent on the depth of submucosal invasion (47, 64, 65). Lesions remaining within the superficial level of the submucosa (66) (T1) are associated with rates of regional lymph node involvement that range from 0% to 5%, while deep submucosal penetration is associated with a 15–20% risk. Invasion through the muscularis mucosa to the muscularis propria, T2 staging, is associated with regional lymph node involvement in up to 50% of cases (47). As such, EMR is appropriate (and potentially curative) only for cancers staged as Tis and T1, with limitation of invasion to the superficial level of the submucosa.

Hurlstone *et al.* prospectively evaluated chromoendoscopy using a high-magnification colonoscope, followed by EMR of flat and sessile colorectal lesions in 1,000 patients undergoing colonoscopy in the UK who were considered high risk for colorectal neoplasia (47). Lesions less than 20 mm without endoscopic criteria, suggesting deep submucosal invasion (*i.e.*, Kudo type V pattern, asymmetric “lifting” or positive non-lifting sign (67) following submucosal injection) underwent EMR using a saline-assisted snare technique.

A total of 599 lesions were removed in this fashion, and complete histological resection was confirmed in 576 (96%) of the lesions. Forty percent of the lesions were flat or depressed, of which 23% contained high-grade dysplasia or more advanced histopathology as compared to 9.0% of the sessile lesions. Bleeding was the most common complication of EMR in the study cohort, and one microperforation was reported. None of the patients required surgery secondary to complications of EMR, and there were no deaths reported.

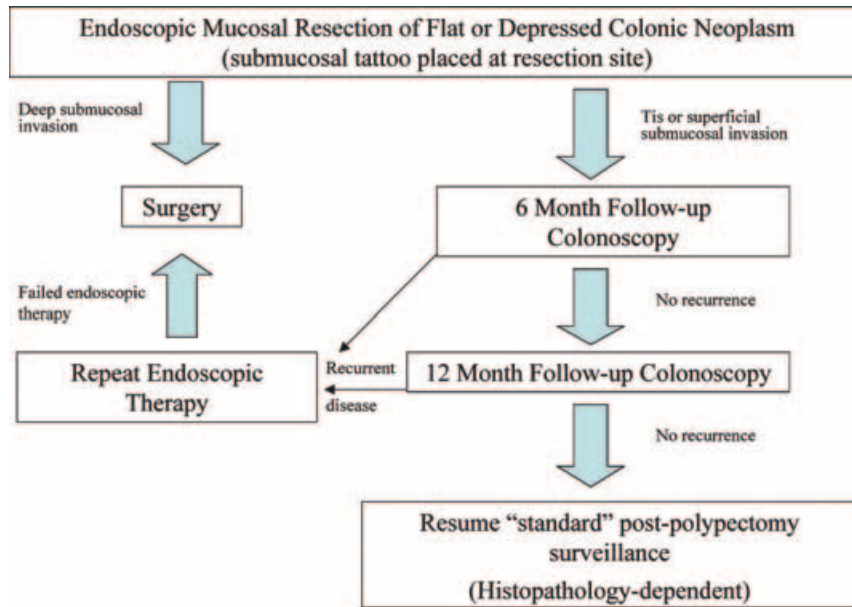
Other studies have found EMR to be equally safe and efficacious in the endoscopic treatment of flat or depressed colorectal lesions (28, 29, 42, 68, 69). Hurlstone *et al.* (28) recently described their experience with LST of the colon, in which 82 identified LST were evaluated for potential EMR. Endoscopic staging of the lesions was accomplished by a

combination of magnification chromoendoscopy and high-frequency probe ultrasonography. Fifty-eight lesions underwent EMR, followed by argon plasma coagulation of the resection margins, an approach which has been found to decrease the rate of recurrence following piecemeal resection of large sessile polyps (70). Local recurrence of adenomatous tissue was found in 10 patients (17%) within 6 months of the initial resection, 8 of whom underwent repeat EMR. Following 2 yr of clinical and endoscopic follow-up, EMR provided adequate curative treatment for 56 of the 58 (96%) of the neoplasms identified.

The high rate of early recurrence (17% at 6 months) demonstrated in the study by Hurlstone *et al.* (28), suggests that close endoscopic follow-up with colonoscopy at 6-month intervals might be necessary following EMR of flat and depressed colonic neoplasms. While this is a more aggressive follow-up regimen than that which is currently recommended following routine endoscopic polypectomy of polypoid adenomas, flat colonic neoplasms have been associated with more aggressive biological behavior and an increased incidence of advanced histopathology in resected lesions. In the absence of prospective data to the contrary, an aggressive endoscopic surveillance strategy following EMR of flat colonic neoplasm seems justified. A proposed algorithm for endoscopic surveillance based on the limited available data is presented in Figure 8.

## CONCLUSIONS

In summary, flat or depressed colonic neoplasms have a significant prevalence in Western populations, and appear to be associated with more aggressive biological behavior than their exophytic counterparts. A heightened awareness for the existence and training in the recognition of these smaller, flat and depressed colorectal lesions are imperative. While the use of advanced imaging modalities such as magnification colonoscopes, ultrasound probes, and chromoendoscopy



**Figure 8.** Proposed management algorithm following endoscopic mucosal resection of flat colonic neoplasms.

have proven to be helpful in the identification and endoscopic staging of flat and depressed colonic neoplasms, the available data suggest that conventional colonoscopes combined with the lack of endoscopic evidence of deep submucosal invasion might accurately predict lesions which are amenable to EMR. The appropriate colonoscopic surveillance interval after EMR remains to be determined.

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