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Editorial

Non-polypoid colorectal neoplasms are no longer unique to Japan, but do not mix up flat and depressed lesions

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ENDOSCOPIC CLASSIFICATION OF EARLY COLORECTAL CANCER AND ADENOMA

EARLY COLORECTAL CANCER and adenoma can be grossly divided into protruded or polypoid (type 0-I) and superficial (type 0-II).[1] Excavated type (type 0-III) was deleted from the recent Japanese classification. The superficial type is further divided into elevated (type IIa), flat (type IIb) and depressed (type IIc). So-called 'flat' adenomas are rarely absolutely flat (type IIb), but are often slightly elevated (type IIa). Depressed-type colorectal cancers can be absolutely depressed (IIc) or can be accompanied by a slightly elevated margin (IIc + IIa and IIa + IIc).

The depressed type was first described in the Japanese language in 1977 and in English in 1993.[2] In the meantime, so-called 'flat adenoma' was first described in 1985.[3] It referred mainly to slightly elevated lesion, but a depressed variety was also included to the category of 'flat adenoma'. The authors emphasized that more than two-fifths of such lesions contained highly dysplastic foci, but this was mainly found in the 'depressed variety'.

Magnifying video-colonoscope became commercially available in Japan in 1993 and accelerated the study of the microsurface pattern of colonic lesions. The combination of dye and zoom was useful for detecting, delineating and characterizing early colorectal neoplasms. Since then, both flat lesions and depressed lesions have been increasingly reported in Japan.

REPORTS ON NON-POLYPOID COLORECTAL NEOPLASMS FROM THE WEST

UNTIL RECENTLY, RELATIVELY few cases of non-polypoid early colon cancers were reported from the West. The cause is speculated that such lesions might have been overlooked as a result of a lack of the concept or because proper diagnostic methods were not used.

Western and Japanese experts gathered and held the International Conference on Endoscopic Classification of Superficial Neoplastic Lesions in Paris, 2002. The adopted classification (so-called Paris classification) was basically in accordance with the Japanese classification.[4]

A review of pathology specimens obtained during the National Polyp Study in the USA found that many flat adenomas had been removed during colonoscopy, but not reported in a separate category and were only referred to as polyps in the endoscopy reports.[5] Recently, an increasing number of articles on non-polypoid colorectal lesions have also been published from outside Japan.[6–12]

DIFFERENCES BETWEEN FLAT LESIONS AND DEPRESSED LESIONS

ACCORDING TO KUDO, the rates of invasive cancer in protruded and flat-elevated lesions between 6 and 10 mm in diameter were 1.3% and 0.18%, respectively.[2] In the meantime, the invasive rate of depressed lesions for the same size group was as high as 43.2%.[2] The rate of invasive cancer was not remarkably different between flat and protruded lesions.

Some previous studies have reported that the malignant potential of flat-elevated adenomas is higher than that of polypoid adenomas, but many other studies have reported that they were not substantially different. In any case, it should be noted that most flat adenomas are not as malignant as thought previously.

Some flat-elevated adenomas spread extensively and circumferentially along the colonic wall although being very short in height, and these were named 'laterally spreading tumor (LST)'.[1,13] They are further divided into granular type which is composed of fine granules, and non-granular type which is devoid of apparent nodules or granules. These lesions are sometimes invasive, but not as advanced as one would expect when compared with their large diameter. It seems that flat-elevated lesions grow very slowly and do not become invasive until they are quite large.

dos Santos *et al*. described that the prevalence of depressed lesions was 0.6–2.9% according to previous

reports.[14] Kudo described that the depressed-type lesion comprised 2.4% of all colorectal neoplasms, but the prevalence of depressed-type jumped to 33% among tumors with cancer invasion into the submucosa.[2] The rate was as high as 60% when only lesions <10 mm were considered.[2] It is speculated that depressed lesions grow rather rapidly, advancing at an early stage.

ADENOMA–CARCINOMA SEQUENCE THEORY AND *DE NOVO* PATHWAY

DEPRESSED-TYPE LESIONS HAVE been reported not to be associated with *K-ras* point mutation.[15] They are regarded as candidates for *de novo* carcinogenesis and seem to be associated with specific genetic alterations different from those in the adenoma–carcinoma sequence, although further investigations are awaited in order to prove the hypothesis.

A significant number of small colonic cancers without any evidence of adenomatous remnant have been reported. In the meantime, it was reported that benign adenomatous tissue was seen only in approximately 20% of advanced colorectal carcinomas.[2] There is no evidence, however, that colon cancers without an adenomatous component actually arise *de novo* from an absolutely normal mucosa. An alternative explanation may be that these lesions arise from microadenomas which are rapidly replaced by the expanding carcinoma. In any case, such a rapid development of cancer looks quite different from a conventional adenoma–carcinoma sequence.

Regarding the natural history of small adenomas, some studies suggested that many small adenomas either do not grow or sometimes diminish in size if followed.[16] As mentioned earlier, the malignant potential of flat-elevated lesions are not so different from that of protruded lesions. It can be speculated that flat-elevated lesions also follow the adenoma–carcinoma pathway.

NEED FOR DIFFERENTIAL DIAGNOSIS BETWEEN FLAT LESIONS AND DEPRESSED LESIONS

SOME BENIGN ADENOMAS appear to have a depression and resemble depressed-type early cancers; however, a 'depression' in flat-elevated benign adenomas is actually a shallow concavity or an ill-defined pseudo-depression and presents a thorny or groove-like appearance (Fig. 1). Flat-elevated adenomas with pseudo-depression should be differentiated from truly depressed lesions, because the former are almost always benign

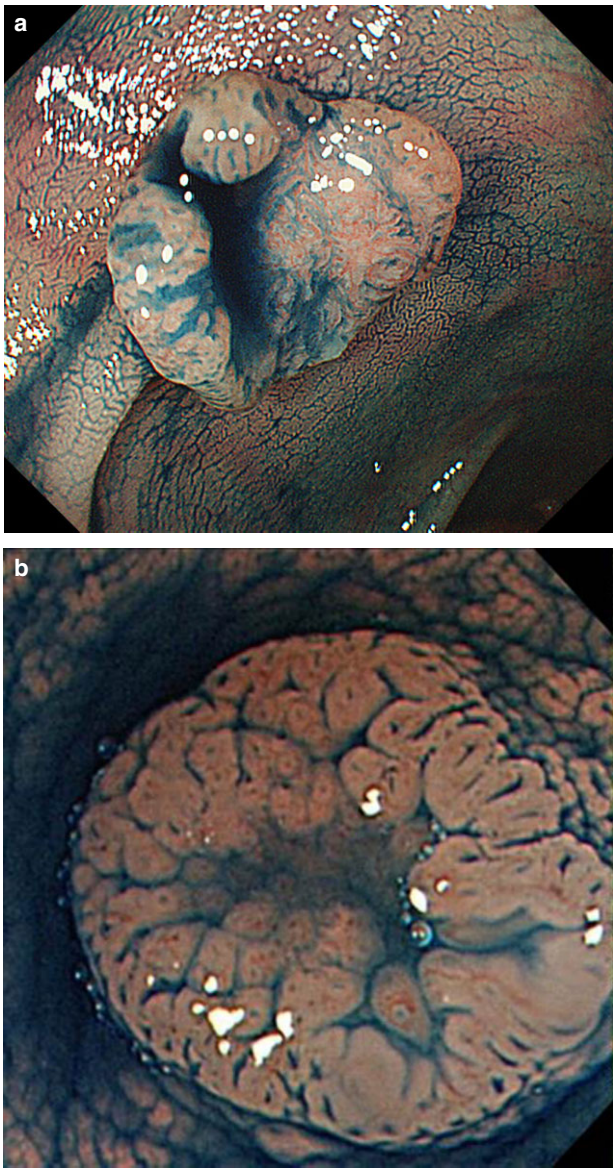

Figure 1 Depressed lesion and flat lesion with pseudo-depression. (a) Truly depressed lesion (IIa + IIc) with extensive depression. Pit pattern in the depression is type VI, whereas that at the marginal elevation is type I. (b) Flat lesion with pseudo-depression. Center of the lesion looks slightly depressed, but the 'depression' is ill-defined and has only a thorny or groove-like appearance. Pit pattern of the lesion is type IIIL both at the periphery and at the center.

Many authors have been discussing flat lesions and depressed lesions mixed together,[3,6–12] but their nature should be discussed separately. Depressed lesion is not a subtype of flat lesion, but a different entity. Comprehensive terms such

as 'non-polypoid' or 'superficial' may also be misleading. Therefore, the use of these descriptions should be chosen carefully.

dos Santos *et al*. reported the prevalence of non-polypoid colorectal neoplasms in southern Brazil and presented the data of flat lesions and depressed lesions separately.[14] The prevalence of depressed lesions and their advanced nature were in accordance with reports from Japan. It would support the speculation that colorectal carcinogenesis may not be as different between the East and West as previously thought.

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