9

Pathological Issues of Ulcerative Colitis/Dysplasia

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1. Introduction

The first ulcerative colitis (UC)-associated carcinoma (colitic cancer) appears to have been 14-year history of UC (Fujii et al., 2002, as cited in Crohn & Rosenberg, 1925). It is widely accepted that inflammation plays important roles in the development of various cancers, and indeed, patients with UC show an increased incidence of colorectal neoplasia, and UC-associate dysplasia/neoplasia represents a major cause of increased mortality in such patients. In order to improve the prognosis of patients with UC-associated dysplasia/neoplasia, diagnosis at an early or precancerous stage is crucial. Predisposition to colorectal dysplasia/neoplasia in UC is generally considered to depend on 2 risk factors, namely the presence of long-standing disease and extensive colitis (Fujii et al., 2008, as cited in Ekbom, et al., 1990, and Eaden et al., 2001). Thus, colitic cancers are believed to arise through a chronic inflammation-dysplasia-carcinoma sequence, and therefore early detection of precancerous dysplasia is very important for optimizing the prognosis of patients with long-standing UC. In a clinical setting, UC patients are monitored for dysplasia endoscopically on a regular basis, but it is difficult to discriminate UC-associated dysplasia/neoplasia from inflamed regenerating epithelium even by pathological examination. Therefore, surveillance colonoscopy with multiple random biopsies has been widely recommended for patients with long-standing and extensive UC. However, because UC-associated dysplasia/neoplasia is often difficult to detect endoscopically and to discriminate from inflammatory regenerative epithelium histologically, it remains a matter of contention whether conventional surveillance colonoscopy is effective for the early detection of UC-associated dysplasia/neoplasia. Here we describe the ulcerative colitis/dysplasia based on pathology and discuss relevant issues in arriving at the correct differential diagnosis based on morphological, immunohistochemical and molecular findings.

2. Risk factor and clinicopathological characteristics of dysplasia/neoplasia development in the patients with ulcerative colitis

The reported prevalence rates of colitic cancer range from 1 to 10% of all patients with UC. This increased risk, above that of the general population, appears approximately 8–10 years after the onset of the disease. The risk increases with the duration of disease and is greater in persons with extensive colitis (Fujii et al., 2002, as cited in Dobbins, 1984). A cumulative

incidence of colorectal cancer was 5–10% with UC of 20 years duration and 12–20% with UC of 30 years duration (Fujii et al., 2002, as cited in Levin, 1995). The risk of colorectal cancer in patients with left-sided colitis was considered to increase 20 years after the onset of UC. Moreover incidence of colitic cancer in patients with left-sided disease did not differ from that in patients with pancolitis. In order to detect UC-associated dysplasia/neoplasia and the early stages of cancer, surveillance colonoscopy has been recommended for patients with long-standing and extensive UC. In Japan, possibly because the number of UC patients with dysplasia/neoplasia is smaller than that in Western countries. We reviewed Japanese case reports of UC-associated dysplasia/neoplasia published between 1990 and 2002 (Fujii et al., 2003b). Of 118 patients with UC-associated neoplasia, 41 underwent surveillance colonoscopy (surveillance group), 64 did not (nonsurveillance group), and the remaining 13 cases were unknown as to surveillance status. The 64 UC associated neoplasias including colitic cancer (UC associated carcinoma) in the nonsurveillance group were found by colonoscopy that was undertaken because of developing symptomatic episode, or for the evaluation of inflammation activities. The depth of tumor invasion, incidence of lymph node metastasis, incidence of liver metastasis, and stage in the two groups are shown in Table 1.

	Surveillance (41)	Nonsurveillance (64)
Depth of neoplastic invasion		
Tis	11	11
T1	12	5
T2	5	6
T3	10	30
T4	0	6
Unknown	3	6
Lymph node metastasis		
Positive	4	25
Negative	25	23
Unknown	12	16
Liver metastasis, positive	1	4
Peritoneal dissemination, positive	0	7
Dukes' stage		
A	22	15
B	2	8
C	4	25
Unknown	13	16

Table 1. Clinicopathological features of neoplasias in the surveillance and nonsurveillance groups (adapted from Fujii et al., 2003b)

Regarding depth of tumor invasion, early colorectal cancer, defined as tumor invading the lamina propria and/or muscularis mucosae and/or submucosa, was more frequent in the surveillance group than in the nonsurveillance group (60.5% vs. 27.6%). The incidence of lymph node metastasis was lower in the surveillance group than in the nonsurveillance group (13.8% vs. 52.1%). Four out of the five tumors associated with liver metastasis and, all seven tumors associated with peritoneal dissemination were in the nonsurveillance group. The distribution of Dukes' stages in the two groups was: A/B/C, 78.6%/7.1%/14.3% in the

surveillance group, compared with 31.2%/16.7%/52.1% in the nonsurveillance group. Similar to Western countries, surveillance colonoscopy in Japan contributes to the early detection of UC-associated dysplasia/neoplasia. The surveillance colonoscopy appears to contribute to the early detection and excellent prognosis of UC-associated dysplasia/neoplasia. But it still remains questionable whether surveillance colonoscopy with multiple-step biopsy effectively enables the early detection of UC-associated dysplasia/neoplasia.

3. The morphological, immunohistochemical and molecular finding of ulcerative colitis/dysplasia

Morphological futures of macroscopic and endoscopic images, UC-associated dysplasia/neoplasias in the precancerous and early stages show various changes. Such dysplasia/neoplasias are often flat, plaque-like, and superficially elevated or even depressed, and frequently appear as faintly red, mildly discoloured, finely villous, and granular (Fig.1).

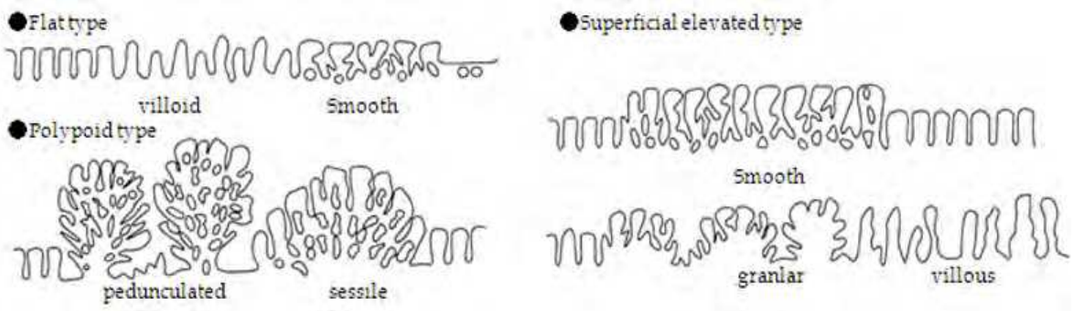


Fig. 1. Morphological classification of dysplastic epithelium in ulcerative colitis. (adapted from Fujii et al., 2002)

Macroscopic and endoscopic changes are not clear, and are sometimes missed in chronically inflamed epithelium. Detecting UC-associated dysplasia/neoplasias in the precancerous and early stages is difficult by macroscopy (Fig.2), endoscopy (Fig.3a), and stereomicroscopic finding (Fig.3b). We retrospectively verified the percentage of UC-associated dysplasia/neoplasias that was detectable endoscopically before surgical resection （Yamagishi et al., 2009）. When classified UC-associated dysplastic/neoplastic lesions according to macroscopic appearance, 79.1% lesions were of flat-type. In detail, 92.5% dysplasias, 80.9% Tis carcinomas, 60% T1 carcinomas were of flat (flat and superficial elevated type), whereas 6 of 7 (85.7%) T2-4 carcinomas were protruding (polypoid type). In each T category, the detection rare of lesions tends to be high in the protruding appearance (Table 2). Most of the undetectable lesions were the flat or flat-elevated type macroscopically. Thus, endoscopic detection of UC-associated dysplasia/neoplasias at the precancerous and early stage appears to be difficult. Therefore, improvements to the current methods of colonoscopy are needed in order to detect UC-associated dysplasia/neoplasias more effectively and accurately. On the other hand, several Japanese investigators reported that observation of the configuration of the outlet of the colorectal surface lesion using high-resolution endoscopy, chromoendoscopy (Fujii et al., 2008, as cited in Rembacken, et al., 2000, and Kudo et al., 1994), increasingly useful for diagnosing and treating colorectal neoplasia. Recent reported the usefulness of high-resolution endoscopy, chromoendoscopy,

and new endoscopic system (NBI, FICE, i-scan) for detecting UC associated dysplasia • neoplasia (East et al., 2006).

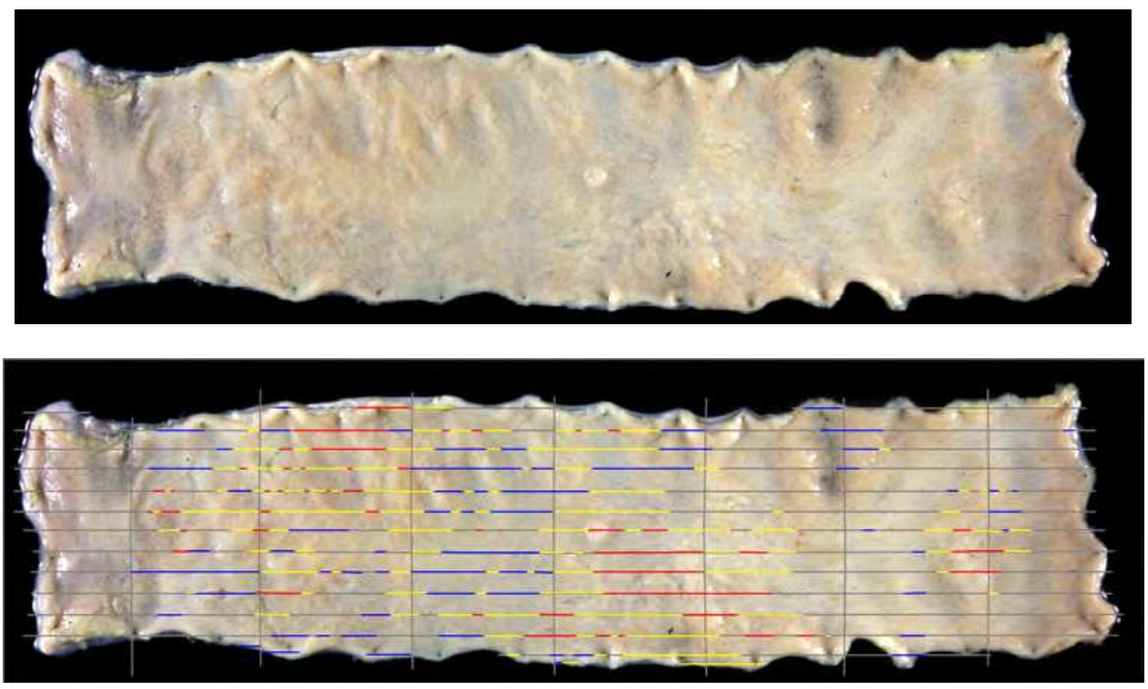
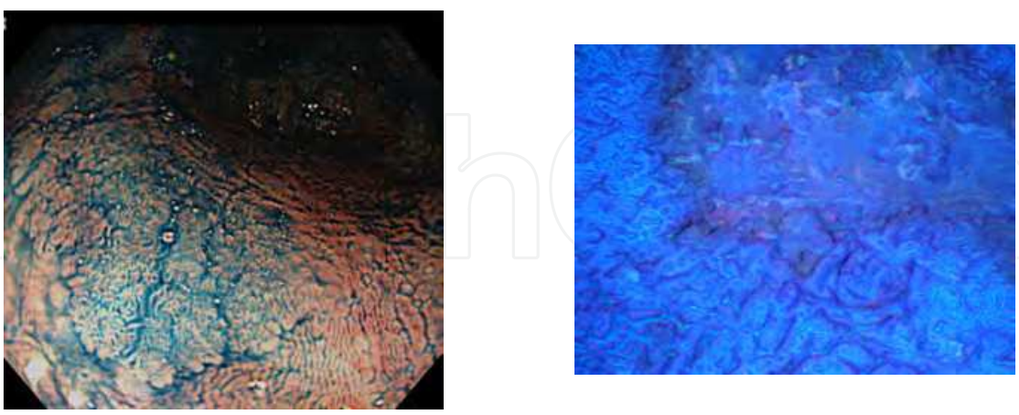


Fig. 2. Macroscopic appearance of ulcerative colitis/dysplasia, post formalin-fixed. Most of the endoscopic undetectable lesions were the flat and superficial elevated type macroscopically. (Red bar: UC-IV, Yellow bar: UC-III, Blue bar: UC-IIb)



(a) Endoscopic finding (b) Stereomicroscopic finding

Fig. 3. Endoscopic finding of the UC-III lesion. In non-dysplastic epithelium, circle and/or oval pits were scattered in the area (a). Stereomicroscopic finding of the UC-III lesion. The mucosal surface shows packed distribution of oval and/or club-like shape and/or branch-like shaped pit (b).

T grade	P value		Protruding	Flat	*P value
Dysplasia(n=40)					
Detectable	19		3	16	0.058
Undetectable	21		0	21	
Tis(n=15					
Detectable	10	0.205[a]	3	7	0.171
Undetectable	5		0	5	
T1(n=5)					
Detectable	2	0.751[a]	2	0	<0.05
Undetectable	3	0.292[b]	0	3	
Advanced (n=7)					
Detectable	7	<0.05 [a]	6	1	ND
		0.082 [b]			
Undetectable	0	<0.05 [c]	0	0	
[a] Compared with dysplasia, [b] Compared with Tis, [c] Compared with T1.					
* Relationship between detection and macroscopic appearance. NF: not determined					

Table 2. Relationship between detection and macroscopic appearance of UC-associated lesions (adapted from Yamagishi et al., 2009)

3.1 Histological diagnosis of ulcerative colitis/dysplasia

UC associated dysplasia was a precursor of colitic cancer in UC, several studies have shown that UC-associated dysplasia correlates with the presence of colitic cancer. The existence of carcinoma at the time of colectomy in UC patients with high-grade dysplasia, as determined by a preoperative rectal biopsy. A presence of dysplasia could identify patients likely either to have or to develop colitic cancer. Thus, dysplasia is not only a precursor of colitic cancer, but may also be a marker for the existence of colitic cancer in other areas of the colorectum. Gastrointestinal surgical pathologist have been diagnosis inflammatory grade and epithelial injury on UC patient using by Matts grading system (Table 3) , The Inflammatory Bowel Disease Morphology Study Group in Western countries attempted to verify a standardized terminology and classification for the assessment of dysplasia in UC (Table 4). However, in Japan, the interpretation of'dysplasia' in UC varies from one pathologist to another. Therefore, the Research Committee on Inflammatory Bowel Disease of the Ministry of Health and Welfare of Japan proposed a new classification for UC associated dysplasia/neoplasia in 1993 (Table 5).

Grade 1	Normal appearance.
Grade 2	Some infiltration of the mucosa or lamina propria with either round cells or polymorphs.
Grade 3	Much cellular of the mucosa or lamina propria and submucosa.
Grade 4	Presence of crypt abscess, with much infiltration of all layers of the mucosa.
Grade 5	Ulceration, erosion, or necrosis of the mucosa, with cellular infiltration of some or all its layer.

Table 3. The value of rectal biopsy in the diagnosis of ulcerative colitis (adapted from Matts , 1961).

Negative
Normal mucosa
Inactive (quiescent) colitis
Active colitis
Indefinite
Probably negative (probably inflammatory)
Unknown
Probably positive (probably dysplasia)
Positive
Low-grade dysplasia
High-grade dysplasia

Table 4. Biopsy classification of dysplasia in inflammatory bowel disease (adapted from Riddle et al., 1983).

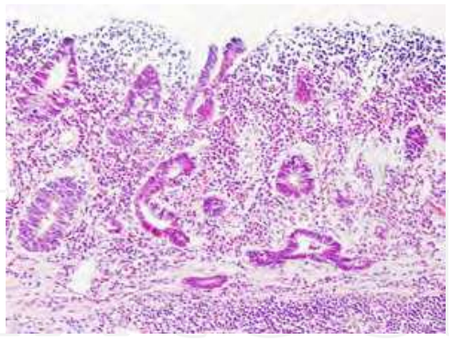
Category	Description
UC-I	Inflammatory change
UC-II	Indefinite
UC-IIa	Probably inflammatory
UC-IIb	Probably neoplastic
UC-III	Neoplastic but not carcinoma
UC-IV	Carcinoma
UC: ulcerative colitis.	

Table 5. Histological classification of the neoplasia epithelium arising in ulcerative colitis (adapted from Konishi et al., 1993).

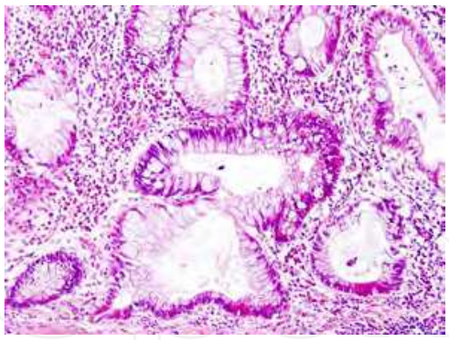
Matts grading system (Table 3) and UC associated dysplasia/neoplastic classification (Table 4 & 5) are used for clinical and research purposes and applies to both colectomy and biopsy specimens. The histological characteristics of each stage of UC-associated dysplasia/ neoplasia with inflammatory lesion (Fig 4). However, it is difficult and sensitive to discriminate between UC-associated dysplasia and regenerative epithelium by the conventional Hematoxylin and Eosin staining section. Histological diagnosis of UC-associated dysplasia/neoplasia is based on a combination of architectural and cytological alterations. The architectural alterations often result in glandular arrangements, e.g., club-shaped villi, crawling glands or bifid formation at the base of the crypts. The cytological alterations comprise cellular and nuclear pleomorphism, nuclear hyperchromatism, loss of nuclear polarity, marked nuclear stratification, dystrophic goble cells and failure of maturation from the crypt base to the surface.

3.2 Immunohistochemical finding of ulcerative colitis/dysplasia

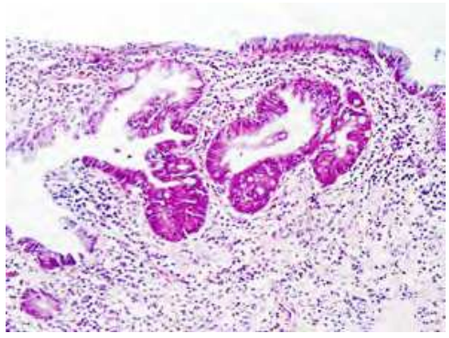
Pathologically, it is not rare those surgical pathologists are unable to distinguish between from UC-associated dysplasia/neoplasia and inflammatory regenerative epithelium using by hematoxylin and eosin staining. Furthermore, there are differences in the diagnostic criteria that different surgical pathologist use for dysplasia/neoplasia. In order to improve the accuracy of pathological diagnosis, it will be necessary to use ordinary method for immunohistochemical technique.



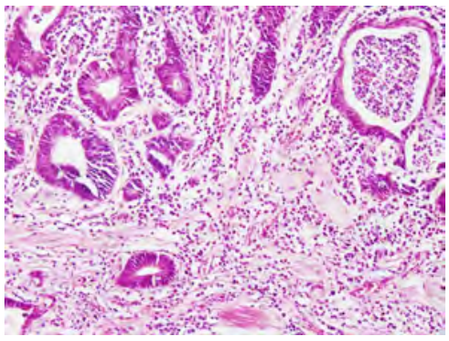
(a) Crawling crypts.



(b) Dystrophic goblet cell



(c) Distorted crypts with cellular atypia



(d) Invasive crypt and crypt abscess

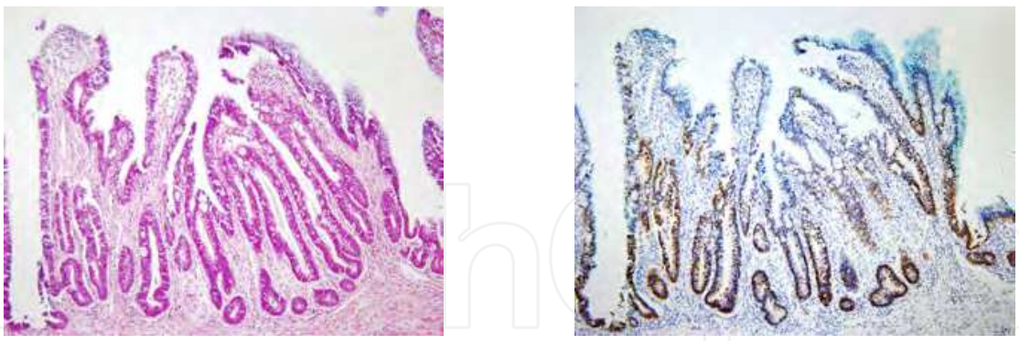
Fig. 4. Histological appearance of UC-associated dysplasia/neoplasia on Hematoxylin and Eosin staining section. There are marked distorted and crawling crypts. This epithelium could be interpreted as UC-IIb with Matts grade 3 (a). There are a lot of goblet cells, so-called dystrophic goblet cell. This epithelium could be interpreted as UC-IIb with Matts grade 3 (b). There are marked distorted crypts with cellular atypia. This epithelium could be interpreted as UC-III with Matts grade 3 (c). Neoplastic crypts with submucosal invasion. This epithelium could be interpreted as UC-IV with Matts grade 4 including crypt abscess. (d).

3.2.1 P53 protein nuclear accumulation

Several reports have shown that the rate of the **t**umor suppressor *p53* gene alteration is high in UC-associated dysplasia/neoplasia (Lashner et al., 1999). Immunohistochemical **a**nalysis of P53 protein is a useful and easy method for detecting *p53* gene alterations. In our study, 59.5% of neoplastic lesions (UC-III and IV) and 40.0% of lesions that were probably neoplastic (UC-IIb) displayed nuclear accumulation of P53 protein (Fujii et al., 2003a). Thus, immunohistochemical analysis of P53 could be a useful marker of UC associated dysplasia/neoplasia in cases where discriminating between neoplasia and regenerative epithelium is difficult (Fig 5) (Table 6)**.**

3.2.2 Increased expression of DNA Methyltransferase -1

Neoplastic progression in UC occurs in a histologically stepwise manner, from chronic epithelial inflammation to dysplasia/neoplasia, and the process of neoplastic progression involves accumulation of genetic and epigenetic alterations. Some of these alterations are



(a) Hematoxylin and Eosin (b) P53 protein

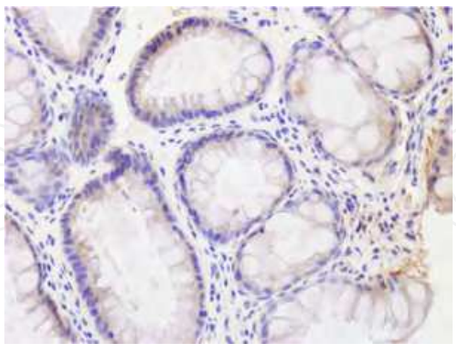
Fig. 5. Mucin droplets are well preserved but have lost their normal polarity, being present apically or basally or lateral to the nucleus (a). This epithelium could be interpreted as UC-IIb. Immunohistochemistry analysis revealed normal accumulated P53 protein in the nucleus (b).

Histological diagnosis	n	Positive staining(%)
Inflammatory change (UC-I)	5	0(0)
Indefinite, probably inflammatory (UC-IIa)	38	0(0)
Indefinite, probably neoplastic (UC-IIb)	35	14(40.0)
Neoplastic but not carcinoma (UC-III)	24	14(58.3)
Carcinoma (UC-IV)	18	11(61.1)

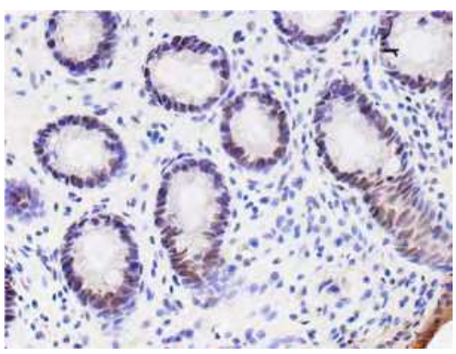
Table 6. Relation between nuclear accumulations of P53 protein and histological diagnosis (adapted from Fujii et al., 2003a)

known to occur in both the neoplastic and nonneoplastic epithelium of UC patients with neoplasia, and are considered to be widespread and to occur early in the process of neoplastic progression. In several types of neoplasia, aberrant methylation of promoter-region CpG islands, as an epigenetic modification of DNA, is associated with transcriptional inactivation of tumor suppressor genes and plays a crucial role in the development and progression of neoplasia (Hsieh et al., 1998). DNA methylation results from a methyl transfer reaction performed by the three active DNA methyltransferases (DNMTs): DNMT1, DNMT3a and DNMT3b (Okano et al., 1999). Of these, DNMT1 is the most abundant DNMT targeted to replication foci and has a preference for hemimethylated DNA substrates. Recent investigations have shown that DNMT1 is overexpressed in tumorigenic cells and several types of human tumors, and that increased expression of DNMT1 is dependent on cell proliferation. We reported that the immunoreactive DNMT1 expression gradually increased from rectal epithelium of UC patients without neoplasia to nonneoplastic rectal epithelium of UC patients with neoplasia ($p < 0.001$), and to colorectal neoplasia ($p < 0.001$) (Fujii et al., 2010). Among 31 neoplasias, there was no difference in the immunoreactive DNMT1 expressions between dysplasia and invasive cancer. Expression of DNMT1 in

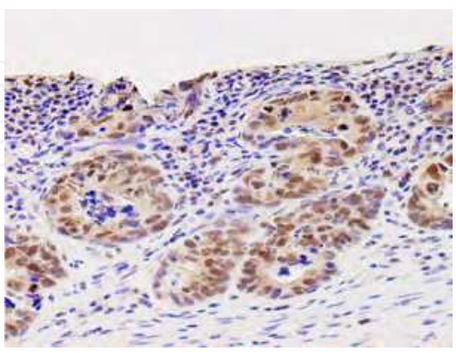
non-neoplastic epithelium may precede or be a relatively early event in UC-associated carcinogenesis (Fig. 6).



(a) Non-neoplastic epithelium without colitic cancer



(b) Non-neoplastic epithelium with colitic cancer



(c) Colitic cancer.

Fig. 6. Immunohistochemical staining for DNMT1 protein in non-neoplastic rectal epithelium from UC patients without neoplasia (a), non-neoplastic rectal epithelium from UC patients with neoplasia (b) and colorectal neoplasia (c).

3.3 Molecular alterations of ulcerative colitis/dysplasia

Numerous reports have revealed molecular alterations (e.g., *K-Ras* gene mutation, *p16* gene hypermethylation, *p14* gene hypermethylation, *p53* gene mutation, DNA aneuploidy, chromosomal instability, microsatellite instability, age-related methylation, telomere length shortening) of nonneoplastic epithelium in UC patients with neoplasia (Brentnail et al., 1994, Holzmann et al., 2001, Fujii et al., 2005). Several of these reports have indicated higher frequencies of molecular alterations to nonneoplastic epithelium in UC patients with dysplasia/neoplasia than in nonneoplastic epithelium in UC patients without neoplasia, suggesting that these molecular alterations may be applicable as new markers for identifying individuals with UC at increased risk of neoplasia.

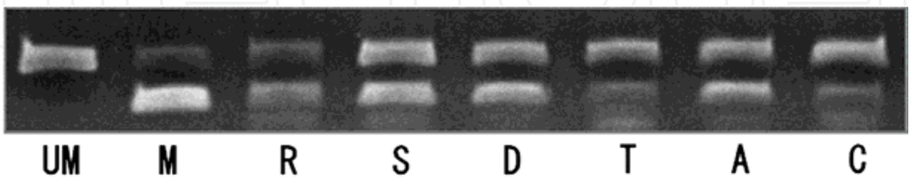
3.3.1 P53 gene abnormalities

In the *p53* gene, point mutations have been reported in 40–50% and LOH in 80% of sporadic colorectal cancers (Baker et al., 1990). However, these genetic alterations of the *p53* gene have only been found in approximately 10% of sporadic adenomas. These data suggest that genetic alterations in the *p53* gene are involved in the progression from adenoma to cancer. Alterations in *p53* gene were reported in both UC-associated dysplasia and colitic cancer at an incidence of about 50–80%.The point mutations in *p53* gene were detected in 48% of case of UC-associated dysplasia, and that both point mutation and allelic loss were found in more than 80% of cases of colitic cancer (Brentnail et al., 1994. When the *p53* gene has a nonsense mutation or frameshift, the P53 protein does not accumulate in the nucleus despite the alteration. In fact, 92.9% of the neoplastic lesions that displayed negative immunohistochemical staining for P53 protein demonstrated a *p53* gene mutation within exons 5–8 under PCR singlestranded conformation polymorphism (Fujii et al., 2003a). This suggests that screening for *p53* gene mutation using PCR single-stranded conformation polymorphism is more accurate than immunohistochemistry for discriminating between UC-associated neoplasia and regenerative epithelium.

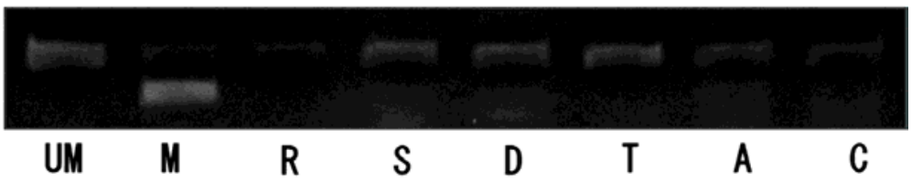
3.3.2 Age-related methylation and methylation analysis of ER Gene

In several neoplasias, aberrant methylation of promoter region Chg. islands, as an epigenetic modification of DNA, is associated with transcriptional inactivation of tumor suppressor genes and plays a crucial role in the development and progression of neoplasia (Hsieh et al., 1998). In normal colorectal epithelium, some genes are methylated with aging, and this alteration is known as age-related methylation. A methylation of the estrogenic receptor (ER) Chg. Island increased with age in no neoplastic colorectal epithelium and that the same methylation occurred in most sporadic colorectal neoplasias (Isa et al. 1994). They concluded that methylation of the *ER* gene in aging colorectal epithelium could represent one of the earliest events predisposing to sporadic colorectal carcinogenesis. Therefore, in our recent study (Fujii et al., 2005 and Tominaga et al., 2005), we analysed *ER* gene methylation in multiple samples taken from 6 regions throughout the colorectum: the rectum, sigmoid colon, descending colon, transverse colon, ascending colon and cecum (Fig. 7). Non-neoplastic colorectal epithelia from patients with longstanding and extensive UC, including 8 UC patients with neoplasia and 10 patients without, were evaluated. The combined bisulfite restriction analysis method (COBRA) was used to determine the methylation status of the *ER* gene. The mean methylation level of the *ER* gene was 25.4% in the nonneoplastic

epithelia from UC patients with neoplasia, whereas it was only4.0 % in those without neoplasia ($P < 0.001$). The methylation level of the ER gene in UC patients with neoplasia was significantly higher than in UC patients without neoplasia throughout the colorectum except for the cecum. In UC patients with neoplasia, the mean ER methylation level in the distal colon was significantly higher than in the proximal colon ($P < 0.001$) Analysis of *ER* gene methylation may have potential as a useful marker for identifying individuals at increased risk of neoplasia among those with longstanding and extensive UC.



(a) Non-neoplastic colon epithelium with colitic cancer



(b) Non-neoplastic colon epithelium without colitic cancer

Fig. 7. COBRA for the *ER* gene in each region of the non-neoplastic epithelium of the colorectum from patient with UC-associated neoplasia (a) and without UC-associated neoplasia (b). UM, the unmethylated breast cancer cell line MCF-7; M, the methylated colon cancer cell line DLD-1; R, rectum; S, sigmoidcolon; D, descending colon; T, transverse colon; A, ascending colon; C, cecum. A, representative samples

4. Conclusion

In this issue, we have discussed the efficacy of surveillance colonoscopy for UC associated dysplasia/neoplasia, several problems related to the diagnosis of UC–associated dysplasia/neoplasia and molecular markers that can be used to identify individuals with UC at increased risk of dysplasia/neoplasia. Current surveillance colonoscopy remains unsatisfactory, due to difficulties with endoscopic and histological diagnosis of UC-associated dysplasia/neoplasia. These difficulties may be overcome by introducing adjunctive techniques for diagnosing UC-associated dysplasia/neoplasia, analysis of *p53* gene alteration and/or new endoscopic system. However, it seems impartial for all UC patients with conventional risk factors, long-standing disease and extensive colitis to undergo close surveillance colonoscopy using such techniques. In order to realize the full potential of close surveillance colonoscopy, higher-risk groups selecting from patients with long – standing and extensive UC. Analyses of age-related methylation and expression of DNMT1 in nonneoplastic epithelium may allow identification of such higher-risk patients.

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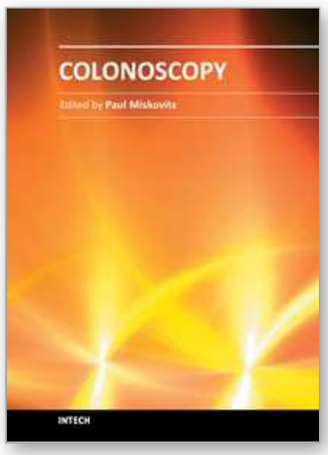

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To publish a book on colonoscopy suitable for an international medical audience, drawing upon the expertise and talents of many outstanding world-wide clinicians, is a daunting task. New developments in videocolonoscope instruments, procedural technique, patient selection and preparation, and moderate sedation and monitoring are being made and reported daily in both the medical and the lay press. Just as over the last several decades colonoscopy has largely supplanted the use of barium enema x-ray study of the colon, new developments in gastrointestinal imaging such as computerized tomographic colonography and video transmitted capsule study of the colonic lumen and new discoveries in cellular and molecular biology that may facilitate the early detection of colon cancer, colon polyps and other gastrointestinal pathology threaten to relegate the role of screening colonoscopy to the side lines of medical practice. This book draws on the talents of renowned physicians who convey a sense of the history, the present state-of-the art and ongoing confronting issues, and the predicted future of this discipline.

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