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Review

Squamous intraepithelial neoplasia of the esophagus: past, present, and future

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With regard to the esophagus, the term "squamous dysplasia" has been used in European countries, the United States, and China, while its use is controversial in Japan. Recently, "low-grade intraepithelial neoplasia" and "high-grade intraepithelial neoplasia" have been used as inclusive terms for dysplasia and carcinoma in situ in the World Health Organization classification. Endoscopically, it is often difficult to identify squamous intraepithelial neoplasia by conventional endoscopy, but application of iodine is useful for the diagnosis of such a lesion. In addition, new types of endoscopic techniques, including magnifying endoscopy, narrow-band imaging (NBI), and endocytoscopy are helpful to detect squamous intraepithelial neoplasia. NBI is very useful for identifying the intrapapillary capillary loop pattern. Regarding the pathological criteria of squamous dysplasia and squamous cell carcinoma, the views of Japanese and Western pathologists have differed significantly. Before the term "intraepithelial neoplasia" was introduced, severe dysplasia as diagnosed by Western pathologists was in fact the same as squamous cell carcinoma in situ or noninvasive carcinoma as diagnosed by Japanese pathologists. This problem has been solved by the introduction of the Vienna classification; however, there are still some issues that need to be resolved. One of them is the presence of basal layer type squamous cell carcinoma in situ, which is often underdiagnosed as low-grade intraepithelial neoplasia by Western pathologists. Endoscopic treatments such as endoscopic mucosal resection and endoscopic submucosal dissection have recently become possible choices for squamous intraepithelial neoplasia; however, these techniques are not in widespread use in the West. We believe that a consensus meeting between Japanese and Western pathologists as well as endoscopists should be held promptly to reach a common ground for the nomenclature.

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Introduction

Of the esophageal cancers, squamous cell carcinoma is the most common carcinoma in Japan. However, in the United States, esophageal squamous cell carcinoma is relatively uncommon, with the incidence of adenocarcinoma being higher and rapidly increasing. Adenocarcinomas of the esophagus usually arise in the setting of Barrett's esophagus.[1,2] Therefore, dysplasia in the esophagus, even in English gastrointestinal textbooks,[3,4] usually refers to glandular dysplasia, especially in Barrett's esophagus, and not squamous dysplasia. Even when searching for articles on esophageal dysplasia, we found that most papers deal with glandular dysplasia in relation to adenocarcinoma derived from Barrett's esophagus.[5] Thus, squamous dysplasia of the esophagus is very rare in the English literature, and most articles are contributed from China or Japan.[6–9] In 2000, the World Health Organization (WHO) classification introduced the term "intraepithelial neoplasia" for the esophagus.[10] Since then, many articles have been using the term "intraepithelial neoplasia" rather than dysplasia or carcinoma in situ (CIS).[11,12] In this review article, we specifically focus on and review squamous dysplasia, not glandular dysplasia. Then, we focus on the squamous intraepithelial neoplasia, including the difference in the clinical and pathological diagnoses between Japan and the West. In addition, the tenth Japanese edition of the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus (Second English edition is now available from Kanehara, Tokyo) as well as the

second edition of the Guidelines for Diagnosis and Treatment of Esophageal Carcinoma were published in 2007.[13,14] Therefore, this article also reviews the present status as well as the historical and prospective aspects of esophageal squamous intraepithelial neoplasia in terms of endoscopy, pathology, and treatment in Japan.

Definition and concept of dysplasia and intraepithelial neoplasia

The term "dysplasia" literally means disordered growth or abnormality of development. However, the pathological definition of dysplasia is alteration in size, shape, and organization of adult cells, which means that it can include pleomorphic cells with hyperchromatic nuclei and mitotic figures.[15] In the field of pathology, the term "dysplasia" is used in relation to some organs such as the uterine cervix and the urinary bladder to indicate a precancerous lesion, while different terminology has been used for the same condition in other organs: for example, "atypical hyperplasia" in the endometrium, "atypical ductal hyperplasia" in the breast, and "prostatic intraepithelial neoplasia" in the prostate. With regard to the esophagus, the term "dysplasia," especially for the squamous epithelium, has been used in European countries and in the United States as well as in China to mean a precancerous lesion, while it is controversial to use it that way in Japan. Therefore, the concept of esophageal dysplasia of the squamous epithelium still remains to be debated.

Dysplasia of the squamous epithelium was defined as precancerous lesions with both architectural and cytological abnormalities by the earlier WHO classification of esophageal tumors.[16] Dysplasia was traditionally classified as mild, moderate, or severe; however, most pathologists prefer to use low-grade and high-grade dysplasia because of the poor interobserver agreement with a three-tier classification. With the increasing grade of dysplasia, atypical cells involve and replace the entire thickness of the squamous epithelium, but the lesion remains confined to the epithelium. This is referred to as CIS, and no evidence of maturation is observed at the surface of the epithelium. Lymph node metastases are not found in CIS. Once the atypical cells invade the lamina propria, the lesion becomes known as invasive carcinoma.[17,18]

Looking back at the history of the term "squamous dysplasia" in Japan, there are two famous round-table talks published in the Japanese literature in 1996 and 2007, called Stomach and Intestine.[19,20] In both round-table talks, active discussions were conducted. Although no definite conclusion was reached on the definition/existence of dysplasia, it is clear that most pathologists who attended these discussions did not use the term "squamous dysplasia" except on very rare occasions. In addition, some pathologists deny the existence of squamous dysplasia in the esophagus as a precancerous lesion, and they classify esophageal atypical squamous epithelium into nonneoplastic atypical epithelium and noninvasive carcinoma. The former lesion includes reactive immature epithelium seen in esophagitis, erosion, ulcers, or hyperplasia, and the latter is divided into low-grade carcinoma and high-grade carcinoma.[21] Thus, most gastrointestinal pathologists in Japan would regard the photographs of high-grade dysplasia, sometimes even low-grade dysplasia, published in recent gastrointestinal pathology textbooks as noninvasive squamous cell carcinoma.[22] This topic is discussed later in the section of pathological findings of squamous intraepithelial neoplasia.

In the recent WHO classification, "intraepithelial neoplasia" has been used as an inclusive term for dysplasia and CIS. High-grade intraepithelial neoplasia is used for severe dysplasia and CIS, since they may have the same clinical implications.[10] The term "esophageal intraepithelial neoplasia" is used in some textbooks.[23,24]

Clinical findings of squamous intraepithelial neoplasia

Generally, patients with squamous intraepithelial neoplasia present no symptoms. Squamous intraepithelial neoplasia of the esophagus may be frequently encountered in biopsy specimens in China and Japan, whereas in the United States and European countries it is more commonly observed in resected specimens of esophageal squamous cell carcinoma. Squamous intraepithelial neoplasia can be present adjacent to squamous cell carcinoma. Dysplasia is found in 60%–90% of the resected cases of squamous cell carcinoma of the esophagus.[25] About 30% of autopsy cases of squamous cell carcinoma of the esophagus are said to reveal squamous dysplasia in varying degrees, including mild, moderate, and severe.[22] According to follow-up studies of Chinese patients with squamous dysplasia, squamous cell carcinoma develops through a progression of dysplastic lesions; in other words, squamous dysplasia plays a role in the genesis of squamous cell carcinoma of the esophagus.[26] Furthermore, DNA methylation was recently found to contribute to the progression of intraepithelial neoplasia to carcinoma.[27]

It is very difficult to detect squamous intraepithelial neoplasia of the esophagus by esophagography, and it is frequently difficult to identify intraepithelial neoplasia by conventional endoscopy. Generally, squamous intraepithelial neoplasia is composed of flat lesions with poor quality color variation, or focal red areas, nodules,

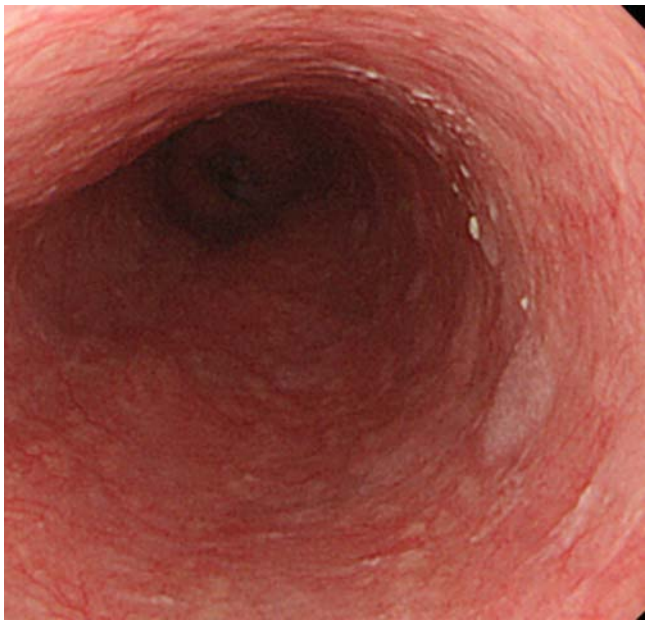

Fig. 1. Endoscopic image of the intraepithelial neoplasia by conventional endoscopy. A flat lesion with poor quality color variation can be seen, although it is not clear

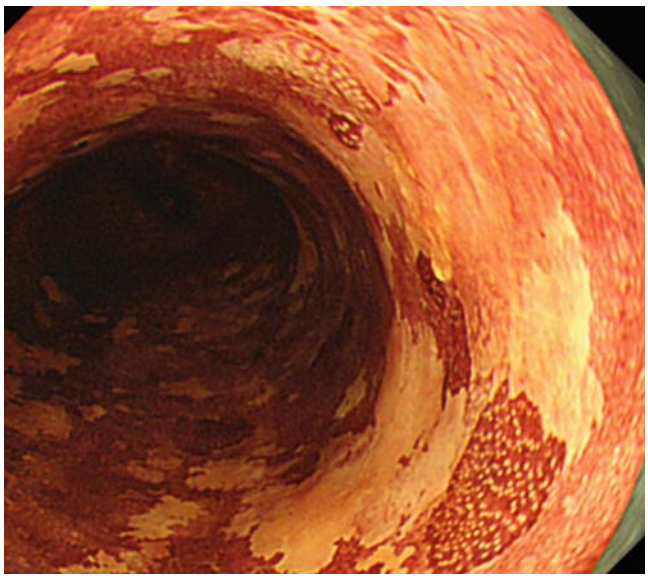

Fig. 2. Endoscopic image of the same intraepithelial neoplasia as in Fig. 1 after iodine staining. Well-demarcated unstained areas are clearly observed

plaques, or erosions (Fig. 1). It can be detected as an unstained area by spraying with iodine (Fig. 2).[28] Since the superficial layers of the normal esophageal squamous mucosa are rich in glycogen, any lesions with a loss of superficial glycogen, such as atrophy, columnar metaplasia, esophagitis, intraepithelial neoplasia, or carcinoma, can be recognized as unstained areas.[26,29]

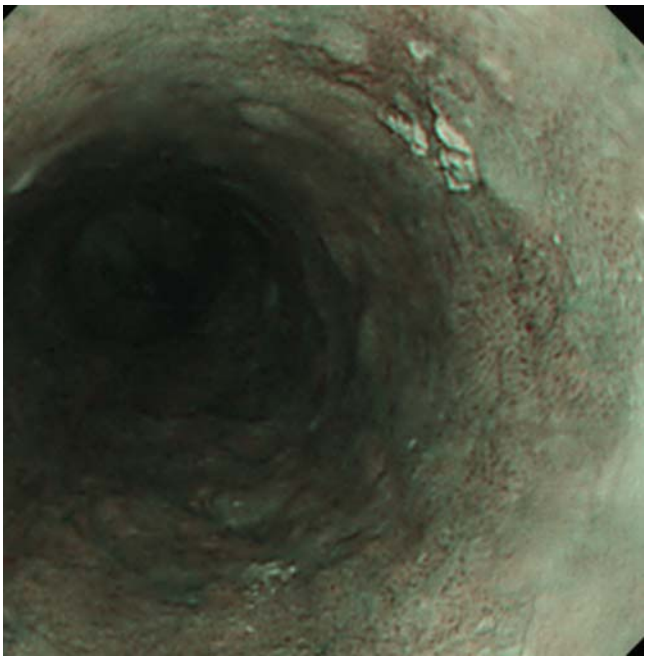

Fig. 3. Endoscopic image of the same intraepithelial neoplasia as in Fig. 1 obtained with a narrow-band imaging (NBI) system. Well-demarcated brown areas are observed

However, even iodine may frequently fail to reveal an unstained area, and show instead a lightly stained area, or the border of the unstained area may not be clear. Recently, new types of endoscopic techniques, including magnifying endoscopy, narrow-band imaging (NBI), and endocytoscopy have been devised.[30–32] With the introduction of the NBI system, intraepithelial neoplasia, which has been difficult to find without application of iodine up to now, is now more clearly detectable (Fig. 3). NBI shows the intraepithelial neoplasia to be a well-demarcated, dark brown mucosal area. When we focus on these brown spots, we observe an intrapapillary capillary loop (IPCL) pattern, which includes such features as dilatation, tortuous running, caliber changes, and different shapes in each IPCL. IPCL was classified into five types by Inoue et al.[33] IPCL type I mainly includes normal epithelium, type II corresponds to inflammatory change or nonneoplastic tissue, and type III reflects either inflammatory or low-grade intraepithelial neoplasia. Type IV suggests high-grade intraepithelial neoplasia (especially severe dysplasia) (Fig. 4), and type V-1 is often equivalent to T1a-EP carcinoma, namely carcinoma limited to squamous epithelium (i.e., CIS) (Fig. 5). Thus, cases of IPCL type III should be followed up, and cases of type IV and V are considered to be treatable in a clinical setting, including endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).[33–36] However, in followed-up cases of IPCL type III, a definite pathological diagnosis of the

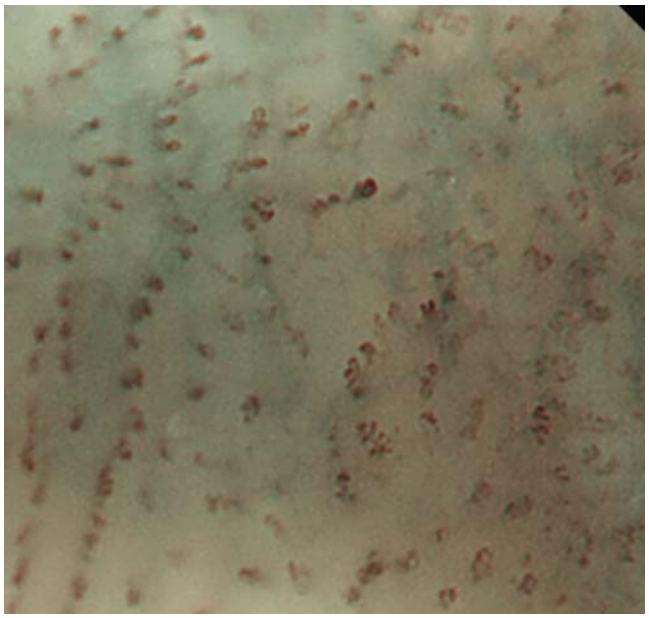

Fig. 4. Magnified endoscopic image of a part of the same intraepithelial neoplasia as in Fig. 1 obtained with the NBI system. Intrapapillary capillary loops (IPCL) show dilatation, tortuous running, and caliber changes. These findings are consistent with Type IV

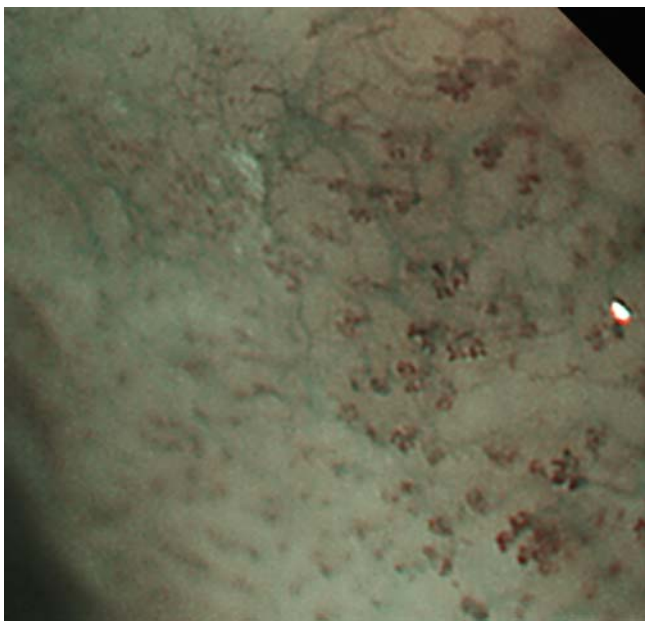

Fig. 5. Magnified endoscopic image of a part of the same intraepithelial neoplasia as in Fig. 1 obtained with the NBI system and diagnosed as IPCL type V-1. All four changes, mild dilatation, tortuous running, caliber changes, and different shapes, in each IPCL are clearly observed

lesion has not been made because biopsy specimens cannot be obtained from the whole lesion. In such cases, therefore, it should be noted that latent carcinoma may be present.

Regarding magnifying endoscopy, Arima et al.[37] divided the microvascular patterns into four types, types 1 to 4. Type 1 is generally seen in normal mucosa, type 2 in inflammatory lesions, type 3 in m_1 (CIS) or m_2 (carcinoma invading the lamina propria) cancer, and type 4 in cancers with m_3 (carcinoma extending to, or invading the muscularis mucosa) or deeper invasion. The characteristic esophageal cancer types of types 3 and 4 are further subdivided.[37] In addition, although it is still preliminary and further study is needed, endocytoscopy may be helpful for differentiating between nonmalignant tissue and malignant tissue.[32]

Pathological findings of squamous intraepithelial neoplasia

Squamous intraepithelial neoplasia is characterized by both architectural and cytological abnormalities that vary in extent and severity according to the degree. The architectural abnormality includes loss of normal cell polarity, overlapping nuclei, and lack of surface maturation. At lower magnification, the nuclei within the epithelium appear denser, and there may be a clear demarcation between dysplastic cells and the overlying nondysplastic cells. The cytological abnormality is characterized by nuclear changes (enlargement, hyperchromasia, and pleomorphism), increased nuclear/cytoplasmic ratio, and increased mitotic activity.[38] Only the basal layer side or the full thickness of the epithelium may be involved, depending on the dysplastic grade. In the case of full-thickness involvement, it is also known as CIS. Squamous intraepithelial neoplasia may extend into the submucosal esophageal glands and ducts; however, in any case there is no evidence of invasion into the lamina propria.[23,39]

As mentioned above, it is preferable to use a two-tier system, namely low-grade and high-grade dysplasia, rather than the three-tier system of mild, moderate, and severe degrees of dysplasia. In such a system, low-grade dysplasia includes mild and moderate dysplasia, and high-grade dysplasia implies severe dysplasia and CIS; this seems to be reasonable because severe dysplasia and CIS may have the same clinical implications (Figs. 6, 7).[17,23,26] In 2000, the term "intraepithelial neoplasia" was introduced as a preferred term in the WHO classification. It is an inclusive term for dysplasia and CIS; intraepithelial neoplasia "results from clonal alterations in genes and carries a predisposition for progression to invasion and metastasis."[10]

A recent study revealed significant differences between Japanese and Western criteria for squamous dysplasia and squamous cell carcinoma of the esophagus. Japanese pathologists mainly focus on individual cells, especially nuclear findings, whereas Western

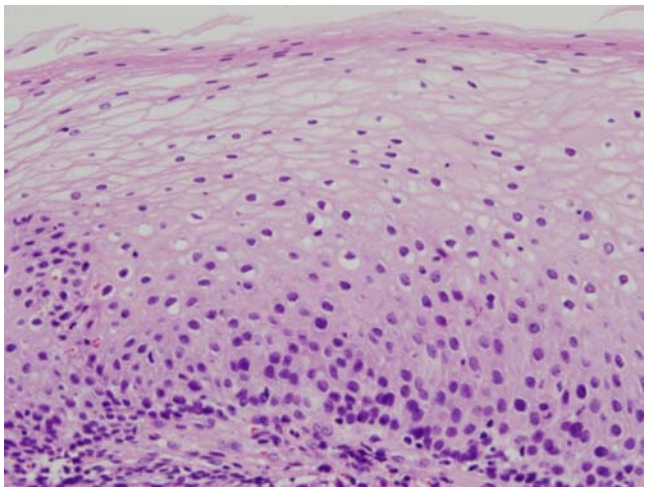

Fig. 6. Low-grade intraepithelial neoplasia. There is an increase in the number of basal cells, and some of them show nuclear overlapping and nuclear hyperchromasia. Less than 50% of the thickness of the epithelium contains such cells (endoscopic submucosal dissection specimen). Hematoxylin and eosin, ×200

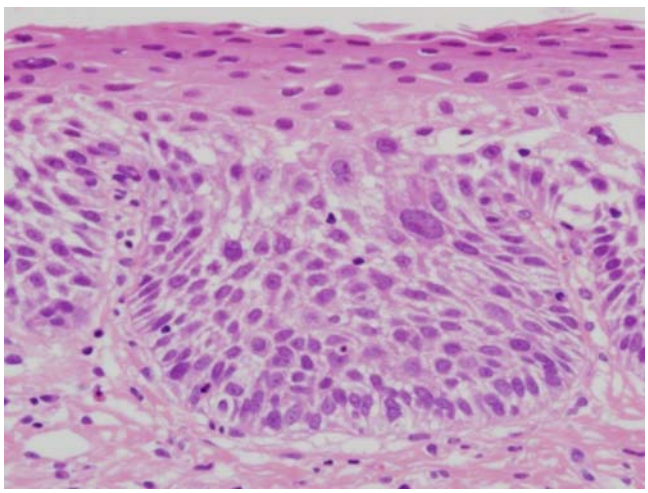

Fig. 7. High-grade intraepithelial neoplasia. More than 50% of the epithelium contains dysplastic cells. Nuclear enlargement and pleomorphism are observed. This lesion is considered to be squamous cell carcinoma in situ (noninvasive squamous cell carcinoma) by Japanese pathologists, and high-grade intraepithelial neoplasia by Western pathologists (endoscopic submucosal dissection specimen). Hematoxylin and eosin, ×200

pathologists pay attention to structural changes of the architecture for the diagnosis of neoplasm. In addition, to make a diagnosis of squamous cell carcinoma of the esophagus, nuclear and structural features are more important diagnostic criteria for Japanese pathologists, while invasion of the dysplastic cells into the lamina propria is the most important finding for Western pathologists.[40,41] This difference implies that Western pathologists would diagnose low-grade dysplasia for the same lesion that Japanese pathologists would diagnose as suspected or definite noninvasive squamous cell carcinoma in biopsy specimens. Furthermore, before the introduction of the Vienna classification, most cases of high-grade dysplasia (i.e., severe dysplasia as used here) diagnosed by Western pathologists in biopsy specimens might be diagnosed as CIS or noninvasive carcinoma by Japanese pathologists.[42] In other words, what is diagnosed as high-grade dysplasia by Western pathologists is the same entity that is called CIS or noninvasive carcinoma by Japanese pathologists. This may explain the higher proportion of early squamous cell carcinoma and relatively good prognosis of superficial esophageal carcinoma in Japan.[43]

Table 1. Vienna classification of gastrointestinal epithelial neoplasia

Category 1	Negative for neoplasia/dysplasia
Category 2	Indefinite for neoplasia/dysplasia
Category 3	Noninvasive low-grade neoplasia (low-grade adenoma/dysplasia)
Category 4	Noninvasive high-grade neoplasia
	4.1 High-grade adenoma/dysplasia
	4.2 Noninvasive carcinoma (carcinoma in situ)[a]
	4.3 Suspicious of invasive carcinoma
Category 5	Invasive neoplasia
	5.1 Intramucosal carcinoma[b]
	5.2 Submucosal carcinoma or beyond

[a] Noninvasive indicates absence of evident invasion
[b] Intramucosal indicates invasion into the lamina propria or muscularis mucosae

To resolve the different pathological criteria between Japan and the West, the Vienna classification was developed (Table 1),[41,42] improving interobserver agreement for conditions of the gastrointestinal tract. Subsequently, the revised Vienna classification (Table 2) was proposed, although it has not been widely adopted.[44,45] This revised Vienna classification is useful because it largely eliminates the diagnostic discrepancy between Japanese and Western pathologists, and each category is associated with different recommendations for further diagnostic and therapeutic measures.[46] From a practical point of view, we recommend use of the revised Vienna classification. This has been further revised to include the term "intraepithelial neoplasia," although the term "Group" is used instead of "Category."[45]

On the other hand, the same consensus study as mentioned above has made the superior diagnostic quality of system used by Japanese pathologists evident.[40] Namely, a comparison study between biopsy-based diagnoses and endoscopic mucosal resection-based diagnoses of the same lesion revealed a significant discrepancy among Western pathologists and a high agreement among Japanese pathologists. The differences

Table 2. The revised Vienna classification of gastrointestinal epithelial neoplasia

Category	Diagnosis	Clinical management
1	Negative for neoplasia	Optional follow-up
2	Indefinite for neoplasia	Follow-up
3	Mucosal low-grade neoplasia Low-grade adenoma Low-grade dysplasia	Endoscopic resection or follow-up[a]
4	Mucosal high-grade neoplasia 4.1 High -grade adenoma/dysplasia 4.2 Noninvasive carcinoma (carcinoma in situ) 4.3 Suspicious for invasive carcinoma 4.4 Intramucosal carcinoma	Endoscopic or surgical local resection[a]
5	Submucosal invasion by carcinoma	Surgical resection[a]

[a] Choice of treatment will depend on the overall size of the lesion; the depth of invasion as assessed endoscopically, radiologically, or ultrasonographically; and on general factors such as the patient's age and comorbid conditions. For gastric, esophageal, and nonpolypoid colorectal well and moderately differentiated carcinomas showing only minimal submucosal invasion (sm1) without lymphatic involvement, local resection is sufficient. Likewise, for polypoid colorectal carcinoma with deeper submucosal invasion in the stalk/base but without lymphatic or blood vessel invasion, complete local resection is considered adequate treatment

among Western pathologists may be due to lack of experience with cases of early squamous cell carcinoma.[40,46] Japanese pathologists have experienced more cases of early invasive carcinoma, in which a low-grade dysplasia-like lesion may invade into the lamina propria, suggesting the presence of basal layer type squamous cell carcinoma in situ (Fig. 8).[22] In other words, early invasive squamous cell carcinoma of the esophagus is not always associated with total layer type squamous cell carcinoma in situ (Fig. 9).[38] Therefore, Japanese pathologists emphasize that the diagnosis of noninvasive squamous cell carcinoma by nuclear findings in biopsy specimens is necessary for the successful early detection and treatment of squamous cell carcinoma.[10,40] This implies that the Western approach may lead to underdiagnosis and delayed treatment, whereas the Japanese approach may cause overdiagnosis and unnecessary treatment. In either case, for both clinical and basic research purposes, an acceptable uniform nomenclature such as noninvasive high-grade neoplasia should be used for high-grade dysplasia, noninvasive carcinoma, and suspected carcinoma.[26,40]

Pathological differential diagnosis and pitfalls of squamous intraepithelial neoplasia

Differential diagnoses include squamous cell papilloma, pseudoepitheliomatous hyperplasia, regenerative/reactive change, radiation or chemotherapy effect, and verrucous carcinoma. Most of these have been described in detail in another paper by one of us.[38] Therefore, we here discuss mainly the differential points between reactive squamous epithelium and squamous intraepithelial neoplasia, because these two lesions may sometimes be difficult to differentiate in biopsy specimens. When it is difficult to classify whether the lesion is neoplastic or nonneoplastic, it can be diagnosed as "indefinite for intraepithelial neoplasia" (Fig. 10).

Compared with squamous intraepithelial neoplasia, reactive squamous epithelium often shows mucosal inflammation, epithelial edema, and vascular congestion. In addition, surface maturation, nonkeratinizing epithelium, fine and homogenous chromatin, and prominent nucleoli are noted in reactive changes (Fig. 11). Regenerative squamous epithelium also lacks irregular nuclear outlines. On the other hand, squamous intraepithelial neoplasia reveals nuclear hyperchromasia and pleomorphism, nuclear overlapping, increased nuclear/cytoplasmic ratio, eosinophilic nucleoli, increased mitotic activity, and abnormal mitoses. In addition, according to the degree of intraepithelial neoplasia, highly atypical cells, keratinizing epithelium, and bizarre cells may be observed.[17,18] In any event, clinical information such as biopsy site, presence of causative agent, and status for radiotherapy or chemotherapy is essential for the pathological diagnosis since the squamous epithelial changes may mimic squamous intraepithelial neoplasia.

The tenth Japanese edition of the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus was just revised in 2007, and the section on squamous intraepithelial neoplasia includes several comments.[13] One addresses the different criteria for squamous cell carcinoma between Japan and the West. Since the concept of noninvasive squamous cell carcinoma has been widely accepted in Japan, most Japanese pathologists still use the term "squamous cell carcinoma in situ" or "noninvasive squamous cell carcinoma" for "high-grade intraepithelial neoplasia" as used by Western pathologists. In addition, Japanese pathologists have noted the presence of a low-grade intraepithelial

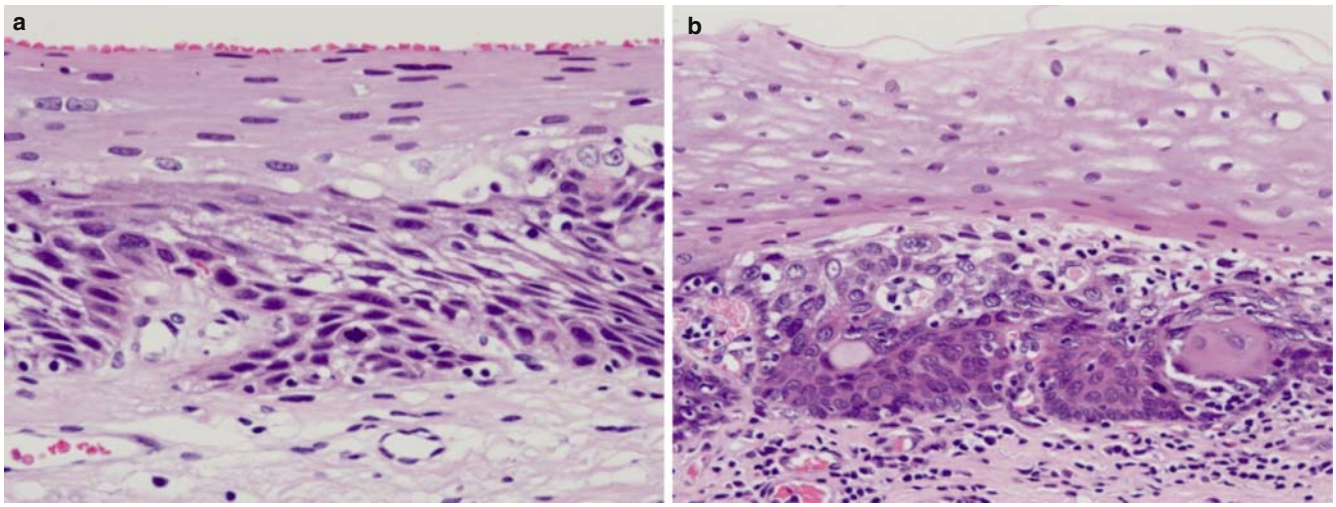

Fig. 8. Basal layer-type squamous cell carcinoma in situ. This type of noninvasive squamous cell carcinoma is frequently called low-grade intraepithelial neoplasia by Western pathologists. Dysplastic cells reveal marked hyperchromatic and pleomorphic nuclei. **a** Abnormal mitosis can also be seen. The entrapped normal epithelium can be seen within the dysplastic area, suggesting a certain kind of, although not conventional, front formation. Findings such as these may suggest basal layer type carcinoma in situ (**b**) (endoscopic submucosal dissection specimen). **a** Hematoxylin and eosin, ×200; **b** hematoxylin and eosin, ×200

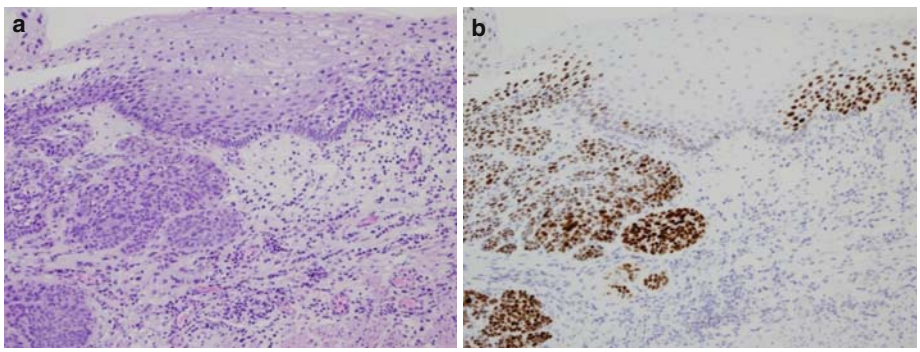

Fig. 9. Early invasive squamous cell carcinoma. This early carcinoma is associated with a low-grade intraepithelial neoplasia-like lesion, suggesting the presence of basal layer-type squamous cell carcinoma in situ (**a**). Note the diffuse immunostaining of dysplastic cells for p53 (**b**) (endoscopic submucosal dissection specimen). **a** Hematoxylin and eosin, ×40; **b** immunostaining for p53, ×40

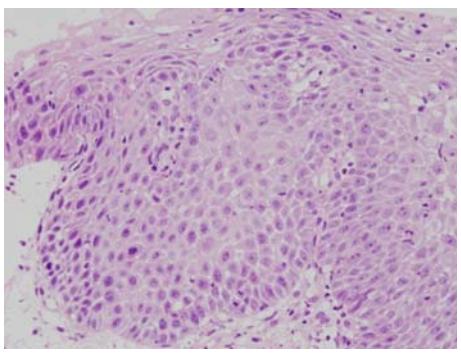

Fig. 10. Indefinite for intraepithelial neoplasia. Cellular maturation from the basal layer toward the surface is observed, and inflammatory cells are present. In addition, nuclear changes are present, but not prominent. Therefore, it is difficult to determine whether this lesion is neoplastic or not (biopsy specimen). Hematoxylin and eosin, ×200

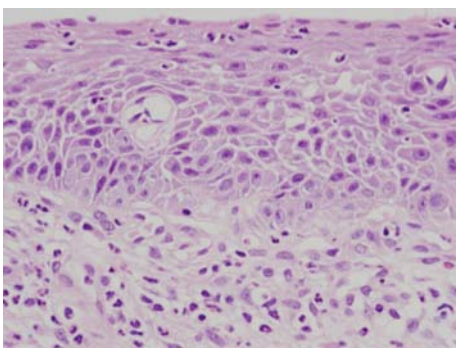

Fig. 11. Reactive squamous epithelium. Squamous epithelium with surface maturation shows fine, homogenous nuclear chromatin and prominent nucleoli. Neutrophilic infiltration is also noted (endoscopic submucosal dissection specimen). Hematoxylin and eosin, ×200

neoplasia-like noninvasive carcinoma. This lesion is a noninvasive carcinoma without full-thickness involvement, also known as basal layer type squamous cell carcinoma in situ (Fig. 8), and is diagnosed mainly by nuclear morphology. Basal layer type squamous cell carcinoma in situ is defined as only the basal half being mostly replaced by carcinoma cells that have a similar cytological appearance to the cells of an invasive squamous cell carcinoma,[22] and it can be seen in thin squamous epithelium. In basal layer type squamous cell carcinoma in situ, cellularity is high in the basal layer and loss of polarity is noted, although surface maturation is present. In particular, if the largest diameter of the lesion is more than 10 mm, it is necessary to make investigations bearing in mind the possibility of noninvasive carcinoma.[13] It should be noted that basal layer type squamous cell carcinoma in situ is frequently called low-grade intraepithelial neoplasia in gastrointestinal textbooks published in Western countries, in analogy to the criteria used for grading dysplasia in the uterine cervix.[22]

Another pitfall is the lateral spread of squamous cell carcinoma, especially in cases of only basal epithelial involvement by carcinoma cells (basal layer type lateral spread). In such cases, very superficial biopsies may miss this intraepithelial spread of carcinoma.[18]

Evaluation of EMR or ESD margins is very important to determine whether further treatment or follow-up should be done. In practice, EMR and ESD specimens should be stretched and pinned on a firm surface such as a wooden, rubber, or wax board with a sheet of paper on top between the surface and the specimen before fixation. After fixation, the specimens should be serially sectioned at 2-mm intervals parallel to the shorter axis (Fig. 12). When the margin's positivity or negativity is questionable, the basic cut line is determined at the nearest distance to observe the area between the lesion and the surgical margin. Then, the specimen is step-sectioned at 2-mm intervals parallel to the basic cut line of the specimen.[47]

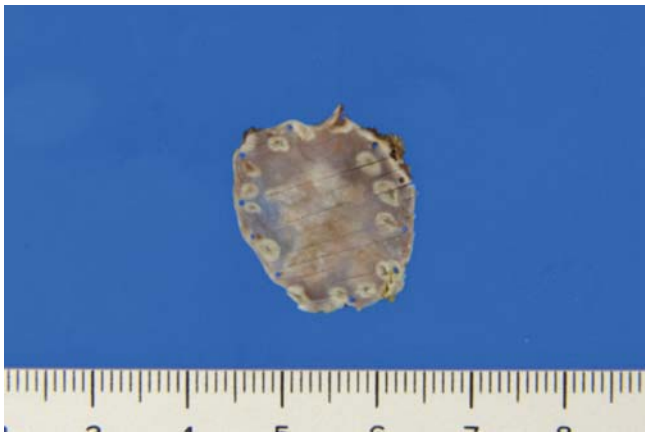

Fig. 12. Specimen obtained by endoscopic submucosal dissection. This stretched specimen was step-sectioned at 2-mm intervals parallel to the minor axis. The pin holes located circumferentially are due to the specimen's being attached to a substrate by pins during fixation

Treatment of squamous intraepithelial neoplasia

According to the revised Vienna classification (Table 2), category 3, namely low-grade intraepithelial neoplasia, is treated by endoscopic resection or follow-up, and category 4, high-grade intraepithelial neoplasia, is adapted for endoscopic or surgical resection, both depending on the overall size of the lesion and the patient's age and comorbid condition. Surgical resection is the general treatment for category 5, submucosal invasion by carcinoma.[45]

Traditionally, pathologically diagnosed esophageal squamous dysplasia, now called squamous intraepithelial neoplasia, has been followed up periodically, and has been treated endoscopically only after it was diagnosed as squamous cell carcinoma. EMR, developed in Japan, is an elective treatment for squamous intraepithelial neoplasia if the lesion is not circumferential and is less than 2 cm in diameter.[48] Complete response is frequently observed if the resection is made in en bloc.[46] However, experience with this procedure is still limited in the West.[49] Another treatment called ESD has recently been considered for early-stage squamous cell carcinoma as well as high-grade intraepithelial neoplasia.[36,50] Here, one consideration requiring caution is that diagnosis from a biopsy specimen is not absolute, since a small piece of tissue does not always reflect the whole lesion. Therefore, endoscopic findings, including the size of the tumor, become important for the treatment.

The Guidelines for Diagnosis and Treatment of Esophageal Carcinoma published in April 2007 indicate the diagnosis and the treatment of esophageal cancer in Japan. Indication for the endoscopic treatment of esophageal squamous cell carcinoma is described as a lesion limited to the squamous epithelium (T1a-EP) or the lamina propria (T1a-LMP), and involving less than two-thirds of the circumference.[14]

It is important to realize that the treatment mentioned above is only an example, because patients with superficial squamous cell carcinoma or intraepithelial neoplasia are usually of advanced age and may have serious complications in the heart or the lung. They may be found to have another cancer in a different organ such as the pharynx, for which treatment may be ongoing. In addition, the natural history of squamous intraepithelial neoplasia of the esophagus is still

unknown. Low-grade intraepithelial neoplasia may regress or disappear, or it may progress to high-grade intraepithelial neoplasia. The precise mechanism of the progression from high-grade intraepithelial neoplasia to superficial squamous cell carcinoma and advanced squamous cell carcinoma has not yet been proven. At present, the EMR or ESD techniques are still being improved in Japan, and they are thought to be safer and less invasive methods, since the reported complications such as hemorrhage and perforation are very rare in some hospitals. However, there is still the possibility of serious complication such as perforation of the mediastinum, especially in older patients who possess other underlying diseases. Therefore, once squamous intraepithelial neoplasia is found, a decision should be made regarding the treatment regimen including follow-up after searching for the patient's general condition and explanation of the pathologic condition to the patient.

In summary, we described the clinical and pathological features of squamous intraepithelial neoplasia. It is important to know the concept and definition of squamous intraepithelial neoplasia. With recent progress in the development of diagnostic and therapeutic tools for this lesion, its concept will be more clarified in the near future. At the present time, we recommend use of the term "squamous intraepithelial neoplasia" and discontinuation of the use of "squamous dysplasia." However, with regard to the term "CIS", it should be realized that there may be two types of squamous cell carcinoma in situ present, one being the total layer type and the other, the basal layer type.[22] In addition, historically, Japanese pathologists have used the term "CIS" or "noninvasive carcinoma" in the gastrointestinal tract in the same way as they have in other organs such as the pancreas, breast, urinary bladder, or prostate. On the other hand, Western pathologists do not use the term CIS for the gastrointestinal tract. This historical difference is still ongoing. Most Japanese pathologists have some resistance to use the term high-grade dysplasia as well as high-grade intraepithelial neoplasia because they include not only severe dysplasia but also CIS. In fact, esophageal CIS does not reveal the same biological behavior as that seen in the uterine cervix, which is closely related to human papillomavirus. Therefore, the pathological criteria used for the uterine cervix cannot be applied in the esophagus. This is one reason why Japanese pathologists hesitate to use the term dysplasia or intraepithelial neoplasia in the esophagus. Historically, it has been recommended in the West not to use the term CIS in order to prevent unnecessary surgery. However, it is not necessary to perform esophagectomy for selective cases of early squamous cell carcinoma, and overtreatment has recently become avoidable as a result of the development of EMR and ESD. Thus, we think the usage of CIS is still debatable. At any rate, we believe that a consensus meeting of Japanese and Western pathologists and endoscopists should be held promptly to come to an agreement about the terminology. In addition, the results should be provided not only to gastrointestinal pathologists but also to general pathologists in each country.

References

1. Siewert JR, Stein HJ. Barrett's cancer: indication, extent, and results of surgical resection. Semin Surg Oncol 1997;13:245–52.
2. Ban S, Mino M, Nishioka NS, Puricelli W, Zukerberg LR, Shimizu M, et al. Histopathologic aspects of photodynamic therapy for dysplasia and early adenocarcinoma arising in Barrett's esophagus. Am J Surg Pathol 2004;28:1466–73.
3. Iacobuzio-Donahue CA, Montgomery E, Goldblum JR. Gastrointestinal and liver pathology. Philadelphia: Churchill Livingstone; 2005. p. 38–65.
4. Day DW, Jass JR, Price AB, Shepherd NA, Sloan JM, Talbot IC, et al. Morson and Dawson's gastrointestinal pathology. Fourth ed. Berlin: Blackwell Science; 2003. p. 59–84.
5. Chatelain D, Fléjou JF. High-grade dysplasia and superficial adenocarcinoma in Barrett's esophagus: histological mapping and expression of p53, p21 and Bcl-2 oncoproteins. Virchows Arch 2003;442:18–24.
6. Nagamatsu M, Mori M, Kuwano H, Sugimachi K, Akiyoshi T. Serial histologic investigation of squamous epithelial dysplasia associated with carcinoma of the esophagus. Cancer 1992;69: 1094–8.
7. Yasuda M, Kuwano H, Watanabe M, Toh Y, Ohno S, Sugimachi K. p53 expression in squamous dysplasia associated with carcinoma of the oesophagus: evidence for field carcinogenesis. Br J Cancer 2000;83:1033–8.
8. Lu N, Hu N, Li WJ, Roth MJ, Wang C, Su H, et al. Microsatellite alterations in esophageal dysplasia and squamous cell carcinoma from laser capture microdissected endoscopic biopsies. Cancer Lett 2003;189:137–45.
9. Zhang W, Wang L, Chang A, Jin Y, Rao J. Immunohistochemical analysis of cyclooxygenase-2 expression in premalignant and malignant esophageal glandular and squamous lesions in Cixian, China. Cancer Detect Prev 2003;27:243–9.
10. Gabbert HE, Shimoda T, Hainaut P, Nakamura Y, Field JK, Inoue H. Squamous cell carcinoma of the oesophagus. In: Hamilton SR, Aaltonen LA, editors. World Health Organization classification of tumours. Pathology and genetics. Tumours of the digestive system, Lyon: IARC Press; 2000. p. 8–19.
11. Geddert H, Kiel S, Heep HJ, Gabbert HE, Sarbia M. The role of p63 and deltaNp63 (p40) protein expression and gene amplification in esophageal carcinogenesis. Hum Pathol 2003;34:850–6.
12. Bax DA, Haringsma J, Einerhand AWC, van Dekken H, Blok P, Siersema PD, et al. MUC4 is increased in high grade intraepithelial neoplasia in Barrett's oesophagus and is associated with a proapoptotic Bax to Bcl-2 ratio. J Clin Pathol 2004;57:1267–72.
13. Japanese Society for Esophageal Diseases. Guideline for the clinical and pathologic studies on carcinoma of the esophagus (in Japanese). 10th edition. Tokyo: Kanehara; 2007.
14. Japanese Society for Esophageal Diseases. Guidelines for diagnosis and treatment of esophageal carcinoma (in Japanese). 2nd ed. Tokyo: Kanehara; 2007.
15. Cotran RS, Kumar V, Robbins SL. Neoplasia. In: Robbins pathologic basis of disease. 5th ed. Philadelphia: Saunders; 1994. p. 241–303.
16. Watanabe H, Jass JR, Sobin LH. World Health Organization. International histological classification of tumours. Histological typing of oesophageal and gastric tumours. 2nd ed. New York: Springer; 1990. p. 1–18.

17. Odze RD, Goldblum JR, Crawford JM. Surgical pathology of the GI tract, liver, biliary tract, and pancreas. Philadelphia: Saunders; 2004. p. 381–408.
18. Fenoglio-Preiser CM, Noffsinger AE, Stemmermann GN, Lantz PE, Isaacson PG. Gastrointestinal pathology. An atlas and text. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 86–109.
19. Round-table talk: squamous dysplasia—how should we think about it? (in Japanese) Stomach and Intestine 1996;31:762–78.
20. Round-table talk: regarding esophageal squamous dysplasia—based on results of case discussions (in Japanese). Stomach and Intestine 2007;42:219–38.
21. Watanabe G, Ajioka Y, Kobayashi M, Aruga Y, Watanabe Y, Nishikura K. Pathological diagnosis of "dysplasia" in the esophageal squamous epithelium (in Japanese with English abstract). Stomach and Intestine 2007;42:129–35.
22. Takubo K. Pathology of the esophagus. An atlas and textbook. 2nd ed. Tokyo: Springer; 2007. p. 145–90.
23. Lewin KJ, Appelman HD. Atlas of tumor pathology, Tumors of the esophagus and stomach. Third series. Washington, D.C.: AFIP; 1996. p. 43–97.
24. Rosai J. Rosai and Ackerman's surgical pathology. 9th ed. Edinburgh: Mosby; 2004. p. 615–47.
25. Wei WQ, Abnet CC, Lu N, Roth MJ, Wang GQ, Dye BA, et al. Risk factors for oesophageal squamous dysplasia in adult inhabitants of a high risk region of China. Gut 2005;54:759–63.
26. Dry SM, Lewin KJ. Esophageal squamous dysplasia. Semin Diagn Pathol 2002;19:2–11.
27. Ishii I, Murakami J, Notohara K, Cullings HM, Sasamoto H, Kambara T, et al. Oesophageal squamous cell carcinoma may develop within a background of accumulating DNA methylation in normal and dysplastic mucosa. Gut 2007;56:13–9.
28. Mori M, Adachi Y, Matsushima T, Matsuda H, Kuwano H, Sugimachi K. Lugol staining pattern and histology of esophageal lesions. Am J Gastroenterol 1993;88:701–5.
29. Dawsey SM, Fleischer DE, Wang GQ, Zhou B, Kidwell JA, Lu N, et al. Mucosal iodine staining improves endoscopic visualization of squamous dysplasia and squamous cell carcinoma of the esophagus in Linxian, China. Cancer 1998;83:220–31.
30. Kumagai Y, Inoue H, Nagai K, Kawano T, Iwai T. Magnifying endoscopy, stereoscopic microscopy, and the microvascular architecture of superficial esophageal carcinoma. Endoscopy 2002;34: 369–75.
31. Yoshida T, Inoue H, Usui S, Satodate H, Fukami N, Kudo S. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc 2004:59: 288–95.
32. Inoue H, Sasajima K, Kaga M, Sugaya S, Sato Y, Wada Y, et al. Endoscopic in vivo evaluation of tissue atypia in the esophagus using a newly designed integrated endocytoscope: a pilot trial. Endoscopy 2006;38:891–5.
33. Inoue H, Kaga M, Sato Y, Sugaya S, Wakamura K, Satodate H, et al. Endoscopic diagnosis of tissue atypia (EA) in esophageal squamous epithelium—IPCL pattern classification and ECA classification (in Japanese with English abstract). Stomach and Intestine 2007;42:161–71.
34. Inoue H. Magnification endoscopy in the esophagus and stomach. Dig Endosc 2001;13 Suppl:S40–1.
35. Ciocirlan M, Lapalus MG, Hervieu V, Souquet JC, Napoléon B, Scoazec JY, et al. Endoscopic mucosal resection for squamous premalignant and early malignant lesions of the esophagus. Endoscopy 2007;39:24–9.
36. Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, et al. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. Clin Gastroenterol Hepatol 2006;4: 688–94.
37. Arima M, Tada M, Arima H. Evaluation of microvascular patterns of superficial esophageal cancers by magnifying endoscopy. Esophagus 2005;2:191–7.
38. Shimizu M, Ban S, Odze RD. Squamous dysplasia and other precursor lesions related to esophageal squamous cell carcinoma. Gastroenterol Clin N Am 2007;36:797–811.
39. Tajima Y, Nakanishi Y, Tachimori Y, Kato Y, Watanabe H, Yamaguchi H, et al. Significance of involvement by squamous cell carcinoma of the ducts of esophageal submucosal glands. Analysis of 201 surgically resected superficial squamous cell carcinomas. Cancer 2000;89:248–54.
40. Schlemper RJ, Dawsey SM, Itabashi M, Iwashita M, Kato Y, Koike M, et al. Differences in diagnostic criteria for esophageal squamous cell carcinoma between Japanese and Western Pathologists. Cancer 2000;88:996–1006.
41. Vieth M, Stolte M. Pathology of early upper GI cancers. Best Pract Res Clin Gastroenterol 2005;19:857–69.
42. Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, et al. The Vienna classification of gastrointestinal neoplasia. Gut 2000;47:251–5.
43. Shimizu Y, Kato M, Yamamoto J, Ono Y, Katsurada T, Ono S, et al. Histologic results of EMR for esophageal lesions diagnosed as high-grade intraepithelial squamous neoplasia by endoscopic biopsy. Gastrointest Endosc 2006;63:16–21.
44. Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. Gut 2002;51:130–1.
45. Lambert R, Hainaut P, Parkin DM. Premalignant lesions of the esophagogastric mucosa. Semin Oncol 2004;31:498–512.
46. Stolte M. The new Vienna classification of epithelial neoplasia of the gastrointestinal tract: advantages and disadvantages. Virchows Arch 2003;442:99–106.
47. Lauwers GY, Ban S, Mino M, Ota S, Matsumoto T, Arai S, et al. Endoscopic mucosal resection for gastric epithelial neoplasms: a study of 39 cases with emphasis on the evaluation of specimens and recommendations for optimal pathologic analysis. Mod Pathol 2004;17:2–8.
48. Makuuchi H. Endoscopic mucosal resection for mucosal cancer in the esophagus. Gastrointest Endosc Clin N Am 2001;11:445–58.
49. Gotoda T. Endoscopic resection for premalignant and malignant lesions of the gastrointestinal tract from the esophagus to the colon. Gastrointest Endosc Clin N Am 2008;18:435–50.
50. Takubo K, Aida J, Sawabe M, Kurosumi M, Arima M, Fujishiro M, et al. Early squamous cell carcinoma of the oesophagus: the Japanese viewpoint. Histopathology 2007;51:733–42.