#### **ORIGINAL ARTICLE**

# Histologic results of EMR for esophageal lesions diagnosed as high-grade intraepithelial squamous neoplasia by endoscopic biopsy

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**Background:** Biopsy specimens obtained from esophageal lesions detected in endoscopic screening with iodine staining have often been diagnosed as high-grade intraepithelial squamous neoplasia (WHO 2000). However, a management strategy for such lesions has not been established. The purpose of this study was to perform EMR for such lesions and to determine the actual tumor stage in patients with complete resection and the outcomes after EMR.

**Patients:** During the study period, 51 patients were found to have esophageal lesions diagnosed as high-grade intraepithelial squamous neoplasia by using endoscopic iodine staining in biopsy specimens. All of the patients underwent EMR, and resected specimens were reviewed microscopically.

**Results:** Histologic examination of totally resected specimens revealed that 12 (23.5%) of the 51 patients had tumor invasion of the lamina propria mucosae and that 4 (7.8%) had tumor invasion of the muscularis mucosae. The remaining 35 patients (68.6%) were confirmed to have high-grade intraepithelial squamous neoplasia. The invasive focus in all of the 16 lesions of invasive squamous-cell carcinoma was surrounded by high-grade intraepithelial squamous neoplasia. After a median of 23 months of follow-up, there were two recurrences, and those patients required second EMR.

**Conclusions:** Histologic results suggested that high-grade intraepithelial squamous neoplasia of the esophagus has characteristics of carcinoma in the preinvasive stage. EMR should be performed for esophageal lesions diagnosed by endoscopic biopsy as high-grade intraepithelial squamous neoplasia, not only because of its probable malignant potential but also because more than 30% of such lesions are actually invasive carcinoma. (Gastrointest Endosc 2006;63:16-21.)

The current widespread use of upper-endoscopic examination and the development in recent years of techniques for endoscopic diagnosis have led to the detection of increasing numbers of early stage esophageal squamouscell carcinoma. EMR has become increasingly popular as a first choice of treatment for patients with early stage esophageal carcinoma, because of its minimal invasiveness and satisfactory outcome. The ability to detect early squamous neoplasia of the esophagus can be considerably enhanced by iodine staining during endoscopic examination. We routinely perform endoscopic screening with

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iodine staining in high-risk populations for esophageal cancer, including men over the age of 50 years with a history of tobacco abuse (defined as more than 20 pack-years) and/or alcohol abuse (more than 5 days of alcohol consumption per week) and patients with other current or prior primary cancers.<sup>3</sup> Biopsy specimens obtained from the lesion detected in endoscopic screening were often diagnosed, by histology, as high-grade intraepithelial squamous neoplasia.<sup>8</sup> Before this new World Health Organization (WHO) classification was established, Western pathologists usually included such lesions under dysplasia, and it has not been determined whether such lesions were malignant or benign. Several investigators have reported the characteristics of intraepithelial squamous neoplasia (carcinoma in situ or dysplasia) adjacent to invasive squamous-cell carcinoma in esophagectomy specimens. 9-11 However, there are very

few reports on the characteristics of such intraepithelial squamous lesions existing solitary (without invasive carcinoma), and a management strategy for such lesions, therefore, has not been established. The purpose of this study was to perform EMR for esophageal lesions diagnosed as high-grade intraepithelial squamous neoplasia by endoscopic biopsy and to determine the actual tumor stage in patients with complete resection and the outcomes after EMR.

#### PATIENTS AND METHODS

Morphologic features of intraepithelial squamous neoplasia of the esophagus include both architectural and cytologic abnormalities. The architectural abnormality is characterized by disorganization of the epithelium and loss of normal cell polarity. The cells exhibit irregular and hyperchromatic nuclei, an increase in nuclear/cytoplasmic ratio, and increased mitotic activity. Intraepithelial neoplasia is graded as high grade when greater abnormalities occur in the upper half of the epithelium.

During the period from April 2001 to September 2004, at Hokkaido University Hospital and associated hospitals, 51 patients were found to have lesions diagnosed as highgrade intraepithelial squamous neoplasia of the esophagus by endoscopic biopsy. In 30 of those patients, the lesions were detected by endoscopic screening with iodine staining for high-risk populations, and the lesions were detected in the other 21 patients by endoscopic follow-up of other diseases or by endoscopic screening for nonspecific complaints (Table 1). (Iodine staining was also performed in those 21 patients after detection of abnormalities of the esophageal mucosa by conventional endoscopy.) All 51 patients were Japanese. None of the 51 patients had symptoms related to esophageal disease such as dysphagia and heart burn. Four of the patients had double lesions diagnosed as high-grade intraepithelial squamous neoplasia by endoscopic biopsy, and one of the patients had triple lesions. (We diagnosed these lesions as independent lesions because they apparently were separated from each other by more than 1 cm.) All patients underwent EUS with the use of a high-frequency catheter probe and were confirmed to have no evidence of submucosal tumor invasion. Subsequently, all patients underwent EMR by one of two endoscopists (Y.S., J.Y.) at Hokkaido University Hospital. Endoscopic examinations were performed with videoendoscopes (XQ-230, Q-240; Olympus Optical Co, Ltd, Tokyo, Japan), and iodine staining methods were performed with 1.5% iodine solution. Follow-up examinations, including GI endoscopy with iodine staining and biopsies, were performed every 3 to 6 months during the first year after EMR and every 6 to 12 months afterward to detect local recurrence.

All biopsy specimens were cut in the center, and all resected specimens were cut into longitudinal slices that measured 2 mm in width. The slices were embedded in

### **Capsule Summary**

#### What is already known on this topic

 Biopsy specimens obtained from esophageal lesions detected in endoscopic screening with iodine staining have often been diagnosed as high-grade intraepithelial squamous neoplasia.

#### What this study adds to our knowledge

 Histologic examination of EMR specimens revealed that more than 30% of such lesions were actually invasive carcinoma.

TABLE 1. Reasons for upper endoscopic examination in the 51 patients who had lesions diagnosed as high-grade intraepithelial squamous neoplasia of the esophagus by endoscopic biopsy

Alcohol and tobacco abuse*/	10
Other primary cancers†	
Head and neck cancer	11
Lung cancer	4
Gastric cancer	5
Follow-up of other diseases	
Gastric ulcer	5
Chronic gastritis	6
Esophagitis	2
Nonspecific complaints	
Epigastralgia	3
Nausea	2
Routine examination (with no complaint)	3

<sup>\*</sup>Men over the age of 50 y with a history of tobacco abuse (defined as more than 20 pack-y) and/or alcohol abuse (more than 5 d alcohol comsumption per wk). All of them were drinkers, and 8 of them were both drinkers and smokers.

paraffin and stained with H&E. All specimens were microscopically reviewed by two pathologists blinded to the clinical characteristics of the patients.

The study was approved by the ethics committee of our institute, and written informed consent for all procedures and for participation in this study was obtained from all subjects.

<sup>†</sup>The 30 patients in high-risk populations underwent endoscopic screening with iodine staining. The other 21 patients underwent conventional endoscopy and subsequently underwent iodine staining after detection of abnormalities of the esophageal mucosa.

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