Utility of Chromoendoscopy with Lugol Solution Spraying in Early Detection of Esophageal Squamous Cell Carcinoma and Dysplasia

Hiroaki Ito, Kazuhiro Kaneko, Kazuo Konishi, Taikan Yamamoto, Atushi Katagiri, Miki Kushima, Ikuo Homma and Keiji Mitamura

Abstract: Patients with esophageal squamous cell carcinoma (ESCC) have a poor prognosis, making early detection vital. Endoscopic screening to detect early signs of ESCC with the hope of preventing disease progression has not yet been established. The aim of this prospective study was to investigate Chromoscopy with Lugol solution spraying as a screening method. A sample group of 1028 asymptomatic subjects, comprising 528 males and 500 females, underwent the videoendoscopy. Biopsies were performed endoscopically on any Lugol-unstained lesions detected by the video screening. ESCC originates from esophageal dysplasia. Therefore, we compared the detection rate of dysplastic lesions using routine endoscopy with that found by chromoendoscopy using Lugol staining. In addition, the clinicopathological characteristics of dysplastic lesions containing ESCC were investigated. Out of 1028 patients, 203 (20%) had Lugol-unstained lesions including 29 (2.8%) dysplastic lesions and 174 (17%) esophagitis. Of the 29 patients with dysplastic lesions, 20 were male and 9 were female. The dysplastic lesions comprised 18 showing low-grade dysplasia (LGD) and 11 showing high-grade dysplasia (HGD) with two intraepithelial carcinomas detected. Sixteen of the 29 dysplastic lesions (55%) measured 5 mm or less in diameter, and 59% of these lesions were located in the middle third of the esophagus. Dysplastic lesions containing intraepithelial carcinoma were detected in 3 of the 1028 biopsied specimens (0.3%) by routine endoscopic observation and in 29 specimens (2.8%) by endoscopic observation with Lugol solution spraying; this difference was significant between the two groups (p<0.0001). Esophageal dysplastic lesions were therefore found in 2.8% of asymptomatic patients. From this study, we conclude that Chromoendoscopy with Lugol solution spraying is a useful screening procedure for the early detection of ESCC.

Key words: esophagus, squamous cell carcinoma, carcinogenesis, videoendoscopy, Lugol staining
Introduction

Carcinoma of the esophagus has one of the worst patient prognoses among digestive tract carcinomas, since more than 90% of patients are diagnosed at an advanced stage. More than half of these patients undergo surgery that is noncurative due to either local tumor invasion of surrounding tissue or distant metastasis being present at the time of operation. Despite recent advances in surgical treatment of esophageal carcinoma around the world, the overall prognosis remains unfavorable in Western countries, and in Japan. In contrast, the prognosis of patients treated for carcinomas confined within the intraepithelium or proper mucosal layer is excellent, with five-year survival rates of 85% to 100%. Endoscopic mucosal resection performed in some patients with superficial cancer has resulted in normal life expectancy and quality. Detecting the development of esophageal squamous cell carcinoma (ESCC) is therefore important not only to enable early treatment of the cancer but also to prevent its progression to an incurable disease.

The Lugol test in gynecologic colposcopy was developed by Schiller for the early diagnosis of uterine cervix neoplasia. Brodmerkel was the first to report the Lugol test in combination with esophagoscopy to diagnose esophageal cancer. With respect to the detection of early lesions, several authors have reported success in endoscopy with Lugol solution spraying to delineate areas of squamous dysplasia and cancer, as well as localized esophagitis. Ina et al. reported that Lugol dye endoscopy is indispensable for monitoring male patients with oral or oropharyngeal cancer to detect an early concomitant esophageal cancer. Mori et al. also reported the usefulness of the Lugol test to delineate precisely the proximal resection line during surgery for esophageal carcinomas with unexpected wide extension.

The progression to esophageal squamous cell carcinoma is a multi-step carcinogenesis mechanism. Genetic analysis indicates that ESCC originates from dysplasia. Shi et al. identified a mutation of the p53 gene in esophageal dysplasia, and concluded that dysplasia could be precancerous. Among esophageal cancers in Japanese patients, 95% are squamous cell carcinomas. In this study, Chromoendoscopy with Lugol solution spraying was performed in asymptomatic subjects to assess this procedure as a means of detecting dysplastic lesions. The clinicopathological findings of dysplasia containing intraepithelial carcinoma were also investigated.

Materials and Methods

Materials

A total of 1028 asymptomatic patients were screened for early carcinoma and dysplasia of the esophagus. Endoscopic observation was performed for all 1028 patients between April 1998 and March 2000. Patients with cancer, a history of surgery or chemoradiotherapy for esophageal carcinoma, or esophageal varices secondary to liver cirrhosis were excluded from the study. All subjects gave informed consent for their participation in this study. The study protocol was approved by the Human Ethics Review Committee of the Showa University School of Medicine. For patients showing Lugol-unstained lesions, only the largest and highest-grade were registered in this study.
**Endoscopic examination**

Patients were examined by videoendoscopy (Q240, Olympus, Tokyo, Japan) with Lugol solution spraying. Initially, a routine endoscopic observation of the entire esophagus was performed in all patients. After the initial inspection, 5 to 10 ml of 4% glycerin-free Lugol iodine solution was sprayed from the gastroesophageal junction to the upper esophageal sphincter using a plastic spray catheter (washing tube PW-5L; Olympus) passed through the biopsy channel of the endoscope. After Lugol solution spraying, the esophagus was observed again, and the epithelial areas were categorized as unstained, normally stained, or overstained. We defined Lugol-unstained lesions as those that stained less intensely than normally stained mucosa, or which were completely unstained (Fig. IA, B). This group of lesions included carcinoma, dysplasia, and esophagitis. Lugol-unstained lesions were sampled with biopsy forceps (Radial Jaw 3, Boston Scientific, Miami, FL, USA) under direct vision.

In routine endoscopic observation prior to Lugol staining, we defined a dysplastic lesion as an area without visible blood vessels or a slightly reddish area in the esophageal epithelium. Visible lesions were recorded as the incisor teeth, and changes around the lesions were also recorded prior to Lugol staining. In order to estimate the detection rate of dysplastic lesions in routine endoscopic observation, patients were classified into two groups; the “should be” group in which Lugol staining should be performed due to the presence of a dysplastic lesion, and the “no need” group in which Lugol staining should not be performed due to the absence of dysplastic lesions.

**Histological evaluation**

Samples were diagnosed according to previously described histological definitions from biopsy specimens. Normal epithelium showed well-oriented squamous epithelium without
evidence of esophagitis, squamous dysplasia, or squamous carcinoma. Specimens with esophagitis fulfilled one or more of three criteria: elongation of lamina propria papillae into the upper third of the epithelium together with basal cell hyperplasia (basal zone thickness exceeding 15% of the total epithelial thickness); epithelial infiltration by neutrophils or eosinophils; or dense nonfollicular mononuclear infiltration or easily recognized infiltration of neutrophils into the lamina propria. Squamous cell dysplasia was characterized by nuclear atypia (enlargement, pleomorphism, and hyperchromasia), loss of normal cell polarity, and abnormal cell maturation in the lower third (mild); in the lower two-thirds (moderate); or throughout the epithelium (severe). Mild dysplasia and moderate to severe dysplasia containing intraepithelial carcinoma were defined as low-grade (LGD) and high-grade dysplasia (HGD), respectively. Squamous cell carcinoma was defined as malignant squamous cells invading the basement membrane. Histological diagnosis was reviewed by one of the authors (M.K.), a pathologist at our university hospital.

Statistical analysis
The significance of differences in proportions was assessed by the chi-squared test and Student's t test. P values less than 0.05 were considered statistically significant.

Results

Patients characteristics
Characteristics of the 1028 patients are listed in Table 1. Of the 1028 patients, 528 were male and 500 were female. The mean age of the patient cohort was 61 years, ranging from 20 to 89 years. Videendoscopy with Lugol solution spraying was performed in all cases, and 203 patients were found to have Lugol unstained lesions. Dysplastic lesions containing two intraepithelial carcinomas were detected in 29 of 1028 patients (2.8%). Of the 29 patients, 4 had two dysplastic lesions and one had 3 dysplastic lesions. Of the remaining 999 patients, 174 (17%) had Lugol-unstained esophagitis. The histological grades of the 29 dysplastic lesions were as follows: 18 of mild dysplasia, 6 of moderate dysplasia, 3 of severe dysplasia, and 2 of intraepithelial carcinoma. The mean lesion size was 7.1 mm in dysplastic lesions (ranging from 3 to 21 mm) and 4.5 mm in Lugol-unstained esophagitis (ranging from 1 to 10 mm). The mean size of the dysplastic lesions was 4.9 mm in mild dysplasia, 7.3 mm in moderate dysplasia, and 11.4 mm in severe dysplasia containing intraepithelial carcinoma. There was no significant difference between the histological grade of the dysplastic lesions and tumor size. Sixteen of 29 dysplastic lesions (55%) measured less than 5 mm in diameter, and 23 of 29 dysplastic lesions (80%) measured less than 10 mm in diameter. Two lesions were located in the upper third (7%), 17 in the middle third (59%), and 10 in the lower third (34%) of the thoracic esophagus.

LGD was found in 10 of 528 male patients (1.9%) and in 8 of 500 female patients (1.6%). No significant difference was found between the two groups (p=0.9035). In contrast, HGD was found in 10 of 528 male patients (1.9%) and in 1 of the 500 female patients (0.2%) (p=0.0195) (Table 2). Dysplastic lesions were found in 3 of 198 patients (1.5%) under 50 years of age, and in 26 of 830 patients (3%) of 50 years and over. No significant difference was found between these two groups (p=0.3191). Of interest, no dysplastic lesion was found in patients under 40 years of age.
Detection rate of dysplastic lesions in routine endoscopy and chromoendoscopy

Dysplastic lesions were suspected in 54 of 1028 patients (5%) during routine endoscopic observations prior to Lugol staining, and hence these patients were considered appropriate for Lugol solution spraying. Fifty-four patients were classified into the “should be” group, while the remaining 974 patients were classified into the “no need” group. However, dysplastic lesions were only found in 3 of these 54 patients (6%) after Lugol staining. No Lugol-unstained lesion was found in the remaining 51 patients. The tumor sizes of these 3 dysplastic lesions measured 15 mm, 20 mm, and 21 mm in diameter, respectively. One of 3 lesions had intraepithelial carcinoma, and the remaining two lesions showed severe dysplasia. The other intraepithelial carcinoma was missed in routine endoscopic observation. The tumor size of this lesion was 5 mm in diameter. Routine endoscopic findings of these lesions showed areas without visible blood vessels or slightly reddish areas in the center of the lesion. The remaining 26 dysplastic lesions detected following videoendoscopy were seen in routine endoscopic observation with Lugol staining. The detection rate of dysplasia containing intraepithelial carcinoma was 0.3% in routine endoscopic observation, and 2.8% in endoscopic observation with Lugol staining (p<0.0001).

Discussion

In this prospective study of individuals representing the general population in Japan, 203 out of 1028 asymptomatic subjects (20%) had Lugol-unstained lesions, indicating dysplasia. In addition, esophageal dysplasia including intraepithelial carcinoma was detected endoscopically in approximately 3% of the group. For several years, Japanese and European authors have reported that staining of the esophageal mucosa with Lugol iodine solution can make the presence and extent of squamous dysplastic and cancerous foci more clear, and therefore be of use to detect dysplasia and intraepithelial carcinoma. Despite this, the technique has not been used widely worldwide. Acceptance of these reports would be enhanced by a comparison of the effectiveness of Lugol solution spraying for the detection of dysplastic lesions containing carcinomas by chromoendoscopy with that achieved by routine endoscopic observation. In this study, we show that videoendoscopy with Lugol solution spraying is a useful and potentially important way to detect dysplasia and intraepithelial carcinoma, since the detection rate of dysplastic lesions by chromoendoscopy with Lugol staining differed significantly from that provided by routine endoscopy. In routine endoscopic observation, larger tumors were detected before Lugol staining, however, the possibility of missing small lesions could not be ignored. We suggest that Lugol staining should be performed together with routine endoscopy so as not to miss any small dysplastic lesions or carcinoma, even in asymptomatic subjects. Furthermore, Lugol iodine solution is not expensive, and no patient experienced a severe toxicity reaction to the dye. We believe that Lugol solution spraying is not only effective in detecting early cancer but is also feasible for routine endoscopy procedures.

Transformation to ESCC has been reported as multi-step carcinogenesis, originating from dysplasia. Shi et al. proposed that dysplasia was the precursor of esophageal carcinoma, since the p53 “hotspot” mutation in dysplasia corresponded to that found in ESCC patients. They concluded that p53 mutations occurred as an early event in esophageal carcinogenesis, with cells harboring such mutations being likely to give rise to carcinoma. In our study, 18 LGD and 11 HGD containing 2 intraepithelial carcinoma were
found in 1028 asymptomatic patients. The mean tumor size enlarged progressively from mild dysplasia to severe dysplasia containing carcinoma, which suggested a multi-step esophageal carcinogenesis as described previously\textsuperscript{17,18}). We propose that mild dysplasia is an important initial event leading to esophageal squamous cell carcinoma.

We believe that early detection of dysplasia is important in endoscopic screening for the prevention of ESCC. However, treatment of LGD remains controversial. Whether patients with LGD should be treated actively with endoscopic mucosal resection, or followed up, has not been established clearly. In our study, the presence of HGD differed significantly between male and female subjects, while the presence of LGD showed no such difference. In previous data concerning 6090 Japanese patients with ESCC, 85% of patients were male\textsuperscript{23}). This prevalence was similar to that of patients with HGD (91%, 10 of 11) in our study. Although LGD is likely to transform to HGD, it remains unclear whether LGD does indeed progress to HGD.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Cancer Research (14–3) from the Ministry of Health, Labour and Welfare, and was also supported in part by a Showa University Grant-in-Aid for Innovative Collaborative Research Projects, and a Special Research Grant-in Aid for Development of Characteristic Education from the Japanese Ministry of Education, Culture, Sports, Science and Technology of Japan.

References


[Received February 3, 2003 : Accepted February 7, 2003]