



Study of the Invasion Depth Diagnosis of Superficial Barrett's Esophageal Adenocarcinoma- Identification of Large Vessels by Magnifying Endoscopy is Useful for the Diagnosis of Sub Mucosal Cancer

Natsuko Yoshizawa^{1,2}, Junko Fujisaki^{1*}, Masami Omae¹, Masahiro Igarashi¹, Satoshi Tanabe² and Wasaburo Koizumi²

¹Department of Gastroenterology, Cancer Institute Hospital, Japan

²Department of Gastroenterology, Kitasato University School of Medicine, Japan

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***Corresponding author:** Junko Fujisaki, Department of Gastroenterology Japanese Foundation For Cancer Research, Cancer Institute Hospital, 3-8-31 Ariake, Koto-ku, Tokyo, 135-8550, Japan.

Abstract

Objective: Superficial Barrett's esophageal adenocarcinoma (S-BEA) has been treated by endoscopic procedures. Especially, intramucosal carcinomas have been treated by endoscopic mucosal resection (EMR) or endoscopic sub mucosal dissection (ESD). It is important to diagnose sub mucosal invasive lesions by endoscopy. However, it is difficult to diagnose with sub mucosal or mucosal BEA. Aim of this study that Observation of large vessels (LVs) by Magnified Endoscopy with narrow band imaging (ME-NBI) is useful for diagnosis of sub mucosal invasive S-BEA.

Methods: We examined 50 cases of S-BEA. We diagnosed the depth of these lesions by white light imaging (WLI) and ME-NBI. Large vessels (LVs) with ME-NBI were defined as a diameter 2-3 times larger than surface capillary. Large vessels (LVs) observed with ME-NBI were defined those having a diameter 2-3 times larger than surface capillaries. If we could observe large vessels, we diagnosed sub mucosal (SM) invasive cancer.

Results: Using WLI, the accurate diagnostic rate (AR) was 72%, sensitivity was 59%, specificity was 79%, positive predictive value (PPV) was 59%, and negative predictive value was (NPV) 79%. With ME-NBI, the AR was 84%, sensitivity was 88%, specificity was 82%, PPV was 71%, and NPV 93%.

Conclusion: Findings large vessels on the tumor using ME-NBI is useful for diagnosis of sub mucosal invasive S-EBA. LV is more objective findings of sub mucosal cancer.

Keywords: Endoscopy; Sub mucosal cancer; Gastro esophageal reflux

Introduction

As the number of patients with gastro esophageal reflux disease (GERD) has increased in Japan recently, there is a growing concern about the increase in the number of patients with Barrett's esophagus and Barrett's esophageal adenocarcinoma, which is thought to be the terminal stage of GERD [1-3]. Endoscopic ultrasonic sonography (EUS) has been mainly used for diagnosis of the depth of the invasion of Barrett's esophageal adenocarcinoma [4,5]. Since Barrett's esophageal adenocarcinoma is most often diagnosed in its early stage thanks to the progress in diagnostic ability of endoscopic equipment, endoscopic treatment has been increasingly used. However, a clear criterion for the use of endoscopic treatment for Barrett's

esophageal adenocarcinoma has not been established. The incidence of lymph node metastasis of mucosal cancer or high-grade dysplasia is said to be 1-2%, and sub mucosal cancers are not treated with endoscopy [6-8].

On the other hand, in esophageal squamous cell carcinoma, the presence of large vessels (LVs), or B3 vessels, that can be observed by magnifying endoscopy was reported to be useful for the diagnosis of sub mucosal infiltration [9,10]. Since the absolute indication for endoscopic treatment was reported to be limited to lesions up to lamina propria mucosa (LPM) [9-11], sub mucosal cancer is not an absolute indication for endoscopic treatment. It was reported that in esophageal squamous

carcinoma, gastric cancer and colon cancer these LVs are recognized to be related to the depth of invasion [12,13]. In the present study, we analyzed findings for S-BAC with sub mucosal invasion or shallower invasion, and examined the propriety of LV observation and the relationship between the presence of LV and its diagnostic ability for invasion depth.

Methods

Study participants were enrolled 50 patients who underwent magnified endoscopy with narrow band imaging (ME-NBI) who were diagnosed as having superficial Barrett's esophageal adenocarcinoma (S-BEA) of SM depth or less and underwent an endoscopic or surgical procedure in our hospital from April 2005 to August 2013. For invasion depth, 17 patients had sub mucosal cancer and 33 patients had mucosal cancer Superficial Muscularis Mucosa (SMM): 21 patients, Deep Muscularis Mucosa (DMM): 12 patients). All participants were diagnosed as having Barrett's esophageal carcinoma by histopathological examination of their resected specimens by expert two gastrointestinal pathologists. Barrett's esophageal carcinoma was defined according to the Japanese classification of esophageal cancer established by the Japan Esophageal Society [11]. We used GIF-H260Z, LUCERA-260SL and CLV-260NBI (Olympus Corporation, Tokyo, Japan) endoscopic systems for the study. Retrospective study was performed.

Invasion depth was diagnosed by conventional endoscopy. The diagnosis of invasion depth was made according to criteria for invasion depth diagnosis of early gastric cancer [14,15]. Because the subjects had adenocarcinoma of the glandular epithelium as part of their background. Thus, findings of protrusion over elevated cancer for the protruded-type cancer and trapezoidal protrusion and sub mucosal-like protrusion for depressed type cancer were diagnosed as sub mucosal invasive cancer. Based on these criteria, patients with mucosal cancer underwent endoscopic treatment and those with sub mucosal cancer underwent surgical operation. Before treatment, Computed Tomography (CT) was performed for all the patients. We defined that they had no metastatic lesion. Endoscopic images of study participants were reviewed, and the images were analyzed by two endoscopic specialists certified by the Japan Gastrointestinal Endoscopy Society.

Table 1: Histologically, most of the submucosal cancer lesions (81%) were mixed with undifferentiated adenocarcinoma.

	SMM (n=21)	DMM (n=12)	SM (n=17)	p-value
Mean Age	66.1	65.3	61.4	NS
Sex (male/female)	18/3	12/0	15/2	NS
Treatment				
Surgical Treatment	5	2	16 (including 6 patients with ESD)	P<0.01
Endoscopic Treatment	16	10	7(ESD)	
Barrett's esophagus(SSBE/LSBE)	18/3	9/3	11/6	NS
Macroscopic classification				P<0.01
0-I,				

In observations by NBI-magnifying endoscopy, findings of LVs with diameters 2-3 times greater than that of capillaries in the superficial mucosa of tumors and tortuosity vessels were judged to be LV-positive (Figure 1) LV could be observed on the lesion and edge of the lesion. Then, images obtained by NBI-magnifying endoscopy were retrospectively reviewed by two endoscopic specialist same as conventional endoscopic picture to examine the propriety of LV observation and its ability to assess invasion depth. We treated these patients by ESD after informed consent was obtained. This study was conducted in accordance with the declaration of Helsinki and the study protocol was approved by the Ethics Committee of the Cancer Institute Hospital of the Japanese Foundation for Cancer. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing).

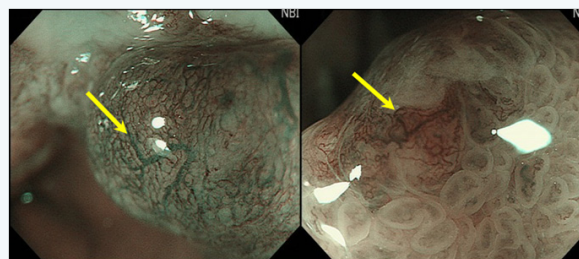


Figure 1: Large vessel: Its diameters 2-3times greater than that of capillaries and tortuosity vessels. Those vessels could be observed on and edge of the lesions.

Results

No significant differences were found in mean age, sex (male/female), and the ratio of short segment Barrett's esophagus/ long segment Barrett's esophagus (SSBE/LSBE) between patient groups classified by invasion depth of Barrett's esophageal carcinoma. Treatment was chosen based on the diagnosis of invasion depth by conventional endoscopy. Endoscopic treatment was chosen for most of the patients with mucosal cancer (SMM and DMM), while surgery was chosen for patients with sub mucosal cancer. Regarding macroscopic classification, the ratio of types IIa + IIc was higher in patients with sub mucosal cancer. Histologically, most of the sub mucosal cancer lesions (81%) were mixed with undifferentiated adenocarcinoma (Table 1).

0-I+IIa,				
0-IIa	12(57.1)	5(41.7)	3(17.6)	
0-IIa+IIc	1(4.8)	2(16.7)	10(58.8)	
0-IIc	8(38.1)	5(41.7)	4(23.5)	
Mean tumor diameter (mm)	17.9	18.9	24.3	NS
Histological classification				
Differential type	21	12	16	P<0.01
Mixed with undifferentiated type	2(9.5)	1(8.3)	13(81.3)	
LV-positive patients	3(14.3)	3(25.0)	15(88.2)	P<0.001

(Table 2) shows a comparison of results of invasion depth diagnosis by conventional endoscopy and by LV imaging. The overall accuracy rate of conventional endoscopy was 72% (36/50); in patients with mucosal cancer it was 78% (26/33) and in those with sub mucosal cancer it was 59% (10/17). On the basis of LV-positive and LV-negative findings the overall accuracy rate was 84% (42/50); in patients with mucosal cancer it was 82% (27/33) and in patients with sub mucosal cancer it was 88% (15/17). The accuracy rate was significantly higher for diagnosis with LV-positive/negative findings than with conventional endoscopy (Table 2). Accuracy rate, Sensitivity, specificity, PPV, NPV showed (Table 3).

Table 2a: Endoscopic findings and Pathological diagnosis.

	P-M	P-SM	
LV+	6	15	15/21(71)
LV-	27	2	27/29(93)
	33	17	

Table 2b: LV using ME-NBI and pathological diagnosis.

	P-M	P-SM	
LV+	6	15	15/21(71)
LV-	27	2	27/29(93)
	33	17	

Table 3: Results of WLI and NBI.

	WLI(95%CI)	NBI(95%CI)
Accuracy rate,%	72(57.5-83.8)	84(70.9-92.8)
Sensitivity,%	59(32.9-81.6)	88(63.6-98.5)
Specificity,%	79(61.1-91.0)	82(65.6-91.4)
PPV,%	59(32.9-81.6)	71(47.8-88.7)
NPV,%	79(61.1-91.0)	93(77.2-99.2)

Case Report

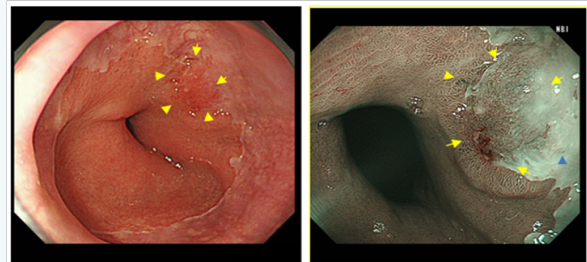


Figure 2a: Reddish are could be seen at 2o'clock lower oesophagus. Slightly depressed lesion with elevation around the lesion. However, it could not be diagnosed submucosal invasion definitely.

Figure 2b: Using NBI, Brownish area could be seen at the same as figure 2a.

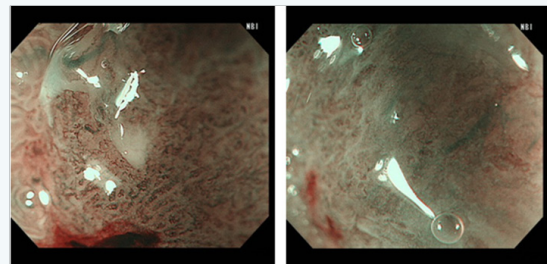


Figure 2c: Using ME we could find large vessel at the upper side of the lesion.

Figure 2d: Also, it could be seen at center of the lesion.

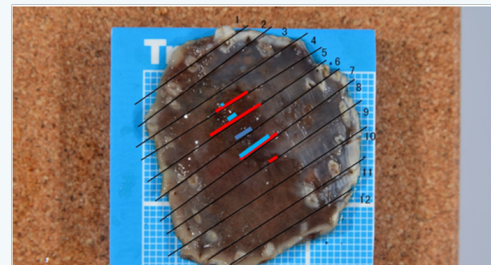


Figure 2e: Histological mapping shows submucosal invasive lesion.

Red line showed intramucosal mapping, blue line showed submucosal invasive mapping.

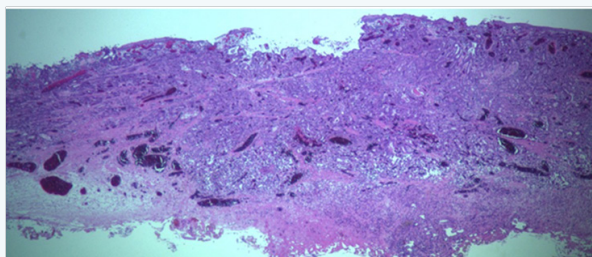


Figure 2f: Histology showed submucosal invasion.

(Figure 2) shows a lesion from a 62-year-old male with LV-positive sub mucosal cancer. Type-IIc was found in the 2 o'clock position of the gastro-esophageal junction. It was diagnosed as mucosal cancer by conventional endoscopy (Figure 2a,2b). NBI-magnifying endoscopy showed LVs on the proximal side of the tumor. The diameter of the LV shown with an arrow was 2-3 times greater than that of the capillaries around it (Figure 2c). The patient underwent ESD. Results of histopathological examinations were as follows: tub1-2 17×9 mm, SM2 (950 μm) ly0, v0, OW/AW (-). In the resected specimen, the tumor was observed in the parts indicated with red lines and sub mucosal infiltration was observed in the parts indicated by blue lines (Figure 2e). Histology showed sub mucosal invasion (Figure 2f,2g). High power view of the lesion showed large vessel on the surface.

Discussion

Endoscopic treatment of S-BEA is mainly performed for mucosal cancer. EUS has been used for invasion depth diagnosis of S-BEA [4,5]. The accuracy rate of EUS for Barrett's esophageal carcinoma was reported to be 74% [5]. Also reported was a 61.9% accuracy rate of EUS for sub mucosal cancer and an over diagnosis rate of 18.6%. A lower accuracy rate for the lower esophagus, that is, 47.6%, has been reported, suggesting the difficulty of diagnosis of invasion depth of Barrett's esophageal carcinoma associated with SBE [5].

With white light imaging (WLI), protruding lesions are observed focusing on the size and height of the protrusion, the shape of the base of the protrusion and the tone and appearance of the protrusion surface, while depressed lesions are observed focusing on the depth of depression, roughness of the bottom of the depression, and the tone and the elevation around the depressed wall. Indicators of sub mucosal cancer are protrusions on an elevated lesion and SMT-like protrusions or trapezoidal protrusions in depressed cancer. However, it is difficult to objectively judge these findings.

Treatment guidelines have been established for esophageal cancer, gastric cancer, and colon cancer in Japan, and the indications for endoscopic treatment are defined in these guidelines. Since deeply infiltrating sub mucosal cancer has the possibility of lymph node metastasis, its treatment requires

surgical operation. Rice et al. [8] reported that lymph node metastasis occurred in 47% of patients with Barrett's esophageal carcinoma, with the following breakdown: epithelial layer (EP), 0%; mucosal layer (LPM and MM), 2.8%; sub mucosal layer (SM), 20.8%; Muscularis propria (MP), 45%; adventitia (Ad), 83.0%; and infiltration to nearby organs, 100%. It has been reported that since lymph node metastasis occurs in 1-2% of patients with intramucosal S-BEA, its treatment by endoscopic operation can be approved, taking surgery-related mortality into consideration [6-8]. Since cancers invading the sub mucosal layer or deeper have the possibility of lymph node metastasis, local treatments including endoscopic treatment, such as EMR and ESD and ablation, are not indicated for these cancers.

In patients with esophageal squamous cell carcinoma, the presence of a type Vn vessel (a large vessel in depth, new tumor vessel) according to the intra-epithelial papillary capillary loop (IPCL) pattern classification and a type B3 vessel (a highly enlarged abnormal vessel; an abnormal vessel of which diameter exceeds 60 μm or 3 times greater than that of a type 2B vessel) according to the new classification of the Japan Esophagus Society [11] have been detected by magnifying endoscopic examinations. Otsuka et al. [12] reported the usefulness of the finding of caliber variation for invasion depth diagnosis of gastric cancer.

In patients with colon cancer, the following are observed in sub mucosal invasive cancer by conventional endoscopy: expansion appearance, disappearance of segmental sulcus, endoscopic hardness, irregularity of surface structure, deep redness, trapezoidal elevation, presence of depressed plaque, protrusion/nodule in depressed lesion, and convergence of fold/deformity. In pedunculated cancers, enlargement of a peduncle or white spots in the normal mucosa of the base of a peduncle are also endoscopic findings for the suspicion of sub mucosal cancer. In addition, it was reported that the presence of long, irregular vessels or the presence of type C3 vessels (irregularly dilated blood vessels) as well as surface pit patterns are magnifying endoscopic findings indicating the advanced invasion of sub mucosal cancer or frequent vascular invasion [16]. Although these reports suggested that the blood vessels in sub mucosal tumors were tumor vessels, there is no way to prove that they were tumor-specific vessels. However, these findings as indicators for judgment of sub mucosal cancer are useful because they enable invasion depth diagnosis without special tools.

Barrett's esophageal adenocarcinoma occurs in few patients, and the characteristic findings of sub mucosal cancer have not been clarified in Japan. In addition, there has been no report on a study of invasion depth diagnosis of S-BEA by magnifying endoscopy. The diagnosis of disease range by NBI [17-19] or acetic acid [20] was reported but it has not been clarified what findings obtained by these methods contribute to invasion depth diagnosis. In the present study, LV was observed in 88.2% of patients with sub mucosal cancer, although the accuracy rate of conventional endoscopy for sub mucosal cancer was only

59%. Therefore, it is considered that the appearance of LV may be a plausible finding indicating sub mucosal cancer. It is difficult to obtain objective indicators for a correct diagnosis by conventional endoscopy because conventional endoscopy cannot always give clear findings on invasion depth and its findings are often judged empirically. Regarding EUS, it is sometimes difficult to obtain appropriate images for diagnosis, especially in patients with SSBE, which is affected by peristalsis. Compared with these methods, the appearance of LV is considered to be useful as a non-empirical objective indicator of sub mucosal cancer.

Conclusion

Depth diagnosis of Barrett's esophageal adenocarcinoma is difficult using conventional endoscopy and EUS. LV findings using ME-NBI were clinically available to distinguish between mucosal and submucosal cancer.

Acknowledgement

Institutional review board statement: This study was performed in accordance with the Declaration of Helsinki and approved by our Institutional Review Board (Registry number: 2015-1179).

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