Original Article

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Flexible Spectral Imaging Color Enhancement (FICE) for the Detection of Early Esophageal Neoplasm in Patients with History of ENT Related Squamous Cell Cancers

Thienchanachaiya P[1]
Rerknimitr R[1]
Wisedopas N[2]
Pittayanon R[1]
Tangjaturonrasme N[3]
Kullavanijaya P[1]

ABSTRACT

Background: Esophageal squamous cell carcinoma (ESCC) is one of important leading cancers in Asia. In symptomatic patients, majority are detected at advanced stages because of the lack of an appropriate surveillance protocol. Therefore, performing a surveillance endoscopy in high risk population such as patients with a history of ENT related squamous cell carcinoma (SCC) may be appropriate. Flexible Spectral Imaging Color Enhancement (FICE) has been reported to increase the detection rate of subtle vascular-pattern changes in many other GI neoplasms, however only a few reports of early ESCC detection by FICE are available.

Objective: To evaluate the sensitivity and detection rate of white light endoscopy (WLE) and WLE plus FICE for the detection of early ESCC and high grade intraepithelial neoplasia (HGIN) in previous history of ENT related SCC patients.

Methods: Between October 2011 and February 2013 at the King Chulalongkorn Memorial Hospital, Bangkok, Thailand, 77 patients with previous ENT related SCC underwent a surveillance EGD by WLE, followed by a dual mode of WLE and FICE endoscopy. Approximately, seventy percent of the patients were previous or current smokers. Demarcated red, elevated or depressed or irregular lesions detected by WLE plus mucosal color changing and dilated with irregularity of intraepithelial papillary loops (IPCLs) were interpreted as possible esophageal neoplastic lesions. Magnifying endoscopy (x50 and x100) under both WLE and FICE were used to further characterize lesions. Esophageal biopsy was performed from all suspicious areas and histopathology results were referred as our gold standard for ESCC diagnosis. In every patient, one control biopsy was taken from WLE and FICE negative area preferably mid esophagus.

Results: There were 61 men and 16 women with a mean age of 56 years (28-74 years). The mean interval time from the diagnosis of ENT related SCC to this surveillance was 55 months (8-234 months). The mean durations for WLE and dual WLE /FICE examinations were 3 minutes and 10 minutes, respectively. There were 5 abnormal lesions detected in 4 patients. Of those, the histological readings showed three ESCCs and two HGINs. FICE was able to detect all 5 lesions whereas WLE missed one early ESCC. The sensitivity for the detection of ESCC and HGIN by WLE was lower than that of dual WLE/FICE (60% vs 100%). The overall prevalence of early ESCC and high grade dysplasia in patients with previous history of ENT related SCC undergoing for endoscopic surveillance in this study was 5.2%.

Conclusion: A surveillance program for early ESCC and HGD in patients with history of ENT related SCC is justified. FICE with magnification can increase the number of positive detection.

Key words : Esophageal squamous cell carcinoma, white light endoscopy, flexible spectral imaging color enhancement, surveillance.

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[1]*Gastroenterology Unit, Department of Internal Medicine,* [2]*Department of Pathology,* [3]*Department of Otolaryngology, Chulalongkorn University, Bangkok 10330, Thailand.*

Address for Correspondence: *Rapat Pittayanon, M.D., Gastroenterology Unit, Department of Internal Medicine, Chulalongkorn University, Bangkok 10330, Thailand.*

INTRODUCTION

Esophageal squamous cell cancer (ESCC) is an important leading cause of cancer-related mortality in Asia[1]. The majority of cases are detected at advanced stages with overall 5-year survival rates of only 10-15%[2]. This poor prognosis can be ascribed to ineffective screening tools and inappropriate surveillance protocol. The sensitivity of conventional endoscopy with a WLE is suboptimal for the detection of ESCC (62.9% compare with NBI[3]). To date, chromoendo-scopy with lugol's solution seems to be the most sensitive technique to detect ESCC[4]. Unfortunately, the lugol's solution leads to mucosal irritation[5] and may increase risk of aspiration[6]. Therefore, this practice has not been popularly adopted worldwide. Recently, a high resolution magnifying digital chromoendoscopy (DC) such as narrow band imaging (NBI) and Flexible Spectral Imaging Color Enhancement (FICE) has been developed. NBI seems to be useful for screening ESCC from preliminary data[3,4,7]. However, only handful reports of early ESCC detection by FICE are available[8,9].

The theory of field cancerization proposed by Slaughter et al. in 1953, they described the development of multiple and independent cancers resulting from the accumulation of genetic alterations in response to repeated exposure to carcinogens[10]. The main predisposing factors for the development of aerodigestive squamous cell cancers including ESCC and ENT related squamous cell cancers (ENT related SCC) are tobacco and alcohol consumption. A recent study in patients with previous ENT related SCC showed that ESCC can appear as synchronous or metachronous tumors with significant prevalence at 9.1% to 22.6%[4]. Therefore, performing a surveillance endoscopy in these high risk populations may be justified.

Carcinogenesis results a dynamic process of tumoral vascularization in which dilated, or irregular tumoral vessels replace normal capillaries[11]. In the esophagus this normal capillaries is named as intrapapillary capillary loops (IPCLs). The recent consensus from Asia-Pacific region supported the role of NBI for the diagnosis of early ESCC by using the criteria as dilatation and caliber change of IPCLs[12]. FICE is a system of DC that reconstructed images by selection only specific wavelengths and this in turn can improve mucosal enhancement in real time. FICE has 10 channels designed to explore entire mucosal surface of different structures and vessels[13]. FICE has been reported to increase the detection rate of subtle vascular-pattern changes in other gastrointestinal neoplasm[13], but the role of FICE in screening of ESCC remains to be determined.

The primary objective of this study was to evaluate the sensitivity of WLE and dual WLE/FICE for the detection of early esophageal neoplasm in patients with previous ENT related SCC. The secondary objective of FICE examination was to characterize the lesions by distinquishing betweeen ESCC and high-grade intraepithelial neoplasia (HGIN). Based on revised Vienna consensus[14], we used the histological diagnosis from mappeds pecimens as the gold standard.

PATIENTS AND METHODS

Study Populations

The protocol and consent form were approved by the Research Ethics Committee of Chulalongkorn University and written informed consent was obtained from all patients. We prospectively recruited patients from October 2011 to February 2013 at the King Chulalongkorn Memorial Hospital, Bangkok, Thailand. The inclusion criteria were patients with previous histologically confirmed ENT related SCC with age of 20 years or older. Patients with prior esophagectomy were excluded. Patients with esophageal obstruction, stricture, esophageal varices, bleeding diatheses or pregnancy were also excluded.

Endoscopic Examination

All patients were fasted for at least six hours before the procedure. To numb the pharyngeal mucosa, two puffs of 10% lidocaine (AstraZeneca, Sweden) were sprayed over. Endoscopy was performed under conscious sedation with intravenous midazolam 2.5 milligrams and meperidine 25-50 milligrams. To decrease esophageal peristalsis, we gave 10 milligrams of hyoscine (Vesco Pharmaceutical, Bangkok) to all patients for decreasing esophageal movement and obtaining the satisfied visualization. Then, the patients were placed in the left lateral decubitus for endoscopy. All patients had their pulse oximetry and blood pressure monitored.

All procedures were performed by two endoscopists (P.T. and R.P.) by using a magnifying endoscope with a high-definition processor (EPX-4450; Fujinon Fujifilm Co., Japan). A transparent soft cap

was inserted at the tip of an endoscope (Fujinon Fujifilm Co., Japan). A careful esophageal examination was performed in a single session. A sequential method starting from WLE followed by a dual WLE/FICE was carried out. Two FICE stations [station 0 (red 525 nm, green 495 nm, blue 455 nm) and station 2 (red 550 nm, green 500 nm, blue 470 nm] and two magnifications (x50 and x100) were chosen (Figure 1). Initially, we noted all abnormalities depicted by WLE such as redness, raised or depressed lesions. Subsequently, a dual WLE/FICE display was used to further depict more lesions that unseen by WLE. All abnormalities including subtle mucosal irregularities or changes of the vascular pattern at the suspicious areas were further characterized by magnifying FICE.

Demarcated red or elevated or depressed or irregular mucosal lesions under WLE were interpreted as possible neoplastic lesions under WLE[3] (Figure 2). Moreover, color changing esophageal mucosal lesion under FICE without magnification and dilatation, irregularity of IPCLs under FICE with magnification x50 or x100 were also interpreted as possible neoplastic lesions under FICE[12] (Figure 3).

All suspicious lesions for neoplasia were noted

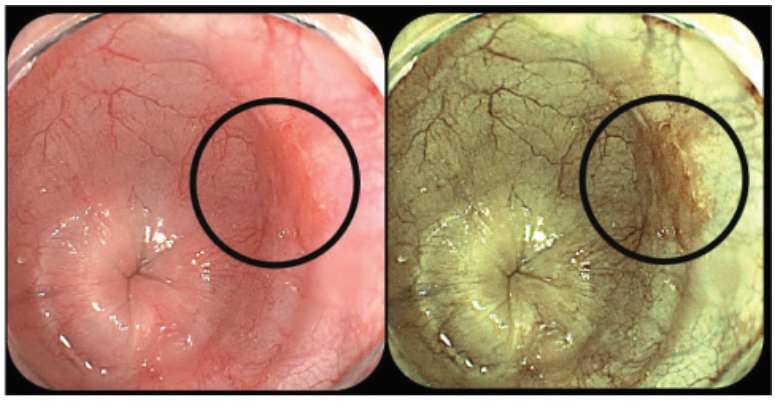

Figure 1. Demonstration dual mode of WLE and FICE can display two pictures simultaneously.

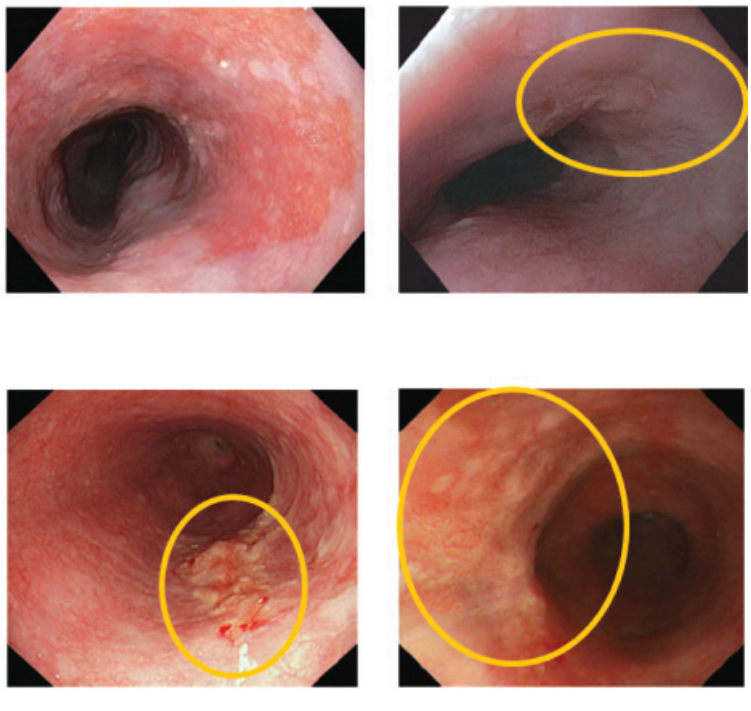

Figure 2. Demonstration diagnostic criteria of neoplastic lesions under WLE.

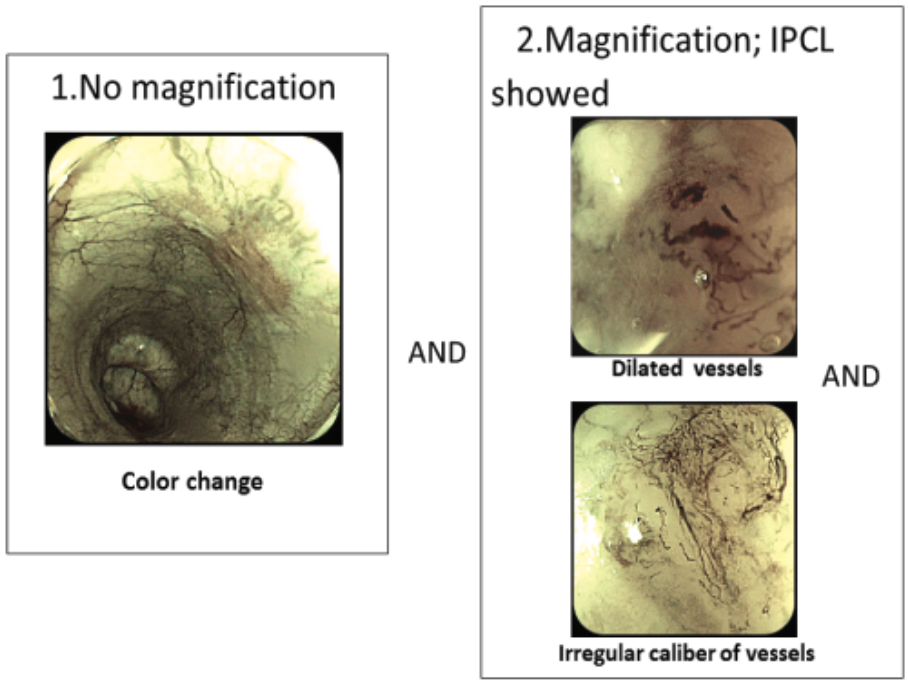

Figure 3. Demonstration diagnostic criteria of neoplastic lesions under FICE.

for the location, distance from the patient's incisor teeth and size of each lesion, and all were recorded as snap shots and VDOs.

Esophageal biopsy was performed from each suspicious area for at least one specimen. Histopathology result was referred as our gold standard for the definite diagnosis. In every patient, a control biopsy was taken from WLE and FICE negative area in mid esophagus at 30 centimeters insertion depth from the incisor teeth (frequent location for ESCC). All specimens were evaluated by a single experienced pathologist (N.W.), who was blinded to the clinical backgrounds of the patients. Histology diagnoses were made accordingly based on the following five categories of the revised Vienna classification[14]; 1) invasive SCC, 2) HGIN, 3) low-grade intraepithelial neoplasia (LGIN), 4) indefinite for neoplasia and 5) negative for neoplasia. All details of the lesions read by FICE including mucosal color change, dilatation, and irregularity of IPCL were noted and further analyzed.

Statistical analysis

The sample size was calculated for the sensitivity as the diagnostic test that estimated for at least 80%. Ninety-five percent confidence intervals (95% CIs) and total width of the confidence interval (CI) of 0.10 were calculated for this estimation. The approximate prevalence of ESCC in previous ENT related SCC patients were 10 percent. Therefore, the estimated sample size for this study was 154 patients. By using histological reading as the gold standard, the sensitivity, specificity, and accuracy of dual WLE/FICE vs. WLE were compared. By using McNemar's test, the *p*-values < 0.05 were considered to be statistically significant.

The result were presented as mean and SD for continuous variables and as proportions or percent for categorical variables. Data were analyzed using a statistical software package (SPSS version 17; SPSS Inc., Chicago, IL).

RESULTS

Seventy-seven patients with previous ENT related SCC (laryngeal cancer; n=7, hypopharyngeal cancer; n=10, tongue cancer; n=19, oropharyngeal cancer; n=2, epiglottic cancer; n=1, and nasopharyngeal carcinoma; n=38) were recruited and underwent a surveillance EGD by WLE and dual WLE/FICE. There were 61 men and 16 women with a mean age of 56 years (28-74 years). Approximately, 70 % of the patients (51 from 77) were previously or currently a smoker and 70% of the patients (56 from 77) had a history of significant alcohol consumptions. Only 4% (3 from 77) had history of betel-nut chewing. Of those 77 patients, 21% (16 from 77) had dysphagia while undergoing this surveillance EGD. All baseline characteristics are sum-

marized in Table 1. The mean interval time from the diagnosis of ENT related SCC to this endoscopic surveillance was 55 months (8-234 months).

The mean duration of endoscopy, including biopsy of esophageal lesions was 20 minutes and the mean duration of WLE and dual WLE/FICE were 3 minutes and 10 minutes, respectively. None of the patients develop allergic reaction to the medications used during the procedure, and no complications occurred during or after the procedures.

During endoscopy, there were 8 abnormal lesions detected in 8 patients using WLE. The endoscopic characters of these 2 abnormal lesions (Figure 4) were slight elevation with slight central deperession (IIa+c, according to the Paris classification[15]) and irregularity of esophageal mucosa by WLE and the histological report confirmed ESCC. Another abnormal lesion showed only well-demarcated red mucosal lesion (IIb, Figure 5) in which the histology revealed HGIN. Dual WLE/FICE mode showed a better delineation of lesions in which demonstrated best under magnifying FICE (Figure 6). Five suspicious well-demarcated red lesions were depicted by WLE, however, magnifying FICE characterized them as normal mucosal and vascular pattern compatible with benign lesion (Figure 7). The final pathologies of these lesion were esophagitis (n=4) and inlet patch (n=1). Another 2 lesions were missed by standard WLE whereas dual WLE/FICE was able to depict color changing and magnifying FICE (x50 and x100) further characterized the lesions by showing dilated and irregularity of IPCL. The histologies confirmed these 2 lesions as HGIN and ESCC, respectively. In total, 3 lesions from different patients were diagnosed as ESCC and the other 2 lesions were HGIN. All 77 control lesions contained no neoplastic cell or inflammation (Figure 8).

Table 1. Clinical features of 77 patients with ENT related SCC.

Mean age (years) (range)	56.6 (28-74)
Male/female (%)	61/16 (79.2/20.8)
Primary cancer site, n (%)	
Larynx	7 (9.1)
Hypopharynx	10 (13)
Tongue	19 (24.7)
Oral cavity	2 (2.6)
Nasopharynx	38 (49.4)
Other	1 (1.3)
Predisposing factors, n (%)	
Tobacco	51 (66.2)
Alcohol	56 (72.7)
Betel-nut chewing	3 (3.9)
Dysphagia, n (%)	16 (20.8)

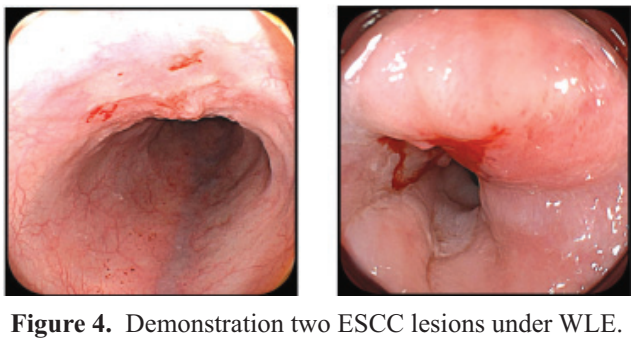

Figure 4. Demonstration two ESCC lesions under WLE.

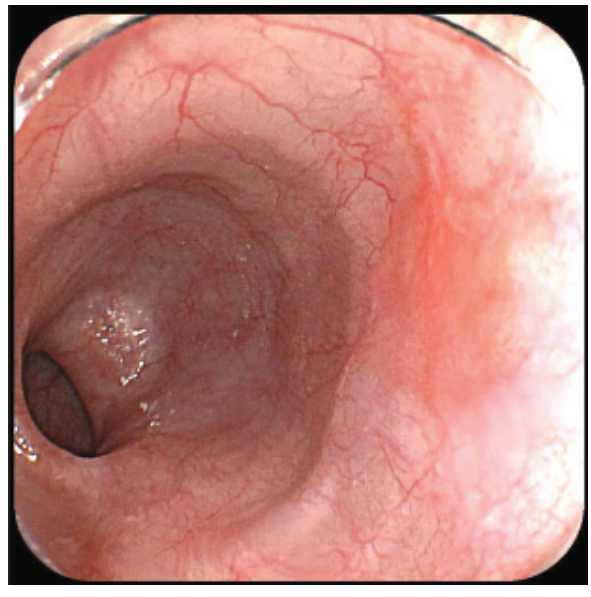

Figure 5. Demonstration the HGIN lesion under WLE.

The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of WLE versus WLE plus FICE for ESCC and HGIN detection by using histological assessment as the gold standard were 60% vs. 100%, 93.9% vs. 98.8%, 37.5% vs. 83.8%, 97.5% vs. 100%, and 92% vs. 99%, respectively (Table 2). The inter-observer agreement (Kappa) of WLE and FICE images interpretation by experienced endoscopists is almost perfect agreement (1.0 and 0.89).

Furthermore, in all 4 patients who diagnosed ESCC or HGIN from this study were changed treatment plans after esophageal neoplasia were detected. All 4 patients with detected with a new esophageal neoplasm demographic data, endoscopic findings, histology and treatment offered are shown in Table 3.

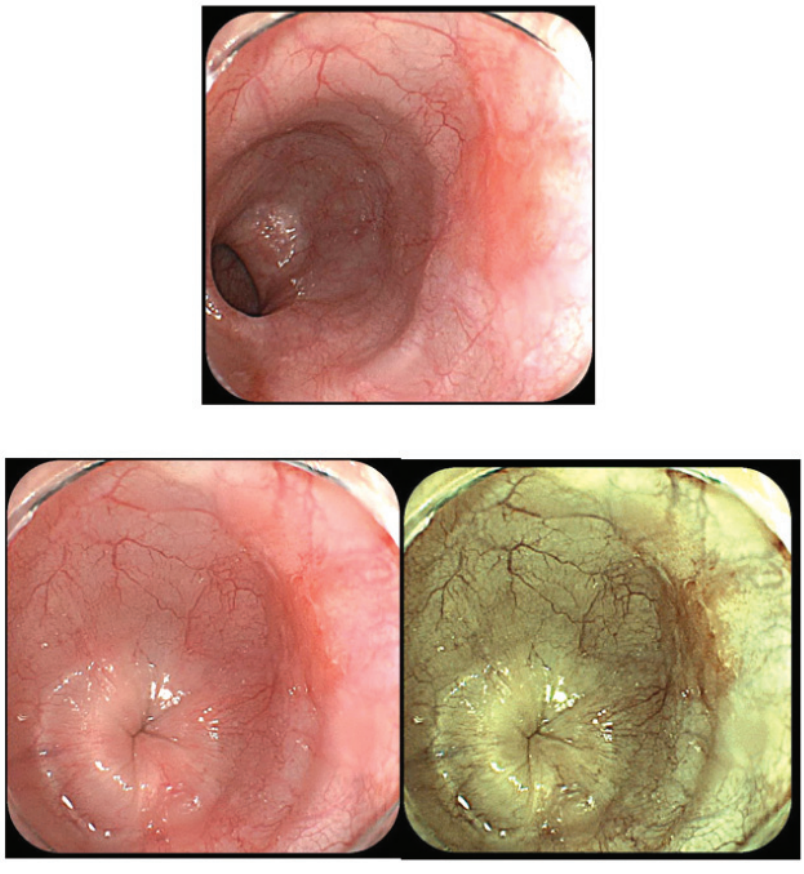

Figure 6. Demonstration one HGIN lesion under WLE and dual WLE/FICE.

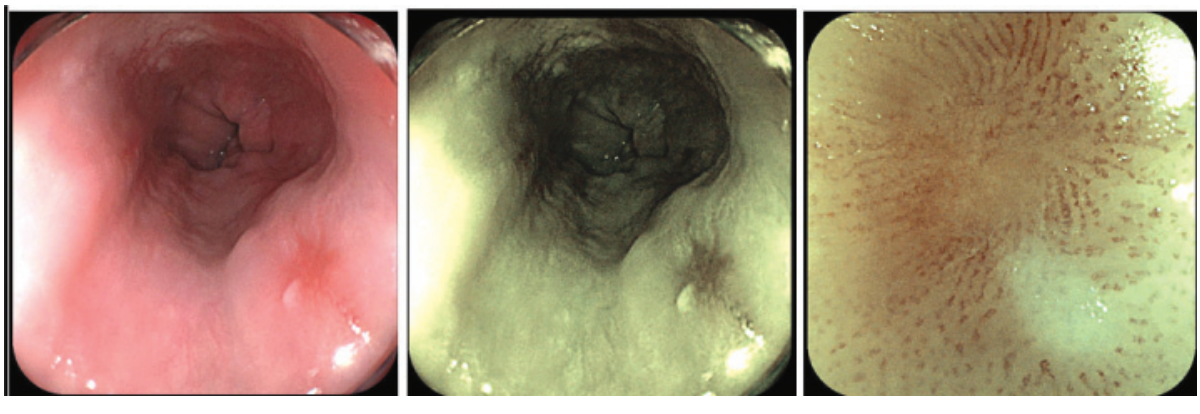

Figure 7. Demonstration benign lesion under WLE and dual WLE/FICE with magnification (100x).

The clinical background and pathological features of the patients who were diagnosed as ESCC or HGIN are summarized in Table 4. Patients diagnosed HGIN and ESCC were evaluated to locoregional staging by computed tomography and/or endoscopic ultrasound. The 3 lesions from 2 patients were classified as HGIN and superficial ESCC and undergo endoscopic mucosal resection (EMR). The other 2 lesions were diagnosed advanced ESCC and these patients were referred to oncologic management with chemo-radiation therapy.

WLE plus FICE can detect all 5 lesions which are diagnosed ESCC or HGIN whereas WLE alone miss two lesions. Therefore the detection rate of ESCC and HGIN was 5.2% in patients with history of ENT related SCC. In our study the interval time from the diagnosis of ENT related SCC to this surveillance is 8-18 months, hence all 4 patients diagnosed metachronous second primary esophageal neoplasia.

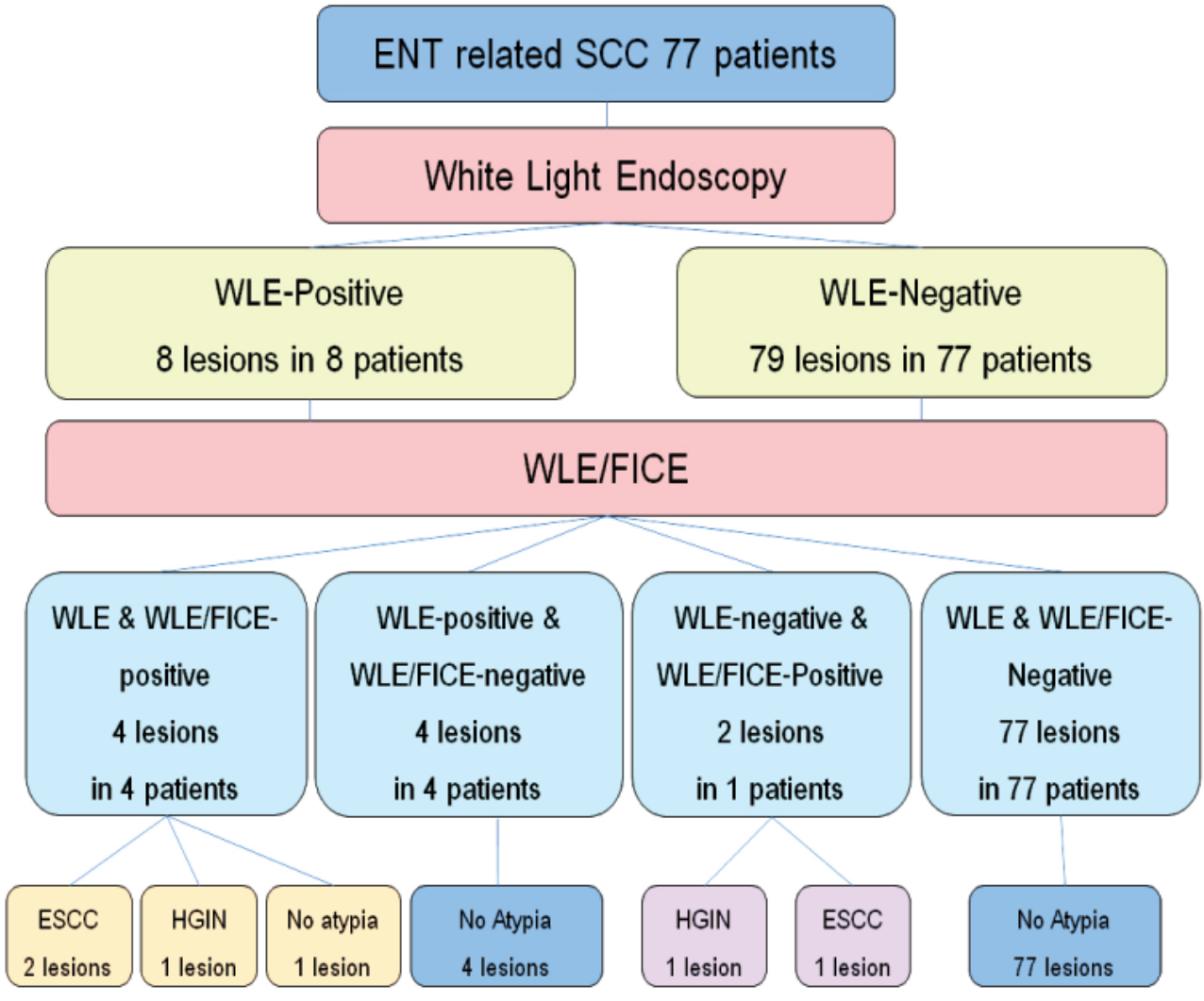

Figure 8. Flowchart of enrolled patients screened by WLE, followed by FICE and results of endoscopic examination and histopathological diagnosis. SCC, squamous cell carcinoma; WLE, white light endoscopy; FICE, flexible spectral imaging color enhancement; ESCC, esophageal squamous cell carcinoma; HGIN, high grade intraepithelial neoplasia.

Table 2. Screening performance of WLE vs FICE for diagnosis of ESCC and HGIN.

Index	WLE	WLE + FICE
Sensitivity (%)	60	100
Specificity (%)	93.9	98.8
PPV (%)	37.5	83.3
NPV (%)	97.5	100
Accuracy (%)	92	99

PPV, positive predictive value; NPV negative predictive value; WLE, white light endoscopy; FICE, flexible spectral imaging color enhancement; ESCC, esophageal squamous cell carcinoma; HGIN, high grade intraepithelial neoplasia.

Discussion

Currently, FICE is one of the novel image enhanced system that provides a clear visualization of the superficial structure and can enhance the vasculature of GI mucosal layer hence it is an interesting platform to detect early mucosal related neoplasm. To date, only a handful of reports on FICE for squamous cell esophageal neoplasm detection[8,9]. We conducted a pilot study comparing WLE and dual WLE/FICE to detect early ESCC and esophageal HGIN. Our results showed the superiority of dual WLE/FICE over WLE

Table 3. Clinical and pathological features of 4 patients diagnosed as ESCC or HGIN.

No.	Age (yrs) /Sex	Primary cancer site	Tumor Diagnosis	Location	WLE detection	FICE detection	Histology	Treatment
1	67/M	Tongue	Inflitrative neoplasia	Upper	Yes	Yes	ESCC	Chemo-radiation
2	61/M	Tongue	Flat lesion	Middle	Yes	Yes	HGIN	EMR
3	65/F	Oral cavity	Flat lesion	Middle	No	Yes	HGIN and ESCC	EMR
4	58/M	Epiglottis	Inflitrative neoplasia	Middle	Yes	Yes	ESCC	Chemo-radiation

M, male; F, female; WLE, white light endoscopy; FICE, flexible spectral imaging color enhancement; ESCC, esophageal squamous cell carcinoma; HGIN, high grade intraepithelial neoplasia; EMR, endoscopic mucosal resection.

alone for the detection of early ESCC and HGIN in patients with history of ENT related SCC. Therefore our study emphasized the benefit of FICE in ESCC and esophageal HGIN detection. These data correspond to the previous ENT study by Arantes V, et al[9]. They applied transnasal endoscopy with FICE system in unsedated patients with head and neck squamous cell cancer (HNSCC) and showed the sensitivity, specificity, and overall accuracy of WLE versus FICE for ESCC were 92.3% vs. 100%, 98.9% vs. 98.9%, and 98.1% vs.99%, respectively. Lee CT, et al. evaluated the feasibility of primary screening with NBI and magnification(NBI-ME) for the presence of esophageal malignancies in patients with head and neck cancers and showed the sensitivity and accuracy of WLE versus NBI-ME for esophageal neoplasia were 62.9 % vs. 100% and 64.4 % vs. 95.6%, respectively[3]. Compared with this NBI-ME study, dual WLE/FICE in our study also had an advantage to increase sensitivity and accuracy from WLE for detection esophageal neoplasia.

Color changing areas detected by nonmagnified dual WLE/FICE was useful to identify suspicious neoplastic lesions. However, they may represent benign pathologies such as erosive changes of the mucosa and may cause false-positive results to be obtained. Using high magnification after detection of suspicious lesion might clarify pathologies with character of IPCLs. In our study, when magnified dual WLE/FICE is compared with nonmagnified dual WLE/FICE, the gain in accuracy increase and up to 40% of nonmagnified dual WLE/FICE-suspected neoplastic lesions (4/10) characterized to be benign in nature, which may demonstrate the better performance provided by magnified dual WLE/FICE.

This study has some limitations. First, it is only a pilot study so the number of patients in the current study is too small. Second, some learning curve is required before the endoscopist can attain the standard skill and competency for the detection of esophageal neoplasm by this new the technique. Third lugol based chromoendoscopy was not used as another control technique; therefore we cannot compare the clinical benefit of FICE to the standard lugol based reading. Lastly, with the sequential design for WLE followed by dual WLE/FICE, the performing endoscopist might be biased to the readings by dual WLE/FICE since she already knew the reading results by WLE already.

In conclusion, a surveillance program for early ESCC and HGIN in patients with history of ENT related SCC is justified. FICE with magnification may increase the number of positive detection and it is also useful to further characterize the lesion.

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