Effectiveness of Unsedated Transnasal Endoscopy With White-light, Flexible Spectral Imaging Color Enhancement, and Lugol Staining for Esophageal Cancer Screening in High-risk Patients

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Background and Aims: Transnasal endoscopy (TNE) has been proposed to screen for esophageal squamous cell cancer (ESCC) in Asia. This study aimed to assess the feasibility and tolerance of Brazilian patients to undergo unsedated TNE for screening, the prevalence of ESCC in this population, and the effectiveness of white-light endoscopy (WLE) and digital chromoendoscopy [flexible spectral imaging color enhancement (FICE)] to diagnose esophageal neoplasia.

Patients and Methods: This was a diagnostic test study that enrolled patients with head and neck squamous cell cancer (HNSCC) referred to ESCC screening. Patients' tolerance was rated by a numeric pain intensity scale. Interventions included unsedated TNE with WLE and FICE examination of the esophagus, in a tandem manner with blinded operators, followed by lugol chromoscopy. Performance of WLE and FICE for neoplasia detection was compared with the reference standard (lugol chromoscopy plus histology).

Results: A total of 106 patients were recruited. TNE was feasible in 99.1%, and 92% of the patients rated the discomfort as absent or minimal. Thirteen ESCC were detected (12.3%), with 10 early cancers (77%). The tests showed an excellent performance and there was no difference between WLE (sensitivity 92.3%, specificity 98.9%, accuracy 98.1%, area under curve 0.995) and FICE (sensitivity 100%, specificity 98.9%, accuracy 99%, area under curve 0.956) for esophageal neoplasia detection.

Conclusions: Unsedated TNE is a feasible, well accepted, and efficient diagnostic tool for the screening of ESCC. The elevated rate of esophageal neoplasia strengthens the recommendations to screen patients with HNSCC. The yields of WLE and FICE were similar for ESCC detection.

Key Words: esophageal squamous cell cancer, transnasal endoscopy, screening, FICE, lugol chromoscopy, head and neck tumors, esophageal cancer

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Esophageal cancer is detected at an advanced stage precluding curative treatment in most patients.[1] Alcohol and tobacco consumption are the main predisposing factors for the development of aerodigestive squamous cell cancer type, according to the theory of field cancerization.[2–4] In addition, recent epidemiological studies have indicated a possible carcinogenetic relationship between human papilloma virus infection and oropharingeal[5] and esophageal cancer,[6] at least in regions with a high incidence of esophageal carcinoma, such as certain Chinese geographic areas.[6,7] The most relevant factor associated with the occurrence of esophageal squamous cell cancer (ESCC) is the history of primary head and neck squamous cell cancer (HNSCC).[8] In these patients, the prevalence of synchronous or metachronous ESCC ranges from 9.1% to 22.6%, according to a compilation of series reviewed by Lee et al.[9] Esophagogastroduodenoscopy (EGD) with lugol staining is the best screening tool for ESCC.[8,10–12] However, lugol staining adds time and costs, and may cause adverse events.[8] Recently, new methods of digital chromoendoscopy such as narrow band imaging (NBI) and flexible spectral imaging color enhancement (FICE) have been developed. Preliminary data have suggested that NBI is beneficial for screening esophageal tumors.[9,13–16] In contrast, the role and effectiveness of FICE chromoendoscopy in the screening of ESCC remains to be determined.

EGD under sedation is the standard approach for endoscopic routine procedures.[17] Moreover, the use of deep sedation with propofol or even anesthesia sedation has gained popularity,[18] an approach that probably increases costs and also raises safety concerns. Transnasal endoscopy (TNE) with ultrathin endoscopes has been proposed by Shaker,[19] but has gained acceptance only in certain countries, such as Japan and France.[20] Using the nasopharynx to access the upper gastrointestinal tract, and sparing the sensitive terminations at the tongue, TNE causes less sensation of nausea and gagging episodes. Therefore, it can be undertaken with minimal discomfort without sedation, which minimizes risks and costs.[20]A new generation of ultrathin endoscopes have been developed with high-resolution images, digital chromoendoscopy capability, and improved maneuverability with functions similar to a standard gastroscope.

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This study followed the rules and recommendations of the Helsinque Declaration.
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In 2009, we initiated at our Institution a program for ESCC screening by means of unsedated TNE with chromoendoscopy in patients with HNSCC. The objectives of this study were: (1) to assess the clinical effectiveness of TNE with white-light endoscopy (WLE), FICE, and lugol staining in patients with HNSCC to screen for ESCC; (2) to assess the feasibility and the acceptance of Brazilian patients to undergo unsedated TNE; (3) to assess the prevalence of esophageal neoplastic lesions in our population; and (4) to determine and compare the performance of WLE and FICE for esophageal cancer detection.

PATIENTS AND METHODS

The investigation and consent form was approved by the Research Ethics Committee of the Federal University of Minas Gerais. This is a diagnostic test study conducted in an academic hospital that enrolled adult patients according to the following inclusion criteria: (1) current or a history of primary HNSCC under treatment or surveillance; (2) absence of distant metastasis or treatment failure of the primary cancer; (3) absence of esophageal symptoms such as dysphagia; (4) agreement to participate in the study with a signed informed consent. Patients with previous nasal surgery, coagulopathy, iodine allergy, thyroid dysfunction, esophagitis, prior esophageal cancer or resection, or using nasogastric feeding tubes were excluded. Patients were interrogated about the duration and the quantity of alcohol and tobacco consumption, and were considered smokers if they consumed >15 packages-years and alcohol abusers if they ingested >80 g of ethanol per day. Patients' enrollment started in June 2009 and finished in May 2011.

TNE Procedures

TNE was performed without sedation with an ultrathin endoscope (EG-530N; Fujinon Fujifilm Co., Japan) that has 5.9 mm of diameter in the distal end, an operating length of 1100 mm, and a 2.0-mm working channel that enables the introduction of catheters for chromoscopy and forceps for biopsies. This slim endoscope has a high-resolution charge-coupled device with 410K pixels, and the image is processed through high-definition processor platforms (EPX-4400). Preparation for the procedure consisted of nasal application of vasoconstrictors (naphazolin) and 2% lidocaine jelly and pharyngeal anesthesia with 10% lidocaine spray. Dimethicone solution (60 mL) was ingested before the procedure, and all patients had their pulse oximetry and electrocardiogram monitored. A water pump infusion (JW2; Fujinon Fujifilm Co.) was connected to the biopsy channel of the endoscope and the esophagus was insistently washed until complete removal of mucus and secretions was achieved.

In a single session, all patients underwent a complete EGD and a meticulous esophageal examination. Esophagoscopy was carried out in a tandem manner (back-to-back), by 2 experienced endoscopists (V.N.A. and W.A.), following the sequence white-light, FICE, and lugol chromoscopy. Both operators have extensive experience in the recognition and management of early neoplastic lesions and were previously trained in FICE and chromoendoscopy in Japan. The endoscopists were randomly allocated by opening sealed envelopes before the procedure. The first operator carried out WLE. The second endoscopist, blinded to the initial findings, performed the esophageal inspection exclusively with FICE. Afterward, both operators joined for lugol chromoscopy and interpretation of the findings. FICE is a modality of digital chromoendoscopy that uses spectral estimation technology[21] and proportionate 10 different combinations of filtered RGB wavelengths' signaling. The original FICE settings from the manufacturer were adopted for esophageal inspection with 2 different combinations of wavelength parameters: (1) red 550 nm, green 500 nm, blue 470 nm and (2) red 550 nm, green 500 nm, blue 400 nm.

TNE was performed as described previously.[22] Patients were examined when fully awake, positioned in the left lateral decubitus. The most patent narine was selected for intubation. The endoscope was introduced into the nasal cavity either along the inferior meatus or between the middle and the inferior turbinate. If the chosen nasal cavity failed to permit smooth passage of the endoscope, the other cavity was attempted. When the passage of the slim endoscope was not possible through both nasal cavities, TNE was considered failed, and the approach was switched to oral EGD. Once the nasal introduction was successful, the endoscope was advanced into the nasopharynx in the direction of the oropharynx, epiglottis, and piriform sinus. The endoscope was then gently negotiated through the upper esophageal sphincter to access the esophagus. A complete EGD up to the second portion of the duodenum was always attempted. Then, a focused examination of the esophagus was performed. The entire length of the esophagus was evaluated thoroughly after vigorous washing and removal of mucus and secretions, with special attention given to the identification of subtle mucosal irregularities or abnormalities of the vascular pattern. Afterward, a 2-mm catheter was inserted and 10 to 15 mL of 0.8% lugol was instilled uniformly over the entire esophagus. The findings after staining with lugol were analyzed by the 2 attending endoscopists, who reached a consensual agreement about the existence (or not) of a neoplastic lesion. The duration of the examination and the postprocedure questionnaire were registered by separate investigators (C.A.F.D. and L.R.A.). Abnormal esophageal mucosal lesions or irregularities suspicious for neoplasia were recorded regarding the distance from the patient's nostrils and size. Static photos of the abnormalities were taken and pediatric forceps were used for sampling. Specimens were processed and embedded in paraffin, and stained with hematoxylin and eosin. Histologic assessment was performed by senior gastrointestinal pathologists blinded to the endoscopic findings. Adverse reactions were documented and managed according to standard of care.

Assessment of Patient Tolerance

Patient tolerance was noted by the attending endoscopists and rated as poor, fair, good, and excellent.[23] After TNE, patients were observed in the recovery room for 30 minutes, and then, were interrogated about pain or discomfort sensation applying a previously used numeric pain intensity scale.[24] The sensation of pain and discomfort were quantified on a 10-mm scale (where "0" represented no discomfort/well tolerated and "10" corresponded to extreme discomfort/poorly tolerated). The results of the pain scale were distributed in the following manner: 0 absent; 1 to 2 minimal; 3 to 7 moderate; 8 to 10 intense. Patients were also questioned about their willingness to

undergo TNE again. Those patients with a previous experience with peroral EGD were asked to compare the sensation of discomfort between TNE and EGD, and if they would prefer to undergo a repeat endoscopic procedure through the oral or the nasal approach.

Definitions

The following definitions were used:

- TNE negative for neoplasia: preservation of the integrity of the esophageal mucosa with homogeneous vascular distribution.
- TNE positive for neoplasia: detection of abnormalities such as elevated, depressed, or stenotic lesions, color alteration, nodularity, friability, or interruption of the blood vessels. Macroscopic description of the superficial lesions followed the Paris Classification.[25]

The reference standard adopted to confirm the diagnosis of neoplasia was lugol chromoscopy with the detection of unstained lesions and biopsy confirmation of either high-grade dysplasia or squamous cell cancer. Well-demarcated unstained areas >5 mm, particularly when there was a color change from yellow to pink within 5 minutes (pink color sign),[26,27] were considered positive for neoplasia, and biopsies were taken for confirmation. Lugol-voiding lesions <5 mm or without the pink color sign, even when multiple, were not considered to be neoplastic. Histologic definitions of neoplastic lesions followed the reviewed Vienna consensus.[28]

Statistical Analysis

The primary outcome measures were the feasibility and acceptance of TNE in a Brazilian high-risk population, and the performance and rates of detection of neoplasia through WLE and FICE examination. The sample size was calculated considering the following parameters: sensitivity and specificity for the diagnostic test ranging from 96% to 99%; total width of the confidence interval (CI) of 0.10; and confidence level for this interval of 95%. The estimated sensitivity and specificity were calculated taking into account the initial results observed during the first 12 months of this investigation. Therefore, the estimated sample size for this study was 15 to 59 patients with neoplasia and the same number of patients without neoplasia.

The results were presented as mean and SD for continuous variables and as proportions for categorical variables. Using lugol chromoscopy and histology as the standard criteria, we calculated the sensitivity, specificity, positive and negative predictive values, overall accuracy, the Youden "J" index, and the likelihood ratios for positive or negative results with WLE and FICE. The tests' performances were compared by means of an receiver operating characteristic curve. Statistical analyses were conducted using a statistical software package (SPSS version 17; SPSS Inc., Chicago, IL).

RESULTS

Demographic Data

During 24 months, 115 patients were referred for esophageal cancer screening (Fig. 1). Nine patients were excluded because of nasoenteral tube use (5 cases), esophageal candidiasis (3 cases), and severe erosive esophagitis (1 case). Therefore, 106 patients were included in the study. Table 1 shows the demographic characteristics of the patients, the site of primary HNSCC, and the prevalence of alcohol and tobacco abuse. Most of the patients (68%) had already finalized their oncological and surgical management against the primary tumor, whereas 30% of the patients underwent TNE ahead of starting their oncological therapy.

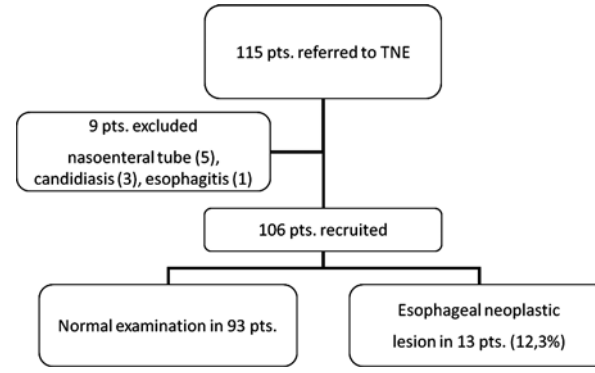

FIGURE 1. Clinical outcome of 115 patients (pts) referred to TNE for esophageal cancer screening. TNE indicates transnasal endoscopy.

Patient Tolerance Assessment

Unsedated TNE was accomplished in 105 patients (99.1%). One individual with narrow nasal cavities had the examination switched to peroral EGD. The examination duration ranged from 10 to 37 minutes (mean, 17 min). Figure 2 demonstrates the assessment of patient's tolerance to TNE according to the endoscopist's evaluation. Figure 3 shows the rate of pain and discomfort sensation reported by the patients according to a pain intensity numeric scale (0 to 10). All patients stated that they would accept to undergo unsedated TNE again if needed in the future. A total of 41 patients (38.7%) informed that they had undergone sedated EGD previously. Considering this group, 12 patients (29.3%) preferred to undergo TNE if needed in the future, 8 (19.5%) had no preference, 17 (41.5%) would rather receive sedated EGD, and 4 (9.7%) declined to answer. There was no episode of epistaxis, nasal trauma, hypoxia, or cardiovascular alteration. Thoracic pain attributed to lugol were reported by 8 patients (7.5%), and successfully managed with analgesics.

Esophageal Cancer Screening Results

Thirteen histologically proven esophageal neoplastic lesions were identified, reaching a detection rate of 12.3%. The histology showed squamous cell cancer in 10 patients and intraepithelial high-grade neoplasia in 3. All neoplastic lesions presented the characteristic color transformation

TABLE 1. Baseline Demographic Characteristics of 106 Patients Subjected to Unsedated Transnasal Endoscopy for Esophageal Cancer Screening

Mean age (y) (range)	60.7 (31-89)
Males/females (%)	86/20 (81/19)
Site of primary head neck neoplasia, n (%)	
Oral cavity	42 (39.6%)
Hypopharynx	24 (22.7%)
Tongue	22 (20.8%)
Larynx	16 (15.1%)
Other	2 (1.9%)
Predisposing factors, n (%)	
Alcohol	87 (82%)
Tobacco	92 (87%)
Alcohol + tobacco	83 (78%)

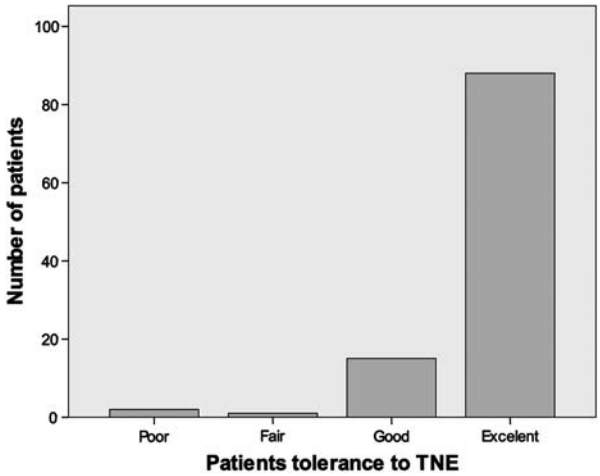

FIGURE 2. Assessment of patients' tolerance to TNE according to the endoscopist's evaluation. TNE indicates transnasal endoscopy.

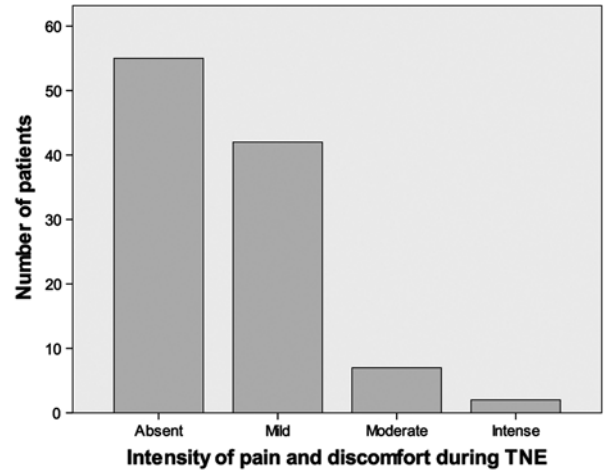

FIGURE 3. Assessment of patients' pain and discomfort sensation according to a pain intensity numeric scale (0 to 10).

from unstained yellow to pink within a few minutes after lugol chromoscopy (pink color sign) as illustrated in Figure 4. FICE examination detected all 13 neoplastic lesions. WLE missed 1 flat (0IIb) dysplastic lesion, measuring 1.5 cm and situated in the distal third of the esophagus (WLE false-negative rate 7.7%). In 5 patients, we observed small well-delineated unstained lesions after lugol application, which went unnoticed on both WLE and FICE evaluations. However, none of these lesions presented the pink color sign and the histologic assessment was negative for neoplasia. There was 1 abnormality depicted only at FICE examination that was primarily considered a flat neoplastic lesion by the examiner. Subsequent lugol chromoscopy demonstrated that this lesion became barely unstained, without the pink color sign and the biopsy was consistent with inflammatory alterations. Therefore, this abnormality was considered as a false-positive result of FICE (false-positive rate 1.1%). Table 2 and Figure 5 show the overall performance of WLE and FICE examinations and the area under the curve for both tests. Both techniques were highly accurate to identify and rule out esophageal neoplastic lesions, and there was no difference between them. We also calculated the tests' performance parameters

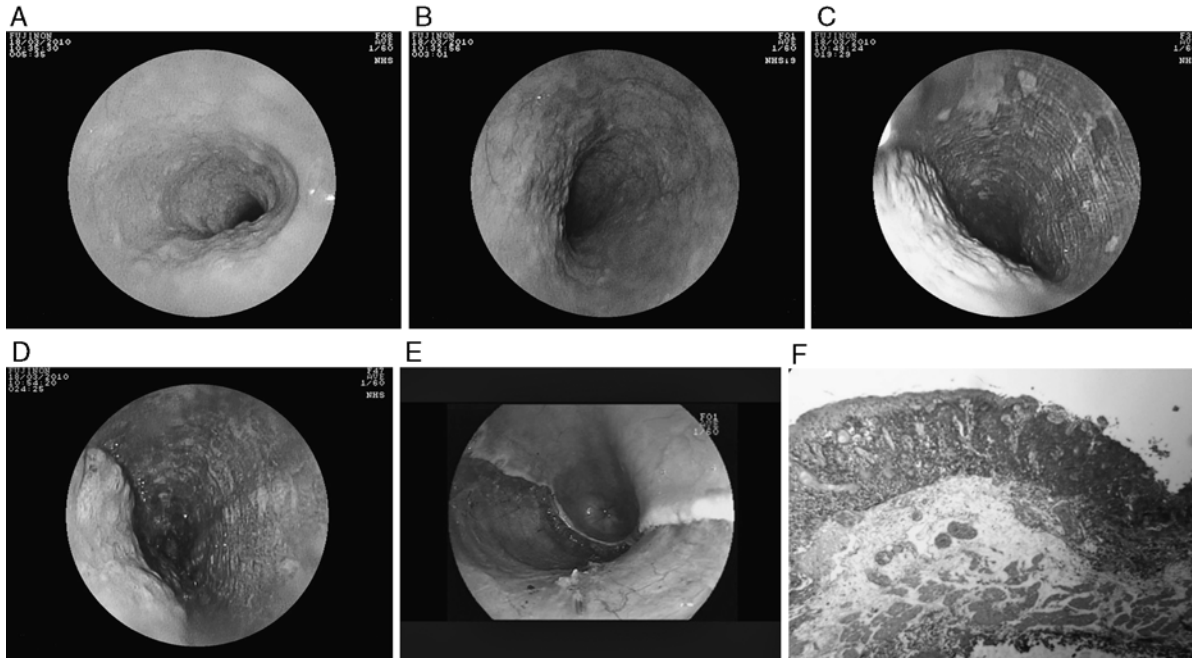

FIGURE 4. Esophageal superficial neoplasia type 0IIA detected on transnasal endoscopy. A, White-light endoscopy. B, Flexible spectral imaging color enhancement. C, Lugol chromoscopy—unstained lesion. D, Lugol chromoscopy—typical "pink color sign" after 5 minutes. E, Complete en bloc resection by endoscopic submucosal dissection. F, Histology of the specimen stained with hematoxylin-eosin shows squamous cell carcinoma limited to the epithelium and lamina propria (M2) without lymphatic or vascular invasion.

TABLE 2. White-light Endoscopy and FICE Examination Performance for the Detection of Esophageal Neoplastic Lesions

Index	White-light	FICE
Sensitivity (95% CI)	92.3% (62.1%-99.6%)	100.0% (71.7%-100.0%)
Specificity (95% CI)	98.9% (93.3%-99.9%)	98.9% (93.3%-99.9%)
Positive predictive value* (95% CI)	92.3% (62.1%-99.6%)	92.8% (64.2%-99.6%)
Negative predictive value* (95% CI)	98.9% (93.3%-99.9%)	100% (95.0%-100.0%)
Disease probability after a negative test* (95% CI)	1.1% (0.08%-6.1%)	0% (0.0%-4.4%)
Likelihood ratio for positive test (presence of lesion)	85.8 (12.1-606.8)	93.0 (13.2-653.6)
Likelihood ratio for negative test (absence of lesion)	0.08 (0.01-0.51)	0.0 (0.0-1.02)
Overall accuracy (95%CI)	98.1% (92.7%-99.7%)	99% (94.0%-99.9%)
Youden "J" Index (95%CI)	96.2% (91.3%-98.8%)	98.1% (92.5%-99.6%)

*Prevalence = 12.3%.
CI indicates confidence interval; FICE, flexible spectral imaging color enhancement.

excluding the 3 advanced lesions from the analysis, and the index values were practically the same as the overall results described in Table 2, with minor variations. Considering only the flat lesions, sensitivity, specificity, and accuracy were 90%, 98.9%, and 98.1%, respectively, for WLE and 100%, 98.9%, and 99%, respectively, for FICE. Therefore, in this population, the performance of both WLE and FICE for the detection of exclusively flat lesions also did not show any superiority of one imaging technique over the other.

Patients with a positive diagnosis of esophageal neoplasia were referred to locoregional staging by computed tomography and endoscopic ultrasound. Neoplastic lesions were classified as superficial (T1) in 10 patients, and 8 of them were scheduled to undergo endoscopic submucosal dissection. Individuals with advanced esophageal neoplasms or flat circumferential tumors were referred to oncological management with chemotherapy and radiotherapy. Patients with early esophageal tumors resected endoscopically, and with favorable results at the specimen histologic analysis, have undergone periodic endoscopic follow-up, ranging from 3 to 18 months, without detection of local recurrence or metachronous tumors. Table 3 summarizes the clinical-pathologic data and the outcome of the patients with esophageal neoplasia.

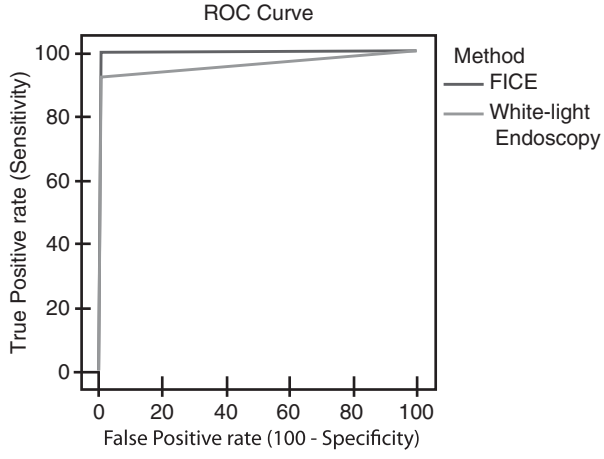

FIGURE 5. Receiver operating characteristic curve calculation for WLE and FICE for detection of esophageal neoplastic lesions (area under the curve for FICE: 0.995; area under the curve for WLE: 0.956). FICE indicates flexible spectral imaging color enhancement; WLE, white-light endoscopy.

DISCUSSION

There is convincing evidence that synchronous or metachronous ESCC occurs frequently in patients with primary HNSCC (oral cavity, oropharynx, hypopharynx, larynx).[3,8,9,12–16,22] In addition, metachronous esophageal cancers have been identified at different intervals, and the risk does not seem to decrease with time.[29] Therefore, according to recent guidelines, at least a single endoscopy may be indicated to search for esophageal cancer in patients with HNSCC.[29] The 12.3% rate of ESCC observed in our study further validates and reinforces these recommendations, also demonstrated previously by other Brazilian investigators.[8,30] It is of note that 77% of the neoplasms identified in our study were staged as superficial, which enables the management by endoscopic resection. These results are in agreement with other series of ESSC screening that showed rates of early cancer detection as high as 62%,[9] 78%,[8] and 80%.[22] Despite this evidence, sufficient data on the cost-effectiveness of this strategy are still lacking and it remains to be proved whether endoscopic screening will ultimately benefit HNSCC patients in terms of increased overall survival and quality of life.

The routine use of sedation for EGD carries a significant economic impact, which may adversely affect the cost-effectiveness of its use as a screening tool. Unsedated endoscopic procedures could be a cost-saving alternative, as long as the detecting capability is not compromised by impaired tolerance or acceptance, or by the use of lower resolution endoscopes, a limitation solved with the new generation of ultrathin endoscopes.[31] The second drawback of EGD is that flat neoplastic lesions in the esophagus often present with discrete alterations, and may be missed if a diligent endoscopic examination with adequate cleaning of the mucus and careful mucosal inspection is not adopted. For this reason, lugol chromoendoscopy is recommended to enhance the detection of early cancer and dysplasia in the esophagus.[12] In a multicenter study for esophageal cancer screening, the authors reported that 20% of the carcinomas and two thirds of the high-grade dysplastic lesions were not recognized by conventional EGD and were detected only after lugol chromoscopy.[12] However, lugol chromoscopy is time-consuming, adds costs, and, among its side effects, it may be painful in about 7.5% of the patients, as noted in our study. The substitution of lugol staining for a reliable,

TABLE 3. Clinical-Pathologic Data and Outcome of 13 Patients With Esophageal Squamous Cell Carcinoma Detected at Screening Transnasal Endoscopy

No.	Age (y)/ Sex	Primary Cancer	Tumor Diagnosis and Staging	WLE Detection	FICE Detection	Treatment (Intent)	Histology	Outcome
1	69/M	Oral cavity	Infiltrative neoplasia (T3)	Yes	Yes	CHT/RT	ESCC	Oncology surveillance
2	54/M	Hypopharynx	Infiltrative neoplasias (T3)	Yes	Yes	CHT/RT	ESCC	Oncology surveillance
3	37/F	Hypopharynx	Protruded neoplasia 0Is (T3)	Yes	Yes	CHT/RT	ESCC	Oncology surveillance
4	46/M	Oral cavity	Circumferential flat lesion 0IIb (T1)	Yes	Yes	CHT/RT	ESCC	Oncology surveillance
5	50/M	Oral cavity	Circumferential flat lesion 0IIb (T1)	Yes	Yes	CHT/RT	ESCC	Oncology surveillance
6	59/M	Larynx	Depressed lesion 0IIc (T1)	Yes	Yes	ESD	ESCC	Failed ESD due to nonlifting sign Referred to CHT/RT
7	58/M	Hypopharynx	Depressed lesion 0IIc (T1sm)	Yes	Yes	ESD	ESCC	SM1 Tumor LØVØ Lateral margin affected Referred to CHT/RT
8	62/F	Oropharynx	Flat lesion 0IIb (T1m)	Yes	Yes	ESD	ESCC	M3 tumor LØVØ Free margins Referred to CHT/RT
9	68/M	Larynx	Flat lesion 0IIb (T1m)	Yes	Yes	ESD	ESCC	M1 tumor LØVØ Free margins
10	48/M	Oral cavity	Flat elevated lesion 0IIa (T1m)	Yes	Yes	ESD	ESCC	M2 tumor LØVØ Free margins
11	49/M	Oral cavity	Flat lesion 0IIb (T1m)	Yes	Yes	ESD	HIEN	M1 tumor LØVØ Free margins
12	69/F	Oral cavity	Flat lesion 0IIb (T1m)	Yes	Yes	ESD	HIEN	M1 tumor LØVØ Free margins
13	53/M	Larynx	Flat lesion 0IIb (T1m)	No	Yes	ESD	HIEN	M2 tumor LØVØ Free margins

CHT indicates chemotherapy; ESCC, esophageal squamous cell cancer; ESD, endoscopic submucosal dissection; F, female; FICE, flexible spectral imaging color enhancement; HIEN, high-grade intraepithelial neoplasia; L, lymphatic invasion; M, male; M1, epithelium; M2, lamina propria; M3, muscularis mucosae; Ø, absence; RT, radiotherapy; SM1, superficial submucosa; V, vascular invasion; WLE, white-light endoscopy.

safer, and more comfortable technique sounds attractive and has been a subject of research with the development of digital chromoendoscopy.[9,13–16,21]

In the present study, we report the results of a screening program designed to detect ESCC in a Brazilian high-risk population by means of unsedated TNE with WLE, FICE, and lugol chromoendoscopy, applied in a sequential manner. Our results show that TNE is feasible, safe, and well accepted. The vast majority of the patients (92%) reported no or minimal discomfort, and the examination was successfully accomplished in all patients, except in 1 individual with narrow nasal cavities. It is noteworthy that the procedures were quite long, ranging from 10 to 37 minutes (mean duration, 17 min), similar to other studies that used TNE with NBI for ESCC screening.[9,22] This may be due, at least in part, to a meticulous esophageal examination. In addition, the ultrathin endoscope has a 2-mm working channel, which requires more time for fluid aspiration. However, this extra time can be compensated by early discharge of patients. The favorable results in terms of patient tolerance observed in this study are in agreement with data from other investigators that used TNE for esophageal screening in patients with primary HNSCC.[9,22] It is interesting that our results are superior to those from clinical trials that compared TNE and peroral EGD in patients referred for endoscopy for other reasons such as dyspepsia or reflux symptoms,[32,33] which demonstrated rates of failed nasal examinations as high as 8%.[32,33] The only adverse event observed in our study was esophageal discomfort due to lugol staining. These results are also in contrast to the use of TNE in general populations, which documented a 5.8% rate of epistaxis.[33] The satisfactory acceptability of TNE and the low rate of adverse events noted in our study may not be representative of the general population of patients referred to routine EGD. We targeted patients with HNSCC, who frequently undergo nasopharyngeal examinations, which may explain why these patients are more tolerant and resilient to TNE.

In terms of cancer detection, either WLE or FICE proved to be highly effective tools to screen for esophageal neoplasia. Elevated rates of sensitivity, specificity, accuracy, predictive values, and likelihood ratios for detecting or ruling out tumors were noted for both techniques. Although the comparative analysis of the receiver operating characteristic curves demonstrated slight superiority of FICE over WLE, the areas under the curve for both tests were very similar, and this minor difference may be attributed to chance. This interpretation is strengthened by the overlapping results of the 95% CIs observed in the tests performance analysis. WLE and FICE findings were compared with a reliable reference standard based on a combination of well-delineated lugol-unstained lesions with a consecutive pink color sign, identified consensually by 2 experienced examiners and followed by a confirmatory histology reported by an independent gastrointestinal pathologist. The ideal gold standard would be the histopathologic examination of the entire esophagus, an approach obviously unfeasible. Therefore, the results presented in this and in other similar studies may in fact overestimate the yield of the endoscopic detection of neoplastic lesions, because the

real rate of false-negative examinations is difficult to be determined.

There is a series of studies dedicated to elucidate the benefit of NBI for the detection of early neoplasia with promising results.[13–16] Lee et al[9] applied NBI with TNE in patients with HNSCC and demonstrated better results with NBI in terms of sensitivity, specificity, and accuracy. Our study is the first investigation performed with TNE that compared FICE with WLE in a blinded manner, by means of a tandem examination (back-to-back) carried out by 2 independent operators. This methodology differs from the study by Lee et al,[9] where all procedures were carried out by the same operator, introducing a possible bias of interpretation that is difficult to rule out. Although WLE in our series did miss 1 flat neoplastic lesion that was recognized by FICE, the data analysis did not demonstrate any significant differences in the overall performance between both techniques. A satisfactory number of patients without neoplasia were recruited, as reflected by the narrow width of the 95% CI for specificity. The limited number of patients with neoplasia, typically observed in screening studies, explains the wide range of the 95% CI for sensitivity. Therefore, it is possible that a difference in terms of sensitivity between WLE and FICE, if existent, could not be demonstrated because of the insufficient number of patients with esophageal cancer. A larger study including more patients with cancer could more confidently ascertain the true sensitivity of both imaging techniques. Our current perception is that the combination of WLE and FICE could replace lugol chromoscopy to screen for esophageal superficial lesions, which would be a significant benefit in terms of cost-savings and improving the efficiency of endoscopic screening. This assumption is supported by the fact that no neoplastic lesions encountered after lugol staining was overlooked by the sum of WLE and FICE evaluations.[8,12] Other authors have also suggested that FICE could improve the ability of ultraslim endoscopy to detect superficial neoplasia in the upper gastrointestinal tract, and replace the use of dye staining.[34] This tendency was also stated in a recent consensus advocating the replacement of lugol chromoscopy by NBI for routine endoscopic procedures.[35] However, further studies are required to clarify whether FICE is in fact a reliable substitute to lugol staining in the esophagus.

In conclusion, this study showed that unsedated TNE is a feasible, well accepted, safe, and efficient diagnostic tool for the screening of esophageal neoplasia in high-risk patients. The elevated rate of esophageal neoplasms observed in this population further strengthen the recommendations to screen these patients. The yield of WLE and FICE were similar for esophageal neoplasia detection, and the combination of both techniques may replace the use of lugol chromoscopy. We envision that TNE with digital chromoendoscopy can potentially expand and facilitate the introduction of programs for screening upper gastrointestinal cancer in high-risk population.

REFERENCES

1. Hölscher AH, Bollschweiler E, Schneider PM, et al. Prognosis of early esophageal cancer. *Cancer*. 1995;76:178–186.
2. Yu MC, Garabrandt DH, Peters JM, et al. Tobacco, alcohol, diet, occupation and carcinoma of the esophagus. *Cancer Res*. 1988;48:3843–3848.
3. Okumura T, Aruga H, Inohara H, et al. Endoscopic examination of the upper gastrointestinal tract for the presence of second primary cancers in head and neck cancer patients. *Acta Otolaryngol*. 1993;501(suppl):103–106.
4. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer*. 1953;6:963–968.
5. Lambert R, Sauvaget C, De Camargo Cancela M, et al. Epidemiology of cancer from the oral cavity and oropharynx. *Eur J Gastroenterol Hepatol*. 2011;23:633–641.
6. Yao PF, Li GC, Xia HS, et al. Evidence of human papilloma virus infection and its epidemiology in esophageal squamous cell carcinoma. *World J Gastroenterol*. 2006;12:1352–1355.
7. Zheng S, Vuitton L, Sheyhidin I, et al. Northwestern China: a place to learn more on oesophageal cancer. Part one: behavioral and environmental risk factors. *Eur J Gastroenterol Hepatol*. 2010;22:917–925.
8. Hashimoto C, Iriya K, Baba ER, et al. Lugol's dye spray chromoendoscopy establishes early diagnosis of esophageal cancer in patients with primary head and neck cancer. *Am J Gastroenterol*. 2005;100:275–282.
9. Lee YC, Wang CP, Chen CC, et al. Transnasal endoscopy with NBI and lugol-staining to screen patients with head and neck cancers whose conditions limit oral intubation with standard endoscope. *Gastrointest Endosc*. 2009;69:408–417.
10. Yokoyama A, Ohmori T, Makuuchi H, et al. Successful screening for early esophageal cancer in alcoholics using endoscopy and mucosa iodine staining. *Cancer*. 1995;76:928–934.
11. Fagundes RB, de Barros SGS, Pütten ACK, et al. Occult dysplasia is disclosed by lugol chromoendoscopy in alcoholics at high risk for squamous cell carcinoma of the esophagus. *Endoscopy*. 1999;31:281–285.
12. Dubuc J, Legoux JL, Winnock M, et al. Endoscopic screening for esophageal squamous-cell carcinoma in high-risk patients: a prospective study conducted in 62 French endoscopy centers. *Endoscopy*. 2006;38:690–695.
13. Takenaka R, Kawahara Y, Ohada H, et al. Narrow-band imaging provides reliable screening for esophageal malignancy in patients with head and neck cancers. *Am J Gastroenterol*. 2009;104:2942–2948.
14. Ishihara R, Takeuchi Y, Chatani R. Prospective evaluation of narrow-band imaging endoscopy for screening of esophageal squamous mucosal high-grade neoplasia in experienced and less experienced endoscopists. *Dis Esophagus*. 2010;23:480–486.
15. Kuraoka K, Hoshino E, Tsuchida T, et al. Early esophageal cancer can be detected by screening endoscopy assisted with narrow-band imaging (NBI). *Hepatogastroenterology*. 2009;56:63–66.
16. Lee CT, Chang CY, Lee YC, et al. Narrow-band imaging with magnifying endoscopy for the screening of esophageal cancer in patients with primary head and neck cancers. *Endoscopy*. 2010;42:613–619.
17. McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. *Gastrointest Endosc*. 2008;67:910–923.
18. Inadomi JM, Gunnarson CL, Rizzo JA, et al. Projected increased growth rate of anesthesia professional-delivered sedation for colonoscopy and EGD in the United States: 2009 to 2015. *Gastrointest Endosc*. 2010;72:580–586.
19. Shaker R. Unsedated trans-nasal pharyngoesophagogastroduodenoscopy (T-EGD): technique. *Gastrointest Endosc*. 1994;40:346–348.
20. Maffei M, Dumonceau JM. Transnasal esogastroduodenoscopy (EGD): comparison with conventional EGD and new applications. *Swiss Med Wkly*. 2008;138:658–664.
21. Teixeira CR, Torresini RS, Canali C, et al. Endoscopic classification of the capillary-vessel pattern of colorectal lesions by spectral estimation technology and magnifying zoom imaging. *Gastrointest Endosc*. 2009;69:750–756.
22. Su YY, Fang FM, Chuang HC, et al. Detection of metachronous esophageal squamous carcinoma in patients with head and neck cancer with use of transnasal esophagoscopy. *Head Neck*. 2010;32:780–785.
23. Trevisani L, Cifala V, Sartori S, et al. Unsedated ultrathin upper endoscopy is better than conventional endoscopy in

routine outpatient gastroenterology practice: A randomized trial. *World J Gastroenterol*. 2007;13:906–911.
24. Murata A, Akahoshi K, Sumida Y, et al. Prospective randomized trial of transnasal versus peroral endoscopy using an ultrathin videoendoscope in unsedated patients. *J Gastroenterol Hepatol*. 2007;22:482–485.
25. Inoue H, Kashida H, Kudo S, et al. The Paris endoscopic classification of superficial neoplastic lesions. *Gastrointest Endosc*. 2003;58(suppl 6):S3–S43.
26. Shimizu Y, Omori T, Yokyama A, et al. Endoscopic diagnosis or early squamous neoplasia of the esophagus with iodine staining: high-grade intraepithelial neoplasia turns pink within a few minutes. *J Gastroenterol Hepatol*. 2008;23:546–550.
27. Ishihara R, Yamada T, Iishi H, et al. Quantitative analysis of the color change after iodine staining for diagnosing esophageal high-grade intraepithelial neoplasia and invasive cancer. *Gastrointest Endosc*. 2009;69:213–218.
28. Schempler RJ, Riddel RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut*. 2000; 47:251–255.
29. American Society for Gastrointestinal Endoscopy. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc*. 2006;63:570–580.
30. Tincani AJ, Brandalise N, Altemani A, et al. Diagnosis of superficial esophageal cancer and dysplasia using endoscopic screening with a 2% lugol dye solution in patients with head and neck cancer. *Head Neck*. 2000;22:170–174.
31. American Society for Gastrointestinal Endoscopy (ASGE). Ultra-thin endoscopes: American Society for Gastrointestinal Endoscopy (ASGE) Technology Status Evaluation Report. *Gastrointest Endosc*. 2010;71:893–898.
32. Preiss C, Charton JP, Schumacher B, et al. A randomized trial of unsedated transnasal small-caliber versus peroral small-caliber EGD versus conventional EGD. *Endoscopy*. 2003;35: 641–646.
33. Yagi J, Adachi K, Arima N, et al. A prospective randomized comparative study on the safety and tolerability of transnasal esophagogastroduodenoscopy. *Endoscopy*. 2005;37: 1226–1231.
34. Tanioka Y, Yanai H, Sakaguchi E. Ultraslim endoscopy with flexible spectral imaging color enhancement for upper gastrointestinal neoplasms. *World J Gastrointest Endosc*. 2011;3: 11–15.
35. Uedo N, Fujishiro M, Goda K, et al. Role of narrow-band imaging for diagnosis of early-stage esophagogastric cancer: current consensus of experienced endoscopists in Asia-Pacific regions. *Dig Endosc*. 2011;23(suppl 1):58–71.