The Value of Virtual Chromoendoscopy in the Workup of Patients with Head and Neck Squamous Cell Carcinoma

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Abstract

Purpose of Review Second primary tumors (SPTs) significantly increase the mortality in patients with head and neck squamous cell carcinomas (HNSCCs). Virtual chromoendoscopy (VCE) could complement or replace lugol chromoendoscopy (LCE) for early esophageal second primary tumor (ESPT) detection. An overview of the existing techniques and their diagnostic performance in early detection of esophageal squamous cell neoplasms is provided.

Recent Findings Nowadays, LCE is the golden standard to detect ESPTs. Recently, multiple new VCE techniques have been developed. Especially narrow-band imaging (NBI) is promising. It shows similar sensitivity to LCE, but a significantly higher specificity.

Summary Patients with HNSCC are prone to develop ESPTs, both synchronous and metachronous, with a substantial negative impact on survival rates. Therefore, active screening and follow-up is necessary. LCE is an effective screening method, but has some disadvantages. Countering these drawbacks, NBI shows a high potential in early ESPT detection in high-risk patients. Additional multicenter studies are needed to compare diagnostic performance and cost-effectiveness of NBI and other VCE techniques with LCE.

Keywords Virtual chromoendoscopy · Lugol chromoendoscopy · Esophageal cancer · Second primary tumor · Head and neck cancer · Enhanced imaging

Abbreviations

AFI	Autofluorescence imaging
BA	Brownish area
BLI	Blue light imaging
DF-NBI	Dual-focus narrow-band imaging
ESPT	Esophageal second primary tumor
FICE	Flexible spectral imaging color enhancement
HNSCC	Head and neck squamous cell carcinoma
HRME	High-resolution microendoscopy

iCLE	Integrated confocal laser endoscopy
LCE	Lugol chromoendoscopy
LVL	Lugol voiding lesion
M	Magnifying
NBI	Narrow-band imaging
NM	Non-magnifying
NPV	Negative predictive value
pCLE	Probe-based confocal laser endoscopy
PPV	Positive predictive value
SFORL	Société Française d' Otorhinolaryngologie
SPT	Second primary tumor
TNE	Transnasal endoscopy
UADT	Upper aerodigestive tract
VCE	Virtual chromoendoscopy
WLE	White light endoscopy

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Introduction

The concept of field cancerization in patients with a primary head and neck squamous cell carcinoma (HNSCC) implies

that exposure to carcinogens, such as alcohol and tobacco, induces the development of second primary tumors (SPTs) within the exposed mucosal membranes, throughout the entire upper aerodigestive tract (UADT) [1]. Thus, one quarter of all HNSCC patients will develop SPTs within 10 years after diagnosis [2]. One third of the mortality of patients with HNSCC is attributed to these neoplasms [2].

Prevalence and Incidence of ESPT

The overall prevalence of synchronous esophageal second primary tumors (ESPTs) in HNSCC patients is 5.1–28% [3, 4, 5, 6]. This observed wide range is due to differences in patient characteristics, location of the index tumor, and the screening techniques that were used in the different studies [7]. The prevalence of synchronous ESPTs differs according to the site and stage of the primary tumor. Most ESPTs occur when the index tumor is located in the oral cavity and hypopharynx, with a prevalence up to 22% and 31% respectively [8, 9, 10].

A study with a 9-year follow-up of 9089 HNSCC patients observed an ESPT incidence of 9.4% over a period of 9 years; 42.1% were synchronous and 57.9% were metachronous [5].

Survival Implications of ESPT

ESPTs can be highly aggressive and bring 5-year survival rates down to 54.9% [11, 12]. One study observed a median overall survival of 38 months and a 5-year overall survival of 40% for patients with hypopharyngeal HNSCC [8]. In patients that were also diagnosed with an early or advanced stage synchronous ESPT, the median survival time was lowered to 36 and 15 months respectively [8]. However, when an ESPT is detected and treated early, the survival rate rises up to 80% [11, 13]. Thus, an active screening program to detect ESPTs early increases survival rates significantly [14].

Risk Factors for Developing ESPT

Alcohol abuse (> 250 g of pure alcohol/day), smoking, lower age at diagnosis (median of ≤ 55 years), and location of the index tumor (e.g., hypopharynx; a fortiori local invasion of ≥ 3 sites in the head and neck region) were found to increase the risk of developing a SPT [7, 8]. Even after treatment of the index HNSCC, the risk of developing a subsequent ESPT remains 8 to 22 times higher than in the general population [3, 7, 15]. This increased number of ESPTs is due to the carcinogenic effects of acetaldehyde, found in smoke and in the breakdown products of ethanol [1, 16]. Two studies have shown that mainly alcohol consumption, but not smoking, implies this higher prevalence of synchronous ESPTs [4, 8]. Another study, however, did identify smoking as an

independent risk factor, while showing no effect of alcohol consumption on developing ESPTs [17]. These conflicting findings are due to the fact that alcohol and tobacco use are often closely linked and their effects difficult to evaluate separately [17]. Other identified risk factors for developing ESPTs are previous radiotherapy for breast cancer, caustic injury of the esophagus, achalasia, thylosis, drinking maté, chewing betelnut, exposure to polycyclic aromatic hydrocarbons, and race [16, 18]. Logically, patients that develop other tobacco- and alcohol-related tumors like HNSCC and tracheobronchial cancer are considered high-risk patients for developing ESPTs [19, 20]. A lower BMI is an additional risk factor [21].

Guidelines for Screening for ESPT in HNSCC Patients

Early screening for ESPT in HNSCC patients is important, yet no global consensus on screening has been established [4]. National consensus documents do exist, and, e.g., in 2013 guidelines of the Société Française d’Otorhinolaryngologie (SFORL) recommended the use of lugol chromoendoscopy (LCE) in addition to white light endoscopy (WLE) in screening for ESPTs in patients with oro- and hypopharyngeal HNSCC and in patients with alcohol abuse [7]. After treating the index tumor, the annual risk of developing an ESPT remains 3–7% [22]. Therefore, a routine screening for metachronous tumors during the follow-up is also indicated, and, thus, the 2015 SFORL guidelines propose that HNSCC patients be screened at 2-year intervals with LCE [22].

Aim of This Study

ESPTs are seen in 16–36% of patients screened using the golden standard, LCE [17]. Virtual chromoendoscopy (VCE) is a group of relatively new endoscopic techniques developed for better, easier, and safer mucosal evaluation. Using VCE, ESPTs are potentially detected earlier, and earlier treatment of these could increase survival rates [14].

This study reviews the diagnostic value of the different VCE techniques in the detection of ESPTs in patients with HNSCC, and compares it with the standard of LCE.

Materials and Methods

A systematic review of the available chromoendoscopic techniques and their diagnostic performance was conducted. PubMed and Embase were searched using (“Head and Neck Neoplasms” [Mesh] AND “chromoendoscopy”) for PubMed and (“head and neck tumor” AND “chromoendoscopy”) for Embase. Articles published between January 1, 1990, and July 1, 2019, were included. This search led to 177 and 95 articles respectively. Afterwards, 8 articles were added by

hand search. Only publications written in English and with an available full text were included. The study types of interest were systematic reviews, narrative reviews, randomized controlled trials, prospective studies, retrospective studies, cohort studies, and guidelines. Other inclusion criteria were human study objects, use of chromoendoscopy, synchronous or metachronous esophagus, and/or stomach neoplasms or dysplasia and patients with primary head and neck cancer. Only studies with numerical data on sensitivity, specificity, accuracy, PPV, and NPV were included. Studies on Barrett's esophagus and case reports were excluded and no abstracts or data from unpublished research were accepted. Duplicate studies were removed.

Retrieved manuscripts were screened according to the PRISMA guidelines [23].

The flow diagram of the search process, using the PRISMA model, is outlined in Fig. 1 [23]. One hundred ninety-six abstracts did not meet the inclusion criteria. Of the remaining 84 articles, only 58 full texts could be obtained. These full texts were assessed for eligibility, including only the articles with numerical content on the diagnostic performances of the imaging techniques discussed in this paper. This resulted in 21 articles of which the data were collected and reviewed. The numerical data, such as sensitivity, specificity, diagnostic accuracy, area under sROC curve, positive predictive value (PPV), and negative predictive value (NPV), were extracted and summarized (Tables 1 and 2); their format, however, did not allow formulating the summary statistics.

Results

Chromoendoscopy and Other Advanced Endoscopic Imaging Techniques

Over the past 50 years, endoscopic imaging techniques have improved significantly. In the past, WLE was the golden standard to screen for ESPTs, but this technique was not very accurate in identifying intramucosal neoplasms such as erosions or flat mucosal lesions [30]. Recently, enhanced identification of suspicious mucosal lesions was observed with chromoendoscopy. This technique uses a dye sprayed on the mucosa to create a contrast between normal and neoplastic mucosa.

Lugol Chromoendoscopy, the Current Golden Standard

LCE is currently considered the golden standard to screen for ESPTs in high-risk patients. Normal glycogen-containing squamous epithelium absorbs lugol's iodine, whereas dysplastic, glycogen-depleted cells do not [39]. Due to the absence of lugol staining in malignant mucosa, visibility of suspicious mucosal lesions within the normal tissue is improved,

and biopsies can be targeted to these lugol voiding lesions (LVLs) [5 · ·, 10 · ·, 39]. When screening HNSCC patients with LCE, 15% are diagnosed with an ESPT, indicating both the high prevalence of SPTs as well as the usefulness of LCE to detect them [10 · ·]. However, there are risks and side effects to the use of lugol, such as laryngospasm, chest pain, acute gastric mucosal damage, allergic reactions, pneumonitis, and nausea [19, 20, 31 · ·]. LCE cannot be used in people with hyperthyroidism [29]. All these factors fed the search for safer methods for detecting ESPTs.

New Advanced Endoscopic Imaging Techniques

In VCE, the contrast to identify suspicious mucosal lesions is created by the endoscope itself, without using a dye. Enhancement of the real-time image can be optical or digital. Optical VCE uses optical filters in combination with high definition imaging incorporated in the light source of the endoscope [40, 41]. Digital VCE uses digital postprocessing algorithms to acquire enhanced images of the white light endoscopic image [40, 41]. Advantages of VCE include safe assessment of the upper third of the esophagus without causing chest discomfort, without the risk of allergic reaction to dyes or pulmonary aspiration [31 · ·]. Disadvantages include training and less known diagnostic performances [5 · ·, 6, 17].

1. Virtual chromoendoscopy with optical filters (preprocessing techniques)
 - a. Narrow-band imaging (NBI)

NBI is an optical VCE technique which is integrated with standard WLE in dedicated endoscopes. By the flick of a switch, the NBI setting filters the white light, leaving only blue and green light wavelengths [40]. These wavelengths uncover mucosal and submucosal vessel structures [40]. The blue 415-nm wavelength is absorbed by hemoglobin in mucosal vessels and the green 540-nm wavelength is absorbed by the submucosal vessels [40]. Evaluating blood vessel structures helps in differentiating normal from suspicious lesions which show intrapapillary capillary loops [40]. Neovascularization and glycogen depletion lead to a brownish color of the mucosa when evaluating with NBI [5 · ·]. These brownish areas (BAs) are considered suspicious and should be biopsied [31 · ·]. A new technique, called dual-focus NBI (DF-NBI), was recently developed [42]. It creates an up to 80 times magnification of the NBI image, improving lesion evaluation.

- b. Blue light imaging (BLI)

BLI is a quite new optical VCE technique. BLI is the blue mode of a four LED-light illumination source consisting of purple, green, red, and blue LEDs [29]. BLI's specific

Table 1 Sensitivity, specificity, accuracy, area under sROC curve, PPV, NPV of imaging methods in detection of esophageal neoplasms in patients with primary head and neck cancer

	Study	Sensitivity	Specificity	Accuracy	Area under sROC curve	PPV	NPV
White light endoscopy							
	Chung et al. [5 · ·]***	56%	98%	66%	0.66		
	Ide et al. [20]	0–85.7%	100%	97.7%		100%	97.6%
	Chung et al. [21]	51.4%	78.3%	61.7%			
	Prueksapanich et al. [24]	43%					
	Wang et al. [25]*			88.7%			89.9%
	Lee et al. [26]	62.9%	70%			88%	
· TNE-WLE	Wang et al. [25]*	47.3%	97.4%			79.4%	
	Arantes et al. [27]	92.3%	98.9%	98.1%	0.956	92.3%	98.9%
	Lee et al. [26]						35%
Dye-based chromoendoscopy							
LCE							
	Chunget al. [5 · ·]***	88%	63%	82%	0.82	37.3%	
	Takenaka et al. [13]	100%	84.7%	85.9%		35.5%	100%
	Carvalho et al. [19]	100%	92%	92%		22%	100%
	Ide et al. [20]		72.5%				
	Chung et al. [21]	97.3%	52.2%	81.7%			
	Nagami et al. [28]*				0.81		
	Wang et al. [25]*	94.7%	90.4%				
· TNE-LCE	Wang et al. [25]*	93.0%	90.7%	91.1%		67.9%	98.4%
Virtual chromoendoscopy							
NBI							
· M-NBI	Chung et al. [5 · ·]***	97%	94%	97%	0.97		
	Takenaka et al. [13]	90.9%	95.4%	95.1%		62.5%	99.2%
	Chung et al. [21]	97.3%	94.1%	96.3%			
	Lee et al. [26]	100%	80%	95.6%		94.6%	100%
· NM-NBI	Ide et al. [20]	100%	86.7%	87.6%		36%	100%
	Lee et al. [26]	100%	40%	86.7%		85.4%	100%
· DF-NBI and LCE	Prueksapanich et al. [24]	85%	62%	70%		54%	89%
TNE-NBI	Wang et al. [25]*	84.2%	95.6%	93.6%		80.0%	96.6%
· TNE-NBI or LCE	Wang et al. [25]*	94.7%	90.4%	91.1%		67.5%	98.8%
· TNE-NBI and LCE	Wang et al. [25]*	82.6%	95.9%	93.6%		81.0%	93.6%
FICE							
· TNE-FICE	Arantes et al. [27]	100%	98.9%	99%	0.995	92.8%	100%
CLE							
· LCE and pCLE	Prueksapanich et al. [24]	83%	92%	89%		83%	92%

LCE lugol chromoendoscopy, *NBI* narrow-band imaging, *M* magnifying, *NM* non-magnifying, *DF-NBI* dual-focus NBI, *FICE* flexible spectral imaging color enhancement, *CLE* confocal laser endoscopy, *pCLE* probe-based confocal laser endoscopy

*Prospective study > 200 patients

***Systematic review

illumination light is used in combination with non-magnifying NBI (NM-NBI) to improve the image of the latter [29]. It allows the endoscopic operator to choose between various light spectra when using NBI. The blue light spectrum increases visualization of mucosal patterns and superficial structures [29]. The distance at which lesions can be recognized as dysplastic or neoplastic is greater in BLI than in NBI, enabling better visualization of surrounding structures [21].

c. Autofluorescence imaging (AFI)

AFI uses the autofluorescent properties of endogenous fluorophores (NADH, collagen, and elastin) in the gastrointestinal tract [39]. These fluorophores emit longer wavelengths when excited with shorter wavelengths [39]. AFI uses a unique optical filter system with a blue excitation filter for inducing autofluorescence and a green filter for generating the

Table 2 Sensitivity, specificity, accuracy, area under sROC curve, PPV, NPV of imaging methods in detection of esophageal neoplasms in high-risk patients including HNSCC patients

	Study	Sensitivity	Specificity	Accuracy	Area under sROC curve	PPV	NPV
White light endoscopy							
	Diao et al. [29]	66.7%	42.3%	56%			
	Nagami et al. [28]*	55.2–62.9%					
Dye-based chromoendoscopy							
LCE							
	Protano et al. [30]	100%	29%	47%	0.9559–0.9685	32%	
	Morita et al. [31 · ·]***	88–92%	37–65%				
	Diao et al. [29]	95.2%	94.6%	91.3%			
	Huang et al. [32]	89.1%	90%			97.6%	64.3%
	Nagami et al. [28]*	94.2%	64%	68%	0.80	28.6%	98.6%
	Christian et al. [33]*	95.5% (M)					
	Li et al. [34]*	88.9%					
	Li et al. [34]*	92.6% (M)					
· LCE and HRME	Protano et al. [30]	95%	79%	83%		60%	
· LCE-PS	Goda et al. [35]**	80.5%	94.3%	90.5%		84.6%	92.6%
	Ishihara et al. [36]	88%	95%	91%		96%	86%
Virtual chromoendoscopy							
NBI							
· NM-NBI and/or M-NBI	Kandiah et al. [11]			76.8–85.2%			
	Morita et al. [31 · ·]***	94–98%	82–88%		0.9587–0.9611		
· M-NBI	Diao et al. [29]	95.2%	92.8%	87.5%			
	Nagami et al. [28]*	88.9–100%					
	Goda et al. [35]**	82.2%	95.1%	91.2%		88.1%	92.4%
· NM-NBI	Nagami et al. [28]*	88.3%	75.2%	77.0%	0.83	34.3%	97.7%
I-Scan	Guo et al. [37]*	78.7%	22.9%	45.3%		40.7%	61.5%
· I-Scan + pCLE	Guo et al. [37]*	74.5%	92.9%	85.5%		87.5%	84.4%
CLE							
· LCE and pCLE	Guo et al. [37]*	94.6%	90.7%	92.3%		87.5%	96.1%
	Pech et al. [38]			95%			
· LCE and iCLE	Huang et al. [32]	95.7%	90.0%	97.8%			
FICE							
· NM-FICE	Li et al. [34]*	92.6%					
· M-FICE	Li et al. [34]*	96.3%					
BLI	Diao et al. [29]	95.2%	91.9%	85.7%			

PPV positive predictive value, NPV negative predictive value, LCE lugol chromoendoscopy, HRME high-resolution magnifying endoscopy, LCE-PS lugol chromoendoscopy pink stain sign, NBI narrow-band imaging, M magnifying, NM non-magnifying, CLE confocal laser endoscopy, pCLE probe-based confocal laser endoscopy, iCLE integrated confocal laser endoscopy, FICE flexible spectral imaging color enhancement, BLI blue light imaging

*Prospective study > 200 patients

**Randomized controlled trial

***Systematic review

reflected images. In conjunction with postprocessing algorithms of the generated images, a purple “red flag” lesion on AFI can be visualized and subsequently evaluated with high-resolution endoscopy and NBI [39].

2. Virtual chromoendoscopy with digital filters (postprocessing techniques)

a. Flexible spectral imaging color enhancement (FICE)

FICE is a digital VCE technique. Here, a video processor disintegrates the endoscopic image into blue, green, and red components, which are then altered and resynthesized to compose a new image [39]. By focusing on different wavelengths and combining them, the contrast is enhanced and vascular

Fig. 1 Search strategy and study selection summarized in a flow diagram based on the PRISMA guidelines

patterns of the mucosa are highlighted [40]. One can choose between 10 different wavelength settings [40]. The image created by FICE, however, is a bit “noisier” in comparison to NBI.

b. I-Scan

I-Scan is a second digital VCE technique. It consists of a combination of three imaging algorithms: surface enhancement, tone enhancement, and contrast enhancement [37]. By adjusting the different settings, the identification of mucosal abnormalities can be improved [37, 40].

3. Endoscopic microscopy

a. Probe-based and integrated confocal laser endoscopy (pCLE and iCLE)

pCLE is a new optical VCE technique that provides real-life histological evaluation, whereas NBI and LCE require further biopsies [24, 32]. pCLE obtains a 1000-fold magnification with high-resolution images of the mucosal layer of the gastrointestinal tract, enabling cellular and intraepithelial papillary capillary loop evaluation [30, 32, 37, 39]. For good tissue contrast, intravenously injected fluorescein sodium is still needed [37]. CLE is very expensive (> \$150,000) and only available in a few tertiary centers worldwide [30]. iCLE is a variant where the endoscope channel can still be used for lugol staining, while confocal images are simultaneously generated [32].

b. High-resolution microendoscopy (HRME)

HRME is a cheaper alternative for expensive techniques like CLE [30]. HRME is portable and battery operated,

enabling its use in remote places and developing countries [30]. By inserting the 1 mm fiber-optic microendoscope in the accessory canal of the endoscope and applying the fluorescent proflavine, it allows delineation of cellular features, such as nuclear size, pleomorphism, and crowding [30]. Combined with LCE, it would increase specificity and decrease unnecessary biopsies [30]. Nowadays, HMRE is not commercially available yet [30].

Summary of the Diagnostic Performance of Standard and Advanced Endoscopic Imaging Techniques

The latest systematic reviews value LCE as a good technique to screen for ESPTs [5 · ·, 31 · ·]. New VCE methods, however, show similar or better results with less risk and complications. Tables 1 and 2 give an overview of the reported diagnostic performance of these new techniques. Table 1 lists the data from studies focusing on patients with HNSCC. Table 2 does the same for studies that do not limit themselves to HNSCC, but also include other high-risk patients, such as patients with a history of esophageal squamous cell neoplasms, patients from high-risk countries, and patients with a score of > 6 on the HRA-F health risk assessment model [28, 31 · ·]. In the literature, no studies evaluating the diagnostic performance of I-Scan, AFI, BLI, and HRME in HNSCC patients were found. Therefore, these techniques are excluded from Table 1. AFI has been excluded from Table 2 for the same reason in high-risk patients.

Diagnostic Performance of Chromoendoscopy in Primary HNSCC Patients

The diagnostic performances of WLE, LCE, NBI, TNE-NBI, FICE, and CLE for detecting ESPTs in HNSCC patients are displayed in Table 1. For LCE, one meta-analysis (16 studies, 4918 patients) found a mean sensitivity, specificity, accuracy, and area under the sROC curve of 88%, 63%, 82%, and 0.82 respectively; in comparison, for NBI, the reported values were 97%, 94%, 97%, and 0.97 respectively [5 · ·]. Area under the sROC curve of the respective techniques showed a higher diagnostic accuracy for NBI than for LCE [5 · ·]. TNE-NBI can be combined with LCE. Its diagnostic performance varies depending on a parallel or serial approach. A parallel approach considers every BA on NBI *or* LVL on LCE as a positive lesion [25]. A serial approach only considers lesions that are BA on NBI *and* LVL on LCE as suspicious [25]. The parallel versus serial approach showed sensitivities of 94.7% versus 82.6%. Specificities, on the other hand, were higher using the serial method or when using NBI alone [25], 95.9% and 95.6% respectively compared with 90.4% when using the parallel method [25]. One small study by Arantes et al. reported promising data for FICE, with a sensitivity, specificity, and accuracy of 100%, 98.9%, and 99% [27].

Diagnostic Performance in High-Risk Patients Including HNSCC

The diagnostic performances of WLE, LCE, NBI, I-Scan, FICE, CLE, and BLI for detecting ESPT in high-risk patients are shown in Table 2. The literature shows similar sensitivities for LCE and NBI (80.5–100% vs. 82.2–100%) [28–36]. One study comparing both methods shows, for both techniques, a high area under the sROC curve (0.95–0.97) and thus a good sensitivity, without a significant difference [31 · ·]. The same study, however, showed a significantly higher specificity when using NBI versus LCE (82–88% vs. 37–65%) [31 · ·]. Nagami et al. showed that, even for non-magnifying NBI (NM-NBI), the accuracy and specificity were significantly higher than with LCE (77% vs. 68% and 75.2 vs. 64%, $p = 0.03$ and $p = 0.01$) [28].

One prospective study comparing I-Scan and LCE concluded a non-inferiority in detection rate between the two techniques (10.4% vs. 12.9%, respectively) [37]. However, I-Scan showed an unsatisfactory screening performance with a sensitivity, specificity, and accuracy of 78.7%, 22.9%, and 45.3% respectively [37]. The accuracy when combining I-Scan and pCLE increases significantly as compared with I-Scan alone (85.5% vs. 45.3%, $p < 0.001$) [37].

Discussion

Studies on Screening for ESPTs in HNSCC Patients—Discussion of the Data in Table 1

LCE is still considered as a reliable procedure for detecting ESPTs in HNSCC patients. The sensitivity of LCE and NBI is considered similar [5 · ·]. However, the specificity of LCE (63–92%) is suboptimal as many non-neoplastic changes, such as atrophic change, create LVLs as well [5 · ·, 13, 19–21, 25]. Due to this non-specificity of LVLs, a lot of unnecessary biopsies are taken [5 · ·, 43]. NBI and especially M-NBI shows a clearly higher specificity (80–95.9%) [5 · ·, 13, 21, 26]. In accordance with our findings, Chung et al. concluded that NBI has a higher diagnostic performance and accuracy than WLE and LCE [5 · ·]. However, a limitation of their systematic review is the lack of a subgroup analysis between patients developing a synchronous and metachronous ESPT. A prospective study evaluating TNE-NBI and LCE, including 441 HNSCC patients, showed that the parallel approach of “NBI or LCE” achieved the highest diagnostic sensitivity (94.7%) [25]. This parallel approach, where every positive lesion (BA on NBI or LVLs on LCE) was included, reduced the number of false negatives. Disadvantages of the parallel approach are longer procedure time, higher cost, and a higher complication rate [25]. In addition, this approach does not increase the specificity as compared with the use of TNE-NBI alone

[25]. Benefits of TNE in general are a higher completion rate (94–99%), better passage of strictures, the absence of sedation, and shorter examination time (mean 17 min) [25, 27]. Wang et al. considered TNE-NBI an effective screening method in detecting ESPTs in HNSCC patients [25].

Looking at NBI, both classical NM-NBI and M-NBI have been well studied. Like LCE, NM-NBI has a high sensitivity and negative predictive value (both up to 100%, Table 1) [13, 19, 20, 26]. No statistically significant difference in sensitivity between NM-NBI and M-NBI has been shown [26]. Nevertheless, specificity of M-NBI (80%) is clearly higher than the specificity of NM-NBI (40%), and this trend was observed by other authors resulting in a preference of M-NBI over NM-NBI [26]. Lee et al. support the routine use of NBI as a screening technique in HNSCC patients, with the caveat that the diagnostic efficacy of NM-NBI vs. M-NBI remains somewhat ambiguous [26]. More prospective studies are needed to confirm these findings.

One prospective study, comprising 106 patients, showed that both WLE and FICE had a high accuracy in detecting and ruling out neoplastic lesions, but for ESPT detection, no significant difference in diagnostic performance between these two techniques was found [27]. This similar performance of FICE and WLE suggests that NBI and LCE are probably also superior to FICE, but formal comparative studies on the diagnostic differences between FICE, NBI, LCE, and other VCE techniques are needed to confirm this.

Studies on Screening for ESPTs in High-Risk Patients Including HNSCC Patients—Discussion of the Data in Table 2

First of all, it is important to note that the greater SPT prevalence in this high-risk population leads to a higher diagnostic yield (PPV) of the VCE techniques. A wide range of diagnostic performance for LCE was seen depending on the power, used methods, and the number of included patients. Overall, studies show no significant difference between the sensitivity of LCE and NBI [31 · ·]. As mentioned before, LVLs are not very specific for ESPTs, leading to unnecessary biopsies [31 · ·]. This fact implies a significant benefit for NBI, with its higher specificity [31 · ·]. Likewise, accuracy of NM-NBI has also shown to be superior to that of LCE, indicating the same potential for avoiding unnecessary biopsies [28]. NM-NBI is widely used when no resources for magnification are available.

The amount of irregular-shaped multiform LVLs positively correlates with the risk of both synchronous and metachronous ESPT development [35, 44]. Takenaka et al. therefore recommended an initial LCE examination to assess the risk, and follow-up with NBI examinations to assess changes in mucosal vessel structures [13]. NBI still has other advantages. Unlike LCE, it is a push-on-a-button method

without the use of a dye and therefore safer to use. NBI detects intrapapillary capillary loop patterns and thus a more exact assessment of diameter of lesions, as well as infiltration depth of neoplasms, influencing further treatment decisions [11, 31 · ·]. Disadvantages include interobserver variability, the focused view (difficult to delineate lesions) and the absence of real-life histologic evaluation as seen in LCE. High NPVs for NBI are seen in less experienced as well as in experienced operators, 98% and 100% respectively, indicating that a patient without lesions on NBI can be spared further examination by LCE [45]. In patients with a lesion detected on NBI, Ishihara et al. still recommend the additional use of LCE, because of their belief in “its unsurpassed capacity to delineate malignant mucosal lesions” [45].

Few studies evaluating FICE, I-Scan and CLE have been conducted. FICE is considered complementary to LCE and has been shown to be a promising technique [27, 34, 37]. M-FICE and NM-FICE have shown similar detection rates as LCE [27, 34]. I-Scan too showed a non-inferiority when compared with LCE, despite its unsatisfactory screening performance (Table 2) [37]. I-Scan combined with pCLE did show a significant increase in overall accuracy [37]. Due to the narrow view, pCLE alone is not suited as a screening method. Nevertheless, pCLE is considered as an excellent method to differentiate between lesions that have been detected by other techniques. It can help target specific biopsies after previous lugol staining, significantly increasing specificity and thereby reducing the number of biopsies [24, 37]. Whether or not the iodine solution may lower image or video quality of pCLE is still uncertain [24, 37]. It also remains unclear whether to use pCLE before or after LCE, NBI, or I-Scan [43]. More studies are needed to compare VCE techniques and their combinations, in order to establish new cost-effective guidelines.

One small study evaluating BLI showed no significant difference in diagnostic performance between M-BLI, M-NBI, and LCE [29]. Larger multicenter studies evaluating BLI will still be needed.

Limitations of the included studies in this review are that many studies struggle with selection bias and a confounded comparison of techniques, as the same operator performs the different VCE examinations. In addition, more than 70% of the included studies were conducted in Asian countries like Japan, China, and Taiwan. This finding correlated with the increased prevalence of head and neck cancer in these regions. One of the main reasons for this racial depending prevalence is the difference in the expression of the ALDH2 gene, which is responsible for the breakdown of acetaldehyde [16]. An inactive ALDH2 allele in the Asian population implies a higher level of acetaldehyde which has been linked to finding more suspicious LVLs [16]. Caucasians do not show polymorphisms in the ALDH2 gene [16]. Only a few European and US studies about this topic have been conducted, bearing the

question whether these innovative techniques are equally cost-effective in lower-risk regions.

Conclusion

Patients with HNSCC, especially of the hypopharynx, are prone to develop ESPTs, both synchronous and metachronous, with a substantial negative impact on survival rates. Therefore, active initial screening and follow-up is necessary. LCE is considered the golden standard for detecting ESPTs, but there are risks and side effects to the use of lugol [19, 20, 31 · ·]. Of new VCE techniques, especially NBI constitutes an improvement in both HNSCC as in other high-risk patients, mainly because of a much higher specificity, decreasing the number of unnecessary biopsies, combined with avoidance of staining-related side effects. For now, I-Scan, FICE, and BLI do not show a significant improvement in diagnostic performance as compared with LCE. pCLE has the advantage that biopsies can be even better targeted due to instant histological evaluation, but availability is limited due to the high cost [30]. Future multicenter studies need to further evaluate and compare the diagnostic value and inter-observer variability of the various VCE techniques, also focusing on cost-effectiveness and implementation strategies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. Ethical approval was provided by the Research Ethics Committee of the KU Leuven.

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- Of importance
- · Of major importance

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