

Is Lugol necessary for endoscopic resection of esophageal squamous cell neoplasia?



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ABSTRACT

Background and study aims Recent evidence suggests that lugol chromoendoscopy (LCE) and narrow-band imaging (NBI) have comparable sensitivity for detection of superficial esophageal squamous cell carcinoma (SCC). However, LCE is time-consuming and associated with side effects. The aim of this study was to compare the effectiveness of NBI and LCE in defining resection margins of esophageal SCC.

Patients and methods This was a retrospective observational cohort study of patients with esophageal SCC and dysplasia who underwent en-bloc resection between 1999 and 2017 at the Cliniques universitaires Saint-Luc, Brussels. Two groups were defined: 1) inspection with NBI only; and 2) inspection with LCE (with or without NBI). The primary endpoint was complete lateral resection rate. Multivariate regression was used to adjust for potential confounders.

Results A total of 102 patients with 132 lesions were included. Lesions were inspected with LCE in 52% (n=68) and with NBI only in 48% (n=64). Lesions 0-IIa were more frequent in the NBI group (37%) and 0-IIb (60%) in LCE. Lesion location, size, and histology and resection technique (endoscopic submucosal dissection in 122/132 cases, 92%) were similar between the groups. The rate of complete lateral resection for invasive carcinoma was 90% in LCE group and 94% in NBI group ($P=0.498$) and 65% and 67% ($P=0.813$), respectively, for dysplasia complete lateral resection. These results remained non-significant after adjusting for potential confounders.

Conclusions Mucosal inspection and delineation of tumors with lugol chromoendoscopy before endoscopic resection of esophageal squamous cell lesions was not associated with increased complete lateral resection rate when compared to NBI.

Introduction

Esophageal cancer is the eighth most common cancer and the sixth leading cause of cancer-related mortality in the world [1]. Squamous cell carcinoma (SCC) is the most frequent histologi-

cal subtype accounting for 90% of cases of esophageal cancer worldwide due to its high prevalence in Eastern Asia [1–3].

Detection and characterization of early stage esophageal SCC can be challenging, since it typically appears as subtle and flat lesions on conventional white light endoscopy [1, 4]. Lugol dye chromoendoscopy (LCE) has long been the gold standard

for detection of superficial SCC and it is based on the lack of absorption of the iodine stain by abnormal squamous tissue [3, 5, 6]. However, lugol staining can cause heartburn and chest discomfort, has risk of pulmonary aspiration and allergic reaction, and increases the duration of the procedure [3, 6]. Moreover, LCE is a highly sensitive but not very specific technique for detecting superficial esophageal SCC since both inflamed and dysplastic/neoplastic lesions can appear as iodine-unstained areas [4]. Therefore, new technologies have been developed to evaluate the esophageal mucosa of high-risk patients, such as narrow-band imaging (NBI, Olympus) [7, 8]. NBI is a virtual chromoendoscopy technique that enhances the mucosa surface and the underlying capillary pattern simply by pressing a button [9]. Early squamous cell lesions can be identified by this technology as brownish, well demarcated lesions [3]. Disadvantages of this technique include the high cost of the device, which decreases accessibility, and its' application requires expertise [3].

Several studies compared the accuracy of NBI and LCE for diagnosing esophageal SCC [4, 10, 11]. A recent meta-analysis showed that NBI has a comparable sensitivity to that of lugol chromoendoscopy (88% vs. 92%), and a superior specificity (88% vs. 82% $P < 0.001$) [12]. However, to our knowledge, there are no data on the effectiveness of NBI in delineating esophageal SCC margin before endoscopic resection.

Therefore, the aim of this study was to compare the effectiveness of NBI and LCE in defining resection margins of esophageal squamous cell cancer and dysplasia. Our hypothesis was that NBI may be equivalent to LCE in determining esophageal SCC limits prior to endoscopic resection.

Patients and methods

We conducted a retrospective observational cohort study of all patients with esophageal SCC and dysplasia who underwent en-bloc resection between 1999 and 2017 at the Cliniques Universitaires Saint-Luc, Brussels, Belgium. The study protocol was approved by our ethical review board in April 2014 (2014/30AVR/210). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the approval by the Comité d'Ethique Hospitalo-Facultaire Université Catholique de Louvain.

Two groups were defined before endoscopic resection: 1) inspection of esophageal lesions exclusively with NBI; and 2) inspection with lugol chromoendoscopy (with or without NBI) (► Fig. 1). The decision to perform each technique was based on availability and endoscopist choice. In the first group, abnormal mucosal areas were identified and resection margins defined by NBI. When NBI was used, brown-stained areas of the mucosa were considered lesions suspected to be neoplasia (compared to "normal" mucosa, which is green independently of changes in surface or vascular texture). Delineation was mainly based on differences between green and brown mucosa, but included analysis of the intrapapillary capillary loop (IPCLs) either considered as normal (type A) vs abnormal (type B1–3), when magnification was available [7]. In the other cases, iodine solution (2%) was sprayed over the entire esophageal

mucosa and areas clearly not stained were suspected to be neoplasia, which is characterized by a yellow color in contrast with brown "normal" areas. The pink sign was not used for delineation since it is usually more centrally seen in the tumour. Delineation of the lesions was always performed immediately before the resection. Markings were placed 2 mm apart from the delineation line and incision a further 2 mm away from markers (► Fig. 2).

Procedures were carried out using Olympus scopes (series 140 and 160 without NBI capability, 180 and 190 including HQ190 with near focus) by six experienced endoscopists. Procedures were performed under deep sedation (propofol) or anesthesia with endotracheal intubation. After delineation of lesions margins, they were resected by en-bloc endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). ESD was the preferred resection technique whenever there was a suspicion of superficial invasive SCC (intramucosal or submucosal) aiming at complete lateral and deep resection (R0 resection) (► Fig. 3) [13, 14].

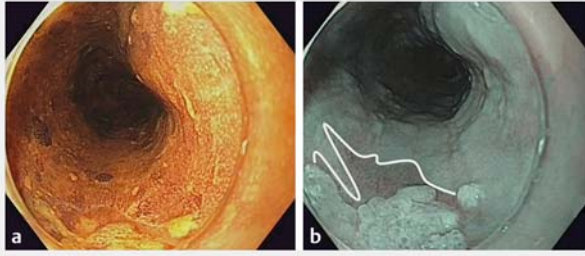
Patient demographic and clinical characteristics were registered including age, gender, smoking and alcohol habits, and previous treatments (EMR, ESD and/or radiotherapy). During endoscopy, lesion location (upper, middle and lower third of the esophagus), size and morphology according to Paris Classification were assessed. We also registered the endoscopist performing the procedure, the scope model and the resection technique (en-bloc EMR or ESD). Histology was assessed and registered according to the following four categories of the World Health Organization (WHO) Classification of tumors of the digestive system: invasive SCC (tumor invading the lamina propria), high-grade intraepithelial neoplasia/dysplasia (HGD) (includes all non-invasive intraepithelial carcinomas formerly called carcinoma in situ), low-grade intraepithelial neoplasia/dysplasia (LGD), and negative for neoplasia/dysplasia (no atypia) [15]. Lateral margins were evaluated in all lesions. In case of invasive SCC, depth of invasion (T1a [intramucosal] and T1b [submucosal]), tumor differentiation, and presence of lymphovascular invasion were also recorded [15, 16]. Need for additional treatment (EMR, ESD, surgery, radiotherapy or chemotherapy) and recurrence rate were also evaluated.

Complete lateral resection rate was defined as cancer/dysplasia free margin where applicable. Complete resection (R0) was defined as resection with lateral and vertical margin free of cancer and dysplasia. Curative resection was evaluated in cases of invasive SCC and defined as lesions that did not need additional treatment. Recurrence was considered local when a new lesion was diagnosed on a scar of a previous resection and metachronous if it occurred in another location.

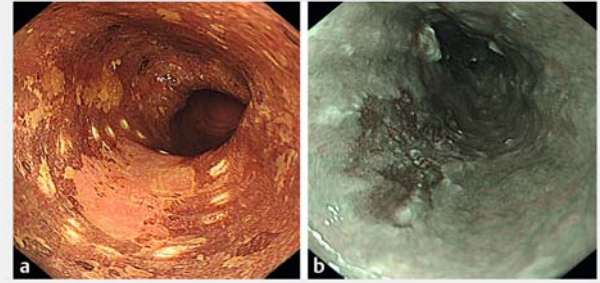
The primary endpoint was complete lateral resection rate – cancer and dysplasia-free margin. Secondary endpoints were R0 resection and recurrence rates.

Statistical analysis

All continuous variables were described as mean and standard deviation or median and range while categorical variables were expressed as frequency and proportions. In case of missing data, the denominator was adjusted to calculate the correct



► **Fig. 1** Esophageal lesion with lugol chromoendoscopy on the left and NBI on the right. The delineated area identified with NBI is high-grade dysplasia (brown and flat, below the nodular whitish lesion) and could have been missed with lugol chromoendoscopy showing normally stained mucosa at the dysplastic site.



► **Fig. 2** Esophageal lesion with lugol chromoendoscopy on the left (iodine-unstained area) and NBI on the right (brown). Markings were placed 2 mm apart from the delineation line (on the left).

proportions. Mean differences of continuous variables with a normal distribution were analysed using an independent Student t-test. The other continuous variables were compared using the Wilcoxon Mann-Whitney test. To explore univariate associations in the distribution of categorical data, the χ^2 test or Fisher's exact test was used as appropriate. For the primary end-point – complete lateral resection – a multiple logistic regression was used to adjust for potential confounders. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the software Statistical Package for Social Sciences (SPSS) (version 23.0).

Results

During the study period, 102 patients were included, 65.7% male, with a mean age of 64.9 ± 9.4 years. ► **Table 1** shows patient demographic and clinical characteristics.

In total, 132 lesions were resected, with a median lesions per patient of 1 (1–6) (► **Table 2**). In 52% ($n = 68$), resection margins were defined by LCE (with or without NBI) and in 48% ($n = 64$) by NBI exclusively. The endoscopy was performed by the same endoscopist in 71% of cases. A H190 or HQ190 scope was used in more than half of patients. About two-thirds of

the lesions were in the middle third of the esophagus, with a median size of 30 mm (5–100). Lesions were classified as 0-IIa in 29% of cases and as 0-IIb in 42%. In total 92% ($n = 122$) of the lesions were resected by ESD and pathological analysis revealed invasive SCC in 77% ($n = 101$). In invasive SCC lesions, 64% were T1a and 36% T1b, 42% (39/93) and 11% (10/93) were well and poorly differentiated, respectively, and lymphovascular invasion was present in 25% (15/61).

The rate of complete lateral resection for invasive carcinoma was 92% (93/101) and 66% (86/131) for dysplasia. Complete lateral and deep resection (R0 resection) was achieved in 49% (64/130). Incomplete R0 resection (66/130) was due to lateral invasion in 53% ($n = 35$), deep invasion in 32% ($n = 21$) and both lateral and deep in 15% ($n = 10$). The curative resection rate was 80.5%.

Of the 102 patients, 21 underwent additional treatment: one with EMR, one with ESD, eight underwent surgery, one radiotherapy and, 10 chemoradiotherapy.

The median time of follow-up was 13 months (0–154). Local recurrence rate was 3% ($n = 4$) after a median time of follow-up of 16 months (1–17).



► **Fig. 3** Esophageal lesion with lugol chromoendoscopy on the left (iodine-unstained area) and NBI in the middle (brown). Stretched resected specimen on the right.

► **Table 1** Patient demographic and clinical characteristics (n = 102).

	Total (n = 102)	LCE (n = 52)	NBI (n = 50)	P value
Age – mean ± SD, years	64.9 ± 9.4	63.4 ± 9.7	66.4 ± 8.7	0.110
Male gender – n (%)	67 (66%)	39 (75%)	28 (56%)	0.043
Smoking habits – n (%)¹				
Never smoker	20 (21%)	7 (14%)	13 (28%)	0.107
Ever Smoker	76 (79%)	42 (86%)	34 (72%)	
Drinking habits – n (%)²				
Yes	69 (71%)	43 (86%)	26 (55%)	0.001
No	28 (29%)	7 (14%)	21 (45%)	
Previous treatment – n (%)				
EMR/ESD	7 (7%)	5 (10%)	2 (4%)	N/A
Radiotherapy	21 (21%)	14 (27%)	7 (14%)	
EMR and radiotherapy	3 (3%)	2 (4%)	1 (2%)	
Number of lesions – n (%)				
1	87 (85%)	44 (85%)	43 (86%)	N/A
2–3	13 (13%)	7 (13%)	6 (12%)	
≥4	2 (2%)	1 (2%)	1 (2%)	

SD, standard deviation; LCE, Lugol chromoendoscopy; NBI, narrow-band imaging; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; N/A, not applicable.

P value comparing LCE group versus NBI group.

¹ Missing data from 6 patients.

² Missing data from 5 patients.

Lugol chromoendoscopy versus NBI

There were more male patients in the LCE group than in the NBI group (75% vs. 56%, $P=0.043$). There were no differences in patient's age between groups.

► **Table 2** shows endoscopy and lesions characteristics in both groups. In the NBI group lesions 0-IIa were more frequent (37%) whereas in the LCE group were 0-IIb (60%). Lesions location and size and resection technique were similar between groups. The scope model was H180/H190/HQ190 in all patients in the NBI group (100% vs. 91%, $P=0.028$). Median follow-up time was longer in the LCE group (18. vs 8 months, 0.006).

The rate of complete lateral resection for invasive carcinoma was 90% in the LCE group and 94% in NBI group ($P=0.715$) and 65% and 67% ($P=0.813$), respectively, for dysplasia complete lateral resection (► **Table 3**). On multiple logistic regression, the results were similar after adjusting for previous local treatment, scope model, lesion size, morphology and histology and resection technique (Odds ratio [OR] 0.544, 95% Confidence interval [95% CI] 0.160–1.847, $P=0.329$ for cancer complete lateral resection; OR 0.590, 95% CI 0.219–1.592, $P=0.298$ for dysplasia complete lateral resection).

Complete lateral and deep resection for cancer and dysplasia was 45% and 54% in LCE and NBI group, respectively ($P=0.295$)

There were four cases of local recurrence: three (4%) in the LCE group and one (2%) in the NBI group ($P=0.627$). Additional treatment was necessary in 15% of patients in LCE group (one EMR, one ESD, four surgery and four chemoradiotherapy) and in 17% in the NBI group (four surgery, one radiotherapy and six chemoradiotherapy) ($P=0.697$).

Predictive factors of complete lateral resection

An exploratory analysis was performed to identify predictive factors for complete lateral resection for invasive carcinoma and dysplasia, namely previous local treatment, scope model, lesion location, size, morphology and histology and resection technique. The scope model (H180, H190 and HQ190 vs. 140 and 160 series) was the only factor associated with a higher cancer and dysplasia-free lateral margin (68% vs 17%, $P=0.017$).

Discussion

Herein, for the first time we compared the effectiveness of NBI and LCE in defining resection margins for esophageal SCC and dysplasia. We found that mucosal inspection with LCE before endoscopic resection of esophageal squamous cell lesions was not associated with increased complete lateral resection rate when compared to NBI alone. The rate of complete lateral and deep resection was also similar between groups. Furthermore,

► **Table 2** Endoscopy and lesion characteristics (n = 132).

	Total (n = 132)	LCE (n = 68)	NBI (n = 64)	P value
Endoscopist – n (%)				
P.D.	94 (71%)	47 (69%)	47 (73%)	N/A
H.P.	15 (11%)	9 (13%)	6 (9%)	
R.Y.	12 (9%)	11 (16%)	1 (2%)	
C.S.	5 (4%)	0(%)	5 (8%)	
R.D.	5 (4%)	0 (0%)	5 (8%)	
T.A.	1 (1%)	1 (2%)	0 (0%)	
Scope model – n (%)¹				
140/160	6 (5%)	6 (9%)	0 (0%)	<0.001
H180	51 (39%)	39 (59%)	12 (19%)	
H190/HQ190	73 (56%)	21 (32%)	52 (81%)	
Lesion location – n (%)				
Upper third	25 (18.9%)	12 (18%)	13 (20%)	0.816
Middle third	80 (60.6%)	43 (63%)	37 (58%)	
Lower third	27 (20.5%)	13 (19%)	14 (22%)	
Lesion size – median ± range, mm	30 (5–100)	22 (5–90)	30 (5–100)	0.123
Lesion morphology – n (%)²				
0-Is	6 (5%)	2 (3%)	4 (7%)	N/A
0-IIa	36 (29%)	13 (21%)	23 (37%)	
0-IIb	53 (42%)	38 (60%)	15 (24%)	
0-IIc	4 (3%)	2 (3%)	2 (3%)	
0-IIa + IIb	6 (5%)	4 (6%)	2 (3%)	
0-IIa + IIc	16 (13%)	3 (5%)	13 (21%)	
0-IIb + IIc	4 (3%)	1 (2%)	3 (5%)	
Resection technique – n (%)				
ESD	122 (92%)	64 (94%)	58 (91%)	0.522
EMR	10 (8%)	4 (6%)	6 (9%)	
Lesion histology – n (%)				
Invasive SCC	101 (76.5%)	51 (75%)	50 (78%)	N/A
High-grade dysplasia	25 (18.9%)	14 (21%)	11 (17%)	
Low-grade dysplasia	6 (4.5%)	3 (4%)	3 (5%)	
Follow-up – median ± range, months	13 (0–154)	18 (0–154)	8 (0–40)	0.006

LCE, Lugol chromoendoscopy; NBI, narrow-band imaging; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; SCC, squamous cell carcinoma; N/A, not applicable.
P value comparing LCE group versus NBI group.
¹ Missing data from two lesions.
² Paris Classification, missing data from seven lesions.

there were no differences in recurrence rate and need of additional therapies.

Esophageal cancers carry a high mortality mainly due to diagnosis in advanced-stage, with a five-year survival rate of less

than 10% [17]. Patients with superficial esophageal SCC, confined to the mucosa or submucosa, have a significantly better prognosis [17], with a 5-year survival rate exceeding 85% for pT1N0 lesions [18]. However, diagnosis of early stage esopha-

► **Table 3** Outcomes in the LCE and NBI group (n = 132).

	LCE (N=68)	NBI (N=64)	P value
Cancer-free lateral margin – n (%) ¹	46 (90%)	47 (94%)	0.715
Dysplasia free lateral margin – n (%) ²	44 (65%)	42 (67%)	0.813
R0 resection – n (%) ³	30 (45%)	34 (54%)	0.295
Local recurrence – n (%)	3 (4%)	1 (2%)	0.627
Metachronous lesions – n (%)	11 (16%)	6 (9%)	0.244

LCE, Lugol chromoendoscopy; NBI, narrow-band imaging.

¹ Included only invasive squamous cell carcinoma (n = 101)

² Missing data from one lesion.

³ Missing data from two lesions.

geal SCC and their precursor lesions can be difficult because of their flat and isochromatic appearance on conventional white-light imaging endoscopy [1, 4]. Lugol staining has long been the gold standard for detection of these lesions [5, 6]. Although it is a low-cost technique, it may have side effects and lead to complications [3, 6]. Therefore, new diagnostic strategies based on virtual chromoendoscopy, such as NBI, have been used for detection of superficial esophageal squamous cells carcinoma and dysplasia [7, 8].

Several studies have compared the accuracy of NBI and LCE for diagnosing esophageal SCC [4, 10, 11]. Only one prospective randomized controlled trial (RCT) have been published on this subject [4]. In this study, Goda et al compared the diagnostic accuracy of NBI magnifying endoscopy (NBI-ME) and lugol chromoendoscopy with pink-color sign assessment (LCE-PS) for superficial esophageal SCC in 294 patients, 147 in each arm. In per-patient analysis, there were no differences between NBI-ME and LCE-PS in sensitivity (82% vs 81%), specificity (95% vs 94%), positive predictive value (88 vs 85%), negative predictive value (92% vs 93%), and overall accuracy (91 vs 91%) for diagnosing superficial esophageal SCC. Median examination time with LCE-PS was 1.5 times longer than NBI-ME ($P < 0.001$). More recently, a meta-analysis compared the diagnostic accuracy of NBI and LCE in identifying esophageal HGD and/or SCC [12]. Twelve studies were included, 11 cross-sectional and one RCT, and 1911 patients were analyzed. The authors showed that NBI has a comparable sensitivity to that of LCE in both per-patient and per-lesion analysis (88% vs 92% and 94% vs. 98%, respectively), and a superior specificity (88% vs. 82%, $P < 0.001$ and 65% vs 37%, $P < 0.001$, respectively). Therefore, NBI presented the same rate of detection of esophageal HGD and SCC when compared to LCE, but was superior in differentiating HGD and SCC from other esophageal mucosa alterations. However, to our knowledge, there are no data comparing the effectiveness of NBI and LCE in delineating the esophageal SCC margin before endoscopic resection. Previous studies on superficial squamous neoplasms in the oropharynx showed that NBI is a useful tool in defining surgical resection margins of oral and oropharyngeal cancers, since it decreases the rate of positive superficial margins [19] and can also decrease recurrence

and improve survival as compared to traditional methods (visual examination alone and white-light nasoendoscopy) [20].

In the current study, the complete lateral resection rate was 66% for dysplasia and 92% for invasive carcinoma, comparable to that described in two single-center and one multicenter study on endoscopic resection of early esophageal SCC (lateral margins positive for carcinoma in 8.3% to 9.5% of lesions) [21–23]. It is interesting to note that local recurrence rate was inferior to complete lateral resection rate for dysplasia which may be due to pathological examination limitations due to cautery artifacts or due to cautery effect on non-resected adjacent mucosa. In the subgroup analysis in our study, the rate of complete lateral resection was similar between NBI and LCE for esophageal SCC (94% vs 90%) and dysplasia (67% vs 65%). The results were similar after adjusting for potential confounders. There were also no differences in the complete lateral and deep resection rate, relapse rate and need of additional therapies. The lower rates than expected for complete lateral resection for dysplasia might be due the fact that in the beginning of our experience we tried to avoid circumferential resections and to leave a small longitudinal band of mucosa. Other explanations may be due to the multifocal disease observed in some patients, rendering both LCE (with multiple unstained areas) and NBI (multiple brown areas) more difficult to assess, and the fact that 41% and 20% in LCE and NBI groups, respectively had undergone previous treatments with scarring and post-radiotherapy mucosal changes. We therefore suggest in multifocal esophageal disease to start delineation with NBI and magnification (and marking), and to use LCE only if multiple brown areas are confounding the global picture. Once LCE is used, the vascular features including IPCLs are lost. We would also like to emphasize that NBI+Nearfocus was able in certain cases to give more information on adjacent dysplastic mucosa (brown area) with normal LCE staining.

Our study has several limitations. First, it is a retrospective study including patients over an 18 years period. As such, different scope models were used during resection, including series 140 and 160 in LCE group which can reduce the rate of complete lateral resection in this group. In fact, we performed an exploratory analysis to detect predictive factors of complete lateral resection and more recent scope models (H180/H190/

HQ190) were associated with a higher cancer and dysplasia-free lateral margin. Moreover, the endoscopists were the same over the study period and therefore their skills in evaluating and resecting lesions improved over time. Second, lesion morphology was different between groups; for example, lesions 0-IIb were more frequent in the LCE group and it might be argued that it is more challenging to assess their lateral margins. Finally, the follow-up time is limited and was significantly longer in the LCE group, since NBI was introduced more recently; this can also influence the recurrence rate and need of additional therapies in the second group.

Conclusion

In conclusion, this is the first study comparing NBI and LCE for resection of esophageal squamous cells lesions and a considerable sample size was included. Mucosal inspection with LCE before endoscopic resection of esophageal squamous cells lesions was not associated with increased complete lateral resection rate when compared to NBI alone. Considering the increased availability of NBI, absence of side effects, possible shorter duration of the procedure as compared to LCE, and similar accuracy in detecting and probably delineating resection margins of SCC and precursor lesions, this technique may become the standard of care for this disease. Further confirmation of our findings in prospective randomized trials is required.

Competing interests

The authors declare that they have no conflict of interest.

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