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Structured oropharynx, hypopharynx and larynx assessment during routine esophagogastroduodenoscopy improves detection of pre- and early cancerous lesions: a multicenter, comparative study

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Authors

Alexander Huelsen[1,2], Andrew T. St John[1,2], Ratna Pandey[3], David E. Vokes[4], Jessica J. McMaster[1,2,5], Russell S. Walmsley[3,6], Gerald J. Holtmann[1,2,5,7]

Institutions

1 Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, Queensland, Australia
2 Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia
3 Department of Gastroenterology, North Shore Hospital, Waitemata District Health Board, Auckland, New Zealand
4 Department of Otorhinolaryngology, Head & Neck Surgery, Auckland City Hospital, Auckland, New Zealand
5 Translational Research Institute, Brisbane, Queensland, Australia
6 Faculty of Medicine, University of Auckland, Auckland, New Zealand
7 Faculty of Health and Behavioural Sciences, University of Queensland, Brisbane, Queensland, Australia

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author
Alexander Huelsen, Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, QLD 4102, Australia
Fax: +61731762111
Alexander.Huelsenkatz@health.qld.gov.au

ABSTRACT

Background and study aims A structured assessment of the oropharynx, hypopharynx and larynx (OHL) may improve the diagnostic yield for the detection of precancerous and early cancerous lesions (PECLs) during routine esophagogastroduodenoscopy (EGD). Thus, we aimed to compare routine EGDs ± structured OHL assessment (SOHLA), including photo documentation with regard to the detection of PECLs.

Patients and methods Consecutive patients with elective EGD were arbitrarily allocated to endoscopy lists with or without SOHLA. All detected OHL abnormalities were assessed by an otolaryngologist-head & neck surgeon (ORL-HNS) and the frequency of PECLS detected during SOHLA vs. standard cohort compared.

Results Data from 1000 EGDs with and 1000 EGDs without SOHLA were analyzed. SOHLA was successful in 93.3 % of patients, with a median assessment time of 45 seconds (interquartile range: 40–50). SOHLA identified 46 potential PECLs, including two benign subepithelial lesions (4.6 %, 95 % CI: 3.4–6.1) while without SOHLA, no malignant and only one benign lesion was found ($P<0.05$). ORL-HNS imaging review classified 23 lesions (2.3 %, 95 % CI: 1.5–3.4) as concerning and ORL-HNS clinic assessment was arranged. This identified six PECLs (0.6 %, 95 % CI: 0.2–1.3) including two pharyngeal squamous cell lesions (0.2 %) demonstrating high-grade dysplasia and carcinoma in situ (CIS) and four premalignant glottic lesions (0.4 %) demonstrating low-grade dysplasia and CIS.

Conclusion In the routine setting of a gastrointestinal endoscopy practice precancerous and early cancerous lesions of the oropharynx, hypopharynx, and larynx are rare (< 1 %) but can be detected with a structured assessment of this region during routine upper gastrointestinal endoscopy.

Introduction

During a standard esophagogastroduodenoscopy (EGD), the oropharynx, hypopharynx, and larynx (OHL) can be visualized on high-definition video imaging with a resolution comparable to standard flexible rhinolaryngoscopes used by otolaryngologist-head & neck surgeons (ORL-HNS). Precancerous or early cancerous lesions (PECLs) in the OHL region are generally asymptomatic unless located on the true vocal cords. They are commonly considered head and neck cancers (HNC) and represent between 3.5% to 4% of cancers diagnosed in Australia, North America, and Europe [1–5]. There is insufficient evidence to justify screening for HNC in the general population [6–8] and in the absence of population screening, most patients remain undiagnosed until the condition has progressed to a symptomatic and more advanced stage [2, 9]. However, the early detection of HNC and its precursors is crucial to minimize the burden of treatment on the patient, and to optimize prognosis and quality of life [10–14].

While occasionally OHL lesions are found during routine endoscopy, a structured OHL assessment (SOHLA) may increase the diagnostic yield of EGDs in relation to the identification of these lesions. Indeed, incorporating an assessment of the OHL during routine EGDs performed for other indications to potentially detect early stage pathology has been suggested as early as 1977 [15]. While some preliminary studies have been performed, they lacked the direct comparison to our recommended quality standard of upper gastrointestinal endoscopy and were not performed with the currently available high-definition imaging equipment [16–21].

Thus, the aim of this study was to determine if the diagnostic yield of a structured OHL assessment during elective EGDs is superior to current practice, with regard to the identification of PECLs [5, 22–24].

Patients and methods

Study design

This prospective, multicenter, non-matched, comparative study was conducted in three Gastroenterology endoscopy units over a 2½-year period, including a large tertiary referral hospital (Australia; main study site), a medium sized secondary level hospital (New Zealand) and a smaller peripheral hospital (Australia). The study protocol was submitted, reviewed and approved by the Human Research Ethics Committees (Metro South HREC/15/QPAH/411; LNR/2020/QTDD/59418; WDHB/Ref:RM14566). Due to the observational nature the study was considered by the Ethics committee as a low risk study and waiver of consent granted. Since the study only reported observations without allocating patients to specific treatments for the purpose of a trial and patient allocation was arbitrarily aligned with routine clinical practice the study was not registered in a trial registry. All authors had access to the study data and reviewed and approved the final manuscript.

Participants

The prevalence of PECLs in the general population is reportedly 0.08% to 1% and therefore, a cohort size of 1000 patients each was deemed appropriate to investigate the study hypothesis [17–21, 25]. The inclusion criteria were adult (age >16) patient and booked for an elective EGD onto one of the participating endoscopists' general gastroenterology procedure lists. During the study, consecutive patients referred for elective EGD were arbitrarily allocated by the administrative staff to a general endoscopy list either with or without SOHLA. Exclusion criteria were non-elective and/or emergent EGDs performed for acute upper gastrointestinal bleeding, foreign body ingestion or EGDs performed under general anesthesia and patients with a prior or current diagnosis of a premalignant lesion or cancer in the upper aerodigestive tract; or a prior or current diagnosis of esophageal squamous cell dysplasia/cancer.

Structured oropharynx, hypopharynx and larynx assessment (SOHLA)

A structured examination of the OHL was performed, which included photo documentation of key anatomical regions, with at least five images. This included views of the palate, posterior oropharynx, larynx (including the post cricoid region), and the left and right piriform fossae (▶ **Fig. 1**). Additional images were captured if any abnormalities were identified.

Data collection and primary and secondary study outcomes

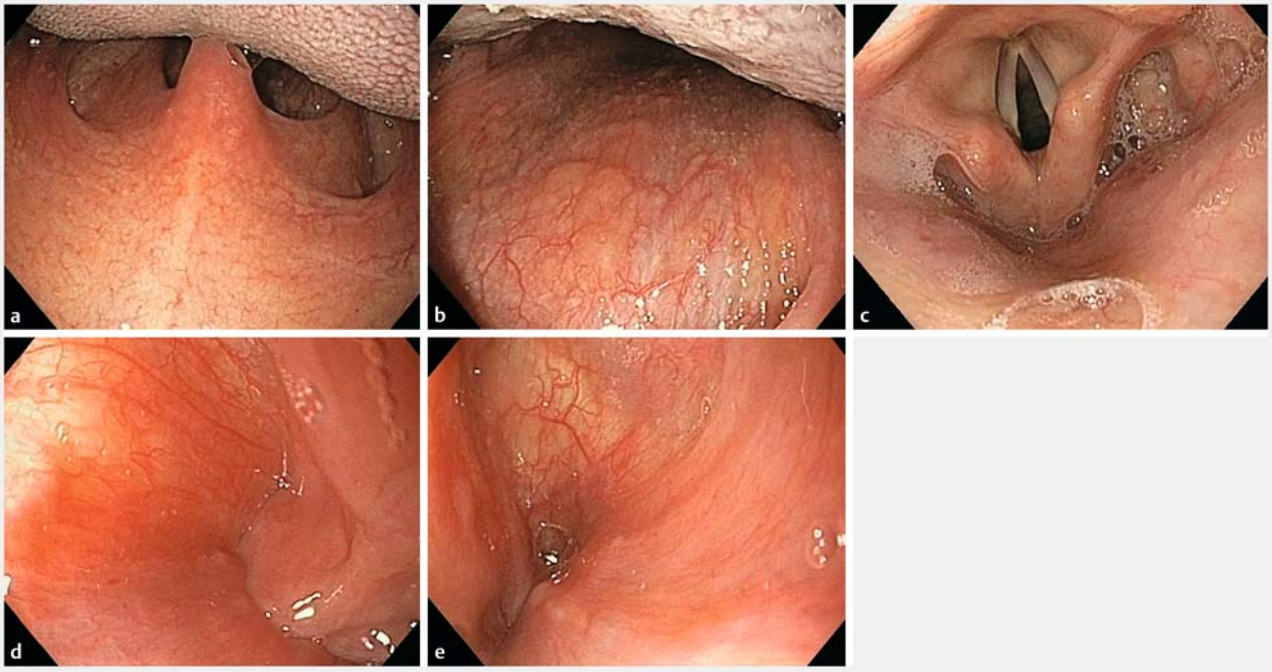
The data collected included patient demographics, type of sedation used, assessment time, completion rate, complications, findings and the details of ORL-HNS/ear, nose and throat (ENT) review, if required.

During the study design phase, the tolerability of the SOHLA (and thus the ability to perform the assessment without interruption) was dependent on the occurrence of gagging and/or coughing, and in the unsedated group, also on patient anxiety. The impact of these factors was graded by the endoscopist on a scale from 0–4 (0 = nil; 1 = mild; 2 = moderate; 3 = assessment interrupted but able to complete EGD; 4 = assessment interrupted and unable to complete EGD). Significant complications were defined as bleeding requiring medical intervention, laryngospasm or injury to the true vocal cords, mucosal tear or perforation.

The primary outcome of this study was PECLs detection rate and secondary outcomes were time required for a SOHLA, SOHLA completion rate and tolerability, detection rate of benign abnormalities, adverse events and health cost analysis.

SOHLA cohort and follow up

The SOHLA cohort included 1000 consecutive elective EGDs performed by three gastroenterologists and experienced endoscopists, each of whom was trained in a different country (Australia, UK, New Zealand) following the national training pathway. The participating endoscopists underwent a single teaching session that included review of the OHL anatomy and common pathological findings. The EGDs were performed with



▶ **Fig. 1** Imaging documentation during structured oropharynx, hypopharynx and larynx assessment. **a** Palate. **b** Posterior oropharynx. **c** Larynx. **d, e** Left and right pyriform fossa.

high-definition adult gastroscopes (GIF-HQ190; Olympus, Tokyo, Japan) using white light as the SOHLA standard. Possible mucosal abnormalities were also assessed with magnifying endoscopy and narrow-band imaging (NBI). A distal cap attachment (12.4 mm; Olympus, Tokyo, Japan) was used at the discretion of the endoscopist. The procedures were performed according to the unit-specific protocols either without sedation, with sedation provided by the endoscopist using a combination of intravenous fentanyl and midazolam, or by an anesthetist using propofol. Topical lignocaine 1 % spray was used at the discretion of anesthetist or proceduralist.

Abnormal findings were discussed with an ORL-HNS, and after imaging review ORL-HNS or ear, nose and throat specialist (ENT) clinic follow-up (depending on study site) was arranged for any concerning lesions.

Non-SOHLA control cohort

The control cohort was composed of 1000 consecutive elective EGDs performed by four experienced gastroenterologists (> 5 years after completion of training and > 5000 endoscopic procedures performed) during the study period, and which fulfilled the inclusion criteria. All procedures were identified and included after the study period to eliminate any change in assessment practice and the reports were reviewed in regard to abnormalities identified in the OHL region. Endoscope insertion time measurements were not available due to the retrospective nature of this cohort. All four endoscopists adhered to the recommended quality standards of upper gastrointestinal endoscopy (as per American Society for Gastrointestinal Endoscopy [ASGE], European Society of Gastrointestinal Endoscopy [ESGE], British Society of Gastroenterology [BSG]/Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland [AUGIS]) which currently do not include a structured OHL assessment [22–24]. Their endoscopy training was undertaken following the Australasian training scheme and three of the specialists also had extensive endoscopy experience within the British system during fellowship training.

Cost analysis

A health economic cost analysis was performed using estimates of $ 1800 (proceduralist sedation or no sedation) and $ 2200 (sedation by an anesthetist with anesthetic nurse support) per 1 hour of endoscopy room time in the tertiary hospital, to calculate the costs of a SOHLA, and per identified PECL.

Statistical analysis

For all quantitative measures, normality of distribution was assessed using the Shapiro-Wilk normality test. All quantitative data was non-parametric, thus the Mann-Whitney U test or Kruskal-Wallis test was used, depending on the number of groups. The Pearson chi-square or Fisher's exact tests were used for all categorical data, depending on the expected value of the cells. Post-hoc subgroup analysis was performed where there were more than two groups and corrected for multiple comparisons (Bonferroni correction). Missing data were not imputed. To apply direct age-adjustment to the PECL rates, the age-specific rate of PECLs in specific age strata of the study population (< 30 years of age, 30 to 50 years of age, and > 50

▶ **Table 1** Comparison table of non-SOHLA and SOHLA cohort.

		Non-SOHLA	SOHLA	*P* value
Age	Median (IQR) in years	57 (44–68)	60 (47–71)	0.001[1]
Gender	female in %	46.7 %	51 %	0.87[2]
Anesthesia type	nil/P/A in %	0.2 / 27.3 / 72.5	28.4 / 32.4 / 39.2	<0.001[2, 3]
Overall findings	n = (%)	1 (0.1 %)	46 (4.6 %)	<0.0001[4]
PECLs	n = (%)	0 (0 %)	6 (0.6 %)	0.03[4]
Aborted procedures	n = (%)	1 (0.1 %)	1 (0.1 %)	>0.99[4]
Complications	n = (%)	0 (0 %)	1 (0.1 %)	>0.99[4]

SOHLA, structured oropharynx hypopharynx and larynx assessment; P, proceduralist sedation using midazolam and fentanyl; A, anesthetist sedation using propofol; PECLs, pre- and early cancerous lesions.
[1] Results analyzed by Mann-Whitney U test
[2] Results analyzed by chi-square test
[3] Bonferroni post-hoc significant ($P<0.05$) for all sedation groups between non-SOHLA and SOHLA groups.
[4] Results analyzed by Fisher's exact test

years of age) was multiplied by the appropriate weight of the control cohort. The sum of these products is the age-adjusted incidence, or age-standardized rate. All statistical analyses were performed with IBM Statistical Package for Social Sciences (SPSS) Version 26 (IBM Corp., Armonk, New York, United States) and figures were generated using GraphPad Prism, Version 8 (GraphPad Software Inc., La Jolla, California, United States). A two-tailed $P<0.05$ was considered statistically significant.

Results

Patient demographics

A total of 2000 eligible patients were recruited over a 30-month period. Patient demographics and patient flow diagram are presented in ▶ **Table 1** and ▶ **Fig. 2**.

Completion rate

A complete SOHLA was successfully performed in 93.3 % of patients requiring a median of 45 seconds (IQR: 40–50 seconds). While we determined the required time for SOHLA (insertion and inspection), the insertion time alone was not captured. A partially successful or unsuccessful assessment was performed in 4.3 % and 2.4 % of patients, respectively. There was a significant difference in completion rates across the different sedation groups ($P=0.001$; ▶ **Table 2**).

All study endoscopy lists were booked and completed within the standard endoscopy unit protocol. Throughout the entire study period, no procedure had to be cancelled as a result of time overruns caused by the addition of SOHLAs.

Tolerability

Of the patients, 32.8 % tolerated the SOHLA without any signs of discomfort (rating 0), while mild or moderate signs of discomfort were documented in 34.3 % and 17.5 % of the cases, respectively (rating 1 and 2). The assessment was completed without interruption in 84.6 % of cases (rating 0–2) and with interruption in 15.3 % of cases (rating 3). The assessment and the entire gastroscopy had to be abandoned in 0.1 % of cases (rating 4) due to severe anxiety in one unsedated patient.

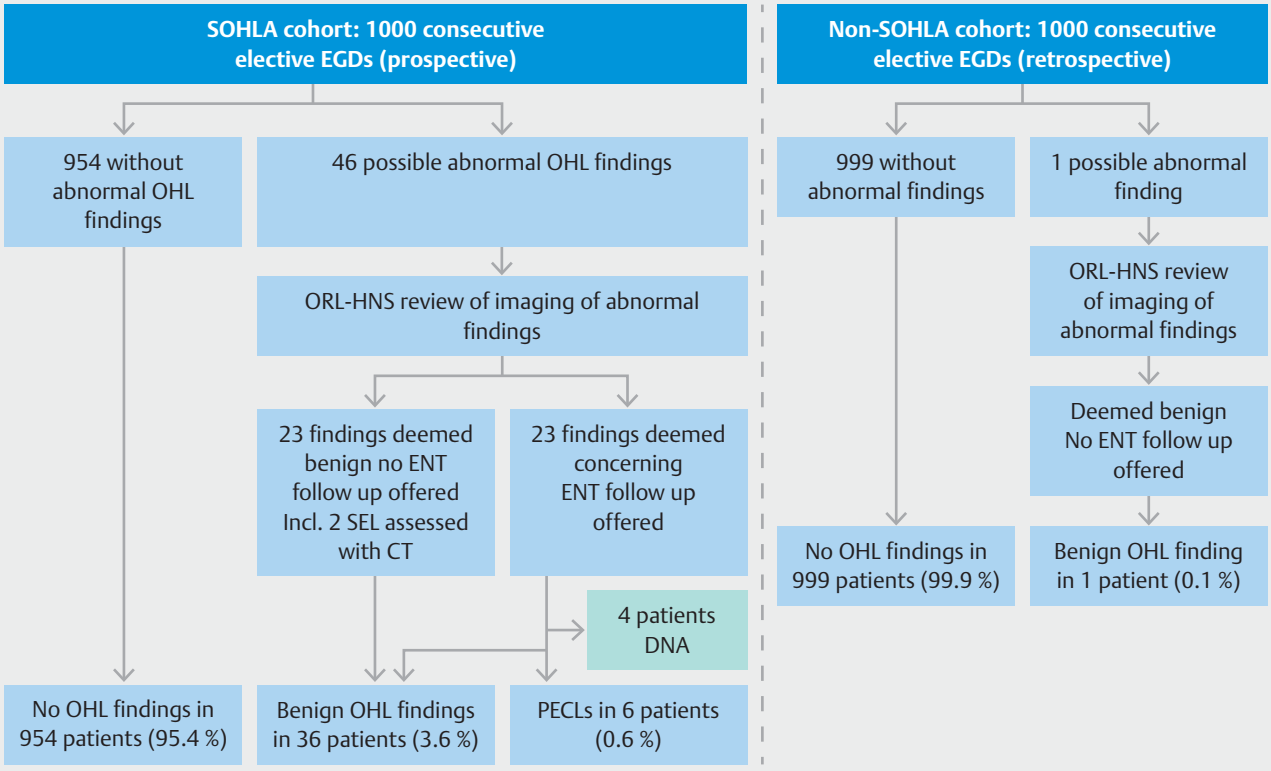
The tolerability of SOHLA was also compared across the various sedation groups by grouping the tolerability ratings into tolerated (= rating 0–2) and not tolerated (= rating 3, 4) and an advantage was identified for proceduralist sedation compared to no sedation ($P<0.01$; ▶ **Table 2**).

SOHLA cohort findings

SOHLA identified 46 abnormalities in 46 patients. The images were reviewed by an ORL-HNS and 21 lesions were classified as benign. This included multiple cases of prominent oropharyngeal lymphoid tissue and tonsils, torus palatinus, pharyngeal mucus retention cysts and denture related mucosal irritation. In two patients, asymmetric pharyngeal anatomy with normal mucosa raised the possibility of subepithelial lesions. These patients underwent contrast computed tomography (CT), which revealed an anterior osteophyte and a medialized carotid artery underlying (▶ **Fig. 3**).

In 23 patients (2.3 %), the lesions appeared concerning and an ORL-HNS/ENT follow-up was offered. This resulted in a histological confirmation of six PECLs (95 % CI 0.2–1.3) with two pharyngeal squamous cell lesions (0.2 %; high-grade dysplasia and carcinoma in situ (CIS)). In four patients, vocal cord lesions were confirmed as leucoplakia (0.4 %) with a histological diagnosis of CIS and low-grade dysplasia. Five lesions were confirmed as squamous papillomas without dysplasia (0.5 %) (▶ **Fig. 4**). The remaining patients demonstrated single cases of neurofibroma, vocal cord granuloma, melanotic lesion, and a denture irritation fibroma. Four patients did not attend follow-up.

With a SOHLA the number needed to diagnose one PECL was 167 cases.



▶ **Fig. 2** Flow diagram of patients in the SOHLA and non-SOHLA cohort. SOHLA, structured oropharynx, hypopharynx and larynx assessment; EGD, esophagogastroduodenoscopy; OHL, oropharynx, hypopharynx and larynx; ORL-HNS, otolaryngologist-head&neck surgeon; ENT, ear, nose and throat specialist; SEL, subepithelial lesion; CT, computed tomography; DNA, did not attend; PECLs, precancerous or early cancerous lesions.

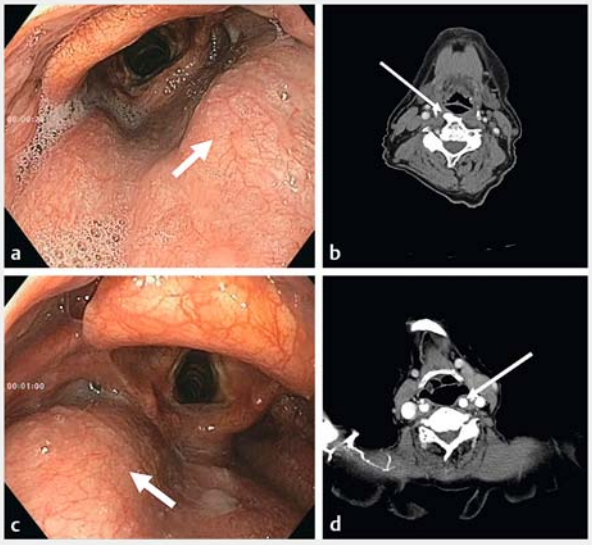
▶ **Table 2** Comparison of procedural outcomes by sedation type in the SOHLA cohort.

	Unsedated	Proceduralist-sedated	Anesthestist-sedated	*P* value
Tolerability (no. who tolerated and %)	226 (79.9 %)	289 (89.2 %)[1]	331 (84.7 %)	0.006[2]
Completion rate (no. who completed assessment and %)	254 (89.4 %)	300 (92.6 %)[3]	379 (96.7 %)[1]	0.001[2]
Assessment time (s)	45 (40–50)	45 (40–50)	45 (40–55)[1]	0.002[4]

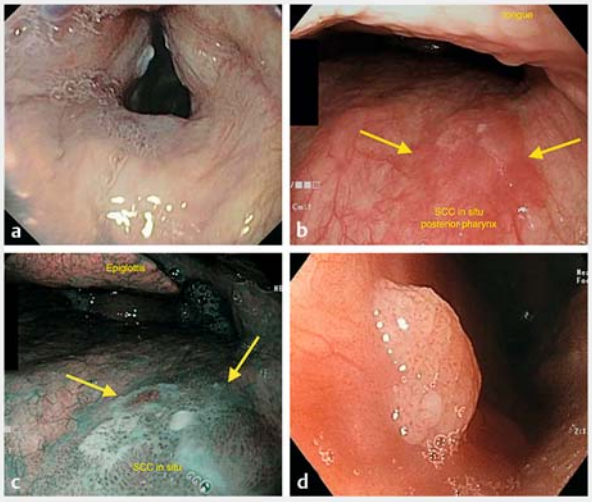
SOHLA, structured oropharynx hypopharynx and larynx assessment.
[1] For Bonferroni post-hoc analysis: $P<0.01$ vs unsedated
[2] Results displayed as number (%) or median (IQR) and assessed by chi-square test for overall comparisons
[3] For Bonferroni post-hoc analysis: $P<0.01$ vs anesthetist-sedated
[4] Results displayed as number (%) or median (IQR) and assessed by Kruskal-Wallis test for overall comparisons

Control cohort findings

The control cohort of 1000 consecutive EGDs performed without SOHLA was gender matched. A median age difference of 3 years between the cohorts was present. Correcting for age did not affect the study results. The OHL region was mentioned in the endoscopy report in three cases (0.3 %). This included a palate lesion documented with a photograph and an ENT referral was recommended. The image demonstrated a benign torus palatinus (▶ **Fig. 5**). The two further endoscopy reports commented on a normal hypopharynx backed by a single image in one case. Imaging documentation without any comments in the report or picture legend were found in 23 reports. In 22 cases, there was a single image of the larynx (with full vision of vocal cords in 15) and in one patient there was a partial view of the posterior oropharynx. In 974 procedures (97.4 %), the OHL region was neither mentioned nor imaged. There was a significant difference in overall findings and identified PECLs between the SOHLA and non-SOHLA cohorts (▶ **Table 1**)



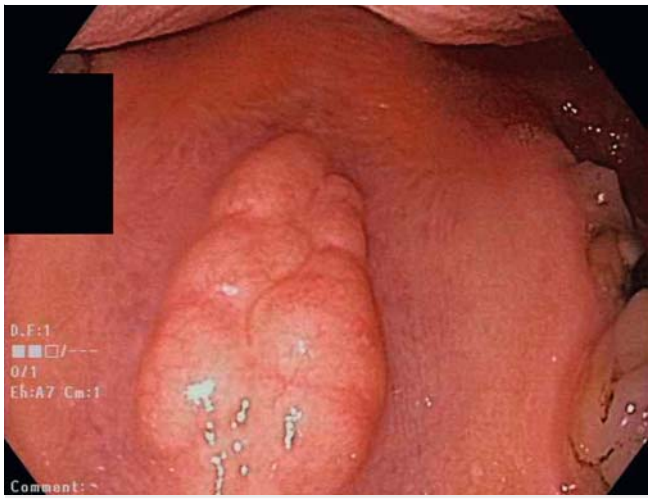
▶ **Fig. 3** Asymmetric posterior oropharynx subepithelial lesions correlated with axial computed tomography image. **a, b** Right-sided anterior osteophyte. **c, d** Prominent left-sided medialized carotid artery.



▶ **Fig. 4** **a** Leukoplakia on the left vocal cord. **b, c** SCC in situ posterior oropharynx in high-definition white light and narrow-band imaging. **d** Benign squamous papilloma posterior oropharynx.

Adverse events

One patient receiving propofol sedation developed a laryngospasm during the SOHLA. The anesthetic team treated the laryngospasm and the EGD was completed without OHL assessment. The patient recovered without any sequelae.



▶ **Fig. 5** Procedure report image of the single abnormality identified in the non-OHL assessment cohort demonstrating a torus palatinus: a benign bony exostosis arising in the midline of the hard palate.

Costs

Using the median SOHLA duration of 45 seconds, the cost per SOHLA was calculated as $ 27.50 with anesthetic support and $ 22.50 without anesthetic support. Therefore, the cost to identify one PECL (1 PECL per 167 cases) was $ 4593 with anesthetic support, and $ 3758 without anesthetic support.

Discussion

This is the first large, prospective study to assess and compare the diagnostic yield of a structured oropharynx, hypopharynx and larynx assessment (SOHLA) utilizing current routine endoscopy equipment with high-definition imaging capabilities with routine clinical practice. While with a SOHLA, PECLs were detected in 0.6 % of patients (95 % CI 0.2–1.3), the detection rate in the control group of routine endoscopies without SOHLA was 0 % ($P < 0.05$).

The SOHLA was completed in > 90 % of all patients with a median assessment time of 45 seconds. The assessment was highly feasible in both unsedated and sedated patients, though sedation improved SOHLA tolerability and completion rates. Neither the completion rate nor the safety of the esophagogastroduodenoscopy (EGD) was compromised by the addition of a SOHLA. Similarly, the overall procedural activity (number of procedures performed per 4-hour list) was not reduced, despite an increase in procedure time with the addition of SOHLA to all elective EGDs.

This study demonstrates for the first time the added benefit of a SOHLA, in the context of routine upper gastrointestinal endoscopies that are performed compliant with the current quality standards for upper gastrointestinal endoscopy (ASGE, ESGE, BSG/AUGIS, [22–24]). SOHLA was able to identify a significant number of structural lesions (PECLs) in the OHL region, which likely would have been missed during routine upper GI endoscopy without SOHLA. Thus, SOHLA significantly im-

proved the value proposition of routine upper gastrointestinal endoscopy.

While we conducted a prospective, controlled multicentre cohort study, very similar results were reported from a retrospective single-center study, where a 0.26 % detection rate of pharyngeal cancer was observed [26]. Similarly, in a study from Greece, precancerous laryngeal lesions were found in 0.35 % of their cases [16]. Other studies reported precancerous and early cancerous lesion detection rates between 0.08 % and 1 % [17–21, 25].

Overall, we identified 46 lesions (4.6 %) in our SOHLA group, including six (0.6 %) PECLs, whereas only a single lesion and no PECLs were identified in our control group. In 97.4 % of cases in the control group, there was no documented evidence that any form of OHL assessment had been undertaken. This supports our hypothesis that with minimal training and the introduction of a structured OHL assessment, endoscopists will identify PECLs that otherwise would be missed in the routine setting. Indeed, a previous editorial has emphasized that passing through the OHL region without adequate examination to identify the subtle changes of early neoplasia is a missed opportunity that should not be accepted anymore [27]. Our data provide further evidence to support this statement.

The six previous studies had limitations that we aimed to address in our study. Some of these studies had small sample sizes [17, 20], or were retrospective [21], or the available imaging technology would now be considered outdated [17, 18, 21] and no study had an appropriate control arm to determine the gain in diagnostic yield [16–21]. In addition, variable criteria to define 'relevant' lesions were used.

Mucus retention cysts and enlarged lymphoid tissue (including tonsils) were reported as pathology, but these findings are not usually associated with symptoms or disease, thus exaggerating the overall prevalence of pathology, which was reported to occur in 0.9 % to 15 % of cases [16–20]. Three of the studies detected mostly laryngitis, whereas the other two studies, as well as the current study, did not report laryngitis at all. This may indicate that prestudy training introduced bias, leading to the preferential diagnosis of specific pathologies by examiners.

The vast majority of premalignant and early malignant lesions in the OHL are squamous cell lesions. The main risk factors are human papillomavirus (HPV) infections, significant alcohol use, and smoking; additional risk factors include low intake of vegetables, male gender and age >50 years [28–30]. Synchronous and metachronous squamous cell lesions in the OHL and esophagus are common [31]. The selection of patients for an OHL assessment on the basis of these risk factors has been proposed to improve the efficiency and detection rate of the OHL assessment. However, given that a SOHLA adds less than a minute to an upper gastrointestinal endoscopy, it may take less time to perform that SOHLA than to review clinical details and determine if a SOHLA should be performed in a given patient. Furthermore, determining the HPV infection risk requires an accurate sexual history of orogenital contact, which may be difficult to elicit in the endoscopy unit. Thus, a structured OHL assessment in all patients is practical, efficient, and may identify squamous and non-squamous pathology that would be overlooked otherwise. However, patients with a known history of squamous cell lesions in the head and neck or esophageal region should preferentially also be screened and surveilled by an otolaryngologist, given the high risk for synchronous or metachronous lesions in the entire head and neck region.

Using the current study's results, it is not required to reduce the caseload of patients undergoing routine upper gastrointestinal endoscopy per hour if SOHLA is done routinely. Thus, while approximately 45 seconds are required to perform a SOHLA, it is likely that this can be delivered without any additional costs. Especially given the consideration that endoscope insertion without SOHLA also does require some time, though this may be only a few seconds in the extreme. However, even considering the full costs of an endoscopy room (in our setting, less than $ 30 per minute) and theoretically comparing it to a scope insertion without SOHLA performed within an instant, it is likely that SOHLA remains cost-effective, given the benefit of an early detection of PECLs. Based upon the number of PECLs identified in our study, this results in less than $ 5000 per detected PECL, which is likely cost-effective, given the costs associated with the treatment of advanced cancers in the OHL region.

The current study is not without limitations. First, participating endoscopists underwent only a single training session, which may have affected the recognition of OHL pathology. Second, high-definition white light (HDWL) endoscopy was the study standard for OHL assessment. Magnification and NBI were used to assess mucosal abnormalities if identified with HDWL. This may have reduced the lesion detection rate based on the excellent and growing evidence demonstrating improved detection and delineation of squamous cell lesions using imaging enhanced endoscopy [32–35]. However, current endoscopy guidelines recommend using enhanced imaging as a general standard only in patients were squamous neoplasia is suspected and such patients were excluded from this study [5, 22]. Third, the ENT assessment may have been affected by the quality of the available images. Thus, while the study's SOHLA may have underestimated the prevalence of clinically relevant lesions, two previous studies which included a video review of all patient exams by an ENT specialist demonstrated a sensitivity of 84.6 % to 100 % and a negative predictive value of 99.3 % to 100 %, suggesting that only a very small number of lesions were missed [16, 19].

Any screening strategy is associated with potential harm, such as psychological consequences owing to false-positive tests, or the treatment of lesions that may not have progressed. However, this is not an additional screening test, as the OHL region is usually visualized with high-definition imaging while passing the endoscope distally. This region should not be ignored during routine upper gastrointestinal endoscopy. As an analogy, it is not considered acceptable for radiologists to focus only on the requested area of interest in a cross-sectional imaging study.

Conclusion

This prospective, controlled cohort study of structured oropharynx, hypopharynx, and larynx assessment (SOHLA) during elective upper gastrointestinal endoscopy demonstrates that it is feasible and superior to current practice in identifying PECLs in this region. Since early detection may allow minimally invasive curative therapy associated with a significantly improved patient outcome, performing a SOHLA during routine endoscopic procedures will add value to clinical practice.

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Competing interests

The authors declare that they have no conflict of interest.

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