The role of NBI with flexible video-endoscope in the follow-up of head and neck cancer patients: a prospective study

Francesca Boscolo Nata[1] · Nicoletta Gardenal[1] · Fabiola Giudici[2] · Giancarlo Tirelli[1]

Abstract

Purpose Narrow band imaging (NBI) enhances mucosal vasculature and could help in the identification of recurrences. We assessed the effectiveness of NBI with flexible video-endoscope in the early detection of recurrence after treatment of head and neck squamous cell carcinoma, its diagnostic advantage over high-definition white-light (HD WL) endoscopy, also in relation to recurrence site, and the influence of previous radiotherapy (RT) or chemotherapy (CT). Moreover, we investigated the association between index tumor site and the risk of developing recurrence, and the relation between index tumor site and recurrence site.

Methods From January 2018 to November 2020, 160 patients previously treated with surgery and/or RT ± CT were evaluated using NBI with flexible video-endoscope. Sensitivity, specificity, positive/negative predictive value, and accuracy were calculated for NBI and HD WL, and compared using the McNemar test. The Fisher exact test was used to compare the other associations investigated.

Results The difference between NBI and HD WL sensitivity was statistically significant ($p < 0.001$). The NBI diagnostic advantage was 62.5%, highest in the hypopharynx ($p = 0.05$), and was not influenced by previous RT or CT ($p = 0.49$). Index tumor site statistically related with recurrence site ($p < 0.001$), but not with the risk of developing recurrence ($p = 0.81$).

Conclusion NBI with flexible video-endoscope could represent a valid option to detect recurrence early during the follow-up, especially in a difficult-to-visualize site such as the hypopharynx.

Keywords NBI-flexible-video-endoscopy · Follow-up · Early detection · Second primary tumor · Recurrence · Radiotherapy

Introducion

According to the "field cancerization" phenomenon, carcinogenic agents act extensively in head and neck mucosa, so that multiple precancerous lesions can develop around the index tumor, each one potentially becoming a new tumor [1]. This explains why, during the follow-up period, patients with head and neck squamous cell carcinoma (HNSCC) are at risk of developing other tumors, which are the most important cause of long-term mortality [2]; additionally, it justifies the lack of improvement in survival reported in recent decades [3].

The Warren and Gates criteria, later modified by Hong et al. allow differentiation between local recurrence (LR) and second primary tumor (SPT). More recently, Braakhuis et al. introduced molecular assessment to discern SPT from secondary field tumor (SFT) [4].

Beyond the definition, it is evident how endoscopy plays a crucial role in detecting these tumors early during the follow-up. Muto et al. [5] were the first to underline the importance of NBI for the early diagnosis of oropharyngeal and hypopharyngeal cancer, validating its use for such a purpose.

NBI is an endoscopic technique that allows the passage of only blue (415 nm) and green (540 nm) light, which are absorbed by mucosal capillaries and submucosal vessels, respectively. This ensures a significantly higher contrast between blood vessels and the surrounding tissue. Changes

✉ Francesca Boscolo Nata
francesca.boscolonata@gmail.com

[1] ENT Clinic, Head and Neck Department, Azienda Sanitaria Universitaria Giuliano Isontina, Strada di Fiume 447, 34149 Trieste, Italy

[2] Unit of Biostatistics, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padova, Italy

in vascular structure and architecture are early phenomena in the carcinogenesis process [6], thus NBI allows the early identification of mucosal tumors by recognizing these vascular alterations.

The utility of NBI has been demonstrated in different scenarios in HNSCC: it allows identification of the primary tumor in the case of neck metastasis of unknown origin [7]; if a tumor is macroscopically visible it better delineates its superficial extension with important implications for guiding the surgical resection [8]. In the case of potentially malignant disorders such as leukoplakia, erythroplakia and oral lichen planus [9] NBI improves the diagnostic accuracy for the early recognition of malignant transformation [10–13].

In consideration of the previously reported risk of recurrence, NBI is extremely important also during the follow-up.

In a previous paper [14], we reported the efficacy of NBI with rigid endoscope for the early diagnosis of oral and oropharyngeal SPT and LR during the follow-up of patients previously treated for HNSCC. However, rigid endoscopy has some limitations: it can cause patient discomfort, especially in the case of important gag reflex, and visualization of the larynx and hypopharynx may be challenging because of the distance of the endoscope from the area of interest. Conversely, the use of NBI with flexible video-endoscope is better tolerated by the patient and allows closer inspection of the laryngeal and hypopharyngeal subsites with the tip of the endoscope, with in-depth visualization of mucosal and submucosal vascular patterns and without the need for local spray anesthesia in the majority of patients.

These advantages are even more important considering that the hypopharynx is the second most frequent location to be affected by SPT, after the oropharynx [2] or oral cavity [15], and that SPT is usually detected at an advanced stage. Visualization of this area is therefore mandatory.

The first aim of the present study was to assess the efficacy of NBI with flexible video-endoscope in the diagnosis of LR, SPT and SFT during the follow-up of HNSCC patients. For practical issues, we globally called "recurrence" the combination of LR, SPT and SFT.

We investigated the NBI advantage in comparison to high-definition (HD) white-light (WL) endoscopy in the diagnosis of recurrence, and the possible impact of previous radiotherapy (RT) ± chemotherapy (CT). Moreover, the NBI diagnostic advantage was stratified according to recurrence site. In consideration of the more accurate examination of hypopharynx allowed by the flexible video-endoscope, we verified whether the early hypopharyngeal lesions revealed by NBI were detectable by radiologic imaging. Moreover, the association between index tumor site and the risk of developing recurrence, and the relation between index tumor site and recurrence site were investigated.

Materials and methods

NBI is routinely used at our Department during the follow-up assessment of patients previously treated with surgery and/or RT ± CT for HNSCC. Specifically, since January 2013 NBI with rigid endoscope (10 mm and 70°) has been used during outpatient visits for the inspection of oral and oropharyngeal subsites.

The present study was prospectively performed from January 2018 to November 2020. Patients previously treated with surgery and/or RT ± CT for oral, pharyngeal, laryngeal or unknown primary cancer, who underwent at least two NBI evaluations at our Department during the study period, were included in the study cohort; patients with previous paranasal sinus and nasopharyngeal cancer were excluded from this study because of the different etiological factors and clinical behavior of such neoplasms. NBI with flexible video-endoscope HD ENF-VH, Visera Elite II OTV-S200 videoprocessor, and OEV 262H full HD monitor (Olympus Medical Systems Corp, Tokyo, Japan) were used for the examinations.

This study was approved by the Trieste University Hospital Institutional Review Board (73/2012) and patients gave their written informed consent for the use of their data and anonymized pictures.

Endoscopic examinations were performed by one of the two ENT doctors experienced in NBI use (FBN, GN), and then recorded and stored for subsequent re-evaluation by the other.

During the outpatient examinations, the flexible video-endoscope was first used to visualize the oral cavity and oropharynx; then the endoscope was passed through the nasal cavity up to the nasopharynx; finally, the base of the tongue, vallecula, larynx, pyriform sinuses, post-cricoid area, and posterior hypopharyngeal wall were visualized. Topical (nasal and oropharyngeal) anesthesia with lidocaine spray 10 g/100 ml was used only if necessary to reduce the patient's discomfort. If mobile dental prostheses were present, the patient was asked to remove them before the examination.

The different anatomic areas were examined both with HD WL and, by pressing a button on the endoscope, with NBI. Patients were asked to say "U" and to perform a modified Valsalva maneuver [16] to better visualize the pyriform sinus.

Endoscopy under WL was considered "positive" in the case of persistent and demarcated red lesions, white lesions, elevated lesions, and ulcerative lesions. NBI was defined "positive" according to the pattern previously described for the oral cavity [17, 18], oropharynx and hypopharynx [5, 8, 19, 20], and larynx [21].

If a positive NBI pattern was found in the oral cavity and oropharynx and the two examiners agreed on the positivity of the findings, an incisional biopsy under local anesthesia was performed. If a suspicious NBI pattern was identified in the hypopharynx and larynx (except for the vocal folds), patients were scheduled for head and neck computed tomography (CT) with contrast and/or magnetic resonance imaging (MRI) with contrast, and incisional biopsy in the operating room on direct laryngoscopy was planned. In the event of a suspicious NBI pattern in the vocal folds, we also performed videolaryngostroboscopy. When the mucosal wave was preserved on videolaryngostroboscopy, patients were subjected to excisional biopsy by subepithelial (type I) or subligamental (type II) cordectomy (according to intraoperative saline infusion into the Reinke space) on direct laryngoscopy [22]. If the mucosal wave was absent, patients underwent contrast-enhanced CT or MRI before incisional biopsy on direct laryngoscopy.

Conversely, in cases of disagreement between the operators, the patient was re-evaluated 1 month later. If persistent, the suspicious lesion was biopsied; if improved, the patient continued the follow-up program.

When patients presented bulky lesions (even if negative under WL), the lesion was positive under WL, or suspicious enhancement was revealed on radiologic imaging, a biopsy for histologic confirmation was obtained even if NBI was negative.

Tumors were staged according to the TNM 8th edition using contrast-enhanced CT scans or MRI [23] and the treatment was discussed and decided at the weekly multidisciplinary meeting.

We compared NBI appearance and histology: a positive NBI lesion with reported different grades of dysplasia (mild, moderate, severe) or squamous cell carcinoma (SCC) at histology was defined true positive (TP); conversely, if no histological alterations were recorded, it was considered false positive (FP). Negative patients underwent repeated NBI evaluations during the follow-up and, if persistently negative, they were considered true negative (TN). If patients developed recurrence before the next scheduled NBI endoscopy, they were considered false negative (FN). The same criteria were used to define TP, TN, FP, and FN with HD WL.

Statistical analysis

Descriptive statistics of patient demographics and clinical characteristics are reported as frequencies (proportions) for categorical variables, and median (range min–max) for continuous variables. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for NBI and WL endoscopy with a 95% confidence interval (CI). The McNemar test was used to compare sensitivity and specificity in the two groups (NBI vs WL). The agreement between the two techniques (NBI and WL) was evaluated by calculating Cohen's kappa coefficient. To interpret Cohen's kappa results, we refer to the Landis and Koch guidelines [24]. If the coefficient was ≤ 0.4, it was interpreted as slight to fair, and if it was > 0.4 or ≤ 0.6, it was interpreted as moderate; if it was > 0.6 or ≤ 0.8, it was interpreted as substantial and, if it was > 0.8, it was almost perfect.

The role of NBI with flexible video-endoscope during the follow-up was assessed by calculating its diagnostic advantage in identifying histological alterations compared to HD WL endoscopy.

We investigated associations between (a) site of index tumor and development of recurrence during follow-up, (b) site of index tumor and site of recurrence, and (c) diagnostic advantage of NBI in relation to site of recurrence. The Fisher exact test was used to evaluate these associations and to verify the impact of previous radiotherapy/chemotherapy on NBI ability to detect recurrence.

All data were analyzed using statistical software R (version 4.0.2, 2020).

Results

A total of 160 patients met the inclusion criteria and were enrolled in the study. Endoscopies were well tolerated by all patients and no complications were recorded.

The patients' characteristics in terms of age, gender, tobacco and alcohol consumption, index tumor site, radiotherapy (RT) ± chemotherapy (CT) as a part of their treatment, recurrence (site and time of appearance), and length of follow-up, are reported in Table 1.

A total of 30 lesions in 21 patients were biopsied: 26 were considered positive under NBI, the remaining 4 were negative under NBI but 2 underwent biopsy because they were bulky lesions, 1 because it was positive under WL and the last was detected by positron emission tomography-computed tomography (PET-CT). Among the 26 NBI-positive lesions, 24 (92.3%) were confirmed positive at histology (dysplasia or cancer) and were considered TP; the remaining 2 were FP because no dysplasia or cancer was revealed at histology. These 2 lesions were also considered FP for WL.

The 24 TP lesions were identified in 16 patients, 5 of whom had two or more recurrences over the study period.

The distribution of NBI TP lesions according to histology at biopsy and lesion site are reported in Table 2.

One patient with moderate dysplasia at biopsy underwent follow-up; the other one underwent surgery, and histology revealed severe dysplasia. The two patients with severe dysplasia at biopsy underwent transoral surgery: cancer was found at definitive histology in both cases, and

Table 1 Patient, index tumor, and recurrence characteristics

Variables	Whole cohort ($n=160$)
Age	
Mean (SD)	68 (11)
Median (range)	69 (39–93)
Gender	
Male	106 (66.3%)
Female	54 (33.7%)
Tobacco	
No	52 (32.5%)
Current	42 (26.3%)
Former	56 (35.0%)
Missing	10 (6.3%)
Alcohol	
No	87 (54.4%)
Current	46 (28.8%)
Former	15 (9.4%)
Missing	12 (7.5%)
Index tumor site	
Oral cavity	76 (47.5%)
Oropharynx	48 (30.0%)
Hypopharynx	1 (0.6%)
Larynx	31 (19.4%)
Unknown	4 (2.5%)
RT ± CT	
Yes	78 (48.8%)
No	81 (50.6%)
Missing	1 (0.6%)
Recurrence	
Patients with recurrence	16 (10%)[a]
Total number of recurrence	24
Recurrence site	
Oral cavity	10/24 (41.7%)
Oropharynx	8/24 (33.3%)
Hypopharynx	6/24 (25.0%)
Larynx	0/24 (0.0%)
Recurrence time of appearance	
Before 1 year	3/24 (12.5%)
1–2 years	7/24 (29.2%)
2–3 years	6/24 (25.0%)
3–4 years	2/24 (8.3%)
4–5 years	0/24 (0.0%)
After 5 years	6/24 (25.0%)
Follow-up (years)	
Median (Min–Max)	2.5 (0.19–16.4)

[a]Sixteen referrers to number of patients who had relapsed: total number of recurrence were 24 because some patients had more than 1 recurrence

Table 2 Distribution of NBI true positive (TP) lesions according to biopsy histology and lesion site

Lesion histology at biopsy (*n*, %)	
Mild dysplasia	0
Moderate dysplasia	2 (8.3)
Severe dysplasia	2 (8.3)
Carcinoma	20 (83.3)
Lesion site (*n*, %)	
Oral cavity	10 (41.7)
Oropharynx	8 (33.3)
Hypopharynx	6 (25)

the lesions were upstaged to pT1. Among the 20 lesions with a biopsy positive for cancer, 12 underwent surgery (10 transoral, 1 transmandibular, 1 lateral pharyngotomy): pathologic tumor stage was pT1 (8 cases), pT2 (2 cases), and pT3 (2 cases). The remaining 8 lesions with cancer at biopsy were treated with CT-RT (3 cases), RT (3 cases), or best supportive care (2 cases with lung cancer or distant metastases). Revision surgery in the neck was performed in 2 patients.

In the 4 NBI negative biopsied lesions, histology was negative for cancer or dysplasia, and they were thus considered TN. The remaining 139 patients were persistently negative at multiple NBI endoscopy examinations and were consequently considered TN.

As regards WL, we recorded 9 TP, 142 TN, 3 FP, and 15 FN.

Among the TP lesions, 15 had not been identified by WL; consequently, in our hands NBI with flexible videoendoscope demonstrated a diagnostic advantage of 62.5%. Specifically, when stratifying according to recurrence site (Fig. 1), NBI demonstrated the highest diagnostic advantage in the hypopharynx (100%), followed by the oropharynx (62.5%), and oral cavity (40%); the difference was statistically significant ($p=0.05$).

Consequently, NBI sensitivity, specificity, PPV, NPV and accuracy were 100% (CI 79.6%; 100%), 98.6% (CI 95.1%; 99.8%), 92.3% (CI 74.9%; 99.1%), 100% (CI 96.2%; 100%), 98.8% (CI 95.8%; 99.9%), whereas WL sensitivity, specificity, PPV, NPV and accuracy were 37.5% (CI 18.8%; 59.4%), 97.9% (CI 94.1%; 99.6%), 75% (CI 42.8%; 94.5%), 90.4% (CI 84.7%; 94.6%), 89.3% (CI 83.7%; 93.6%).

NBI sensitivity was significantly higher than WL sensitivity ($p<0.001$), while specificity was comparable ($p=0.99$).

Considering the entire cohort, we found a moderate agreement (Cohen's kappa = 0.53, CI 0.32–0.75) between NBI and WL. When focusing on TP lesions only, we found a slight agreement (Cohen's kappa = 0.0, CI − 0.31–0.31), while for TN lesions there was a substantial agreement (Cohen's kappa = 0.8, CI 0.40–1.00).

Only 2 (33.3%) hypopharyngeal carcinomas revealed by NBI were detectable by imaging, one of them by CT

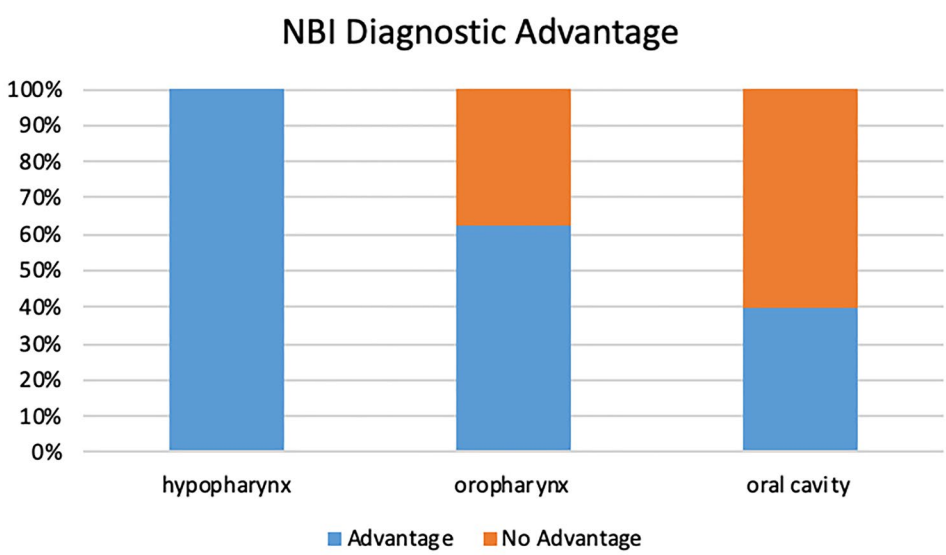

Fig. 1 Distribution of the NBI diagnostic advantage according to recurrence site

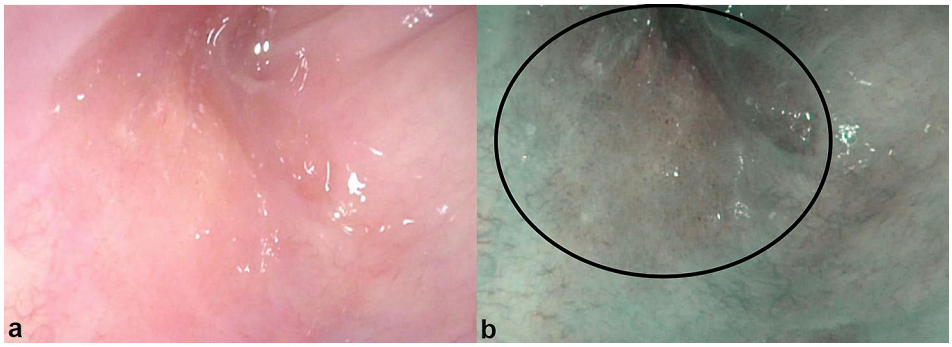

Fig. 2 cT1 squamous cell carcinoma of the right pyriform sinus revealed by NBI and not visible on radiologic imaging. **a** Lateral wall of the right pyriform sinus under HD WL: no lesions are appreciable. **b** Lateral wall of the right pyriform sinus under NBI: a well-demarcated brownish area (circle) with scattered brown dots is visible

Table 3 Distribution of recurrence according to index tumor site

	Recurrence site			
	Hypopharynx	Oral cavity	Oropharynx	Total
Index tumor site				
Larynx	2 (40.0%)	0	3 (60.0%)	5 (100%)
Oral cavity	0	9 (90.0%)	1 (10.0%)	10 (100%)
Oropharynx	4 (44.4%)	1 (11.1%)	4 (44.4%)	9 (100%)
Total	6	10	8	24

scan with contrast and the other one by MRI with contrast (Fig. 2).

The index tumor site was not statistically significantly related with the risk of developing recurrence ($p = 0.81$), even if there was a higher incidence of recurrence in patients with index tumor located in the oropharynx.

We noted a statistically significant association between index tumor site and recurrence site ($p < 0.001$). Specifically, as reported in Table 3 and Fig. 3, laryngeal index tumors showed recurrence in the oropharynx (60%) and hypopharynx (40%); oral cavity index tumors presented recurrence in the oral cavity (90%) and oropharynx (10%); finally, oropharyngeal index tumors presented recurrence in the oropharynx and hypopharynx (44.4% each) and in the oral cavity (11.1%).

We did not find any relation between previous RT ± CT and the risk of recurrence ($p = 0.99$).

Previous RT ± CT did not impact on NBI ability to diagnose recurrence. Specifically, only two cases were considered FP under NBI, and neither underwent RT ± CT as a part of their treatment (2/81 = 2.5%); conversely, FP were 0% among patients who underwent RT ± CT. This difference was not statistically significant ($p = 0.49$).

Discussion

Patients with previous head and neck cancer are at risk of developing recurrence in the upper aerodigestive tract according to the field cancerization hypothesis proposed by Slaughter [1, 4].

The incidence of LR and SPT is reported between 2 and 30% in the previous literature [3, 15, 25–28]. This variability depends on differences in the population tested (in terms of

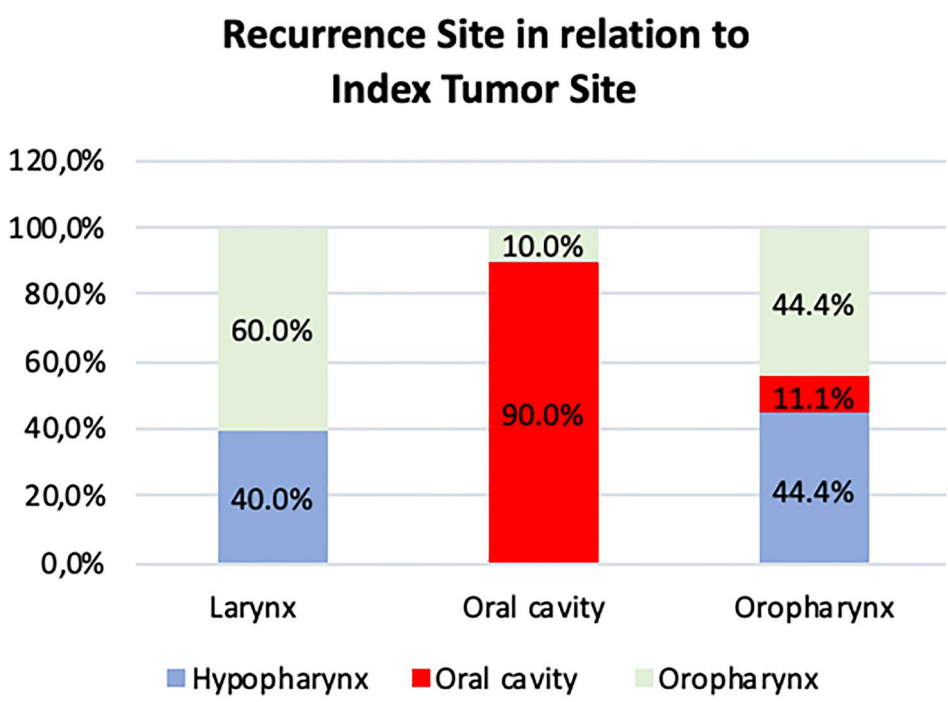

Fig. 3 Recurrence site (*y*-axis) in relation to index tumor site (*x*-axis)

index tumor site, follow-up duration and systematic screening of patients with HNSCC); moreover, SPT of the lung and esophagus besides those in the head and neck mucosal sites, have been included in some studies. The 14.2% of recurrence found in the present study is in line with previous results.

As regards the timing of appearance, in our cohort 41.7% of recurrences were discovered in the first 2 years of follow-up, a result in line with that previously reported by Haughey et al. [26]. Moreover, we diagnosed 75% of recurrences within 5 years from the index tumor, a percentage similar to that found by Panosetti et al. [29]. However, we should underline that about one-fourth of recurrences may be discovered more than 5 years after the index tumor: in the light of these results, we agree with other authors who advocated long-term surveillance for these patients [26, 29].

Bertolini et al. recently found that patients with an oropharyngeal index tumor had a higher incidence of recurrence [30]. In our cohort, we observed a similar pattern even though this finding did not reach statistical significance ($p = 0.81$), possibly as a result of the smaller number of patients considered in our study.

Interestingly, investigation of the relation between index tumor site and recurrence site revealed a statistically significant association ($p < 0.001$). This was particularly evident in the oral cavity. A recurrence in the oral cavity after an oral index tumor has been previously reported also by Rogers et al. [31], and could be explained with a strong local effect of carcinogens in this area.

In the light of the high risk of recurrence, clinicians play a crucial role in detecting LR and SPT in asymptomatic patients early during the follow-up, as this allows for minimally invasive treatment and minimal impact on functionality and quality of life. Conversely, recurrence could be diagnosed accidentally during the follow-up visits if a visible lesion is appreciable by the clinician, or could be detected as a result of a patient's complaint (but in this situation the lesion would likely be larger and need a more invasive treatment).

Thus we need a sensitive and easy-to-apply method to assist in early diagnosis. Possible solutions have been proposed such as panendoscopy (which, however, requires general anesthesia), toluidine blue staining, and Lugol staining which, although used in the esophagus, cannot be used in the head and neck region because of severe mucosal irritation, with patient pain and discomfort [32, 33]. Ongoing studies are trying to identify patients at higher risk of SPT by using oncogene expression, but the results are not conclusive and cannot be applied to clinical practice yet [3].

We think NBI endoscopy could fulfill the requirements of ease of application, speed of execution, and patient safety.

Since its first application in head and neck in 2004 by Muto et al. [5], NBI has become popular in otolaryngology for tumor diagnosis, surgical treatment and follow-up [34, 35].

Specifically, as regards NBI utility in the follow-up of HNSCC, previous studies reported a sensitivity between 90 and 100%, specificity between 76 and 97%, and accuracy between 86.3% and 100% [8]. Our findings of 100% sensitivity, 98.6% specificity, and 98.8% accuracy are in line with the higher values reported by previous studies.

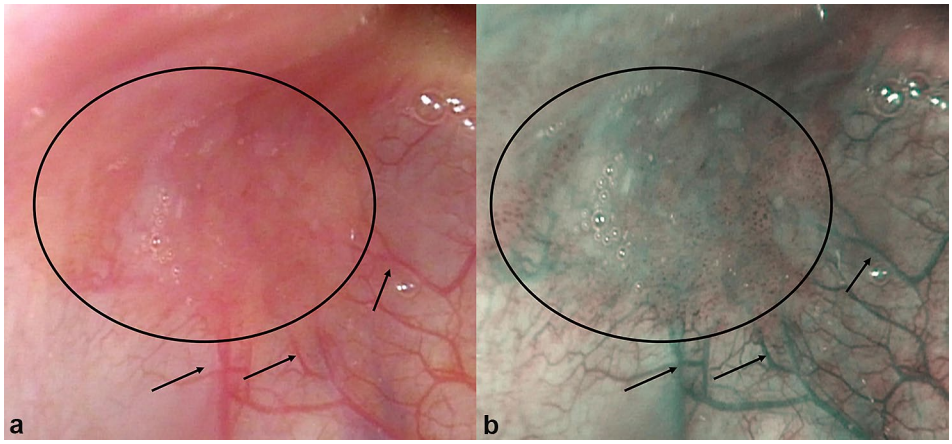

Fig. 4 **a** Lateral wall of the right pyriform sinus under WL: a flat reddish area is appreciable (circle) with dilated feeding vessel (arrows), but dots are not visible. **b** Lateral wall of the right pyriform sinus under NBI: a well-demarcated brownish area with scattered brown dots (circle) is visible; dilated feeding vessel (arrows) can be seen

Consistent with Muto et al. [36] we found a statistically significant difference between the sensitivity of NBI and WL ($p < 0.001$). During the follow-up we used to dealing with selected patients because of their previous history and risk of recurrence, thus a highly sensitive method is mandatory. Previous studies [4] underlined how a stricter follow-up in patients who have developed recurrence is mandatory to identify additional tumors arising in the same area. We agree with this statement considering that 5 patients in our cohort developed two or more recurrences during the follow-up period.

The slight agreement between WL and NBI in detecting TP lesions demonstrates that WL allows the identification of TP results only in cases of ulcerative, vegetating lesions or elevated erythroplakia, but our aim should be to discover flat superficial lesions in asymptomatic patients, as NBI did. In fact, biopsies based solely on NBI findings diagnosed 4 patients with dysplasia and 18 with early tumor (14 cT1, 4 cT2) in our cohort.

Conversely, we found a substantial agreement in the case of TN lesions, justifying the use of HD WL in low risk patients.

Previous studies have investigated the NBI advantage to diagnose recurrences only in oral and oropharyngeal cancer, with values between 27% and 88.2% [14, 37]. In the present study, we found 62.5% of diagnostic advantage and, for the first time in the literature, we stratified this result according to the recurrence site. The highest diagnostic advantage was recorded in the hypopharynx (100%), followed by the oropharynx (62.5%) and oral cavity (40%) ($p = 0.05$).

Considering that the national survey by Morris et al. [2] highlighted that the hypopharynx is the second most frequent location affected by SPT after the oropharynx, visualization of this area during endoscopy is crucial.

Hypopharyngeal cancer is often detected at an advanced stage, with a consequent poor prognosis [38]. The treatment of advanced hypopharyngeal cancer requires destructive surgery and chemoradiotherapy with a reduction in quality of life [23]. Conversely, superficial hypopharyngeal cancer can be treated with endoscopic submucosal dissection (ESD) [39], transoral laser microsurgery (TLM), and transoral robotic surgery (TORS) [40–42].

Among the 6 lesions found in the hypopharynx, only 2 were detectable by imaging, namely those appearing slightly elevated at endoscopy. In our opinion it is important to underline the ability of NBI to highlight flat lesions not otherwise detectable. As also reported by Watanabe et al. [43], positive NBI lesions in the hypopharynx appeared as a well-demarcated brownish area with scattered brown dots on close view; dilated feeding vessels were visible in one patient (Fig. 4). None of the hypopharyngeal carcinomas were visible under WL at a first observation: in hindsight, when returning to WL no dots were visible, but a flat reddish area could be appreciated in some cases.

As previously reported [14, 44], despite the small number of cases (only 2 FP cases), the present study confirmed that previous RT does not influence NBI ability to recognize atypical vascular patterns.

We should remember that NBI is characterized by a learning curve and it is an operator-dependent investigation: the clinicians performing NBI in this study were experienced in this technique, justifying the very good results found in our experience.

Conclusions

The risk of recurrence in HNSCC patients is considerable, and an early diagnosis to reduce treatment-related effects and improve survival is mandatory.

The routine application of NBI endoscopy during follow-up visits could represent a valid option to detect recurrences early. The use of NBI with flexible video-endoscope may further improve this ability, especially in a difficult-to-visualize site such as the hypopharynx.

Acknowledgements The authors thank Itala Mary Ann Brancaleone, MA, RSA Dip TEFLA, teacher of Medical English at the University of Trieste, for her support in editing the manuscript.

Funding Olympus Europa SE & CO. KG provided the endoscopic equipment of the study.

Declarations

Ethical approval This study was approved by the Trieste University Hospital Institutional Review Board (73/2012).

Conflict of interest Authors declare they have no conflicts of interest.

References

1. Slaughter DP, Southwick HW, Smejkal W (1953) Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 6:963–968. https://doi.org/10.1002/1097-0142(195309)6:5%3c963::aid-cncr2820060515%3e3.0.co;2-q
2. Morris LGT, Sikora AG, Patel SG, Hayes RB, Ganly I (2011) Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol 20(29):739–746. https://doi.org/10.1200/JCO.2010.31.8311
3. Leon X, Quer M, Diez S, Orús C, López-Pousa A, Burgués J (1999) Second neoplasm in patients with head and neck cancer. Head Neck 21:204–210. https://doi.org/10.1002/(sici)1097-0347(199905)21:3%3c204::aid-hed4%3e3.0.co;2-7
4. Tirelli G, Zacchigna S, Biasotto M, Piovesana M (2016) Open questions and novel concepts in oral cancer surgery. Eur Arch Otorhinolaryngol 273:1975–1985. https://doi.org/10.1007/s00405-015-3655-0
5. Muto M, Nakane M, Katada C, Sano Y, Ohtse A, Esumi H, Ebihara S, Yoshida S (2004) Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer 15(101):1375–1381. https://doi.org/10.1002/cncr.20482
6. Kumagai Y, Toi M, Inoue H (2002) Dinamism of tumour vasculature in the early phase of cancer progression: outcomes from oesophageal cancer research. Lancet Oncol 3:604–610. https://doi.org/10.1016/s1470-2045(02)00874-4
7. Di Maio P, Iocca O, De Virgilio A, Giudeice M, Pellini R, D'Ascanio L, Golusiński P, Ricci G, Spriano G (2019) Narrow band imaging in head and neck unknown primary carcinoma: a systematic review and meta-analysis. Laryngoscope 130:1692–1700. https://doi.org/10.1002/lary.28350
8. Boscolo Nata F, Tirelli G, Capriotti V, Marcuzzo AV, Sacchet E, Ŝuran-Brunelli AN, de Manzini N (2021) NBI utility in oncologic surgery: an organ by organ review. Surg Oncol 36:65–75. https://doi.org/10.1016/j.suronc.2020.11.017
9. Ganesh D, Sreenivasan P, Öhman J, Wallström M, Braz-Silva PH, Giglio D, Kjeller G, Hasséus B (2018) Potentially malignant oral disorders and cancer transformation. Anticancer Res 38:3223–3229. https://doi.org/10.21873/anticanres.12587
10. Deganello A, Paderno A, Morello R, Fior M, Berretti G, Del Bon F, Alparone M, Bardellini E, Majorana A, Nicolai P (2021) Diagnostic accuracy of narrow band imaging in patients with oral lichen planus: a prospective study. Laryngoscope 131:E1156–E1161. https://doi.org/10.1002/lary.29035
11. Bertino G, Cacciola S, Bastos Fernandes Jr WB, Muniz Fernandes C, Occhini A, Tinelli C, Benazzo M (2015) Effectiveness of narrow band imaging in the detection of premalignant and malignant lesions of the larynx: validation of a new endoscopic clinical classification. Head Neck 37:215–222. https://doi.org/10.1002/hed.23582
12. Rzepakowska A, Sielska-Badurek E, Żurek M, Osuch-Wójcikiewicz E, Niemczyk K (2018) Narrow band imaging for risk stratification of glottic cancer within leukoplakia. Head Neck 40:2149–2154. https://doi.org/10.1002/hed.25201
13 Kim DH, Kim SW, Lee J, Hwang SH (2021) Narrow-band imaging for screening of oral premalignant or cancerous lesions: a systematic review and meta-analysis. Clin Otolaryngol 46:501–507. https://doi.org/10.1111/coa.13724
14 Tirelli G, Piovesana M, Bonini P, Gatto A, Azzarello G, Boscolo Nata F (2017) Follow-up of oral and oropharyngeal cancer using narrow-band imaging and high-definition television with rigid endoscope to obtain an early diagnosis of second primary tumors: a prospective study. Eur Arch Otorhinolaryngol 274:2529–2536. https://doi.org/10.1007/s00405-017-4515-x
15. Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP (2001) Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. J Clin Oncol 1(19):1358–1362. https://doi.org/10.1200/JCO.2001.19.5.1358
16 Spragss PD, Harries ML (1995) The modified Valsalva manoeuvre to improve visualization of the hypopharynx during flexible nasopharyngoscopy. J Laryngol Otol 109:863–864. https://doi.org/10.1017/s0022215100131512
17 Takano JH, Yakushiji T, Kamiyama I, Nomura T, Katakura A, Takano N, Shibahara T (2010) Detecting early oral cancer: narrowband imaging system observation of the oral mucosa microvasculature. Int J Oral Maxillofac Surg 39:208–2013. https://doi.org/10.1016/j.ijom.2010.01.007
18 Tirelli G, Marcuzzo AV, Boscolo Nata F (2018) Narrow-band imaging pattern classification in oral cavity. Oral Dis 24:1458–1867. https://doi.org/10.1111/odi.12940
19. Fujii S, Yamazaki M, Muto M, Ochiai A (2010) Microvascular irregularities are associated with composition of squamous epithelial lesions and correlate with subepithelial invasion of superficial-type pharyngeal squamous cell carcinoma. Histopathology 56:510–522. https://doi.org/10.1111/j.1365-2559.2010.03512.x
20 Nonaka S, Saito I (2008) Endoscopic diagnosis of pharyngeal carcinoma by NBI. Endoscopy 40:347–351. https://doi.org/10.1055/s-2007-995433
21. Arens C, Piazza C, Andrea M, Dikkers FG, Tjon Pian Gi REA, Voig-Zimmermann S, Peretti G (2016) Proposal for a descriptive guideline of vascular changes in lesions of the vocal folds by the committee on endoscopic laryngeal imaging of the European Laryngological Society. Eur Arch Otorhinolaryngol 273:1207–1214. https://doi.org/10.1007/s00405-015-3851-y
22 Mora F, Carta F, Missale F, Laborai A, Parrinello G, Piazza C, Puxeddu R, Peretti G (2020) Laryngeal mid-cord erythroleukoplakias: how to modulate the transoral CO_2 laser excisional biopsy. Cancers (Basel) 4(12):2165. https://doi.org/10.3390/cancers12082165
23. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed 30 Mar 2021
24. Landis JR, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33:159–174
25. Simple M, Suresh A, Das D, Kuriakose MA (2015) Cancer stem cells and field cancerization of oral squamous cell carcinoma. Oral Oncol 51:643–651. https://doi.org/10.1016/j.oraloncology.2015.04.006
26 Haughey BH, Gates GA, Arfken CL, Harvey J (1992) Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. Ann Otol Rhinol Laryngol 101(2Pt1):105–112. https://doi.org/10.1177/000348949210100201

27. Cooper JS, Pajak TF, Rubin P, Tupchong L, Brady LW, Leibel SA, Laramore GE, Marcial VA, Davis LW, Cox LD et al (1989) Second malignancies in patients who have head and neck cancer: incidence, effect on survival and implications based on the RTOG experience. Int J Radiat Oncol Biol Phys 17:449–456. https://doi.org/10.1016/0360-3016(89)90094-1
28. Schwartz LH, Ozsahin M, Zhang GN, Touboul E, De Vataire F, Adolenko P, Lacau-Saint-Guily J, Laugier A, Schlienger M (1994) Synchronous and metachronous head and neck carcinomas. Cancer 1(74):1933–1938. https://doi.org/10.1002/1097-0142(19941001)74:7%3c1933::aid-cncr2820740718%3e3.0.co;2-x
29 Panosetti E, Luboinski B, Mamelle G, Richard JM (1989) Multiple synchronous and metachronous cancers of the upper aerodigestive tract: a nine-year study. Laryngoscope 99:1267–1273. https://doi.org/10.1288/00005537-198912000-00011
30. Bertolini F, Trudu L, Banchelli F, Schipilliti F, Napolitano M, Alberici MP, Depenni R, D'Angelo E, Mattioli F, Rubino L, Presutti L (2020) Second primary tumors in head and neck cancer patients: the importance of a "tailored" surveillance. Oral Dis. https://doi.org/10.1111/odi.13681
31. Rogers SN, Swain A, Carroll C, Lowe D (2019) Incidence, timing, presentation, treatment, and outcomes of second primary head and neck squamous cell carcinoma after oral cancer. Br J Oral Maxillofac Surg 57:1074–1080. https://doi.org/10.1016/j.bjoms.2019.09.018
32 Emura F, Baron TH, Gralnek IM (2013) The pharynx: examination of an area too often ignored during upper endoscopy. Gastrointest Endosc 78:143–149. https://doi.org/10.1016/j.gie.2013.02.021
33. Piazza C, Dessouky O, Peretti G, Cocco D, De Benedetto L, Nicolai P (2008) Narrow band imaging: a new tool for evaluation of head and neck squamous cell carcinomas. Review of the literature. Acta Otorhinolaryngol Ital 28:49–54
34 Tirelli G, Boscolo Nata F, Bussani R, Gatto A, Quatela E, Rigo S, Piovesana M (2019) How we improve the transoral resection for oral and oropharyngeal cancer: the CO_2 waveguide laser. Eur Arch Otorhinolaryngol 276:2301–2310. https://doi.org/10.1007/s00405-019-05473-x
35. Tirelli G, Boscolo Nata F, Gatto A, Bussani R, Spinato G, Zacchigna S, Piovesana M (2019) Intraoperative margin control in transoral approach for oral and oropharyngeal cancer. Laryngoscope 129:1810–1815. https://doi.org/10.1002/lary.27567
36. Muto M, Minashi K, Yano T, Saito Y, Oda I, Nonaka S, Omori T, Sugiura H, Goda K, Kaise M, Inoue H, Ishikawa H, Ochiai A, Shimoda T, Watanabe H, Tajiri H, Sato D (2010) Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol 28:1566–1572. https://doi.org/10.1200/JCO.2009.25.4680
37. Piazza C, Cocco D, Del Bon F, Mangili S, Nicolai P, Majorana A, Bolzoni Villaret A, Peretti G (2010) Narrow band imaging and high definition television in evaluation of oral and oropharyngeal squamous cell cancer: a prospective study. Oral Oncol 46:307–310. https://doi.org/10.1016/j.oraloncology.2010.01.020
38 Eckel HE, Bradley PJ (2019) Treatment options for hypopharyngeal cancer. Adv Otorhinolaryngol 83:47–53. https://doi.org/10.1159/000492308
39. Hanaoka N, Ishihara R, Takeuci Y, Suzuki M, Uemara H, Fujii T, Yoshino K, Uedo N, Higashino K, Ohta T, Kanzaki H, Hanafusa M, Nagai K, Matsui F, Iishi H, Tatsuda M, Tomita Y (2013) Clinical outcomes of endoscopic mucosal resection and endoscopic submucosal dissection as a transoral treatment for superficial pharyngeal cancer. Head Neck 35:1248–1254. https://doi.org/10.1002/hed.23106
40 Martin A, Jäckel MC, Christiansen H, Mahmoodzada M, Kron M, Steiner W (2008) Organ preserving transoral laser microsurgery for cancer of the hypo-pharynx. Laryngoscope 118:398–402. https://doi.org/10.1097/MLG.0b013e31815aeda3
41 White HN, Moore EJ, Rosenthal EL, Carroli WR, Olsen KD, Desmond RA, Magnbuson JS (2010) Transoral robotic-assisted surgery for head and neck squamous cell carcinoma: one- and 2-year survival analysis. Arch Otolaryngol Head Neck Surg 136:1248–1252. https://doi.org/10.1001/archoto.2010.216
42. Muto M, Satake H, Yano T, Minashi K, Hayashi R, Fujii S, Ochiai A, Ohtse A, Morita S, Horimatsu T, Ezoe Y, Miyamoto S, Asato R, Tateya I, Yoshizawa A, Chiba T (2011) Long-term outcome of transoral organ-preserving pharyngeal endoscopic resection for superficial pharyngeal cancer. Gastrointest Endosc 74:477–484. https://doi.org/10.1016/j.gie.2011.04.027
43 Watanabe A, Tsujie H, Taniguchi M, Hosokawa M, Fujita M, Sasaki A (2006) Laryngoscopic detection of pharyngeal carcinoma in situ with narrow band imaging. Laryngoscope 116:650–654. https://doi.org/10.1097/01.mlg.0000204304.38797.34
44. Piazza C, Cocco D, De Benedetto L, Bon FD, Nicolai P, Peretti G (2010) Role of narrow-band imaging and high-definition television in the surveillance of head and neck squamous cell cancer after chemo- and/or radiotherapy. Eur Arch Otorhinolaryngol 267:1423–1428. https://doi.org/10.1007/s00405-010-1236-9