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Narrow-Band Imaging in Transoral Laser Surgery for Early Glottic Cancer: A Randomized Controlled Trial

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Abstract

Objective. Assessing whether the additional use of narrow-band imaging (NBI) in transoral laser surgery (TOLS) for early laryngeal cancer improves clinical outcomes.

Study Design. Randomized controlled trial, performed between September 2015 and November 2022.

Setting. A tertiary referral hospital in The Netherlands.

Methods. TOLS was carried out in 113 patients. The procedure was performed with white light imaging (WLI, n = 56) alone, or combined with NBI (n = 57). Patients received frequent follow-up laryngoscopy. Resection margin status, recurrence rate, and recurrence-free survival at 12 months, 18 months, and after study termination (maximum 86 months) were analyzed.

Results. Thirty-one cases in the WLI group had a positive resection margin, versus 16 in the NBI group ($p = .002$). After 12 months, the recurrence-free survival was 92%: 87% for WLI versus 96% for NBI, $p = .07$. The recurrence rate was 7/56 (13%) for WLI, versus 2/57 (4%) for NBI, $p = .09$. After 18 months, the recurrence-free survival was 84% for WLI versus 96% for NBI, $p = .02$. The recurrence rate was 9/56 (16%) for WLI, versus 2/57 (4%) for NBI, $p = .02$. After study termination, the recurrence-free survival was 71% for WLI versus 83% for the NBI group ($p = .08$). The recurrence rate was 16/56 for WLI, versus 10/57 for NBI ($p = .16$).

Conclusion. The additional use of NBI during TOLS significantly decreased the number of positive resection margins. Although not statistically significant at all time points, patients treated with NBI-supported TOLS showed a lower recurrence rate and better recurrence-free survival. Further studies in larger patient groups are needed to confirm these results.

Keywords

early glottic cancer, head and neck cancer, laryngeal cancer, narrow-band imaging, squamous cell carcinoma, transoral laser surgery

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Transoral laser surgery (TOLS) is a well-established treatment modality for early-stage laryngeal cancer.[1-3] The main goal of TOLS is complete tumor resection with adequate negative resection margins.[4,5] The secondary goal is the preservation of the laryngeal function by leaving as much healthy tissue as possible untouched.[2,6] To achieve both goals, it is important to find a balance between a sound oncologic resection and optimal functional results. Adequate visualization of the mucosa is important for determining the precise tumor extension.

The techniques for visualization of the larynx have improved over the last years, due to the use of novel endoscopic devices and techniques, including the use of high-definition video laryngoscopy and narrow-band imaging (NBI). NBI uses an optical filter to filter blue (415 nm) and green light (540 nm) which, due to their small wavelengths, only penetrate into the superficial layers of the mucosa and submucosa and highlight the superficial vascular structures located therein.[7-9] By identifying specific superficial vessel changes, (pre)malignant lesions can be easily detected.[7,8,10] Previous studies showed that the use of NBI enables an easier and more accurate determination of the exact resection margins.[5,7,10-15]

In 2017, our group published a retrospective study on the effect of the application of NBI preceding TOLS of early glottic cancer.[16] Patients treated with TOLS based

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on an NBI-conducted strategy had a significantly lower recurrence rate than patients in which the treatment was based on traditional white light imaging (WLI). The 2-year recurrence-free survival was significantly higher in the NBI-treated group (82% vs 98%).[16] However, due to the retrospective nature, this study might have suffered from selection bias. Therefore, a prospective randomized controlled study was conducted to assess whether the additional use of NBI in TOLS for early laryngeal cancer improves clinical outcomes.

Materials and Methods

Between September 2015 and January 2020, 206 patients, who were seen in our outpatient clinic with a lesion on the vocal folds suspicious of dysplasia or early-stage glottic cancer, were included. Data was collected prospectively after approval by the Medical Ethical Committee of the University Medical Center Groningen (NL53152.042.15). All patients signed informed consent. In November 2022, the last patients' recordings were checked. All patients underwent rigid laryngoscopy under general anesthesia and, in case of early-stage glottic carcinoma, TOLS was carried out at the Department of Otorhinolaryngology, Head and Neck Surgery of the University Medical Center Groningen, a tertiary referral hospital in The Netherlands. All TOLS procedures were carried out by 4 experienced head and neck surgeons. Randomization was carried out in Microsoft Excel by M.A.Z., deciding whether the procedure was performed with WLI alone or combined with NBI. Block randomization was used to achieve equal sample sizes. Blinding was impossible for both the surgeon and the patient. M.A.Z. and J.M.W. enrolled the participants and assigned participants to the intervention. Patients were excluded during surgery if the tumor was unfavorable for TOLS, and patients were excluded when pathology results came back, in cases in which the histopathology was benign. **Figure 1** shows the study population flow diagram. The CONSORT 2010 checklist is provided as Supplemental Data available online. Prior to this study (in 2015), no data was available on the recurrence-free survival of patients treated with NBI CO_2 laser resection for early glottic cancer. The sample size calculation was based on the assumption that the median survival for WLI and NBI were 6 and 12 months, respectively. It was determined that we needed to study 40 experimental subjects and 40 control subjects to be able to reject the null hypothesis, with a power of 0.80. The probability of a type I error was 0.05. It was decided to include at least 55 patients per group. A second sample size calculation was performed in 2017, based on the available data on recurrence-free survival.[17] A power analysis was conducted using MedCalc (MedCalc Software Ltd), to determine the minimum sample size required to test the study hypothesis, based on survival analysis (log rank). The available 2-year recurrence-free survival for WLI and NBI were 82% and 98%, respectively. The required sample size to achieve 80% power, at a significance criterion of $\alpha = .05$, was 60 patients per group. Thus, the aim of the sample size of 55 seemed reasonable.

Rigid laryngoscopy under general anesthesia was carried out with a 0° Olympus camera system (Olympus OTV-S7ProH-HD12E HD autoclavable camera head, Olympus EVIS EXERA CLV-180 light source, 300 W xenon with NBI filter; Olympus EVIS EXERA CV-180 processor, high-definition television; Olympus Nederland BV). The tumor extension was evaluated carefully and photo and video documentation were saved in the electronic patient records. The tumor was excised by using a Lumenis Laser (Lumenis) in continuous superpulsed mode.

All histopathology results were discussed in our multidisciplinary head and neck tumor board. Patients received frequent follow-up visits after complete tumor resection: every 3 months during the first 2 years after TOLS, then every 6 months during the following 2 years, and a final check-up 1 year later, which is the standard clinical practice in The Netherlands. In patient-specific cases, additional check-ups after 5 years of follow-up were carried out, for example, due to physical complaints or anxiety. In case of incomplete tumor resection, adjuvant treatment consisted of a re-resection. In 10 cases with positive superficial resection margins, a wait-and-see policy with check-ups every 6 weeks was opted for, based on the surgeon's opinion. After the procedure, patients visited our outpatient clinic for follow-up with flexible high-definition video laryngoscopy (Olympus Nederland BV). Follow-up laryngoscopy was performed with WLI alone or with WLI combined with NBI, depending on the randomization: if surgery was performed with WLI alone, follow-up was performed with WLI alone and if surgery was performed with additional NBI, follow-up was performed with additional NBI. Patients were excluded if during follow-up endoscopic evaluation was performed with WLI in the NBI group or NBI in the WLI group, more than once consecutively as a result of accidental errors in executing the protocol (n = 2). A local recurrence was defined as high-grade dysplasia or carcinoma at the same location as the original tumor. The 12 months, 18 months, and overall recurrence-free survival were analyzed. Recurrence-free survival was defined as the number of months between TOLS and the moment of histological confirmation of a local recurrence, the last follow-up date, or the date of death. A minimum follow-up period of 24 months was aimed, for analysis in this study, though all patients were offered a 5-year oncologic follow-up which is standard practice in The Netherlands.

Statistical Analysis

SPSS version 28 statistical software (IBM Corp) was used for performing statistical analysis. Kaplan-Meier plots

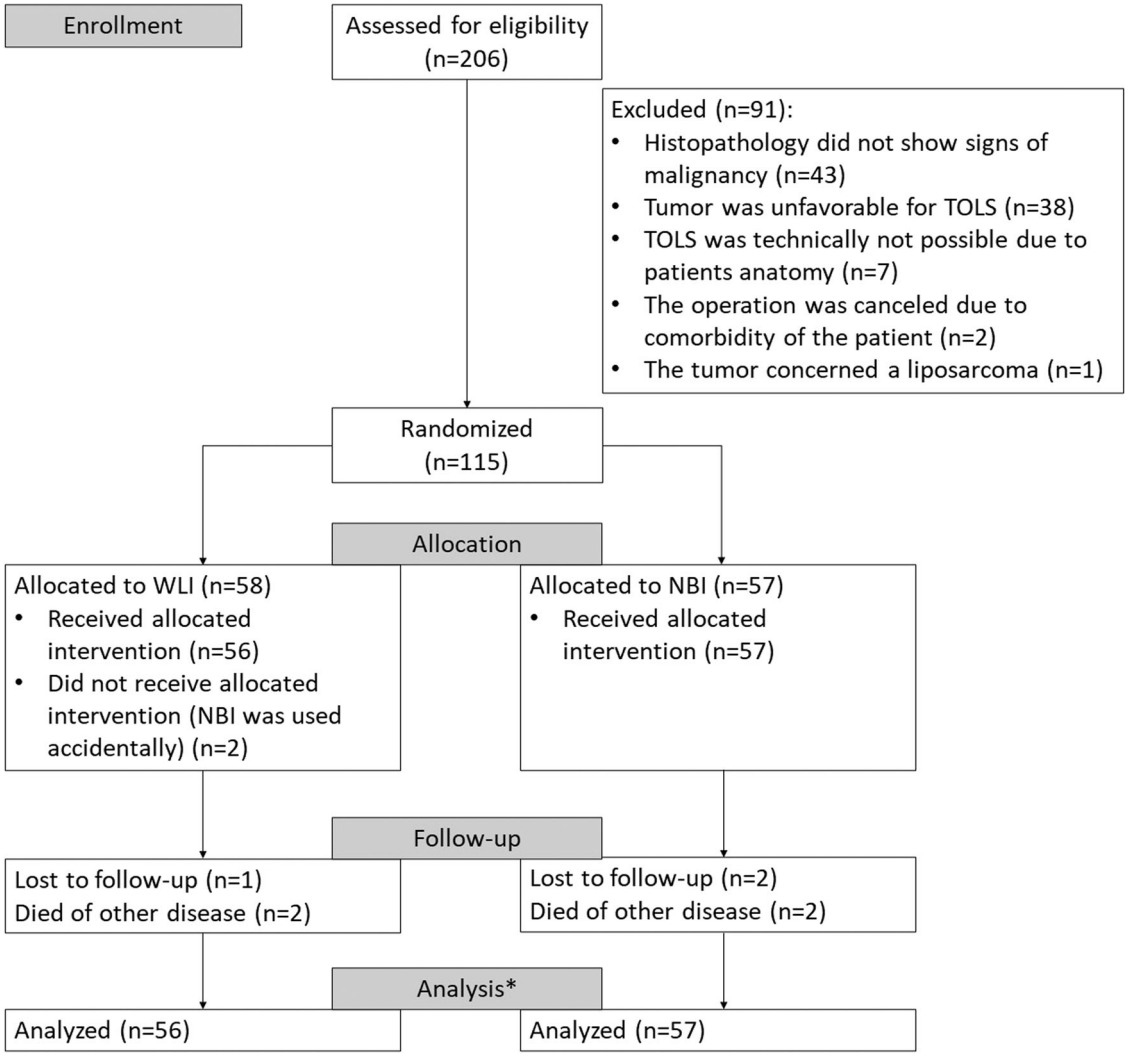

Figure 1. Flow diagram of the study population. *Patients lost to follow-up and patients who died of other diseases were also included for analysis. NBI, narrow-band imaging; TOLS, transoral laser surgery; WLI, white light imaging.

were constructed and differences between survival plots were compared by the Breslow test. Pearson's χ^2, Fisher's exact test, or independent-samples T test were used for analyzing differences between groups. Univariate and multivariate logistic regression analyses were performed to assess the relationship between variables in relation to outcome data. $p < .05$ were considered statistically significant.

Results

A total of 113 patients underwent TOLS with CO_2 laser resection of early glottic squamous cell carcinoma. The patient characteristics are presented in **Table 1**. The median follow-up period was 46 months (range: 4-86 months): 44 months in the WLI group and 48 months in the NBI group. **Figure 2** shows an example of a left-sided T1a glottic laryngeal carcinoma: **Figure 2A** and **B** shows images of the laryngoscopy in our outpatient clinic and **Figure 2C** and **D** shows the rigid laryngoscopy under general anesthesia.

The resection margin status is presented in **Figure 3**, including the number of re-resections carried out. Thirty-one tumors in the WLI group had a positive resection margin, versus 16 tumors in the NBI group ($p = .002$). One patient with unclear resection margins in the WLI group received a re-resection in which no carcinoma (in situ) was found. A total of 38 re-resections were carried out and residual carcinoma was found in 11 (29%) of these cases.

A total of 18 patients had an examination under general anesthesia with biopsy taking with benign pathology results during their follow-up, although a suspicious lesion was visible during laryngoscopy in the outpatient clinic: 6 patients in the WLI group (11%) versus 12 in the NBI group (21%), $p = .13$.

Recurrence-Free Survival and Recurrence Rate

After 12 months, the recurrence-free survival was 92%: 87% in the WLI group versus 96% in the NBI group, $p = .07$ (**Table 1**). The recurrence rate was 8%: 7 recurrences in the WLI group (13%), and 2 in the NBI

Table 1. Patient Characteristics

	Total group	WLI group	WLI + NBI group	*p* value*
Total	113 (100%)	56 (50%)	57 (50%)	
Gender				.97
Male	99 (88%)	49 (88%)	50 (88%)	
Female	14 (12%)	7 (13%)	7 (12%)	
Median age ± SD [range]	69 ± 10.5 [41-90]	71 ± 10.8 [42-87]	68 ± 10.1 [41-90]	.33
Smoking status				.08
Never smoker	24 (21%)	8 (14%)	16 (28%)	
Former smoker	56 (50%)	27 (48%)	29 (51%)	
Active smoker	33 (29%)	21 (38%)	12 (21%)	
Alcohol consumption				.56
Never drinker	41 (36%)	18 (32%)	23 (40%)	
Former drinker	8 (7%)	5 (9%)	3 (5%)	
Active drinker	64 (57%)	33 (59)	31 (54%)	
T stage				.19
Tcis	29 (26%)	11 (20%)	18 (32%)	
T1a	81 (72%)	42 (75%)	39 (68%)	
T1b	1 (1%)	1 (2%)	-	
T2a	2 (2%)	2 (4%)	-	
Median FU (±SD) in months [range]	46 ± 20.1 [4-86]	44 ± 20.4 [4-82]	48 ± 19.3 [5-86]	.63
N. of recurrences at				
12 mo	9 (8%)	7 (13%)	2 (4%)	.09
18 mo	11 (10%)	9 (16%)	2 (4%)	.02
Study termination	26 (23%)	16 (29%)	10 (18%)	.16
Recurrence-free survival at				
12 mo	92%	87%	96%	.07
18 mo	90%	84%	96%	.02
Study termination	77%	71%	83%	.08
Average time to recurrence in months ± SD [range]	27 ± 19.5 [4-71]	24 ± 19.6 [4-62]	33 ± 19.0 [8-71]	.56

Percentages are rounded up to whole numbers.

Abbreviations: cis, carcinoma in situ; FU, follow-up; N., number; NBI, narrow-band imaging; SD, standard deviation; T, tumor; WLI, white light imaging.

*p value comparing the WLI group with the WLI + NBI group.

group (4%), $p = .09$. After 12 months, negative resection margins were a significant predictor for a lower chance of developing a recurrence, $p = .01$, odds ratio (OR): 0.16 (95% confidence interval [CI]: 0.04-0.69). The recurrence rate in tumors with unclear or positive resection margins was higher than in tumors with negative resection margins, namely 5% versus 25% ($p = .007$).

After 18 months, the recurrence-free survival was 90%: 84% in the WLI group versus 96% in the NBI group, $p = .02$. The recurrence rate was 10%: 9 recurrences in the WLI group (16%), and 2 in the NBI group (4%), $p = .02$. After 18 months, positive resection margins were a significant predictor for developing a recurrence, $p = .05$. In multivariate analysis, randomization in the NBI group and complete resection of the primary tumor were both significant predictors for a smaller chance of developing a recurrence within 18 months, $R^2 = 0.16$, $p = .01$: randomization in the NBI group $p = .04$, OR = 0.19, (95% CI: 0.04-0.96) and negative resection margins $p = .05$, OR = 0.24 (95% CI: 0.06-0.99). The recurrence rate in tumors with unclear or positive resection margins was higher than in tumors with negative resection margins, namely 7% versus 25% ($p = .026$).

At study termination, the overall recurrence rate was 23%. In the WLI group, 16 patients (29%) developed a recurrence and in the NBI group, 10 recurrences (18%%) were detected $p = .16$. All recurrences developed at the original tumor site. Resection margin status was not a significant predictor for developing a recurrence at study termination, $p = .40$. The recurrence rate in tumors with unclear or positive resection margins was 31%, versus 22% in tumors with a negative resection margin ($p = .40$).

The mean time between TOLS and the development of a local recurrence for the whole group was 27 months (±19.5 standard deviation): 24 months in the NBI group versus 33 months in the WLI group, $p = .56$. The overall recurrence-free survival was 71% in the WLI group versus 83% in the NBI group, $p = .08$. **Figures 4** and **5** show the recurrence-free survival in the WLI and NBI groups after 18 months and at study termination, respectively. After 18 months of follow-up, 5 cases were censored: 2 in the NBI group and 3 in the WLI group. The NBI censored cases

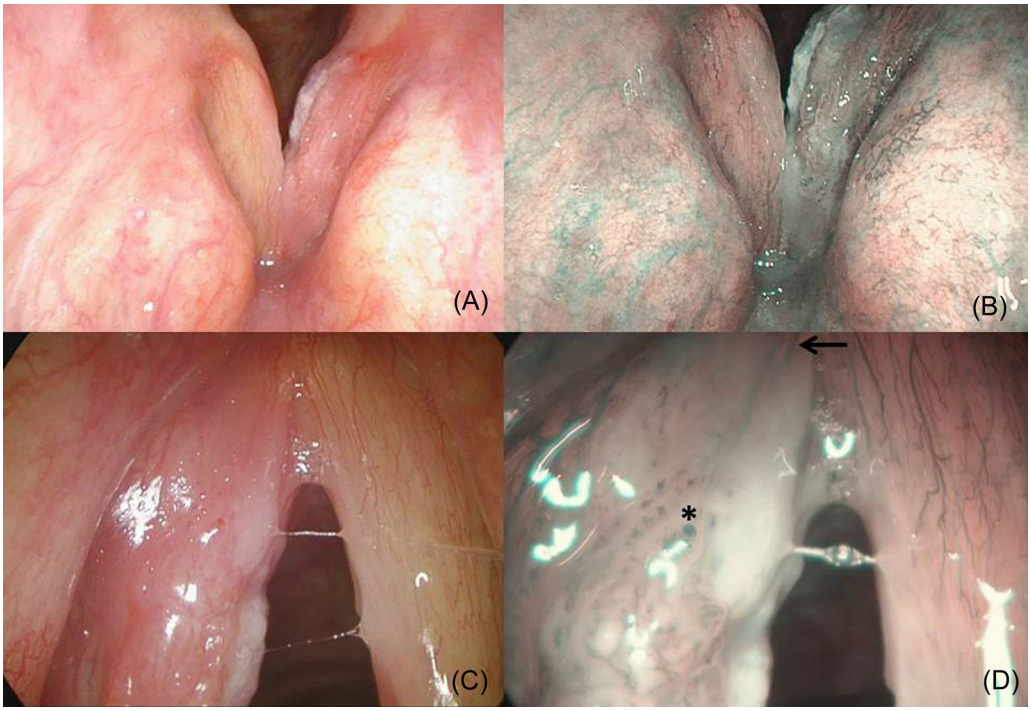

Figure 2. T1a glottic laryngeal carcinoma with white light imaging and narrow-band imaging, in the outpatient clinic (A and B) versus under general anesthesia (C and D). Arrow, normal vessels; asterisk, malignant vessel loops.

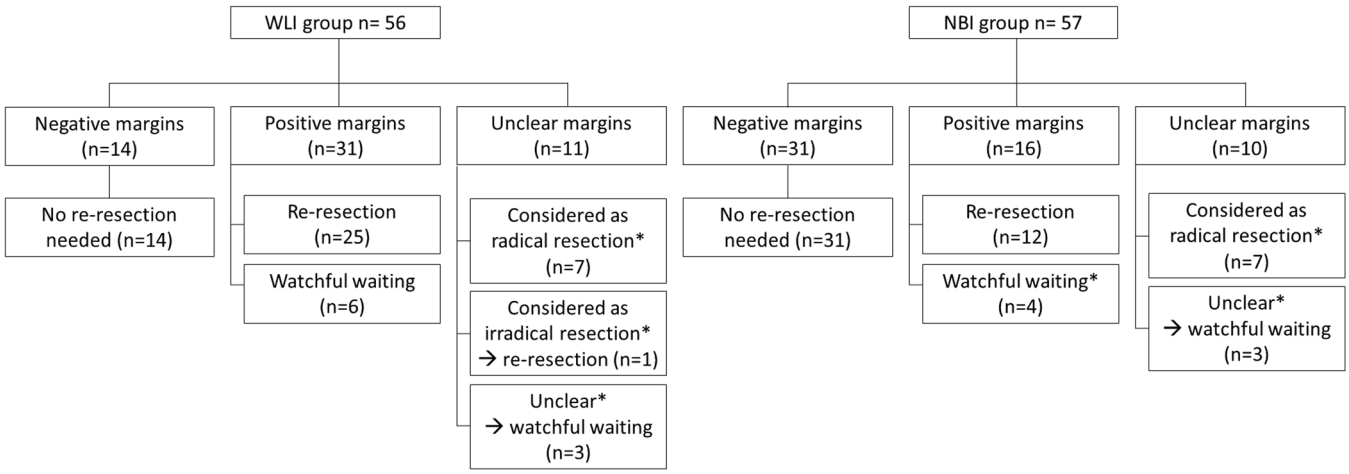

Figure 3. Flowchart of tumor margin status and treatment policy. NBI, narrow-band imaging; WLI, white light imaging.

concerned 1 patient who died of another disease and 1 patient lost to follow-up at 16 months. The WLI censored cases concerned 1 patient who died of other diseases at 12 months, and 2 patients lost to follow-up at 7 and 12 months. In both univariate and multivariate analysis, the variables "positive resection margin," "age," and "randomization in the WLI or NBI group," were not significant predictors for developing a recurrence before study termination.

Discussion

This prospective randomized controlled trial in TOLS for early glottic cancer shows a beneficial effect of NBI. NBI reduces the number of positive resection margins and decreases local recurrence rates.

Resection Margins

CO_2 surgical laser resection of glottic carcinoma was introduced by Strong in 1975.[18] Today, TOLS is the treatment of choice for early-stage laryngeal cancer.[1-3,19] Since the goal of TOLS is finding a balance between sound oncologic resections and laryngeal function preservation, the number of close and positive margins is reported up to 50%.[20,21] In this study the number of positive resection margins was significantly higher in the WLI group ($p = .002$). This suggests that tumor extension

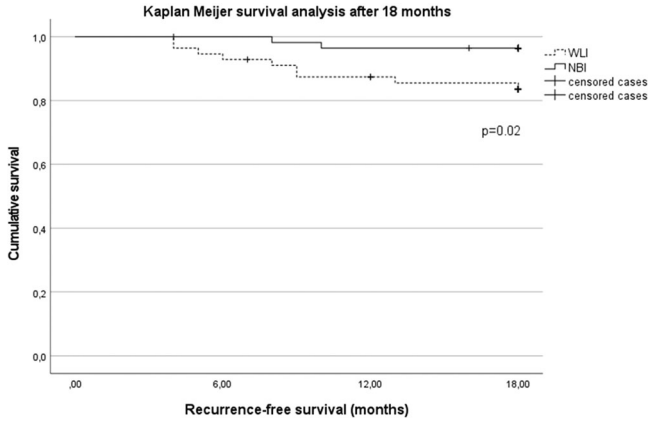

Figure 4. Recurrence-free survival after 18 months. NBI, narrow-band imaging; WLI, white light imaging.

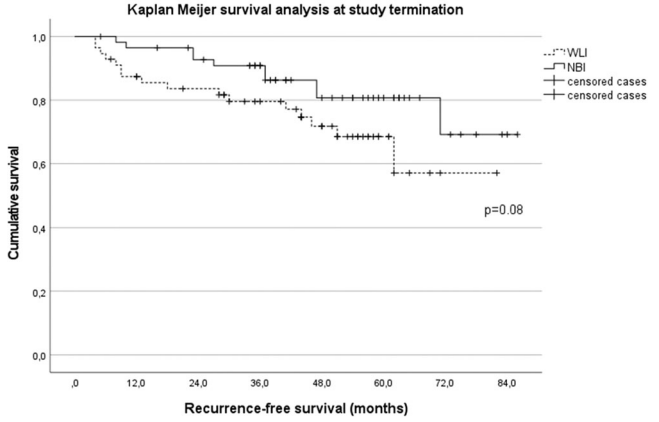

Figure 5. Recurrence-free survival at study termination. NBI, narrow-band imaging; WLI, white light imaging.

can be more accurately determined with NBI, which is in line with previous studies showing that additional use of NBI improves the accuracy of tumor detection and staging.[5,15,22] A recent systematic review by Campo et al shows that the use of NBI significantly reduces the number of positive resection margins.[11] However, our study provides stronger evidence due to its prospective randomized study design. The relevance of positive margins after TOLS on local tumor control, however, is unclear, and widely debated.[5,23] Several studies showed that positive resection margins do not have a negative impact on oncologic local control.[23-28] There are several explanations for the fact that not all patients with positive resection margins will develop recurrences, such as thermal damage of the wound bed, the small size of the specimen, and shrinking of the resection specimen.[5,29] Up to 80% of the positive margins (and close margins) are believed to be false positive and often no residual carcinoma is found in re-excision specimens, which is consistent with the percentage (29%) of residual carcinoma we found in our re-resections.[19,29] Other studies, however, showed that positive resection margins do lead to more recurrences,[20,29,30] which is consistent with our results showing that negative tumor resection margins lead to a significantly lower amount of recurrences after 12 months ($p = .007$) and after 18 months ($p = .026$).

Recurrences

The 5-year overall survival of early-stage laryngeal carcinoma reported in the literature is high: 88% to 94%,[19,24,31] and the reported 5-year disease-specific survival is even better 97% to 99%.[19,28,32] Although the survival is favorable, the recurrence rate is considerable: percentages between 10% and 31% are reported,[19,24,27,33-37] which is consistent with the recurrence rate of 23% we found. The recurrence rate is largely dependent on the follow-up duration that was maintained in different studies, for instance, the recurrence rate of 31% was found in a cohort with a follow-up duration of 15 years.[36] Results of this study show that the number of recurrences is statistically significantly lower in the NBI group than in the WLI group after 18 months ($p = .02$). However, at study termination, the difference in recurrence rate and recurrence-free survival between NBI and WLI was in favor of NBI, but not statistically significant ($p = .16$ and $p = .08$, respectively).

The effect of negative resection margins decreases over time ($p = .007$ after 12 months, $p = .026$ after 18 months, and $p = .40$ at study termination), possibly due to the development of new primary tumors in a field of dysplasia. Until 18 months after TOLS, the recurrence rate in tumors with negative resection margins was significantly lower, than in tumors with positive resection margins (7% vs 25%, $p = .026$). However, at study termination, the rate of new tumors in the group with negative resection margins is comparable with the recurrence rate in the group with tumors with positive resection margins (22% vs 31%, $p = .40$), suggesting that these tumors are in fact new primary tumors arising in a field of preneoplastic altered mucosa. One could argue whether the development of a new tumor more than 18 months after TOLS truly reflects the efficacy of the specific surgical oncologic procedure. Consensus in literature is needed on what we define as a "recurrence," and what is defined as a "new primary tumor," since that fact is critical to assess the success of the surgical procedure. A limitation of this study is that it turned out to be underpowered since the variables needed for an adequate power calculation were not available in 2015. The additional value of NBI on recurrence-free survival we found in this study, was lower than suspected, compared to our assumptions at the start of the study in 2015, and compared to the results of our retrospective study.[17] Based on the current findings (recurrence-free survival of 84% for WLI and 96% for NBI), the needed sample size per group would be 102 (MedCalc V20.210; MedCalc Software Ltd).

There is a 6-month learning curve for the evaluation of NBI images.[38] In our clinic, we have been using NBI for

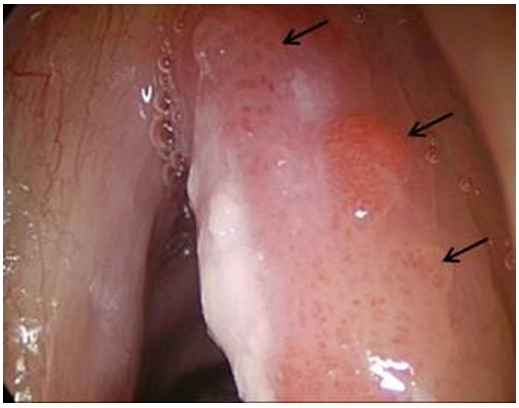

Figure 6. Right-sided T1a laryngeal carcinoma: Evaluation with white light imaging shows the typical intraepithelial capillary loops (arrows) pathognomonic for malignancy, even without using narrow-band imaging.

over 10 years, and we noticed that the typical intraepithelial capillary loops (IPCL), in some cases, were also visible when evaluated with WLI alone. This may have influenced the beneficial results of NBI in a negative way when the results are compared with the results of our retrospective study.[16] An example of IPCLs visible with WLI is given in **Figure 6**.

The WLI group has 3 cases of more advanced tumors (1 T1b and 2 T2a), whereas the NBI group's highest T stage was T1a. This may have influenced the results in favor of the NBI group. Future studies, with larger inclusion of T1b and T2a lesions, must show whether the positive effect of additional NBI and negative resection margins, indeed decreases the risk of developing recurrences.

The results of this study are mostly consistent with the results from our previously published retrospective study.[16] What corresponds is that more recurrences are found in the WLI group. What differs is that the difference between WLI and NBI is not as large as previously observed. The follow-up period was longer in this prospective study, which influenced the overall recurrence rate.

More patients in the NBI group (but not statistically significant) underwent a biopsy after the initial resection, with benign pathology results, because during follow-up flexible laryngoscopy a concerning lesion was visible. It is known that NBI can cause false positive assessments: false positive assessments occur in 7% to 14% of the cases described in the literature, especially in the early phase of the learning curve.[10,39-41]

Conclusion

In this study, the use of additional NBI during TOLS significantly decreased the number of positive resection margins. Patients treated with NBI-based TOLS showed a lower recurrence rate and better recurrence-free survival, than patients in which only traditional WLI was used, which was statistically significant only at 18 months ($p = .02$). Further investigation is required to see whether NBI actually improves clinical outcomes in larger groups of patients, given the in retrospect underpowered sample size of this study. The inclusion of a patient group treated with NBI-based TOLS, and follow-up with conventional WLI would give more insight into the actual effect of using additional NBI during TOLS.

Author Contributions

Manon A. Zwakenberg, designed and directed the study, patient inclusion, data analysis, interpretation of data, wrote the paper with input from all the authors; **Jeroen M. Westra**, patient inclusion, data analysis, interpretation of data, discussed the results and contributed to the final manuscript; **Gyorgy B. Halmos**, interpretation of data, discussed the results and contributed to the final manuscript; **Jan Wedman**, interpretation of data, discussed the results and contributed to the final manuscript; **Bernard F.A.M. van der Laan**, interpretation of data, discussed the results and contributed to the final manuscript; **Boudewijn E.C. Plaat**, designed the study, data analysis, interpretation of data, supervised the work, discussed the results and contributed to the final manuscript.

Disclosures

Competing interests: Boudewijn E.C. Plaat has received research funding from Olympus Medical Systems EU.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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