Chapter 2

Narrow band imaging is a new technique in visualization of recurrent respiratory papillomatosis

Robin E.A. Tjon Pian Gi¹, Gyorgy B. Halmos¹, Bettien M. van Hemel², Edwin R. van den Heuvel³, Bernard F.A.M. van der Laan¹, Boudewijn E.C. Plaat¹, Frederik G. Dikkers¹.

¹ Department of Otorhinolaryngology/ Head & Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
² Department of Pathology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
³ Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Abstract

Objectives: Recurrent respiratory papillomatosis (RRP) is a rare, benign, wart-like disease for which no curative treatment exists. Goal of treatment is total surgical removal of the epithelial lesions in order to keep the airway open and the voice sufficient. Therefore it is essential to visualize all papillomatous lesions. The present study aims to evaluate the sensitivity of additional use of narrow band imaging (NBI) in detecting RRP during microlaryngoscopy.

Study Design: Prospective study.

Methods: Between January and July 2011 patients with RRP underwent systematic inspection during microlaryngoscopy using conventional white light (WL) immediately followed by inspection with NBI. Consensus was achieved about the number of lesions and number of RRP suspect lesions. All lesions were subsequently excised and sent for histopathological examination.

Results: Eighty-six excisional biopsies were taken in 24 microlaryngoscopies performed in 14 RRP patients. Eleven out of the 13 additional biopsies taken, induced by the second inspection with NBI, proved to be papillomata after histopathological examination. The sensitivity increased from 80% with WL up to 97% with WL+NBI (p<0.01), while the specificity remained poor (32% and 28%, respectively).

Conclusions: NBI is an additional diagnostic tool increasing the sensitivity of visualizing papillomata during microlaryngoscopy.

Key words: endoscopy, microlaryngoscopy, imaging, narrow band imaging, NBI, laryngeal papillomatosis, papilloma, recurrent respiratory papillomatosis, RRP.
Introduction

Narrow band imaging (NBI) is an in vivo optical image enhancement technique that increases the visibility of blood vessels on mucosal surfaces. Narrow band light exists of 2 wavelengths, is strongly absorbed by hemoglobin in blood vessels and only penetrates the surface of the tissue. The short wave length (390-445 nm) of the light source penetrates only in the superficial layer of mucosa, and is absorbed by capillary vessels. Longer wave lengths (530-550 nm) however, penetrate deeper and are absorbed by more deeply located veins. As a result, under narrow band illumination, capillaries on the mucosal surface are displayed in the color brown on the monitor, but veins in the submucosa are displayed in cyan. NBI has already successfully been used in screening and diagnosis in multiple regions of aerodigestive tract, including the tracheobronchial tree, esophagus, stomach, duodenal ampullary, and colorectal region (1,2). Muto et al. introduced NBI in head and neck oncology, to detect carcinoma at oropharyngeal and hypopharyngeal mucosal sites (3). Later, the NBI endoscopy improved diagnostic accuracy, sensitivity, and negative predictive value in detecting squamous cell carcinoma of the head and neck in patients with esophageal cancer (4). Nowadays, NBI is primarily used in head and neck oncology for better detection, improving location of surgical margins and for definition of tumor staging (1,5).

Recurrent respiratory papillomatosis (RRP) is caused by human papilloma virus (HPV) 6 and 11, and is characterized by wart-like lesions spread throughout the respiratory tract with a preferred location in the larynx. The characteristic histopathologically appearance of RRP is the typical finger-like projections of the squamous epithelium each with a core of vascular connective tissue (6). The incidence of RRP according to the literature is 3.84 per 100,000 (7). Even though the incidence is very low, the burden for a patient and his/her family can be very high. Some patients will need over a 100 operations for removal of RRP. There is no curative therapy. The goal of treatment is total surgical removal of the epithelial lesions in order to keep the airway open and the voice sufficient. Papillomata are often missed during microlaryngoscopy due to their small size or due to granulations as a result of previous interventions in an adjacent area. Small RRP lesions can grow in areas where papilloma tissue remains after incomplete surgical excision. Therefore, it is important to visualize the complete RRP lesion for complete surgical removal. The purpose of this study is to evaluate the sensitivity
of narrow band imaging (NBI) - as an additional tool - in detecting RRP during microlaryngosurgery.

Materials and methods

Patients and procedure
The present study was prospectively conducted between January and July 2011 at the department of Otorhinolaryngology, Head and Neck Surgery of the University Medical Center Groningen (UMCG), a tertiary referral hospital in the Netherlands. The human-study internal review board of the UMCG assessed that there were no needs for permission based on the Dutch Medical Research Law (Wet Medisch Onderzoek, WMO).

All patients with lesions suspect for RRP or had histopathologically proven history of RRP, who were planned for routine microlaryngoscopy, were included in the study. No exclusion criteria were used.

All procedures have been performed under general anesthesia. After orotracheal intubation the patient’s upper aerodigestive tract was examined by a telescope indirectly coupled to HDTV (Olympus OTV-S7ProH-HD-12E HD autoclavable Camera Head, with a 0° telescope Ø5.4mm, Olympus EVIS EXERA CLV-180 light source, 300 Watt Xenon with Narrow Band Imaging filter, Olympus EVIS EXERA CV-180 processor, HDTV). As in the normal procedure, an experienced laryngologist performed a systematic inspection under conventional white light (WL). During this inspection he and another doctor (an experienced otolaryngologist in training) completed a form, which consisted of three questions:

1. How many lesions have you seen?
2. How many RRP suspect lesions have you seen?
3. Where were they located?

The diagnostic criteria used during the two inspections were determined in advance:

1. Diagnostic criteria of RRP suspected lesion by conventional WL: a lesion with multi-nodular growth and possible vascularities in the respiratory tract.
2. Diagnostic criteria of RRP suspected lesion by NBI: a lesion with typical brown dots or increased intra-epithelial papillary capillary pattern, within a shimmering pale mass in the respiratory tract.

After the first inspection the two doctors listed the number of lesions, the number of RRP suspect lesions and their locations. Consensus was obtained after interpretation of the endoscopic images. Pictures of all lesions were taken with conventional WL. With the knowledge of the first inspection, the second inspection was performed in the same way by using NBI. After the second consensus between the same two doctors, NBI pictures were taken of the lesions.

WL pictures were made of the lesions missed during the first inspection. In this way every RRP suspect lesion was photographed twice; once using WL and once using NBI. All lesions, suspect for papilloma or for other pathology, possibly influencing the voice, diagnosed with any modality (WL and NBI) were then surgically removed under WL. Following to this procedure, all lesions were separately sent to the pathologist. The experienced head and neck pathologist with knowledge of RRP was blinded for detection method.

Statistical Analysis
Sensitivity and specificity for detecting RRP were calculated and compared. The McNemar’s test was conducted to compare the WL and the combination of WL and NBI. All tests were two-sided and conducted at the significance level of 0.05. Analyses were performed with SAS (version 9.2) and Excel (2007).

Results
Twenty-four microlaryngoscopies were performed in 14 patients. The study population consisted of nine men and five women, with a mean age of 35 years (range 3-57). Five out of 14 had juvenile RRP: they were diagnosed with RRP when they were younger than 14 years (8). The additional time necessary to complete the NBI inspection never lasted longer than five minutes. There were no complications registered.
Of the 86 detected and excised lesions, 79 were suspect for papilloma. The remaining seven biopsies were not suspect for papilloma but for aberrant mucosa (granuloma or scar tissue, which possibly influence voice). One of these, however, was histopathologically diagnosed as papilloma.

The group had a mean of 3.3 RRP suspect lesions (range 0-10) per microlaryngoscopy. In four microlaryngoscopies in patients with a history of RRP, no RRP suspect lesions were seen. Histopathology revealed 61 papillomata out of 86 biopsies. The remaining 25 biopsies were not histopathologically considered papilloma.

The clinical findings during endoscopy and histopathological findings are schematically depicted in Figure 1. Thirteen additional biopsies were taken after NBI was performed (cases 1-8 in Figure 1). Eleven out of these 13 biopsies (colored green in cases 1-8, Figure 1) were histopathologically confirmed as papillomata, but two were not. Without NBI, these eleven papillomata would have been missed. In two microlaryngoscopies (cases 9 and 10 in Figure 1), two RRP suspect lesions were seen during inspection with WL, while they did not appear as RRP suspect during the NBI inspection. Therefore these lesions would have been surgically removed if only inspected by WL, while in combination with NBI these lesions would not have been surgically removed. These lesions have been biopsied and one was histopathologically positive (case 9 in Figure 1) while the other was negative for papilloma (case 10 in Figure 1).

Based on the observed lesions and histopathology the sensitivity and the specificity of conventional WL in detecting papillomata was 80% (49 of 61) and 32% (8 of 25), respectively (Table 1). The sensitivity and the specificity of WL in combination with NBI were 97% (59 out of 61) and 28% (7 of 25), respectively (Table 2). Using McNemar’s test, the p-values for testing equality of sensitivity and specificity separately between WL and WL in combination with NBI were obtained at p<0.01 and p= 1.0, respectively, using an exact calculation.
Figure 1. Figure showing the number of additional biopsies taken in individual microlaryngoscopies because of NBI-induced presumed presence of papilloma, and the corresponding histopathological diagnosis. Hist P+: Histopathologically confirmed papillomata. Hist P-: Histopathologically not confirmed as papillomata.

<table>
<thead>
<tr>
<th></th>
<th>histopathology</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>papilloma</td>
<td>nonpapilloma</td>
<td></td>
</tr>
<tr>
<td>White light</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion suspect for</td>
<td>49</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>papilloma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion not suspect</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>for papilloma</td>
<td>61</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Clinical and histopathological results of WL in detecting papillomata. Total number of biopsies is 86.

<table>
<thead>
<tr>
<th></th>
<th>histopathology</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>papilloma</td>
<td>nonpapilloma</td>
<td></td>
</tr>
<tr>
<td>White light + NBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion suspect for</td>
<td>59</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>papilloma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion not suspect</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>for papilloma</td>
<td>61</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Clinical and histopathological results of WL in combination with NBI in detecting papillomata. Total number of biopsies is 86.
Figure 2, Figure 3 and Figure 4 show cases where RRP lesions were missed using WL, but where they were visualized during the second inspection by NBI. Histopathologically all these lesions were positive. The figures demonstrate that there is much greater contrast between lesion and healthy tissue with NBI inspection than in inspection with conventional WL. Figure 5 shows a HE (hematoxylin and eosin) stain with the typical RRP finger-like projections of the squamous epithelium with a core of vascular connective tissue. This lesions was not seen using conventional WL but clearly presented itself using NBI.

![Figure 2](image1.png)

**Figure 2.** (a) Endoscopic view of the trachea with optical focus on most proximal (4th) tracheal ring. No lesions were seen using conventional white light. (b) With narrow band imaging inspection, these lesions cleared up, and were histopathologically confirmed as papillomata. Visible are several typical brown dots (black arrows) within a shimmering pale mass.

![Figure 3](image2.png)

**Figure 3.** (a) Endoscopic view of the aryepiglottic fold. No lesions were seen using conventional white light. (b) With narrow band imaging inspection these lesions cleared up and were histopathologically confirmed as papillomata.
Figure 4. (a) Endoscopic view of the epiglottic. No lesions were seen using conventional white light. (b) With narrow band imaging inspection these lesions cleared up and were histopathologically confirmed as papillomata.

Figure 5. Typical recurrent respiratory papillomatosis finger-like projections of the squamous epithelium (arrow). The core of vascular connective tissue (arrowhead) (magnification, 100).
Discussion

To the best of our knowledge, this is the first study describing the additional use of NBI in combination with WL in the diagnosis of RRP. This novel technique significantly increases the sensitivity of detecting RRP. Eleven additional papillomata were found, while only one papilloma was missed by NBI while seen by the WL inspection. Capillary vessels in RRP absorb the narrow band light and show typical brown or increased intra-epithelial papillary capillary pattern within a lobular shimmering pale wart-like mass.

A concern of the study is the estimation of specificity. It is ethically unjustified to take biopsies of healthy tissue without lesions. This issue can explain the low specificity. Piazza et al. showed that the number of false positives using NBI are related to the period of practicing with the NBI and is the highest in the first 6 months (9). The endoscopist in our series had no previous experience with NBI. Therefore, a learning curve of the new technique can be expected, which can lead to less false positive results and a better specificity. The specificity slightly decreased from 32% to 28% with additional use of the NBI. However, this decrease is out weighted by the improvement in sensitivity (or false negatives), which increased from 80% to 97%.

Eleven additional histopathologically confirmed papillomata were found by NBI. These papillomata were seen in seven out of 24 different microlaryngoscopic interventions. This implies that approximately for every 3.4 interventions additional papillomata are found in case NBI is used as additional tool.

In retrospect it is remarkable that eleven seemingly obvious RRP lesions were missed during the WL examination. After having used NBI, some of these lesions could easily be visualized using WL. Two reasons can explain this phenomenon. On one hand, higher optical zoom was used while taking the WL pictures than during the laryngoscopic procedure. On the other hand there is foreknowledge of narrow band imaging.

Although the otorhinolaryngologists found NBI simple to use (one button to switch between WL and NBI), the NBI method has some limitations. NBI is less suitable during surgery where high amounts of blood are released, because the
Narrow band imaging

Narrow band light is absorbed by the bloody environment. This leads to darker images.

In the study setup we aimed to optimize the study design by adding a second observer during microlaryngoscopy. The advantage of the chosen study design over a patient control study is that all individual variables did not give bias. Unfortunately a crossover study was clinically impossible to arrange.

During inspection, the otorhinolaryngologists felt that they could better separate papilloma from healthy tissue with NBI than without. In some cases the otorhinolaryngologist decided to take a wider margin in response to the NBI inspection. The potential curative effect of this wider margin is not analyzed in this study, and should be investigated in future studies.

The purpose of this study was not to demonstrate the clinical outcome of NBI. It cannot determine whether the additional use of NBI decreases the recurrence rate or the number of surgical interventions. In addition the authors experienced that RRP can be earlier visualized and therefore it is easier to remove, causing less damage by surgical excision than if it were larger.

Conclusion

This is the first study showing increased sensitivity of histopathologically confirmed RRP lesions using NBI as an additional technique as compared with conventional WL alone.

In conclusion: NBI is an additional diagnostic tool that increases the sensitivity of visualizing RRP during microlaryngoscopy. Since this is the first report of using NBI in RRP patients, there remains much research to be done.
Chapter 2

References


Part II
Clinical Course