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Laryngeal Dysplasia and narrow band imaging: secondary analysis of published data supports the role in patient follow up

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Abstract:

Background: Clinicians have recognised the role of narrow band imaging (NBI) in the management of head and neck cancer in several studies. However, a recent systematic review was unable to pool the data on diagnostic efficacy in this setting owing to the heterogeneity in the published data.

Methods: Secondary analysis of data, utilising Bayes' theorem, from meta-analyses and randomised trials

Results: In patients with a histological diagnosis of mild dysplasia who show no abnormalities on NBI, the post-test probability of malignancy is 2.3%, compared to 10.3% with conventional white light imaging (WLI). For severe dysplasia, similar post-test probabilities after NBI and WLI are 8.0% and 29.7% respectively. Post-test probabilities in this setting indicate the chance of missing malignancy following a negative NBI or WLI in patients who undergo no further intervention. This paper also provides a nomogram designed for use in this setting.

Conclusions: This paper identifies the evidence base for use of NBI in the follow up for laryngeal dysplasia.

Introduction

The management of laryngeal dysplasia has historically been subject to significant variation, and practice was largely based on personal and institutional policies [1]. However, ENT UK has led on the formulation of multispecialty consensus management guidelines for laryngeal dysplasia, based on robust analysis of published data and professional opinion prevalent in 2010 [2]. This has helped to streamline the provision of laryngeal dysplasia services [3].

Diagnosis is established by tissue biopsy and follow up is needed for high risk patients. The consensus guidelines recommend flexible nasolaryngoscopy and colour photo-documentation as a minimum follow up as standard. Change in the appearance of the dysplastic lesions is usually a trigger for a biopsy, and accurate photo documentation of the lesion enables such change to be detected.

The authors recently performed systematic review to pool published data on the diagnostic efficacy of narrow band imaging (NBI) within head and neck practice [4]. Although the available data pertaining to laryngeal dysplasia could not be pooled due to significant heterogeneity and was presented in a descriptive fashion, a careful assessment, re-analysis and re-interpretation of the published data, in conjunction with pooled data on malignant transformation rates published earlier [5], suggests an important role that NBI that can play in patient follow up. We present an interpretation of data based on further analysis of two studies using Bayes' theorem.

Ethical considerations:

Being a secondary analysis of published data, no ethical considerations arise in this study.

Studies used in the analysis:

A systematic review on the role of NBI in dysplastic lesions [4] identified the study by Muto et al [6] as the only randomised controlled study in the literature that uses NBI in the diagnostic setting, comparing the detection rate for superficial squamous cell carcinoma in the head and neck region using NBI with conventional white light imaging (WLI). The study enrolled 333 patients with histologically confirmed oesophageal squamous cell carcinoma, aged 20 years or older, newly diagnosed or on follow up. As this patient group has a high prevalence of synchronous or metachronous malignancies, the upper aerodigestive tract (UADT) mucosa was assessed during oesophagoscopy. Patients were randomised to primary WLI followed by NBI, performed back to back at the same sitting, or primary NBI followed by WLI. The primary outcome was to identify lesions that that appeared as slightly elevated lesions lower than 5 mm, flat lesions, and lesions with a shallow depression that were later histologically proven to be carcinoma in situ or microinvasive squamous cell carcinoma (SCC). These were characterised by a well demarcated brownish area with irregular microvascular patterns. Overt lesions with an elevation greater than 5mm or those with apparent deeper ulceration were not evaluated.

Of the 333 patients enrolled, 13 were excluded and the analysis included 320 randomly allocated patients. In the primary WLI group (n=162), one of 13 superficial squamous cell cancer was detected in the UADT mucosa, compared with 15 detected in 15 patients in the primary NBI group. This difference was statistically significant ($p< 0.01$). This paper reported in detail the diagnostic accuracy of WLI and NBI, shown in Table 1.

Weller et al [5] reported a systematic review of observational studies on laryngeal dysplasia and pooled selected data as a meta-analysis, one aspect of which focused on the malignant transformation rates (MTR). The data from nine studies including 940 cases suggested that overall malignant transformation rate was 14% (95%CI: 8%, 22%); the malignant transformation rate was higher with severe dysplasia/carcinoma in situ (30.4%) compared to mild/moderate (10.6%) ($p< 0.0002$).

Secondary analysis and interpretation of the above data:

Further analysis, utilising Bayes' theorem, allows the post-test probability of disease to be calculated by combining the pre-test probability with the likelihood ratio for the test [7]. A pre-test probability for mild/moderate dysplasia is estimated as 10.6% (95% CI: 5.1–20.7) and for severe dysplasia as 30.4% (95% CI: 16.1–49.9) from Weller et al [5] .

The negative likelihood ratio (-LR), the probability of testing negative with disease compared to the probability testing negative when not, can be calculated using estimates of sensitivity and specificity from the test. Estimates of sensitivity and specificity for WLI and NBI (Table 1) are taken from the Muto et al trial [6]. The -LRs with associated 95% confidence intervals (calculated using the bootstrapping method of Marill et al [8]) are 0.97 (0.70 - 1.00) and 0.00 (0.00 - 0.20) for WLI and NBI respectively. When the -LR is <0.1 (as is the case with the point estimate for NBI), it can be

interpreted as a large and often conclusive decrease in likelihood of disease. However, when the -LR is 0.5 – 1 (as is the case with WLI) only minimal decrease in likelihood of disease can be expected. Thus, if follow up assessment using NBI does not have findings suggestive of superficial cancer as per the description above, the clinician can have confidence that the lesion has not undergone malignant transformation.

The pre-test probability can be combined with the -LR of the test, using Bayes' theorem, to obtain a post-test probability of malignancy. The calculation proceeds by first converting the pre-test probability to pre-test odds, multiplying by the –LR, then converting the post-test odds to a post-test probability. These calculations could also be shown on a Bayes' nomogram [7], adapted from Fagan's nomogram [9, 10].

Given that the sample -LR for NBI is zero, the upper bound of the 95% confidence interval (0.00 - 0.20) is used in place of the point estimate in subsequent calculations. This is a conservative choice and follows the advice of Marill et al [8], who suggest that the upper bound is the critical metric to use when evaluating a diagnostic test in this scenario. For WLI, the point estimate of the -LR of 0.97 is used in subsequent calculations, this estimate is very close to the upper bound of the 95% confidence interval (0.70 - 1.00).

Let us consider a patient who has a histological diagnosis of mild dysplasia who is under follow up with a pre-test probability of malignancy of 10.6%. An NBI with no abnormalities gives the post-test probability of malignancy to be 2.3%. The interpretation for a negative NBI in this setting is thus: the probability of testing negative for a malignancy, and thus missing a diagnosis if no intervention were to be performed on this basis is 2.3%, an acceptable margin of error. Using WLI, the post-test probability of missing a malignancy is 10.3%. This margin of error would be unacceptable in most clinical situations.

Let us now assume a patient with a histological diagnosis of severe dysplasia with a pre-test probability of 30.4%. The post-test probability, and thus the chance of missing malignancy in a patient with severe dysplasia who has a negative result from NBI and undergoes no further intervention on the basis of this test is 8.0%. For WLI, the post-test probability and the chance of missing malignancy is 29.7%. These figures would be considered too high in clinical practice. Other pre-test probabilities, for example based on local population data, can be used to work out post-test probabilities, as illustrated in Figure 1.

Discussion:

As recent literature review has not shown a clear way forward, and prospective studies on this specific group are awaited, we elected to perform this secondary analysis to make the best use of available data. Our findings suggest that NBI could play a significant role in follow up of patients with laryngeal dysplasia. Across all histological grades of dysplasia, WLI has greater chance of missing malignant transformation during follow-up compared with NBI. For patients with mild laryngeal dysplasia, the point estimate and the upper limit of confidence interval for the -LR are both low enough to consider a non-intervention policy based on the clinical findings. However, for patients

with severe dysplasia, greater caution should be exercised, although the clinician is four times less likely to miss malignant transformation when NBI is used for follow up.

Strengths and weaknesses of the analysis:

Although the Muto et al [6] paper included all UADT mucosal sites, and did not present data on laryngeal sites separately, the patient selection with appropriate risk factors and the exclusion of previously radiated patients make for a reasonably comparable group. The median age for the population was 64, with alcohol use reported in over 94% of patients and 90% being smokers. Recent papers [11] provide further data on the diagnostic efficacy rates of NBI in laryngeal precancer that are similar to the figures identified in the study by Muto et al [6]. Clinically, the interpretation of NBI for laryngeal and other mucosal sites remain uniform; thus, we do not have major concerns with the applicability of this data to the laryngeal dysplasia population. However, the study was performed on a Japanese population and we recommend that the reader carefully peruse the data in this trial. It is the publication of the robust MTR that allows us to be confident in our recommendation. Indirect proof of this recommendation can also be found in studies that use NBI to define superficial resection margins during transoral laser surgery for early laryngeal cancers [12]; the positive margin rate drops significantly (3.6% vs 23.7%) when the mucosal cuts are performed using NBI than with WLI. Similarly, Staníková et al [13] identified close concordance between NBI endoscopy findings are histological evidence malignant transformation (kappa index 0.77, $p < 0.001$) in their prospective cohort of 63 patients; they conclude in their study that a "negative NBI endoscopy may be an indication for long-term endoscopy follow-up without histological evaluation".

We acknowledge the variability in the sensitivity and specificity estimates used to derive the likelihood ratio due to the small number of cancers observed in the Muto study. As such, it is recommend that further confirmation of the conclusions of this re-analysis be sought in the real world from clinical trials. A major caveat is the thick keratotic lesion that prevents assessment of the submucosal vessels, negating the added value of NBI.

Clinical applicability of the data:

In a retrospective analysis of laryngeal biopsies performed in North Glasgow, Scotland, between 2001 and 2010, Lim et al [14] showed that there has been a significant increase in the number of biopsies performed from 2005; Between 2004 and 2005, the number of biopsies in the dysplasia category increased by 20%, with the increasing number primarily in the severe dysplasia and carcinoma in situ category ($p<0.001$). It is widely recognised that repeated laryngeal biopsies can have an adverse effect on the voice outcomes. Based on this analysis, we believe that a negative NBI test should allow more confident outpatient management of patients on follow up for laryngeal dysplasia, and avoid general anaesthetic and biopsy. This analysis also supports the need for a prospective trial in this setting.

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