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WILEY
INTRODUCTION

Early diagnosis and assessment of upper aerodigestive tract (UADT) lesions is paramount to avoid treatment delays. This is especially true when UADT cancer is suspected. Timely diagnosis will allow for earlier start of treatment. It will also reduce patient anxiety while waiting for results, and help adherence to national targets in management of patients with suspected cancer. Rigid endoscopy and biopsy under general anesthesia (GA) continues to be widely utilized as a diagnostic aid when assessing UADT lesions and looking for simultaneous pathologies. It also offers a therapeutic opportunity in cases of small laryngeal tumors. There has been some recent debate with regard to the role of rigid endoscopy both in terms of safety and yield.¹,² Major complications of rigid endoscopy, such as esophageal perforation, are rare, with a perforation rate of 0.2% to 0.6%.³,⁴ However, it is still a life-threatening complication. The yield of second primary tumor of rigid endoscopy reported in the literature is small and ranges from 0% to 1.8%.⁴,⁶

Additionally, rigid endoscopy was found to be inferior to both esophago-gastro-duodenoscopy (OGD)⁷ and positron emission tomography–computed tomography⁸ in terms of detecting a second primary. Moreover, there is a significant rate of abandoned rigid endoscopy procedures that amount to ~10%.⁴ This can carry significant implications in terms of diagnosis delay. In addition, it was reported in the literature that upper esophageal neoplasia could be missed by rigid endoscopy.⁹

When compared with OGD, transnasal esophagoscopy (TNE) is a recent diagnostic and procedural instrument. Flexible scopes in fields other than ear, nose, and throat (ENT) were introduced around 1960. It was not until 1964 that the first flexible scope with biopsy ability was introduced.¹⁰ TNE was introduced in the early 1990s, and since then it became widely available in units across the United States and the United Kingdom.¹¹ The first reports on utilization of TNE in ENT practice were very encouraging in terms of image quality and patient acceptance, enabling the procedure to be performed under local anesthesia without sedation.¹² As such, it provides the option of assessing UADT in the outpatient settings with the possibility of taking biopsies from suspicious areas and perform procedures such as secondary puncture of voice prosthesis or removal of foreign body,¹¹ in addition to flexible CO₂ laser delivery¹³ and to guide injection thyroplasty.¹⁴ TNE also offers a good alternative in patients with large tumors or with multiple comorbidities in whom a general anesthetic would pose a risk to their general health. It also allows for biopsies to be...
taken in addition to allowing inspection of UADT to look for a second primary.

In meta-analysis of the literature, it was shown that 6.4% of patients who were diagnosed with upper gastrointestinal cancer did have negative OGD in the previous year. Additionally, OGD is not without complications, primarily due to anesthetic factors (0.14% nonfatal) and even death (0.04%), with higher rates found in therapeutic OGD. TNE, on the other hand, has a long record of safety with only one major complication (perforation) and no deaths reported in the literature. Such differences in major complication rate might be explained by the different spectrum of patients and pathologies assessed and/or treated by each method.

A review of the literature shows that TNE was used in the past to guide biopsies. The largest number of patients reported was 96, all of whom underwent laryngeal biopsies. Sensitivity and specificity varied between studies ranging from 30% false-negative rates in a study where patients with TNE-guided laryngeal biopsies were rebiopsied using traditional techniques and pathological findings, compared to a 100% accuracy rate in a series of 17 patients when compared with standard panendoscopy performed on the same patients afterward. Other studies seem to have focused mainly on the feasibility and safety of performing biopsies via TNE rather than the actual results. One potential critique is that the number of procedures performed in these studies is relatively small, and no information was offered about sensitivity and specificity except in the study involving laryngeal lesions.

The aim of this project, which is to date the largest report on TNE-guided biopsies, was to present yield of TNE biopsies of UADT lesions. We also aimed to define the role of TNE as a safe alternative to rigid endoscopy.

MATERIALS AND METHODS

This study received approval by the local clinical research and audit governance committee. All patients provided informed consent before commencing treatment, and information was stored in a secure location with anonymous evaluation of results. All patients in whom TNE-guided biopsies were attempted over a 2-year period in an ENT outpatient setting were included. Patients' demographic data were recorded as well as the site of the lesions biopsied and the final histological diagnosis. The outcomes recorded were the success in completion of the procedure, success in obtaining sufficient biopsies, and the need for further biopsy before treatment. The procedure was performed with no fasting requirements and no sedation. All patients had their larynx, pharynx, and esophagus visualized before obtaining biopsies. Local anesthesia was applied in the nose and the back of the mouth in addition to installation of local anesthesia directly into the lesion. For further details on setup of TNE (Pentax 80 K Series Digital Video Endoscope; Pentax, Slough, UK) and anesthesia technique, please refer to the earlier work from our institution. To obtain the biopsies, the senior author used the help of a trained doctor to maneuver the scope. A small biopsy forceps (Pentax KW1811S 1.8-mm flexible biopsy forceps; Pentax) is then used to obtain between two and three biopsies from the lesion. In cases of tongue base lesions, more biopsies were taken including deeper biopsies, which was achieved by taking biopsies from the same spot and getting deeper each time. Biopsies were preserved in formalin and sent for histological assessment, results were reported back to patients after 1 week, and further biopsies were arranged under general anesthesia if necessary. All procedures were recorded in a diary that was used to identify patients. Additionally, coding of office records was used to corroborate the number of patients identified. Office letters and patient notes were retrieved if there was any ambiguity.

RESULTS

Patients included 26 (19.8%) females and 95 (72.5%) males. At the time of the procedure the mean age was 65.8 years, and the standard deviation was 14.34. A flowchart of the study cohort is presented in Fig. 1. The study included 134 procedures on 121 patients. Of these, there were 19 abandoned procedures. This leaves 115 successful procedure where biopsies were taken, giving an overall procedure success (of obtaining biopsies) rate of 86%. All further analysis will be made on these 115 procedures.

The abandoned procedures numbered 19 in total. In most of these procedures, the TNE was performed down to the lesion but biopsy was not possible. Patients were offered another TNE appointment and were listed for panendoscopy and biopsy as a provision. Thirteen patients of the 19 refused a further TNE-guided biopsy and went on to have panendoscopy and biopsy. Only six procedures were repeated; five procedures were successful and one had to be abandoned again, and the patient then went on to have a successful one (undergoing a total of three procedures). It is worth noting that most of the abandoned procedures were for glottic lesions (11 patients).

Biopsies were taken from UADT lesions, with the glottis being the most common site. Further details of the subsites are shown in Figure 2. The histology showed benign lesions in 46 patients and malignant and premalignant lesions in 64 patients; biopsies were not sufficient in five (nondiagnostic in four and necrosis in one) patients. For further details please refer to Table I.

Out of 115 patients, only 13 procedures (11%) biopsy results were deemed not sufficient due to one of three reasons: high clinical suspicion (in malignancy-negative TNE biopsy results) (six patients including the patient who was found to have necrosis on his TNE-guided biopsy), when there were neck nodes requiring fine-needle aspiration (FNA) (three patients), or when biopsies on TNE were nondiagnostic (four patients, including one patient who had a neck node and went on to have a core biopsy).

Further procedures under GA (with an intention to perform biopsies) were performed in eight cases. An example of high clinical suspicion is persistent pain even after treatment with antibiotics or a persisting suspicious lesion. Patients with UADT cancer diagnosed on FNA went on to have further investigations per multidisciplinary team (MDT) recommendations. The details of these 13 procedures, including findings and subsites, are summarized in Table II. No patient suffered airway or bleeding complications during any of the procedures, and all were discharged home after their appointment in the office.
DISCUSSION

Many hospitals are experiencing constraints in bed and operating room capacity. There is also a drive in the United Kingdom toward more day case procedures. The option of assessing and taking biopsies from the UADT in the outpatient setting using transnasal endoscopy is attractive. It is more convenient to the patient, because it does not involve the usual routine of a GA procedure. Complications from GA are higher in the older, comorbid group, from which head and neck cancer patients are most commonly drawn. Although American Society of Anesthesiologists (ASA) 1 patients have a GA-related mortality of 0.4/100,000, this rises to 27/100,000 in ASA 3 patients. Patients aged 40 to 75 years have a GA related mortality of 5.2/100,000, rising to 21/100,000 in those over 75 years. TNE also offers a solution to patients with inaccessible biopsy sites when traditional methods are used. In addition, the procedure can be done

![Flowchart of the study cohort. *Includes nondiagnostic biopsies and necrosis. **Includes rigid pharyngoscopy and microlaryngoscopy. FNA = fine-needle aspiration, SCC = squamous cell carcinoma, ND = Non diagnostic. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]](image1)

![Number of biopsies performed per subsite, PNS = postnasal space. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]](image2)
in a timely fashion, as there is more flexibility in the outpatient office and planned lists are not disrupted. Furthermore, performing TNE-guided biopsy early in the process has the added benefit of potentially avoiding the need to coordinate between the radiology department and operating room coordinator, which is advisable if rigid endoscopy is to be performed to avoid false-positive radiological findings.

TNE-guided biopsy expenditure should include the initial cost of setting up a TNE office. However, even when that cost is included, the economic analysis presented in previous articles suggest a significant advantage with this technology. The cost calculation is not limited to the avoidance of general anesthesia; it also precludes the need for preoperative assessments and minimizes the administration burden associated with each patient episode, as usually TNE can be arranged at the first appointment with the benefit of avoiding potential future cancellations or nonattendance.

This is the largest series to date of biopsies using transnasal endoscopy in one center. More than 800 procedures were carried out over the study period for a variety of reasons, and 16.2% (134/824) required a single/multiple biopsy for suspicious lesions.

Success rate of obtaining a TNE-guided biopsy is smaller than that of TNE alone (86% vs. 94%). This can be explained by patient anxiety, which is understandably more due to the presence of a lesion, and the extra time required.

### Table I.

<table>
<thead>
<tr>
<th>Subsite</th>
<th>Benign</th>
<th>Premalignant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inflammatory/ Reactive/Normal</td>
<td>Papilloma</td>
</tr>
<tr>
<td>Glottis</td>
<td>5 inflammatory</td>
<td>2 (one with severe dysplasia)</td>
</tr>
<tr>
<td>Supraglottis</td>
<td>1 inflammatory</td>
<td>2†</td>
</tr>
<tr>
<td>Tongue base</td>
<td>3 inflammatory, 5 benign, 2 normal</td>
<td>1</td>
</tr>
<tr>
<td>Oropharynx§</td>
<td>1 inflammatory, 1 benign</td>
<td>1</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>1 inflammatory</td>
<td>1 atypia</td>
</tr>
<tr>
<td>Neopharynx</td>
<td>5 normal, 2 hyperplasia, 3 benign</td>
<td>1 oncocyotma</td>
</tr>
<tr>
<td>Esophagus</td>
<td>29</td>
<td>3</td>
</tr>
</tbody>
</table>

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*Two nodules, two keratosis (one dysplastic), one polyp.
†Cyst and venous malformation.
‡Hyperplasia.
§Other than tongue base.
CIS = carcinoma in situ; HPV = human papillomavirus; PNS = postnasal space; SCC = squamous cell carcinoma; TNE = transnasal esophagoscopy; AC = Adenocarcinoma.

### Table II.

<table>
<thead>
<tr>
<th>Subsite</th>
<th>High Clinical Suspicion</th>
<th>Neck Lump</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TNE Result</td>
<td>Further Procedure</td>
</tr>
<tr>
<td>Glottis</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Supraglottis</td>
<td>Inflammatory</td>
<td>Radionecrosis</td>
</tr>
<tr>
<td>Tongue base</td>
<td>1 benign, 2 benign</td>
<td>1 recurrent SCC, 2 benign</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Inflammation</td>
<td>Recurrent SCC</td>
</tr>
<tr>
<td>Neopharynx</td>
<td>Inflammation</td>
<td>Recurrent SCC</td>
</tr>
<tr>
<td>PNS</td>
<td>Necrosis</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

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*Patient went back to primary treating hospital.
CIS = carcinoma in situ; FNA = fine-needle aspiration; PNS = Postnasal space; SCC = squamous cell carcinoma; TNE = transnasal esophagoscopy.
needed for the procedure. Additionally, factors such as a strong gag reflex, persistent cough, and narrow nasal passages were among reasons leading to patients not tolerating the procedure.

When compared with rigid endoscopy, our results suggest a favorable complication rate and comparable abandonment rate. When comparison is made with OGD, the success rate seems to be slightly better. It is important to point out the very high rate of nondiagnostic TNE-guided biopsies of the tongue base. We recommend that unless the lesions are obvious or the patient is not fit for GA, other methods should be considered.

Esophageal tumors are normally referred to the gastroenterology MDT for discussion and management. In these circumstances, performing TNE biopsies will save time and might prevent the need for further biopsies. Additionally, availability of digital recording will obviate the need for an OGD before discussion.

When considering patients for TNE-guided biopsy, anatomical as well as patient-related factors play an important role in candidacy (i.e., narrow nasal passages, hyperfunctional cricopharyngeus, patient preference, and anxiety). Anxiolytic medications can help if given 2 hours before the procedure. Regarding a narrowed nasal passage, the transoral route can be used with a caveat that no nasopharyngeal biopsies can be obtained. A potential difficulty encountered with TNE relates to the difficulty with cannulating the cricopharyngeus/esophageal inlet. In contrast, GA offers the advantage of muscle relaxants that can be effective in relieving the tension. OGD continues to be a step in the middle. However, in the current National Health Service (NHS) setting, it is not as flexible in timing as TNE and normally restricted to the gastroenterology department (making routine inpatient/outpatient referral more formal and less practicable).

Limitations

Effects of early biopsies on imaging quality were not formally assessed. However, the effect is thought to be minimal. Only patients referred via cancer pathway were included, which might have some confounding effect on the results of biopsies taken and might be responsible for the high number of malignant and premalignant lesions. Immunohistochemistry was not performed in all patients included in this study. Assessment of p16INK4A status in TNE-guided biopsies is possible. It is advised to include human papillomavirus status in any future research, especially when biopsies of the tongue base and tonsils are included.

Clinical suspicion was a factor that led to some patients undergoing further procedures. In this study, factors such appearance of the lesion, presence of high-risk factors such as smoking and alcohol consumption, in addition to presence of referred pain were used to identify this subgroup of patients. It might be debated that some patients with possible malignancy might be missed. However, it may be impractical to rebiopsy every patient with benign histopathology.

CONCLUSION

This article is the largest to date to report on TNE-guided biopsy yield. The results suggest that the TNE-guided biopsy procedure has the potential become a first-line assessment tool for suspicious lesions in UADT. In the current NHS environment, where bed space is limited and in an aging society where more people with multiple comorbidities are presenting to the NHS with suspected cancer, TNE-guided biopsy offers a viable solution. It also helps prevent disruption to planned operating room lists. Risk and safety assessment, especially in regard to presence of the resuscitation trolley and an ENT consultant when the procedure is performed, will ensure safer implementation.

BIBLIOGRAPHY


