



Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Laryngeal biopsies in the outpatient setting in people with suspected head and neck dysplasia/cancer
Topic exploration report number:	TER304

Introduction and aims

Patients with suspected head and neck cancer are routinely seen in outpatients for a diagnostic endoscopy procedure. If an area of clinical suspicion exists, patients usually have to wait for a theatre space to have a biopsy taken with a rigid laryngoscope, commonly under general anaesthetic in a day-case setting. Flexible transnasal video laryngoscopes can be used with local anaesthetic in the outpatient setting at the time of the initial diagnostic laryngoscopy procedure: one such example, submitted by the topic proposer, is the Olympus ENF-VT3. This particular laryngoscope uses narrow-band imaging (NBI), which uses two specific wavelengths of light that are strongly absorbed by haemoglobin, allowing improved visualisation and delineation of mucosal microvascular patterns for the detection of malignant lesions. Other flexible laryngoscopes with different enhanced imaging techniques, including iScan and Spectra A/Spectra B imaging, also exist.

Health Technology Wales researchers searched for evidence on the use of flexible transnasal video laryngoscopes for biopsies in the outpatient setting in people with suspected head and neck dysplasia/cancer, particularly those with suspected laryngeal cancer. We focussed on evidence that compared flexible transnasal video laryngoscopes with enhanced imaging to rigid laryngoscopes with enhanced imaging. We also included studies that did not include enhanced imaging techniques, and those that compared different flexible video laryngoscopes and enhanced imaging techniques, where this was available.

The Scottish Health Technologies Group (SHTG) published advice on outpatient biopsies for the diagnosis of suspicious lesions of the larynx, pharynx and tongue base. SHTG conducted their literature search from 2008 until 22 February 2018, so we focused our search after this date.

Summary of evidence

We identified relevant advice from SHTG and the National Institute for Health and Care Excellence (NICE). Since this advice, we identified one meta-analysis and two additional observational studies investigating diagnostic accuracy of flexible video laryngoscopes, one observational study and one prospective analysis investigating the diagnostic work-up and time-to-treatment when using flexible video laryngoscopes, and one systematic review looking at cost.

In 2018, SHTG published advice on outpatient biopsies for the diagnosis of suspicious lesions of the larynx, pharynx and tongue base. They recommended that outpatient biopsies safely allow elected patients the possibility of a more rapid diagnosis through the avoidance of biopsy under general anaesthetic in the operating theatre, and that the availability of outpatient biopsy is likely to result in resource saving for NHS Scotland.

NICE Guideline *Cancer of the upper aerodigestive tract* (NG36) recommends that NBI endoscopy should be considered to identify a possible primary site in the upper aerodigestive tract when it has not been possible to do so using a fluorodeoxyglucose positron emission tomography (FDG PET)-CT scan. It also states that NBI could be considered to improve detection of recurrence or second primary cancer in the upper aerodigestive tract (NICE, 2016). The evidence used to inform these recommendations in NG36 can be found in the 'Brief Literature Search' section.

Diagnostic accuracy

SHTG (2018) recommended that where there is clinical suspicion of malignancy, the high specificity of outpatient biopsy is sufficient to rule-in a diagnosis of malignancy. Low sensitivity of outpatient biopsy means that where there are negative findings, patients will require a further biopsy under general anaesthetic in an operating theatre for confirmation. This recommendation was based on two prospective observational studies (n = 186) and four retrospective observational studies (n = 420 [number of people who had both outpatient biopsy and operating theatre biopsy taken]). None of the diagnostic accuracy studies used to inform SHTG advice (2018), nor any of the studies identified by HTW researchers, compared outpatient biopsy and enhanced imaging techniques with operating theatre biopsy and enhanced imaging techniques.

We identified one meta-analysis published since the SHTG advice in 2018. This assessed the effectiveness of outpatient NBI in people presenting with cervical metastasis from head and neck squamous cell carcinoma of unknown primary origin, where standard work-up with white light endoscopy and conventional imaging did not reveal any primary tumours, and therefore only covers a subset of the population of interest. Based on five studies analysing outpatient NBI use in 169 patients, pooled sensitivity and specificity were 83% and 88%, respectively, which allowed localisation of the primary tumour in 61 out of 169 patients, otherwise not detected by the usual diagnostic work-up (Di Maio et al, 2020).

We also identified two observational studies, published since publication of SHTG advice in 2018 (Galli et al, 2021; Hassan et al, 2019). Both of these studies compared outpatient biopsies using flexible video laryngoscopes with operating theatre biopsies using rigid laryngoscopes. Participants in the study by Galli et al (2021) underwent outpatient endoscopic examination with white light endoscopy and NBI, or white light endoscopy alone. The study showed improved diagnostic accuracy of NBI during videolaryngoscopy compared with white light endoscopy alone. Hassan et al (2019) reported a specificity of 75.6% and sensitivity of 100% in their small study of outpatient biopsies using flexible laryngoscopes (n = 47). However, the endoscope used in the study by Hassan et al was transoral as opposed to transnasal and did not use NBI.

Diagnostic work-up and time-to-treatment

Since publication of SHTG advice (2018), Lee et al (2018) conducted a retrospective observational study of 114 patients: 44 outpatient and 70 operative endoscopic biopsies. The mean time from consultation to biopsy was 17.4 days for the operative endoscopy group and 1.3 days for the outpatient group. The mean time from initial otolaryngology consultation to initiation of treatment was not significantly different (51.7 days and 44.6 days for the operative endoscopy and in-office groups, respectively).

A prospective analysis of 188 people with laryngeal, oropharyngeal, and hypopharyngeal lesions suspicious for carcinoma found that diagnostic work-up time and time-to-treatment for rigid laryngopharyngoscopy were longer than those compared to outpatient flexible endoscopic biopsies, with waiting times of 16 days versus 2 days, and 41.5 days versus 27 days, respectively (Schutte et al, 2018).

Clinical outcomes

Neither SHTG (2018) nor HTW researchers identified any studies comparing clinical outcomes, such as cancer survival or recurrence rates, between patients receiving outpatient biopsy and those undergoing operating theatre biopsy.

Safety

SHTG (2018) reported that outpatient biopsy was generally found to be safe with low complication rates. Although most complications were minor and self-limiting, one case of subglottic oedema requiring tracheostomy was described in the literature. The procedure appeared to be well-tolerated by most patients. This was supported by the prospective analysis of 188 people identified by HTW researchers (Schutte et al, 2018).

Cost

SHTG (2018) advice stated that provision of outpatient biopsies is likely to reduce laryngoscopy costs to the NHS, although initial investment will be required to purchase the additional equipment needed to obtain biopsies in the outpatient setting. SHTG identified five studies that reported cost items as a study outcome. They noted that in NHS-relevant settings, there is evidence that the cost of the outpatient biopsy procedure is consistently lower than that of biopsy under general anaesthetic in an operating theatre. Healthcare Improvement Scotland developed a budget impact model to inform NHS Scotland. The results of the analysis found outpatient biopsy to be resource-saving over a period of five years. Accounting for initial investment costs of approximately £1.5m in the first year and on-going annual costs of £200,000, the average resource saving per annum over five years was in excess of £400,000.

HTW researchers identified a systematic review by Schimberg et al (2019), which found that all 13 of the included studies reported lower costs for outpatient endoscopic transnasal surgery when compared to theatre-based procedures. This included, but was not limited to biopsies: the costs of flexible endoscopic laryngopharyngeal biopsies ranged from €57 to €10, whereas costs for biopsies obtained under general anaesthetic varied between €22 and €101.

Areas of uncertainty

It is unclear whether the flexible transnasal video laryngoscope would be used in sites other than the larynx, or whether it would also be used in adjacent sites. The majority of the studies identified are retrospective observational studies, and none of the studies identified were conducted in a UK setting. However, the ongoing meta-analysis is being conducted in Scotland, and current advice for outpatient biopsies for the diagnosis of suspicious lesions of the larynx has been published in Scotland. We identified a number of different models of video laryngoscope in the published evidence. It is not clear if all of these specific devices are relevant to clinical practice in Wales, or whether conclusions on the effectiveness of different individual devices can be drawn based on the available evidence. None of the studies identified compared outpatient biopsies using enhanced imaging techniques with operating theatre biopsies using enhanced imaging techniques, and so the effect of enhanced imaging remains unclear.

Conclusions

Outpatient biopsy has been the subject of a recent health technology assessment by SHTG (2018), who recommended that it safely allows selected patients the possibility of a more rapid diagnosis through the avoidance of biopsy under general anaesthetic in the operating theatre. Neither SHTG nor HTW identified any studies directly comparing outpatient biopsies using enhanced imaging techniques with operating theatre biopsies using enhanced imaging techniques, but the mainly retrospective observational studies that were identified demonstrated a high specificity, but lower sensitivity, of outpatient biopsy. Studies also suggest that outpatient biopsy may reduce diagnostic work-up and time to treatment compared to operating theatre biopsy. SHTG advice and evidence published since then states that the availability of outpatient biopsy is likely to result in resource savings. A further detailed evidence review would be required to determine the effectiveness of video laryngoscopy with enhanced imaging in the exact scenario of interest.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	SHTG Advice Statement 012-18, and Evidence Note 84: Outpatient biopsy for diagnosis of suspicious lesions of the larynx, pharynx and tongue base (2018): https://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/topics_assessed/shtg_012-18.aspx
Health Technology Assessment Group	We did not identify any relevant evidence from this source
Health Information and Quality Authority	We did not identify any relevant evidence from this source
EUnetHTA	We did not identify any relevant evidence from this source
International HTA Database	We did not identify any relevant evidence from this source
UK guidelines and guidance	
SIGN	We did not identify any relevant evidence from this source
NICE	<ul style="list-style-type: none"> NG36: Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (2016, last updated: 2018): https://www.nice.org.uk/guidance/ng36 <p>Five studies were identified that investigated the accuracy of narrow band imaging for identifying an occult primary tumour of suspected upper aerodigestive tract origin, including a total of 136 patients:</p> <ul style="list-style-type: none"> Hayashi, T., Muto, M., Hayashi, R., Minashi, K., Yano, T., Kishimoto, S., and Ebihara, S. Usefulness of narrow-band imaging for detecting the primary tumor site in patients with primary unknown cervical lymph node metastasis. <i>Japanese Journal of Clinical Oncology</i> 2010. 40(6): 537-541 Masaki, T., Katada, C., Nakayama, M., Takeda, M., Miyamoto, S., Seino, Y., Matsuba, H., Okamoto, T., Koizumi, W., Tanabe, S., Horiguchi, S., Okamoto, M., and Muto, M. Usefulness and pitfall of Narrow band imaging combined with magnifying endoscopy for detecting an unknown head and neck primary site with cervical lymph node metastasis. <i>Auris Nasus Larynx</i> 2012. 39(5): 502-506 Ryu, I. S., Choi, S. H., Kim, D. H., Han, M. W., Roh, J. L., Kim, S. Y., and Nam, S. Y. Detection of the primary lesion in patients with cervical metastases from unknown primary tumors with narrow band imaging endoscopy: Preliminary report. <i>Head and Neck-Journal for the Sciences and Specialties of the Head and Neck</i> 2013. 35(1): 10-+ Sakai, A., Okami, K., Ebisumoto, K., Sugimoto, R., Maki, D., and Iida, M. New techniques to detect unknown primaries in cervical lymph node metastasis. <i>Laryngoscope</i> 2010. 120(9): 1779-1783 Shinozaki, T., Hayashi, R., Ebihara, M., Miyazaki, M., Daiko, H., Saikawa, M., and Ebihara, S. Narrow band imaging endoscopy for unknown primary tumor sites of the neck. <i>Head and Neck</i> 2012. 34(6): 826-829

	<p>Based on the pooled results of these studies, the sensitivity and specificity of NBI was estimated to be 0.77 (95 % confidence interval [CI] 0.50, 0.921) and 0.84 (95% CI 0.68, 0.927), respectively. Three out of five studies were at risk of bias due to lack of clear reporting on how patients were selected; in the same three studies, it is unclear if all the patients were relevant to the review question, due to a lack of reporting of patient characteristics. All five studies reported limited details of what reference standard was used, and whether this was the same for all patients.</p> <ul style="list-style-type: none"> • Cancer service guideline (CSG6). Improving outcomes in head and neck cancers (2004): https://www.nice.org.uk/guidance/csg6
Secondary literature and economic evaluations	
https://www.epistemonikos.org/en/	<p>Di Maio P, Iocca O, De Vergilo A, Giudice M, Pellini R, D'Ascanio L, Golusiński P, Ricci G, Spirano G (2020). Narrow band imaging in head and neck unknown primary carcinoma: A systematic review and meta-analysis. <i>The Laryngoscope</i>, 130 (7): pg 1692-1700: https://doi.org/10.1002/lary.28350</p> <p>Schimberg AS, Wellenstein DJ, van den Broek EM, Honings J, van den Hoogen FJA, Marres HAM, Takes RP, van den Broek GB (2019). Office-based vs. operating room-performed laryngopharyngeal surgery: a review of cost differences. <i>European Archives of Oto-Rhino- Laryngology</i>, 276: pg 2963-2973: https://doi.org/10.1007/s00405-019-05617-z</p>
https://www.tripdatabase.com/	We did not identify any relevant evidence from this source
Cochrane library	We did not identify any relevant evidence from this source
Medline (via Ovid or Pubmed)	We did not identify any relevant evidence from this source
Primary studies	
https://www.epistemonikos.org/en/	We did not identify any relevant evidence from this source
https://www.tripdatabase.com/	<p>Schutte HW, Takes RP, Sloopweg PJ, Arts MJPA, Honings J, van den Hogen FJA, Marres HAM, van den Broek GB (2018). Digital Video Laryngoscopy and Flexible Endoscopic Biopsies as an Alternative Diagnostic Workup in Laryngopharyngeal Cancer: A Prospective Clinical Study. <i>Annals of Otolaryngology, Rhinology and Laryngology</i>, 127 (11); 770-776: https://doi.org/10.1177/0003489418793987</p>
Cochrane library	We did not identify any relevant evidence from this source
Medline	<p>Whited CW, Lubin J, Marka N, Koszewski IJ, Hoffman MR, Schoeff S, Dailey SH (2020). Pain experience and tolerance of awake in-office upper airway procedures: influencing factors. <i>Laryngoscope</i>, 131: :E1580-E1588: DOI: 10.1002/lary.29238</p>
Ongoing primary or secondary research	
PROSPERO database	<p>Mervyn Owusu-Ayim, Sushil Ranjan, Pavithran Maniam, Susanne Flach, Shiyang Hey, Jaiganesh Manickavasagam. Outcomes of office-based (outpatient) biopsy for laryngopharyngeal tumours: a systematic review and meta-analysis.</p>

	<p>PROSPERO 2019 CRD42019158186 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019158186</p> <p><i>A meta-analysis, with an anticipated completion date of February 2021 (although at the time of writing this report we were unable to find it published), which will investigate the outcomes of outpatient biopsy for laryngopharyngeal tumours (the main outcomes will include safety, diagnostic yield, time to treatment and cost), compared to patients who have received a biopsy under general anaesthetic for a laryngopharyngeal lesion. It is unclear whether enhanced imaging techniques will be incorporated into this review.</i></p>
Clinicaltrials.gov	We did not identify any relevant evidence from this source
Other	
Evidence provided by Topic Proposer	<p>Galli J, Settimi S, Mele DA, Salvati A, Schiavi E, Parrilla C, Paludetti G. Role of Narrow Band Imaging Technology in the Diagnosis and Follow up of Laryngeal Lesions: Assessment of Diagnostic Accuracy and Reliability in a Large Patient Cohort. J Clin Med. 2021 Mar 16;10(6):1224. doi: 10.3390/jcm10061224. PMID: 33809578; PMCID: PMC8002249.</p> <p>Hassan NH, Usman R, Yousuf M, Ahmad AN, Hirani I. Transoral flexible laryngoscope biopsy: Safety and accuracy. World J Otorhinolaryngol Head Neck Surg. 2018 Nov 17;5(1):30-33. doi: 10.1016/j.wjorl.2018.09.003. PMID: 30775699; PMCID: PMC6364665.</p> <p>Lee F, Smith KA, Chandarana S, Matthews TW, Bosch JD, Nakoneshny SC, Dort JC. An evaluation of in-office flexible fiber-optic biopsies for laryngopharyngeal lesions. J Otolaryngol Head Neck Surg. 2018 May 9;47(1):31. doi: 10.1186/s40463-018-0275-x. PMID: 29739442; PMCID: PMC5941642.</p> <p>Mozzanica F, Ottaviani F, Ginocchio D, Schindler A. Office-Based Laryngeal Biopsy in Patients Ineligible for General Anesthesia. Iran J Otorhinolaryngol. 2020 Nov;32(113):373-378. doi: 10.22038/ijorl.2020.42544.2436. PMID: 33282785; PMCID: PMC7701486.</p> <p>Schimberg AS, Wellenstein DJ, van den Broek EM, Honings J, van den Hoogen FJA, Marres HAM, Takes RP, van den Broek GB. Office-based vs. operating room-performed laryngopharyngeal surgery: a review of cost differences. Eur Arch Otorhinolaryngol. 2019 Nov;276(11):2963-2973. doi: 10.1007/s00405-019-05617-z. Epub 2019 Sep 5. PMID: 31486936; PMCID: PMC6811667.</p> <p>Townsley RB, Anderson J, Yiannakis CP (2020). Awake transnasal laryngeal and pharyngeal biopsy in the unsedated patient. ENT and Audiology News, 29(1): https://www.entandaudiologynews.com/development/how-i-do-it/post/awake-transnasal-laryngeal-and-pharyngeal-biopsy-in-the-unsedated-patient</p>

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Concepts used:

Video laryngoscopes (and synonyms), outpatient biopsy, office-based biopsy, laryngeal biopsy, Olympus ENF-VT3, narrow band imaging, iScan, Spectra A/B