Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Pharyngolaryngeal biopsies for people with suspected head and neck cancer in the outpatient setting

Executive summary

The aim of this review was to address the following research question: What is the diagnostic accuracy, clinical effectiveness, and cost-effectiveness of pharyngolaryngeal biopsies with local anaesthetic (OLB) in the outpatient setting for people with suspicious laryngeal or pharyngeal lesions, compared to undergoing biopsy in an operating theatre (OTB) under general anaesthetic?

The Scottish Health Technologies Group (SHTG) in 2018 identified two prospective observational studies (Castillo Farías et al. 2015, Cohen & Benyamini 2014) and five retrospective studies (Cha et al. 2016, Cohen et al. 2018, Lippert et al. 2015, Richards et al. 2015, Saga et al. 2018). Health Technology Wales researchers have identified a further four observational studies (Hassan et al. 2019, Lee et al. 2018, Mohammed et al. 2019, Schutte et al. 2018). Relevant outcome measures include diagnostic accuracy (sensitivity, specificity, positive predictive values, and negative predictive values), time to biopsy procedure, diagnosis, and treatment, procedure success rate, and complication rates. Of the studies identified by SHTG (2018), sensitivity values ranged from 60% to 81.1% and the specificity values ranged from 87% to 100%. HTW identified a further study that reported the sensitivity value as 75.6% and the specificity value as 100%.

From consultation to biopsy procedure, the mean number of days was 1.3 for OLB compared to 17.4 days under OTB ($p < 0.0001$) (Lee et al. 2018). From consultation to diagnosis under OLB, the mean number of days was 7.5 compared to 23 days under OTB ($p < 0.0001$) (Lee et al. 2018). For Schutte et al. (2018), the mean time from consultation to start of treatment was 27 days for OLB compared to 41.5 days for OTB ($p < 0.0001$). Of the studies identified by SHTG (2018), the proportion of patients experiencing complications was low and ranged from 0 to 2.6%. Three out of four observational studies identified by HTW did not report any complications (Lee et al. 2018, Mohammed et al. 2019, Schutte et al. 2018).

Due to a lack of identified cost-effectiveness data, HTW developed a de-novo cost-utility analysis comparing OLB to OTB over a lifetime horizon. Inputs were sourced from the SHTG budget impact analysis, updated with values more relevant to a Welsh setting where possible. Sensitivity and specificity of OLB were sourced from SHTG, updated with the additional identified study by HTW, and OTB was assumed to have perfect diagnostic accuracy - 100% sensitivity and specificity. In a population with 2,183 at risk patients, OLB when compared to OTB was considered a cost-effective diagnostic strategy over a lifetime horizon. OLB was associated with less costs and fewer QALYs than OTB, corresponding to an ICER of £21,011 – a cost-effective result when costs and QALYs are lower than the comparator. Scenario analyses demonstrated that the proportion of patients who

go on to have treatment following a false positive diagnosis can mean that OLB is no longer cost-effective – this occurs when more than 42% of patients are undetected as false positive during conventional staging.

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question:

What is the diagnostic accuracy, clinical effectiveness, and cost-effectiveness of pharyngolaryngeal biopsies (OLB) with local anaesthetic in the outpatient setting for people with suspicious laryngeal or pharyngeal lesions compared to undergoing biopsy in an operating theatre (OTB) under general anaesthetic?

As per the protocol, studies that evaluated narrow-band imaging alone, and those evaluating endoscopies only, have been excluded from this rapid review. The reference standard and usual care is OTB using general anaesthetic. See Appendix 1 for further details.

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of published evidence identifying the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Head and neck cancers are malignancies occurring within the larynx, oral cavity, salivary glands, regions of the pharynx and the paranasal sinuses (Cancer Research Wales 2022b). Squamous cell carcinoma represents 90% of head and neck cancer cases, and these cancers usually begin in the squamous cells that line the mucosal surfaces of the head and neck, for example, inside the mouth, throat, and voice box (Sanderson et al. 2002). If left untreated, metastasis can occur through spread to local and distant area, most commonly the lymph nodes (Macmillan Cancer Support 2018). Head and neck cancers are strongly associated with alcohol and tobacco use and human papillomavirus virus, Epstein-Barr virus, and occupational hazards also considered as risk factors (Macmillan Cancer Support 2018).

The symptoms of head and neck cancers that typically lead to clinical suspicion vary depending on the area of cancer subtype. General symptoms may include a hoarseness voice persisting for more than six weeks, oral swellings which persist for more than three weeks, unresolved neck masses, ulceration of oral mucosa persisting for more than three weeks, difficulty swallowing, and shortness of breath (Sanderson et al. 2002). NICE guidelines on recognition and referral for suspected cancer outline that for head and neck cancer, a referral to an appropriate suspected cancer pathway should be made for the following population: people with an unexplained lump in the neck or unexplained ulceration in the oral cavity for more than three weeks; people with a red or white patch in the oral cavity consistent with erythroplakia or erythroleukoplakia; and people aged 45 years and over with persistent unexplained hoarseness (NICE 2015).

In the UK, over 12,400 new cases of head and neck cancers are reported yearly (NHS 2021) and in Wales, there are around 500 cases per year (Cancer Research Wales 2022a). The net survival rates for head and neck cancers vary greatly depending on the cancer subtype (Cancer Research UK 2022). Based off figures between 2009 and 2013 in England, 85% of men survive laryngeal cancer for at least one year, with declining survival to 65% at five years and 55% at ten years (Cancer Research UK 2022). The net survival rates for hypopharyngeal cancer are among the lowest with 60% of men surviving hypopharyngeal cancer for at least one year, and this is predicted to fall to

27% for five years and 18% for ten-year survival (Cancer Research UK 2022). 84% of men survive oropharyngeal cancer for at least one year, this falls to 66% for five years or more, and 57% for ten years or more (Cancer Research UK 2022). For women, the one year and five year survival rates for oropharyngeal cancer are the same as that of men, at 84% and 66% respectively, this falls to 59% for ten years or more (Cancer Research UK 2022).

Alongside mortality, head and neck cancers can have a major impact on people's quality of life. A recent study of 100 cancer patients found that people with head and neck cancers experience major changes in their appearance, speech, eating pattern, work efficiency and deteriorations in emotional, social, and cognitive functioning (Bhardwaj 2021).

3. Health technology

The Scottish Health Technologies Group (SHTG) have previously published advice on outpatient biopsies for the diagnosis of suspicious lesions of the larynx, pharynx, and tongue base. Health Improvement Scotland recommended that a suspicion of malignancy using outpatient biopsies is sufficient to rule-in a diagnosis due to its level of specificity (SHTG 2018). However, due to their level of sensitivity, negative findings would require a further biopsy under general anaesthesia and there was remaining uncertainty about its benefit.

When certain head or neck cancers are suspected, pharyngolaryngeal biopsies can be used to take a tissue sample for examination. Pharyngolaryngeal biopsies have typically been conducted under general anaesthesia with a scope used to provide a view of the area of suspicion and sample tissue. This means that there is a period of delay between referral and biopsy being completed, usually with the patient attending hospital as a day-case. However, the procedure can also be performed in an outpatient clinic under local anaesthetic. This approach may reduce time to diagnosis and treatment and may lead to a reduction in the need for biopsy. However, there is uncertainty around the diagnostic accuracy of OLB, with a risk of both false positives and negatives leading to inappropriate treatment responses. Due to this, the need for further diagnostic procedures might limit the benefits that the technology can deliver.

When assessing whether a person should be put forward for either OLB and/or OTB, consensus among experts stated that the level of suspicion does have a bearing on the choice of procedure. For example, if there is a high level of suspicion that the person has malignancy, OLB would reduce the delay in starting treatment. Consensus among experts also state that other clinical factors are taken into consideration when putting people forward for OLB and/or OTB such as a person's choice, and the patient's suitability and general tolerance for undergoing the procedure awake under local anaesthetic.

An example of a biopsy, provided by the topic proposer, is the Olympus ENF-VT3. This laryngoscope is compatible with both narrow-band imaging (NBI) and white light imaging, although other manufacturers in this setting can be carried out without enhanced imaging. The Olympus device uses two specific wavelengths of light that are strongly absorbed by haemoglobin, allowing improved visualisation for the detection of malignant lesions. Tissue samples can be taken with forceps guided by this imaging.

Health Technology Wales have identified several other devices in the literature, including:

- FNL-10 RP3, Pentax.
- VNL-1570STK, Pentax.

Consensus among experts suggest that opto-digital technologies such as NBI can improve the diagnostic accuracy of the OLB procedure. NBI enables the detection and differentiation of laryngeal lesions which would otherwise not be detected by white light endoscopy (Popek et al.

2019). Another observational study in a cohort of people with suspected cancer of the hypopharynx and larynx concluded that NBI when compared to white light endoscopy, improves the visualisation of the mucosal and submucosal microvascular patterns of observed pathologies (Wacławek et al. 2019). However, studies that evaluated NBI alone, or included comparison of imaging techniques have been excluded from this rapid review as they fall out of scope.

4. Clinical effectiveness

In their evidence note, SHTG conducted their literature search in 2018 and included studies published since 2008. Due to this, our rapid review has included evidence that was published after this date. For full details on the methods for this evidence review, see Section 11.

4.1 Overview

SHTG (2018) conducted a review of the literature on OLB to support advice for NHS Scotland. The SHTG evidence note identified two prospective observational studies (n=186) and four retrospective observational studies (n=420) reporting diagnostic accuracy outcomes (SHTG 2018). Two prospective observational studies examined the diagnostic accuracy of OLB when compared to OTB under general anaesthetic (Castillo Farías et al. 2015, Cohen & Benyamini 2014). One study recruited people with suspected malignant pharyngolaryngeal tumours (Castillo Farías et al. 2015), and the other study recruited people with suspicious-appearing lesions of the larynx (Cohen & Benyamini 2014).

Of the four retrospective studies, two studies performed outpatient biopsies in people with suspicious laryngeal lesions (Cha et al. 2016, Cohen et al. 2018), one study performed biopsies on people with suspected laryngeal and pharyngeal lesions (Richards et al. 2015) and one study performed biopsies on people with suspected pharyngolaryngeal lesions (Saga et al. 2018). One further retrospective study (n=116) (Lippert et al. 2015) identified by SHTG (2018) examined the effect of outpatient biopsy on time to diagnose data for people with suspicious lesions who underwent OLB of the larynx (n=73), oropharynx (n=35), and hypopharynx (n=8) (SHTG 2018).

The full details of all included studies and outcomes identified by SHTG (2018) can be found in Tables 1 and 4. In their evidence note, no studies compared OLB with OTB using enhanced imaging and no studies were identified comparing the safety of OLB with OTB. No randomised controlled trials were identified comparing clinical outcomes, such as cancer survival or recurrence rates, between patients undergoing OLB or OTB.

Health Technology Wales researchers have identified four observational studies (Hassan et al. 2019, Lee et al. 2018, Mohammed et al. 2019, Schutte et al. 2018) that have been published since the SHTG search. Two studies included people with suspicious lesions of the larynx, supraglottis, oropharynx, pharynx, and glottis (Mohammed et al. 2019, Schutte et al. 2018). One study included people with suspicious lesions of the larynx (Hassan et al. 2019) and one study included people with suspicious lesions of the pharynx and larynx (Lee et al. 2018). Full details of included studies and outcomes can be found in Tables 2 and 3.

The choice of manufacturer varied across identified studies. Of those studies identified by SHTG (2018), two studies, Castillo Farías et al. (2015) and Cha et al. (2016) used an Olympus made scope. Three studies, Richards et al. (2015), Cohen & Benyamini (2014) and Lippert et al. (2015) used a Pentax made scope (a Pentax-FNL-10 RP3 or VNL-1570STK). Two retrospective studies, Cohen et al. (2018) and Saga et al. (2018) either did not specify the manufacture used, or used various manufacturers, including both Olympus and Pentax. Of those studies identified by Health

Technology Wales, one study Hassan et al. (2019) used an Olympus made scope. One study, Schutte et al. (2018) used a Pentax made scope (VNL-1570STK) and two studies, Lee et al. (2018) and Mohammed et al. (2019) either used various manufacturers or did not specify the manufacturer used. See Tables 1 and 2.

Six out of ten observational studies in this evidence appraisal report are retrospective in nature, which may lead to methodological variations of the measurement of outcomes and classification systems. Different techniques used among different studies, and the availability of OLB in different locations may also contribute to bias in overarching conclusions. All studies except for Mohammed et al. (2019) are non-UK based and thus, the overarching conclusions of the studies may not be generalisable to settings in Wales or the UK. Several authors note the potential for selection and referral bias, in addition to the potential limitation of shorter follow-up periods which may not allow for assessment of longer-term complications.

Outcomes include sensitivity, specificity, time to diagnose and time to treatment, positive and negative predictive values, and procedure success rate.

4.2 Sensitivity and specificity

No identified studies compared the sensitivity and specificity of OLB to OTB.

SHTG (2018) reported the sensitivity and specificity of OLB from six individual studies (Castillo Farías et al. 2015, Cha et al. 2016, Cohen & Benyamini 2014, Cohen et al. 2018, Richards et al. 2015, Saga et al. 2018). Sensitivity values ranged from 60% (Richards et al. 2015) to 81.1% (Castillo Farías et al. 2015). Specificity values ranged from 87% (Richards et al. 2015) to 100% (Castillo Farías et al. 2015, Cha et al. 2016, Saga et al. 2018).

Health Technology Wales researchers identified a further study that reported the sensitivity and specificity values of OLB (Hassan et al. 2019). In this study, the sensitivity was reported as 75.6% and the specificity was reported as 100%.

The diagnostic accuracy of OLB may vary greatly depending on the technique and imaging used. Consensus among experts highlighted that the experience of the professional, the responsiveness/sensitivity of the larynx and pharynx, and the quality and size of the sample are all important factors that may alter the diagnostic accuracy of the procedure.

4.3 Positive and negative predictive values

No identified studies compared the positive and negative predictive values of OLB when compared to OTB.

SHTG (2018) reported the positive and negative predictive values of OLB across five individual studies (Castillo Farías et al. 2015, Cha et al. 2016, Cohen & Benyamini 2014, Richards et al. 2015, Saga et al. 2018). Positive predictive values ranged from 78% (Richards et al. 2015) to 100% (Castillo Farías et al. 2015, Cha et al. 2016, Saga et al. 2018). The negative predictive value ranged from 20% (Castillo Farías et al. 2015) to 87.3% (Cha et al. 2016).

Health Technology Wales researchers identified a further two studies reporting the positive and negative predictive values of OLB (Hassan et al. 2019, Schutte et al. 2018). Both studies reported the positive predictive value as 100%. In Hassan et al. (2019), 31 true positives were reported in comparison to 0 false positives. The negative predictive value was 17% in Hassan et al. (2019) with 10 false negative values and 2 true negative values. The negative predictive value reported in Schutte et al. (2018) was 33%.

Consensus among experts suggested that false negative results could potentially lead to untreatable cancer, along with increased anxiety and disruption to daily life among patients. Such risk should be addressed and communicated with patients and safeguards should be in place to ensure that risks are minimised.

4.4 Time to biopsy procedure, diagnosis, and treatment

SHTG (2018) reported two retrospective studies assessing the time to treatment for the OLB when compared to OTB, although the statistical significance of the values were not reported (Cohen et al. 2018, Lippert et al. 2015).

In Lippert et al. (2015), the total time to treatment for OLB was 24.2 days with a range of 13.9 days, whereas the time to treatment reported for OTB was 48.8 days with a range of 49.4 days. Cohen et al. (2018) reported the mean days from biopsy to treatment for both OLB and OTB. Patients with a positive result during OLB received their diagnosis within a mean value of 10.7 days (95% CI, 8.6-12.8), including a two-to-six-day period for the pathology report (Cohen et al. 2018). People who had a negative (benign path) result on OLB who subsequently tested positive for squamous cell carcinoma identified in OTB (n=10) received their diagnosis within a mean value of 49.1 days (95% CI, 38.1-60.1) (Cohen et al. 2018). People who were identified as having carcinoma in situ with OLB and subsequently had squamous cell carcinoma identified in OTB (n=6) received their diagnosis within a mean value of 36.1 days (95% CI, 15.1-57.1) (Cohen et al. 2018).

Health Technology Wales researchers identified a further two studies reporting the time from consultation to diagnosis, time from consultation to biopsy procedure and time from consultation to treatment (Lee et al. 2018, Schutte et al. 2018). From consultation to biopsy procedure, the mean number of days was 1.3 for OLB compared to 17.4 days under OTB ($p < 0.0001$) (Lee et al. 2018). From consultation to diagnosis under OLB, the mean number of days was 7.5 compared to 23 days under OTB ($p < 0.0001$) (Lee et al. 2018). The mean number of days from ENT consultation to multidisciplinary oncology consultation (MDOC) was 19 days (95% CI, 16.0–22.0) for OLB compared to 23.4 days (95% CI, 19.4–27.4) for OTB and this difference was reported as not significant (Lee et al. 2018). The mean number of days from MDOC to treatment under OLB was 32 days (95% CI, 28.3–35.7) compared to 33 days under OTB (95% CI, 27.0–39.0) and this difference was reported as not significant (Lee et al. 2018).

Both studies reported the time from consultation to treatment. For Lee et al. (2018), the mean time from the initial ENT consultation to treatment for OLB was 49.6 days (95% CI, 44.6–54.6) compared to 51.7 (95% CI, 46.6–56.8) under OTB, however this result was reported as not significant, and the p value is not reported. For Schutte et al. (2018), the mean time from consultation to start of treatment was 27 days for OLB compared to 41.5 days for OTB ($p < 0.0001$).

4.5 Procedure success rate

One study, Mohammed et al. (2019) reported the procedure success rate of outpatient biopsy as 85.8%, however the statistical significance of this result is unclear. 102 out of 115 (88.7%) procedures were not followed up by a further procedure where 46 results were benign, 10 results were pre-malignant, 54 were malignant and 5 were categorised as other, including non-diagnostic biopsies and necrosis. 13 out of 115 (11.3%) procedures were followed by a further procedure with three ultrasound and fine-needle aspiration procedure finding three cases of squamous cell carcinoma (SCC), nine OTB procedures including rigid pharyngoscopy and micro laryngoscopy finding four cases of SCC, one non-diagnostic and four benign cases, and one core biopsy found one case of lymphoma.

4.6 Safety and Complications

No studies identified by SHTG (2018) compared the safety of OLB with OTB. Across their studies, the proportion of patients experiencing complications was low and ranged from 0 to 2.6% (SHTG 2018).

Cohen et al. (2018) did not report any severe complications, although the study did report four mild complications (1%), compromising epistaxis (n=2), hematoma in the vocal fold (n=1), and an aspiration event (n=1). Lippert et al. (2015) did not report any complications, although two people did not tolerate the procedure. Castillo Farías et al. (2015), Cha et al. (2016) and Richards et al. (2015) did not report any complications. Cohen & Benyamini (2014) reported post-procedure aspiration in one person without serious consequences and two cases of self-limited epistaxis. A further retrospective study identified by SHTG (2018) (Wellenstein et al. 2017) reported four complications out of 187 patients (201 procedures). Complications included laryngospasm which were self-limiting (n=1), anterior epistaxis which required intervention (n=1), laryngeal bleeding which required intervention (n=1), and supraglottic oedema resulting in tracheostomy (n=1).

Three out of four observational studies identified by Health Technology Wales researchers did not report any complications (Lee et al. 2018, Mohammed et al. 2019, Schutte et al. 2018). One study, Hassan et al. (2019) observed participants for 30 minutes after the procedure. One participant developed post procedure blood-tinged salivation and choking sensation, and the patient was admitted for overnight observation and treated conservatively.

4.7 Survival and other clinical outcomes

None of the identified studies included reported outcomes relating to survival and other clinical outcomes.

4.8 Health-related quality of life and patient satisfaction

None of the identified studies included reported outcomes relating to quality of life and/or patient satisfaction.

4.9 Ongoing trials

No ongoing trials were identified.

Table 1. Observational studies: design and characteristics: SHTG (2018)

Study reference	Methods and setting	Participants	Intervention(s)	Outcomes	Follow-up	Comments
Castillo Farías et al. (2015)	• Prospective study • Study period: April 2008 - December 2011 and January 2012 – November 2012. • Location: Spain	• N = 88 • Mean age: 65 years • Males: 81 • Females: 7	• OLB • Manufacturer: Olympus • Reference standard: OTB	• Sensitivity • Specificity • Positive and negative predictive values	NR	A key consideration as stated by the author/s is that it is important to consider that laryngeal sensitivity is variable among patients, as well as being difficult to evaluate objectively.
Cohen & Benyamini (2014)	• Prospective study • Study period: N/A • Location: Israel.	• N = 117 • Males: 94 • Females: 23 • Median age: 66 years	• OLB • Manufacturer: FNL-10 RP3, Pentax. • Reference standard: OTB	• Sensitivity • Specificity • Complications	NR	Of the 17 people who were diagnosed with CIS, five people refused to undergo OTB and were excluded from the final statistical analysis.
Cha et al. (2016)	• Retrospective study • Study period: January 2011 to November 2014. • Location: Republic of Korea.	• N = 581 • Males: 516 • Females: 65 • Median age: 67 years	• OLB • Manufacturer: Olympus. • Reference standard: OTB	• Sensitivity • Specificity • Positive and negative predictive values	Min: 6 months	A key limitation as noted by the author/s includes the possibility of an underdiagnosis of premalignant lesions as the participants in this study were closely followed without re-biopsy after an initial diagnosis for over 6 months.
Richards et al. (2015)	• Retrospective chart review • Study period: January 2010 – July 2013. • Location: US.	• N = 261 (76 subset) • Male: Female ratio of 5:1. • Median age: 62	• OLB • Manufacturer: VNL-1570STK, Pentax. • Reference standard: OTB	• Sensitivity • Specificity • Positive and negative predictive values	NR	A limitation of this study as noted by the author/s is selection bias determining the candidacy or need for OTB. Another noted consideration is the different techniques and forceps that are used which may influence results.
Cohen et al. (2018)	• Retrospective cohort study • Study period: June 2013 – January 2017. • Location: Israel.	• 390 procedures • N = 355 • Mean age: 63.6 • Male: Female ratio of 4.3:1.	• OLB Procedures • Manufacturer: not specified. • Reference Standard: OTB	• Time to diagnose • Complication classification as severe, mild, and self-limited. • Delay in diagnosis as a complication. • Sensitivity	2 – 4 weeks.	Follow-up period may not allow for longer-term complications.

Study reference	Methods and setting	Participants	Intervention(s)	Outcomes	Follow-up	Comments
				• Specificity • Complications		
Saga et al. (2018)	• Retrospective study • Study period: 2006 – 2016 • Location: Spain	N = 30	• OLB • Manufacturer: Various manufactures. • Reference standard: OTB	• Sensitivity • Specificity • Positive and negative predictive values	NR	Follow up data was not reported in the evidence note. Original paper is published in Spanish.
Lippert et al. (2015)	• Retrospective review • Study period: 2007 – 2013 • Location: US	N = 116	• OLB • Manufacturer: VNL-1570STK, Pentax. • Reference standard: OTB	• Time to treat	NR	Participants had appropriate follow-up in accordance with the standard of care for their disease process. The duration of follow-up depended on the lesion present. The author/s notes the common limitations of the study design used in this paper, in addition to the sample size. The author/s noted that due to the study design, participants received their diagnosis outside of the institution.

*Abbreviations: OLB, outpatient pharyngolaryngeal biopsies; OTB, operating theatre biopsy; SCC, squamous cell carcinoma; CIS, carcinoma in situ; ENT, ear nose and throat; MDOC, multidisciplinary oncology consultation; 95% C.I., 95% confidence; NR, Not reported; IQR, the interquartile range;

Table 2. Observational studies: design and characteristics: HTW

Study reference	Methods and setting	Participants	Intervention(s)	Outcomes	Follow-up	Comments
Hassan et al. (2019)	• Prospective diagnostic study • Study period: 1 December 2013 - 31 August 2015 • Location: Pakistan.	• N = 47 • 47 patients underwent OLB, out of these patients 16 patients were referred for OTB. • Males: 32 • Females: 15	• OLB • Manufacturer: Olympus. • Reference standard: OTB	• Positive and negative predictive value • Sensitivity • Specificity • Complications	30 minutes – 10 days.	The author/s do not report the statistical significance of their outcomes (e.g., 95% CI). Follow-up period may not allow for longer-term complications.
Lee et al. (2018)	• Retrospective case-control study • Study period: 1 January 2010 – 31 December 2015 • Location: Canada.	• N = 114 • (44 people for in-office biopsy, 70 for operative endoscopic biopsies) • Mean age: 62.3 years OLB: • Males: 36 • Females: 8 OTB: • Males: 64 • Females: 6	• OLB • Manufacturer: not specified. • Reference Standard: OTB	• Delay to the initiation of treatment • Delay from consultation to biopsy • Time from cancer diagnosis to multidisciplinary oncology consultation (MDOC), • Time from consultation to treatment.	NR	The author/s note the study's retrospective design and the potential for referral bias.
Schutte et al. (2018)	• Prospective analysis • Study period: 2010 – 2013 • Location: Netherlands.	• N = 180 (53 for OLB, 135 OTB)	• OLB • Manufacturer: VNL-1570STK, Pentax. • Reference Standard: OTB	• Success percentage of initial biopsies per site • Predictive values • Time from diagnosis to start of treatment.	NR	The exact P values in this study are unknown. The author/s acknowledged that a selection bias was introduced as participants were not randomised,

Study reference	Methods and setting	Participants	Intervention(s)	Outcomes	Follow-up	Comments
Mohammed et al. (2019)	• Retrospective case series • Audit of UK hospital use • Location: UK.	• N = 121 • (134 procedures, 121 people)	• OLB • Manufacturer: Various manufacturers. • Reference standard: OTB	• Procedure success rate • Number of cases who underwent further diagnostic procedures	NR	The author/s note the potential for referral bias.

*Abbreviations: OLB, outpatient pharyngolaryngeal biopsies; OTB, operating theatre biopsy; SCC, squamous cell carcinoma; CIS, carcinoma in situ; ENT, ear nose and throat; MDOC, multidisciplinary oncology consultation; 95% C.I., 95% confidence; NR, Not reported; IQR, the interquartile range;

Table 3. Outcomes reported by Health Technology Wales

Outcome	Evidence source(s)	Absolute and relative effect	Number of participants	Comments on reliability
Diagnostic accuracy				
Sensitivity	Hassan et al. (2019)	OLB: 75.6% (95% CI, NR)	N = 47	P value and confidence internal not reported
Specificity	Hassan et al. (2019)	OLB: 100% (95% CI, NR)	N = 47	P value and confidence internal not reported
Positive predictive value	Hassan et al. (2019)	100% (95% CI, NR) True positive: 31 False positive: 0	N = 47	P value and confidence internal not reported
	Schutte et al. (2018)	100% (95% CI, NR)	N = 180	P value and confidence internal not reported
Negative predictive value	Hassan et al. (2019)	17% (95% CI, NR) True negative: 2 False negative: 10	N = 47	P value and confidence internal not reported
	Schutte et al. (2018)	33% (95% CI, NR)	N = 180	P value and confidence internal not reported
Time to diagnose/treat				
Time to diagnose (ENT consultation to diagnosis)	Lee et al. (2018)	OLB: 7.5 days (95% CI, 5.5–9.4) OTB: 23.0 (95% CI, 18.8–27.2) P < 0.0001	N = 114	
Time from consultation to biopsy (ENT consultation to Biopsy)	Lee et al. (2018)	OLB: 1.3 days (95% CI, -0.2–2.9) OTB: 17.4 days (95% CI, 13.5–21.3) P < 0.0001	N = 114	

Outcome	Evidence source(s)	Absolute and relative effect	Number of participants	Comments on reliability
Time from consultation to MDOC (ENT Consultation to MDOC)	Lee et al. (2018)	OLB: 19 days (95% CI, 16.0–22.0) OTB: 23.4 days (95% CI, 19.4–27.4)	N = 114	Results reported as not significant, Although the P value was not reported.
Time from MDOC to treatment	Lee et al. (2018)	OLB: 32 days (95% CI, 28.3–35.7) OTB: 33 days (95% CI, 27.0–39.0)	N = 114	Results reported as not significant, Although the P value was not reported.
Time from consultation to treatment (ENT Consultation to Treatment)	Lee et al. (2018)	OLB: 49.6 days (95% CI, 44.6–54.6) OTB: 51.7 days (95% CI, 46.6–56.8)	N = 114	Results reported as not significant, Although the P value was not reported.
Time from consultation to start of treatment	Schutte et al. (2018)	OLB: 27 days OTB: 41.5 days P < 0.0001	N = 180	IQR range: 13 days
Time from initial consultation to board meeting (diagnostic workup time)	Schutte et al. (2018)	OLB: 2 days OTB: 16 days P < 0.0001	N = 180	IQR range: 14 days
Overall success percentage of OLB compared to OTB	Schutte et al. (2018)	OLB: 92.5% OTB: 91.1% (95% CI, NR)	N = 180	Results reported as not significant, Although the P value was not reported.
Outcomes relating to procedure success rate				
Procedure success rate	Mohammed et al. (2019)	85.8% 115/134 successful procedures	N = 121	The statistical significance of this result is not reported

Outcome	Evidence source(s)	Absolute and relative effect	Number of participants	Comments on reliability
Number of people who did not require further interventions for histological diagnosis	Mohammed et al. (2019)	88.7% 102/115 remaining procedures were not followed up by a further procedure.	N = 121	The statistical significance of this result is not reported
Number of OLB procedures followed by a further procedure	Mohammed et al. (2019)	11.3% 13/115 procedures were followed by a further procedure including three ultrasound and fine-needle aspiration procedure, nine OTB procedures including rigid pharyngoscopy and microlaryngoscopy, and one core biopsy).	N = 121	The statistical significance of this result is not reported

Table 4. Outcomes reported by SHTG

Outcome	Evidence source(s)	Absolute and relative effect	Number of participants
Diagnostic accuracy			
Sensitivity	Cohen et al. (2018)	OLB: 77.8%	N = 35
	Castillo Farías et al. (2015)	OLB: 81.1% (95% CI, 72.6–89.3)	N = 88
	Cohen & Benyamini (2014)	OLB: 70.6%	N = 117
	Cha et al. (2016)	OLB: 78.2% (95% CI, 72.25–83.34)	N = 581
	Richards et al. (2015)	OLB: 60%	N = 261 (76 subset)
	Saga et al. (2018)	OLB: 73%	N = 30
Specificity	Cohen et al. (2018)	OLB: 95.1%	N = 355
	Castillo Farías et al. (2015)	OLB: 100% (95% CI, 100–100)	N = 88
	Cohen & Benyamini (2014)	OLB: 96.7%	N = 117
	Cha et al. (2016)	OLB: 100% (95% CI, 98.93–100)	N = 581
	Richards et al. (2015)	OLB: 87%	N = 261 (76 subset)
	Saga et al. (2018)	OLB: 100%	N = 30
Positive predictive value	Castillo Farías et al. (2015)	OLB: 100% (95% CI, 100–100)	N = 88
	Cohen & Benyamini (2014)	OLB: 98%	N = 117
	Cha et al. (2016)	OLB: 100% (95% CI, 97.96–100)	N = 581
	Richards et al. (2015)	OLB: 78%	N = 261 (76 subset)
	Saga et al. (2018)	OLB: 100%	N = 30
Negative predictive value	Castillo Farías et al. (2015)	OLB: 20% (95% CI, 2.5–37.5)	N = 88
	Cohen & Benyamini (2014)	OLB: 57%	N = 117

Outcome	Evidence source(s)	Absolute and relative effect	Number of participants
	Cha et al. (2016)	OLB: 87.3% (95% CI, 83.61–90.43)	N = 581
	Richards et al. (2015)	OLB: 74%	N = 261 (76 subset)
	Saga et al. (2018)	OLB: 30%	N = 30
Time to diagnose/treat			
Time to treatment	Lippert et al. (2015)	OLB: 24.2 to 3.9 days OTB: 48.8 to 49.4 days	N = 116
	Cohen et al. (2018)	Total for OLB: 10.7 days (95% CI, 8.6-12.8) (2-6 days for a pathology report) for positive result DL: 49.1 days (95% CI, 38.1-60.1) (After a benign result in OLB) for a malignancy result. DL: 36.1 days (95% CI, 15.1-57.1; P< 0.05) (after a benign result in OLB) for a positive result (carcinoma in situ to malignant, squamous cell carcinoma)	390 procedures N = 355

5. Economic evaluation

5.1 Health economic literature review

We conducted an update to a systematic literature review conducted by the Scottish Health Technology Group, SHTG (2018), to answer the following research question: what is the cost-effectiveness of pharyngolaryngeal biopsies (with or without narrow-band imaging) with local anaesthetic in the outpatient setting for people with suspected head and neck cancer? Based on the titles and abstracts of records identified in the search, 13 health economic studies were deemed potentially relevant, including the SHTG review itself and five studies identified in their review. The full texts of these studies were reviewed against the inclusion/exclusion criteria. Following consideration of the full texts, 12 studies were excluded from the review as they were not full cost analyses or were not as applicable as the UK SHTG model. The remaining relevant study was the literature review and budget impact model conducted by SHTG) (SHTG 2018), which was considered applicable to the research question as it was conducted in a UK setting.

The SHTG budget impact analysis aimed to establish whether additional costs associated with purchasing new equipment for OLB would be offset by the potential savings over a five-year time horizon from displacing OTB with OLB. They compared the use of OLB with topical anaesthesia against biopsies in an inpatient or daycase setting under general anaesthesia and conducted the analysis from an NHS Scottish perspective. Sensitivity and specificity were derived from the clinical systematic literature review undertaken prior to the analysis. The analysis was based on 2,264 patients being screened for head and neck cancer annually and found that although costs were expected to be increased in the initial year of uptake by £589,442, due to the additional investment in equipment, subsequent years saw an annual cost-saving of £673,865 due to the reduced number of patients having to undergo the procedure in a daycase or inpatient setting under general anaesthetic. As such, it was found that over a five-year time horizon, OLB was associated with average cost savings of £421,204 per year.

An important consideration of the analysis is that patients who test negative through OLB were assumed to undergo an additional OTB to confirm the result. Therefore, in the base case analysis, around 83% of patients were expected to undergo a daycase or inpatient procedure. There is uncertainty as to whether this approach would be adopted in routine clinical practice, with some studies suggesting that only those patients whose result is suspected to be incorrect would undergo an additional biopsy (Naidu et al. 2012). The SHTG analysis reported that, should no patients have to have results confirmed, this could translate to cost savings of £2,655,906 in the first year alone.

The budget impact analysis was conducted both deterministically (using mean values for model inputs) and probabilistically (using values sampled from a distribution to account for uncertainty). Both analyses result in the same conclusions (additional costs in the first year offset by savings in subsequent years), however due to fairly large differences in predicted costs in the initial year, the average cost savings over five years varies by £203,724. This suggests that there is some uncertainty around modelled results, particularly in terms of upfront costs. Additionally, one-way sensitivity analyses were conducted to account for uncertainties in the parameters used in the analysis. Results were most sensitive to the number of laryngoscopes required per health board, expected patient numbers, disease incidence and procedure costs.

Table 5. Summary of the included health economic study: SHTG

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: SHTG 2018 (SHTG 2018) **Country:** Scotland **Type of economic analysis:** Budget impact analysis **Perspective:** NHS Scotland **Currency:** GBP (£) **Price year:** 2018 **Time horizon:** 5 years **Discounting:** NR **Potential conflict of interest:** None	**Population** Patients with suspicious laryngeal and/or pharyngeal lesions (N=2,264) **Interventions** Flexible laryngoscope with outpatient-based biopsies under local anaesthetic **Comparator** Operating theatre biopsy (OTB) in a day case setting with general anaesthetic **Study design** Budget impact analysis based on findings of rapid literature review conducted by SHTG.	**Source of baseline and effectiveness data:** A rapid literature review conducted by SHTG was used to derive the sensitivity and specificity of outpatient biopsies. The value used appears to be a weighted average of the reported sensitivity and specificity from 6 identified studies; 2 prospective studies conducted in Spain and Israel, and 4 retrospective studies conducted in South Korea, the USA, Israel, and Spain. Data on disease prevalence, incidence and the eligible population has been sourced from the Information Services Division (ISD) Cancer incidence data and clinical advice. The risk of complications following procedure was based on clinical advice about the frequency of oesophageal perforation and difficult airway cases. **Source of resource use and cost data:** Costs of the technology itself, as well as information on the life expectancy of the technology were sourced from discussions with National Services Scotland (NSS), the manufacturer and clinical opinion. Staff resource use was derived following discussions with staff working in the relevant departments and at Health Facilities Scotland. The number of procedures performed was requested from ISD. Average costs of visits were taken from ISD. Costs of laryngoscopes and stack equipment, maintenance and working channel costs were estimated following discussions with each of the manufacturers and weighted by their market share. Costs of topical anaesthesia were taken	**Base case results (Probabilistic)** **Costs** Overall, 5-year costs of £3,732,470 with intervention and £4,153,674 with comparator, resulting in total 5-year cost saving of £421,204 **Subgroup analysis** Analysis was conducted for each health board in Scotland, with cost-savings of between £9 - £87,511 being realised over 5-years **Sensitivity analysis** One-way sensitivity analysis was used to investigate key inputs including assumptions around the number of new laryngoscopes needed, tolerability of the procedure, maintenance costs, procedure time and risk of complications. The results were found to be sensitive to the proportion of patients undergoing OLB (83% in base case). Probabilistic sensitivity	**Applicability** The study is directly applicable as it was conducted from the Scottish NHS perspective. **Limitations** True positives did not receive a daycase procedure or second outpatient-based procedure to confirm their diagnosis. However, false positive results were assumed to be corrected by a daycase procedure (33%), a second outpatient-based procedure (33%), or other correction during treatment planning (33%). This means that no patients who receive a false positive result will receive treatment. This may underestimate the implications of false positive results. It is also unclear whether costs were applied for the 33% of people who had their diagnosis corrected during treatment planning. The model assumes that all patients testing negative for the outpatient procedure would still need this confirmed by the daycase procedure. A lot of inputs have been sourced using clinical advice and from

Study details	Study population and design	Data sources	Results	Quality assessment
		from BNF (Joint Formulary Committee 2022) for lidocaine with phenylephrine. Costs were included for staff time during procedure and decontamination, with unit costs sourced from PSSRU. Costs of the procedures were taken from the average ENT speciality costs, with additional bed days calculated from ISD.	analysis (PSA) was conducted (PSA results used as base case). Deterministic results (based on mean values) predict savings of £217,480)	Scottish specific sources, which may not be reflective of a Welsh population. Diagnostic accuracy data has been sourced from multiple studies from various country settings. Full results of deterministic sensitivity analysis not presented. Fairly large difference between PSA and mean values results suggesting that there is high degree of uncertainty around modelled results. Costs don't include cost of consumables or decontamination costs (other than staff costs). Another potential benefit of outpatient biopsy is the shorter wait time for a diagnosis which isn't captured in this analysis.

*Abbreviations: QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; SHTG: Scottish Health Technologies Group; BIM: budget impact model; NR: not reported; OTB: operating theatre biopsy; ISD: Information Services Division; PSA: probabilistic sensitivity analysis

5.2 De novo cost utility analysis

As there was a lack of published evidence on the cost effectiveness of OLB, HTW developed an economic analysis to estimate cost effectiveness compared to inpatient/daycase procedures. The model developed on the budget impact model created by SHTG (SHTG 2018), to include life years and health-related quality of life, following a hypothetical cohort of patients with suspicious laryngeal or pharyngeal lesions for a lifetime.

The model comprises a short-term decision tree and lifetime predictions of mortality and quality of life to evaluate the cost effectiveness of diagnostic strategies for suspected head and neck cancer. The following two strategies were included:

1. Operating theatre biopsy (OTB)
2. Outpatient pharyngolaryngeal biopsy (OLB)

The analysis took the perspective of the UK NHS and personal social services (PSS). A lifetime time horizon (40 years) was considered, and future costs and benefits were discounted at rate of 3.5%. Full details of the methods and results are available in Appendix 5.

The results of the base case analysis are presented in Table 6. Despite a reduction in in quality adjusted life years (QALYs) compared with OTB (-0.04 QALYs), this strategy is considered cost-effective under base case assumptions due to the cost-savings associated with OLB (£816 per person). The ICER result indicates that £21,011 is saved for each QALY that is lost with the OLB approach. Since this saving is greater than the threshold of £20,000 per QALY, OLB is considered to be cost effective. Note the interpretation of the ICER changes in scenarios where an intervention is less effective and less costly, with values above the threshold considered cost effective because higher values indicate greater savings for each QALY lost.

Table 6. Summary of base case results

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Operating theatre biopsy (OTB)	£7,718	-	9.24	-	-
Outpatient pharyngolaryngeal biopsy (OLB)	£6,902	-£816	9.21	-0.04	£21,011

*Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Base case results were robust in probabilistic and deterministic sensitivity analyses, as well as scenario analyses. Probabilistic sensitivity analysis (PSA) also indicated that the strategy is likely to be cost-effective compared to OTB with a probability of 96.77% at a willingness-to-pay threshold of £20,000 per QALY.

Scenario analyses also highlighted the importance of key assumptions in the model. Within the model, all patients who are diagnosed with advanced stage cancer undergo a PET-CT scan and any false positive diagnoses are assumed to be detected. Those who are not diagnosed with advanced disease undergo conventional staging, where 20% of false positive cases are missed under base case settings. Threshold analysis demonstrated that when this value goes above 42%, OLB is no longer considered a cost-effective strategy.

6. Organisational Issues

One study identified in the evidence literature highlighted that the ability to obtain high diagnostic yield biopsy can depend on the experience of the surgeon (Richards et al. 2015).

Consensus among several experts imply that there would be no major adaptions within the outpatient department such as the need for additional equipment, apart from the preference of a larger clinic room and the recommendation to make appointments longer so they can be undertaken efficiently without much intrusion on to clinical activity in the rest of the department. Consensus among experts suggested that OLB would be an aerosol generating procedure and would therefore require suitable ventilation and more air circulation time. OLB would likely require additional staff to assist the procedure, the use of FFP3 masks and local anaesthetic spray. If OLB were to be rolled out more widely in Wales, it is possible that further training may be necessary, although consensus among experts imply that laryngologists would have the necessary transferable skills to deliver this service. Additionally, it is likely that the increased use of OLB would be helpful in reducing demands on operating theatre time, as confirmed among experts. The procedure would enable other patients to be treated that would have otherwise waited a prolonged period.

7. Patient issues

Health Technology Researchers did not identify any studies that reported on patients' perspectives or experiences of OLB using local anaesthetic.

Consensus among experts imply that the choice of procedure should be judged on a case-by-case basis depending on patient tolerability, patient preference, and clinical need. Additionally, patient education may be required from the outset to inform patient expectations. OLB does have the potential to shorten the time to diagnosis and treat, which subsequently could reduce anxiety for the patient due to a shorter waiting time, fewer visits and less time spent in hospital, indicating a faster diagnostic pathway.

8. Conclusions

This evidence review summarised published evidence on the clinical and cost effectiveness of OLB with local anaesthetic in the outpatient setting for people with suspicious laryngeal or pharyngeal lesions compared to undergoing OTB under general anaesthetic.

Relevant outcome measures included diagnostic accuracy (sensitivity, specificity, positive predictive values, and negative predictive values), time to biopsy procedure, diagnosis, and treatment, procedure success rate, and complication rates. Sensitivity values ranged from 60% to 81.1% and the specificity values ranged from 87% to 100%. However, consensus among experts highlight that the experience of the professional, the responsiveness/sensitivity of the larynx and pharynx, the quality and size of the sample, and the type of imaging used, are all important factors that may alter the diagnostic accuracy of the procedure. Across the studies, the positive predictive values ranged from 78% to 100% and the negative predictive values ranged from 20% to 87.3%. From consultation to biopsy procedure, the mean number of days was 1.3 for OLB compared to 17.4 days under OTB ($p < 0.0001$) (Lee et al. 2018). From consultation to diagnosis under OLB, the mean number of days was 7.5 compared to 23 days under OTB ($p < 0.0001$) (Lee et al. 2018) For Schutte et al. (2018), the mean time from consultation to start of treatment was 27 days for OLB compared to 41.5 days for OTB ($p < 0.0001$). Across the studies, the proportion of patients experiencing complications was low and ranged from 0 to 2.6%.

The only identified economic analysis comparing OLB and OTB was the budget impact analysis conducted by SHTG. This analysis looked at the two strategies over a period of 5 years from a Scottish health care perspective and found that despite initial upfront cost increase with OLB, these costs would be later offset by the reduction in the number of patients having to undergo OTB. The average annual cost savings over the considered 5-year time horizon was £421,204.

Due to a lack of identified cost-effectiveness data, HTW developed a de-novo cost-utility analysis comparing OLB to OTB over a lifetime horizon. The SHTG budget impact analysis was used to derive inputs for the model, and these were updated with values more relevant to a Welsh setting where possible. Sensitivity and specificity of OLB were sourced from SHTG, updated with the additional identified study by HTW, and OTB was assumed to have perfect diagnostic accuracy, i.e., 100% sensitivity and specificity. Costs were sourced from a combination of expert advice and NHS Reference Costs (NHS England 2021), and inputs relating to quality adjusted life years were sourced from NICE Guideline 36 (NICE 2016). Costs and benefits were discounted at an annual rate of 3.5%.

In a population with 2,183 at risk patients, OLB was considered a cost-effective diagnostic strategy when compared to OTB over a lifetime horizon. OLB was associated with less costs and fewer QALYs than OTB, corresponding to an ICER of £21,011. Note the interpretation of the ICER changes in scenarios where an intervention is less effective and less costly, with values above the threshold considered cost effective because higher values indicate greater savings for each QALY lost.

Probabilistic sensitivity analysis demonstrated that the results of the base case analysis were robust. Scenario analyses, however, showed that changes to the proportion of patients who undergo unnecessary treatment following a false positive result from OLB can impact cost-effectiveness conclusions. OLB became a non-cost-effective strategy when more than 42% of patients who have been diagnosed as false positive are not detected during conventional imaging. Results of the deterministic sensitivity analysis further highlighted some key input changes that could impact conclusions of the analysis. Those with the biggest impact were changes to the time horizon, sensitivity, and specificity of OLB.

9. Contributors

This topic was proposed by Alex Zervakis, General Manager, Health Economics and Market Access, Olympus Medical.

The HTW staff and contract researchers involved in writing this report were:

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The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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11. Evidence review methods

We searched for evidence that could be used to answer the review question: What is the diagnostic accuracy, clinical effectiveness, and cost-effectiveness of laryngeal biopsies with local anaesthetic in the outpatient setting for people with suspected head and neck cancer?

The criteria used to select evidence for the appraisal are outlined in Appendix 1. These criteria were developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts.

SHTG conducted their literature search from 2008 until 22 February 2018, so our rapid review has included evidence that was published after this date.

As detailed in Appendix 1, we prioritised existing systematic reviews or other sources of secondary evidence, such as previous health technology assessments or evidence-based guidelines, as sources of quantitative outcome data. However, we did not identify any relevant secondary evidence, systematic reviews or any randomised controlled trials and therefore searched for and included evidence from observational studies as our main source of outcome data. We only included evidence where the intervention used was outpatient pharyngolaryngeal biopsies with local anaesthetic. As per the protocol, studies that evaluated narrow-bang imaging alone, and those evaluating endoscopies only, have been excluded from this rapid review. The included population must be people with suspected head and neck cancer and not those under routine follow-up. The reference standard and usual care is a biopsy in an operating theatre (OTB) using general anaesthetic.

The systematic search followed HTW's standard rapid review methodology. A search was undertaken of Medline, Embase, CINAHL, Cochrane Library, the International Network of Agencies for Health Technology Assessment (INAHTA) HTA database, the Centre for Reviews and Dissemination (CRD) database & Epistemonikos. Additionally, searches were conducted of key websites and clinical trials registries.

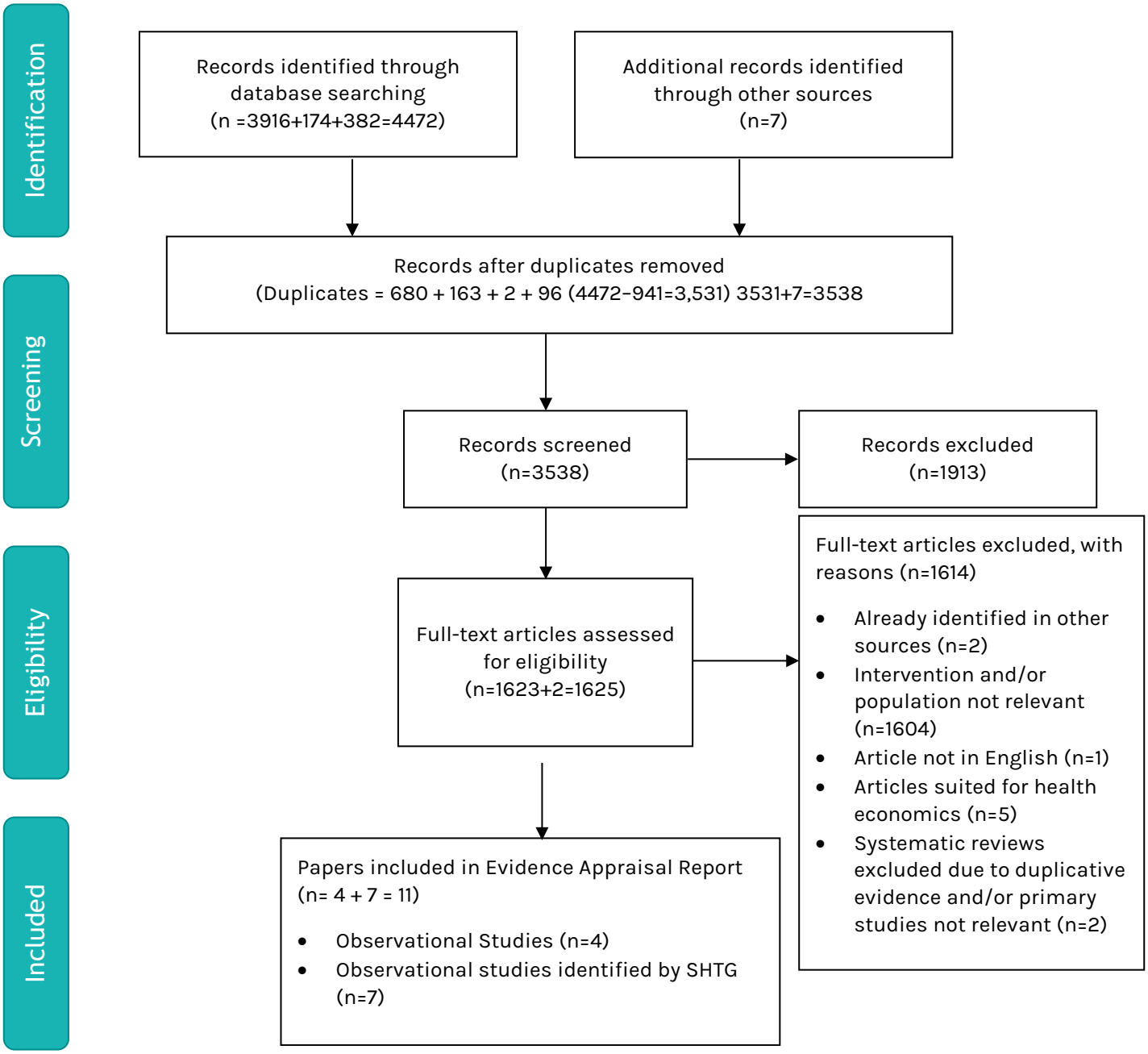
The searches were conducted on 15 November 2021 and then updated on 7 April 2022. Appendix 4 gives details of the search strategy used for MEDLINE. Search strategies for other databases are available on request.

Appendix 2 and Appendix 3 summarise the selection of articles for inclusion in the clinical and economic review, respectively.

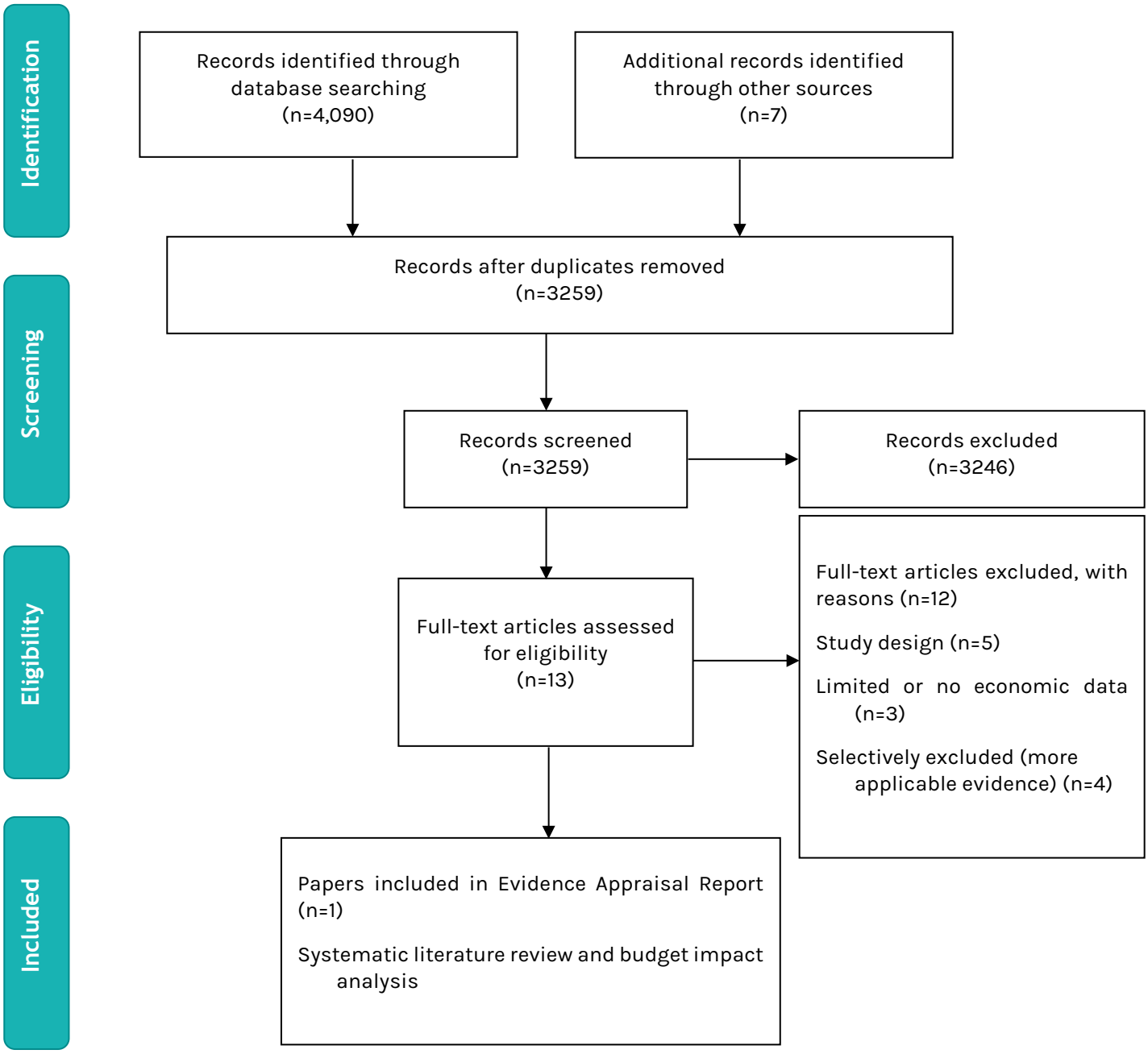
Appendix 1. Inclusion and exclusion criteria for evidence included in the review

	Inclusion criteria	Exclusion criteria
Population	People with suspected head and neck cancer	Follow-up procedure/routine follow up (must be those with suspected cancer)
Intervention	Pharyngolaryngeal (Laryngeal/pharyngeal) biopsy (OLB) with local anaesthetic in the outpatient setting	Exclude narrow-band imaging (NBI) only (must be biopsy with or without imaging, not just imaging) Exclude endoscopy only.
Comparison/ Comparators	Reference standard and usual care - OTB	
Outcome measures	Diagnostic accuracy (e.g., sensitivity, specificity, positive predictive value, negative predictive value, ROC curve) Clinical outcomes (e.g., time to diagnosis and treatment, mortality, adverse events) Patient-reported outcomes (e.g., health-related quality of life, patient satisfaction) Healthcare utilisation and economic outcomes (e.g., intervention delivery, number of procedures under general anaesthesia, hospital admission, length of stay, cost-effectiveness)	
Study design	We will prioritise the following study types, in the order listed: • Systematic reviews of randomised controlled trials. • Randomised controlled trials. • Non-randomised comparative trials. • Single-arm (no control group) trials that report any relevant outcome. We will only include evidence from "lower priority" sources where this is not reported by a "higher priority" source. This could be because higher priority evidence: • Does not cover all relevant populations • Does not compare the technology of interest to all relevant comparators • Does not cover all outcomes of interest • Reports over short-term follow up periods and longer follow up data is required to facilitate decision making. Where relevant and well-conducted systematic reviews exist, we will use these by: • Reporting or adapting their reported outcome measures where these are fully relevant to the scope of our review, and appropriate synthesis methods have been used • Using these reviews as a source of potentially relevant studies where the review cannot be used as a source of outcome data We will also include evidence from lower priority sources where they relate to organisational issues, PPI and health economics.	
Search limits	Search date limits have been applied to include only evidence published since the SHTG advice	
Other factors	English language only	

Appendix 2. Flow diagram outlining selection of relevant clinical evidence sources



Appendix 3. Flow diagram outlining selection of relevant economic evidence sources



Appendix 4. MEDLINE strategy

Ovid MEDLINE(R) ALL 1946 to April 06, 2022		
Head and Neck Population (including larynx, oropharynx, hypopharynx and pharynx)		
1	exp "Head and Neck Neoplasms"/	335468
2	exp Otorhinolaryngologic Neoplasms/	93007
3	((upper respiratory or upper airway* or upper aerodigestive or "head and neck" or UAT or UADT or head or neck) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or oncolog* or malignan* or metast* or lesion* or mass or masses or disorder*)).tw,kf.	78304
4	((otorhinolaryng* or laryng* or pharyng* or oropharyng* or hypopharyng*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or oncolog* or malignan* or metast* or lesion* or mass or masses or disorder*)).tw,kf.	29476
5	Laryngeal Diseases/	7802
6	Pharyngeal Diseases/	5641
7	Otorhinolaryngologic Diseases/	6142
8	Esophageal Diseases/	10230
9	Respiratory Tract Diseases/	22974
10	Otolaryngology/	14034
11	exp Head/	223330
12	exp Neck/	32370
13	exp Larynx/	42024
14	exp Oropharynx/	15136
15	exp Hypopharynx/	2495
16	exp Pharynx/	49530
17	(head or neck or larynx or oropharynx or hypopharynx or pharynx or endolaryngeal or dysplasia).tw,kf.	598057
18	or/1-17	1149199
Setting of the Biopsy (including outpatients and in-office)		
19	Ambulatory Care/	45576
20	Ambulatory Surgical Procedures/	12911
21	Outpatients/	19275
22	Office Visits/	7344
23	Anesthesia, Local/	17966
24	Minimally Invasive Surgical Procedures/	28436
25	Neoplasms, Unknown Primary/	3810
26	ambulatory.tw,kf.	86179
27	(outpatient* or out-patient*).tw,kf.	208906
28	office-based.tw,kf.	5305
29	in-office.tw,kf.	5487
30	cup forcep*.tw,kf.	58
31	local an?esthetic.tw,kf.	18993
32	minimal* invas*.tw,kf.	88014
33	unsedated.tw,kf.	983
34	(awake adj3 laryng*).tw,kf.	121
35	(unknown primar* or primar* unknown).tw,kf.	4619
36	or/19-35	454085
Biopsy		
37	Biopsy/	184682
38	Biopsy, Fine-Needle/	14861
39	Image-Guided Biopsy/	4944
40	Biopsy, Needle/	49634
41	biops*.tw,kf.	438246
42	Narrow Band Imaging/	1117

43	narrow* band* imag*.tw,kf.	2342
44	narrowband* imag*.tw,kf.	83
45	NBI*.tw,kf.	2759
46	Video Recording/	27203
47	Otorhinolaryngologic Surgical Procedures/	5402
48	Natural Orifice Endoscopic Surgery/	3386
49	Laryngoscopy/	13644
50	Laryngoscopes/	3920
51	(laryngoscop* or videolaryngoscop* or laryngovideostroboscop* or videostroboscop*).tw,kf.	17396
52	fiberoptic.tw,kf.	9469
53	flexible.tw,kf.	125774
54	oesophagoscop*.tw,kf.	510
55	esophagoscop*.tw,kf.	2228
56	working channel*.tw,kf.	1025
57	or/37-56	745523
Set Combinations (including language, date and exclusions filters)		
58	18 and 36 and 57	3372
59	((outpatient* or out-patient* or ambulatory or office* or in-office) adj2 (otorhinolaryng* or laryng* or pharyng* or oropharyng* or hypopharyng*)).tw,kf.	286
60	(distal* chip* adj3 (laryngoscop* or videolaryngoscop* or laryngovideostroboscop* or videostroboscop* or endoscop*)).tw,kf.	23
61	or/58-60	3577
62	limit 61 to (english language and yr="2017 -Current")	1006
63	Letter/	1175282
64	Editorial/	600792
65	News/	211856
66	exp Historical Article/	408079
67	Anecdotes as Topic/	4746
68	Comment/	957822
69	Case Reports/	2260447
70	(letter or comment*).ti.	175500
71	or/63-70	4727219
72	Randomized Controlled Trial/ or random*.ti,ab.	1433685
73	71 not 72	4697112
74	exp Animals/ not Humans/	4985821
75	exp Animals, Laboratory/	938111
76	exp Animal Experimentation/	10117
77	exp Models, Animal/	626490
78	exp Rodentia/	3440367
79	(rat or rats or mouse or mice).ti.	1395347
80	or/73-79	10525566
81	62 not 80	796
82	62 not 81	210

Appendix 5. Cost-effectiveness analysis

1. Background and objective

An economic analysis was developed to estimate the cost effectiveness of outpatient pharyngolaryngeal biopsies (OLB) under topical anaesthesia for patients with suspicious laryngeal or pharyngeal lesions compared to undergoing an inpatient or day case biopsy under general anaesthetic.

The economic analysis built upon the budget impact analysis (BIA) conducted by SHTG (SHTG 2018), extending their analysis to a full cost effectiveness analysis, capturing both costs and benefits of both diagnostic procedures over a lifetime horizon.

2. Methods

2.1 Model structure

A decision tree analysis was developed using Microsoft Excel to compare the cost effectiveness of diagnostic strategies for suspected head and neck cancer. The analysis took the perspective of the Welsh NHS and personal social services (PSS). The model comprises a short-term decision tree and lifetime (40 years) predictions of mortality and quality of life to evaluate the cost-effectiveness of diagnostic strategies for suspected head and neck cancer. The following two strategies were included:

1. Outpatient pharyngolaryngeal biopsy (OLB)
2. Operating theatre biopsy (OTB)

Future costs and benefits were discounted at a rate of 3.5%.

A simplified version of the decision tree is provided in Figure 1 and the two strategies considered in the analysis are briefly described below:

1. Outpatient pharyngolaryngeal biopsy (OLB)

   Patients undergo an OLB during their outpatient visit under topical anaesthesia. Most patients are assumed to tolerate the biopsy (86.6%) and are either diagnosed as having head and neck cancer or receive a negative test result. All patients diagnosed with advanced stage cancer (T4 or N3) are assumed to undergo a PET-CT scan for staging. At this stage, those who were misdiagnosed as positive would be detected and therefore not be subject to unnecessary treatment. Those diagnosed as non-advanced stage cancer undergo conventional imaging, at which point it is assumed that 80% of patients with a false positive diagnosis would be detected. The remaining patients with a false positive diagnosis are assumed to be identified following treatment initiation. As the readings from an OLB can be subject to doubt, a proportion of negative results would be subject to suspicion and would subsequently undergo an additional OTB in a daycase or inpatient setting. Those that do not undergo an additional procedure but are incorrectly identified as negative are assumed to be detected according to a background rate of diagnosis but miss out on immediate treatment.

2. Operating theatre biopsy (OTB)

   Patients undergo an operating theatre biopsy in a daycase or inpatient setting under general anaesthesia. A proportion of patients will experience either major or minor complications following the procedure and require an inpatient stay at the hospital. As OTB is the current reference standard diagnostic for head and neck cancer, it is assumed to have 100% sensitivity and specificity.

Patients who do not tolerate the OLB, experience complications with the procedure, or have a suspicious negative result are assumed to undergo an additional OTB. This procedure is assumed to be associated with 100% sensitivity and specificity, and so results are treated as confirmatory of diagnosis.

The model structure is an adaption of the SHTG BIA (SHTG 2018), and as such includes many of the same assumptions and inputs, however the structure has additionally been guided by the NICE pathway (NICE 2016) for upper aerodigestive tract cancer .

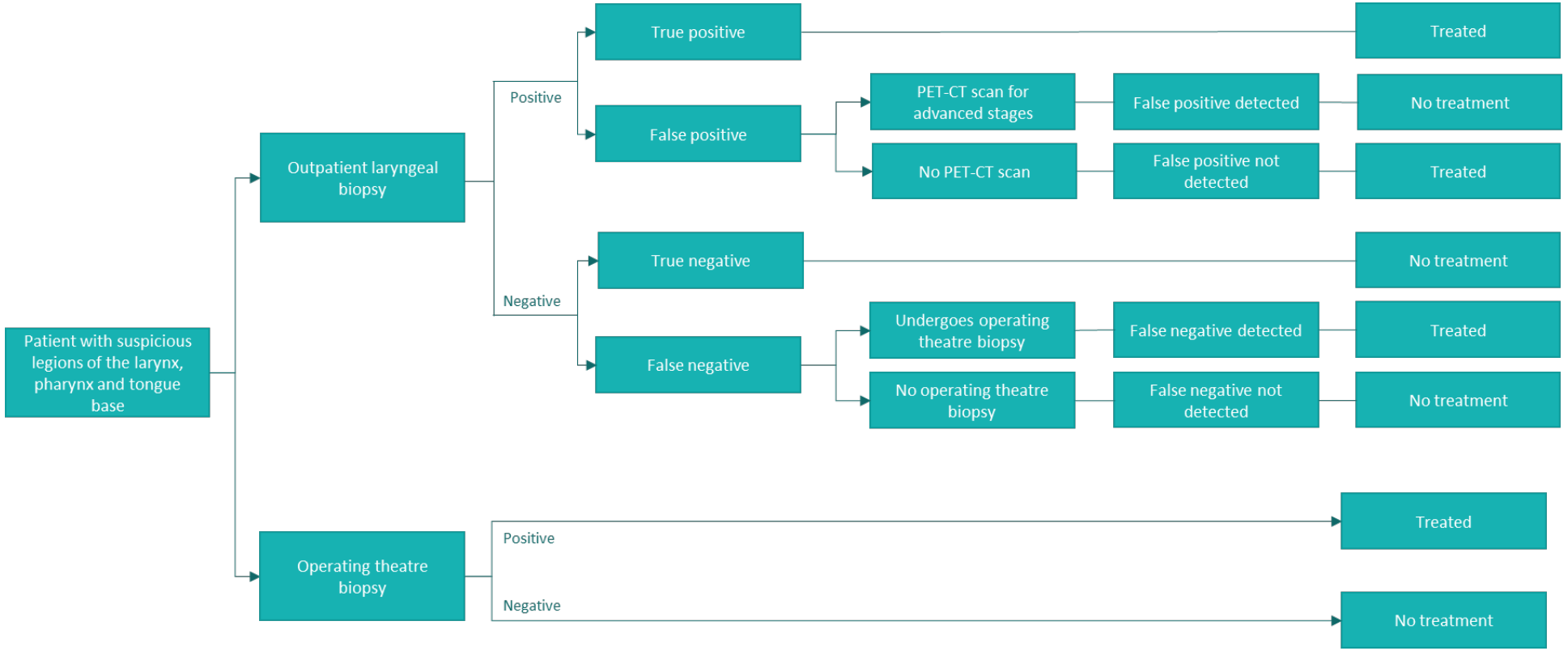


Figure 1. Modelled decision tree

2.2 Clinical data

2.2.1 Prevalence and accuracy data

Welsh statistics on the annual number of new diagnoses of head and neck cancer (Macmillan Cancer Support 2017) were used to calculate the number of patients who present with suspicious laryngeal or pharyngeal lesions. Under the assumption that patients presenting with suspicious laryngeal or pharyngeal lesions would have the same probability of having head and neck cancer as in Scotland, the prevalence rate amongst this patient group was taken from the SHTG BIA (SHTG 2018).

Of those that are diagnosed with head and neck cancer, 54% are assumed to be diagnosed as advanced stage (Gatta et al. 2015). These patients will undergo a PET-CT scan to gather more information on the stage and prognosis of their cancer. A small proportion of patients are not indicated for PET-CT scan and will instead undergo conventional imaging.

The population entering the model was 27.5% female with a baseline age of 65.8, based on the only UK study identified in the clinical literature review (Mohammed et al. 2019).

Table 1. Model inputs: Prevalence inputs

	Mean value	SE/α, β, distribution	Source
Patients with suspicious lesions	2,183	449.6, normal	Macmillan Cancer Support (2017)
Prevalence amongst these patients	30.6%	687.89, 1,560.11, beta	SHTG (2018)
Patients with advanced stage at diagnosis	54.0%	128,848, 109,760, beta	Gatta et al. (2015)
Patients with advanced stage indicated for PET-CT scan	95.3%	41, 2, beta	NHS England (2018)

The diagnostic accuracy was derived using a weighted average from values reported from SHTG (SHTG 2018), updated with the additional study identified in the clinical review (Hassan et al. 2019). As readings from an OLB can be subject to doubt, a proportion of negative results would subsequently undergo an additional OTB to confirm the negative result. The proportion of patients in the base case analysis who would undergo an additional OTB following OLB has been derived from Naidu et al. (Naidu et al. 2012), however values between 0% and 100% have been explored in scenario analyses to evaluate the impact of no patients undergoing an additional biopsy, or all patients with a negative OLB result undergoing an additional biopsy.

Where patients do not undergo an additional OTB and have been incorrectly diagnosed as negative, they are assumed to be identified as such at a later stage. The model assumes that all patients with a false negative result will be detected within a year of the initial biopsy, with a value of 2 months being explored in scenario analyses, Similarly, patients who are incorrectly diagnosed as positive and are not detected during staging will be identified within three months of initial diagnosis.

OTB procedures are assumed to be confirmative of diagnosis with 100% diagnostic accuracy. As this is the reference standard, this is deemed to be an appropriate assumption and as such, is not varied in sensitivity analysis.

Table 2. Model inputs: Diagnostic accuracy of procedures

Input	Mean	α, β, distribution	Source
Outpatient pharyngolaryngeal biopsy (OLB) diagnostic accuracy			
Sensitivity	76.12%	848.65, 251.35, beta	SHTG (2018) & Hassan et al. (2019)
Specificity	97.93%	1,065.89, 34.11, beta	SHTG (2018) & Hassan et al. (2019)
Operating theatre biopsy (OTB) diagnostic accuracy			
Sensitivity	100%	-	SHTG (2018)
Specificity	100%	-	SHTG (2018)
Proportion of negatives undergoing additional biopsy	33.3%	4.00, 8.00, beta	Naidu et al. (2012)

2.2.2 Complications

Complications relating to both biopsy procedures were incorporated in the analysis using estimates applied in the BIA conducted by SHTG (SHTG 2018). The risk of complication applied in the analysis per procedure are provided in Table 3.

Patients undergoing an OLB are at risk of experiencing complication or intolerance to the procedure, requiring them to switch to an OTB.

An OTB can lead to both minor and major complications, each of which require an inpatient stay. In addition, patients may need to stay overnight following OTB, regardless of complications, due to their individual circumstances.

The SHTG BIA based major complication estimates on clinical opinion of the proportion of oesophageal perforations and difficult airway cases which could potentially require a tracheotomy. The risk of minor complication following OTB, and the risk of intolerance or complication from an OLB was sourced from their literature review.

Table 3. Model inputs: Complications of procedures

Input	Mean	α, β, distribution	Source
Outpatient pharyngolaryngeal biopsy (OLB) complications			
Complication or intolerance	13.4%	301.23, 1,946.77, beta	SHTG (2018)
Operating theatre biopsy (OTB) complications			
Minor complication	1.0%	22.48, 2,225.52, beta	SHTG (2018)
Major complication	2.7%	60.70, 2,187.30, beta	
Overnight stay due to patient circumstance	15.0%	337.20, 1,910.80, beta	

2.2.3 Mortality

Mortality for the general population is derived using published life tables for Wales (Office for National Statistics 2021), and is weighted annually according to the baseline gender distribution in the analysis.

Mortality data for patients treated with head and neck cancer has been derived from age-specific one- and five-year survival rates published by Public Health Wales (Public Health Wales 2021) . The trend of these values was used to extrapolate survival estimates over the 40-year time horizon using the exponential distribution. The predicted 10-year survival for patients in different age categories is provided in Table 4. Depending on the baseline age of the population being modelled, the corresponding survival rates were applied in the analysis.

Table 4. Model inputs: 10-year survival for head and neck cancer patients

	15 - 54		55 - 64		65 – 74		75 +	
	Male	Female	Male	Female	Male	Female	Male	Female
0	100%	100%	100%	100%	100%	100%	100%	100%
1	94%	96%	91%	92%	90%	92%	89%	88%
2	88%	91%	83%	84%	81%	84%	79%	77%
3	83%	87%	76%	77%	73%	77%	70%	67%
4	77%	83%	69%	71%	65%	70%	62%	59%
5	73%	79%	63%	65%	59%	64%	55%	52%
6	68%	76%	58%	60%	53%	59%	49%	45%
7	64%	72%	53%	55%	47%	54%	44%	40%
8	60%	69%	48%	51%	42%	49%	39%	35%
9	56%	66%	44%	47%	38%	45%	35%	30%
10	53%	63%	40%	43%	34%	41%	31%	27%

To account for patients with advanced stage cancer, a hazard ratio of 2 has been applied to mortality estimates, sourced from a study by Cadoni et al. (2017) which evaluated the prognostic factors in head and neck cancer in Italy. A similar study in a Welsh or UK setting was not identified. For patients who are not treated immediately due a false negative diagnosis, a hazard ratio of 1.06 has been applied to mortality estimate. This value, sourced from Hanna et al. (2020), looked at the impact of delaying cancer treatment on survival for a number of different cancer sites.

2.3 Resource use and costs

The costs considered in the analysis reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2021 prices. Where costs were reported in a different cost year, they were inflated to 2021 prices using the CCEMG – EPPI Centre Cost Converter (CCEMG - EPPI-Centre 2019).

In the base case analysis, costs have been sourced from NHS Reference Costs (NHS England 2021) to account for all resource use associated with each of the procedures. Costs for HRG code CA69A have been used as this corresponds to Diagnostic, Laryngoscopy or Pharyngoscopy, in patients 19 years and over, and includes biopsy. The cost of the OLB procedure is assumed to be the ENT outpatient cost. For OTB, costs for the daycase procedure have been applied, unless patients experience complications which require hospital stay, whereby inpatient costs have been applied.

2.3.1 OLB costs

Initial upfront costs associated with OLB includes the purchase of new laryngoscopes and new imaging stacks plus peripherals. Some health boards may already have existing imaging stacks which could be utilised for the outpatient biopsies; therefore, the analysis assumes that not all hospitals require new imaging stack and peripheral equipment. Upfront and maintenance costs of laryngoscopes have been provided by the manufacturer, and costs of imaging stack and associated equipment has been sourced from experts.

2.3.2 Visit costs

All patients in the model attend an initial outpatient appointment. Patients undergoing OLB will undergo the procedure during this appointment. Patients undergoing the OTB will usually undergo the procedure in a daycase setting following initial outpatient visit unless there are complications. If complications occur and patients need to remain in hospital, they will incur the cost of an inpatient visit. Table 5 provides the costs per visit of each type of stay.

Table 5. Model inputs: Costs associated with visit type

Resource	Mean	α, β, distribution	Source
Outpatient visit	£135.59	3,546,567.32, 0.00, gamma	NHS Reference costs 2019 – 2020 (NHS England 2021)
Daycase visit	£1,100.00	63,786.06, 0.02, gamma	
Inpatient visit	£1,854.33	22,287.57, 0.08, gamma	

2.3.3 Treatment and staging costs

Patients who are identified as having advanced stage cancer following biopsy are assumed to undergo a PET-CT scan, or conventional imaging if unsuitable for PET-CT. Costs of £667.62 and £46.10 for PET-CT scan and conventional imaging, respectively, have been sourced from NHS reference costs 2019 – 2020 (NHS England 2021).

Treatment costs have been sourced from NICE Guideline 36 (NICE 2016) where a weighted average of treatments per stage of various head and neck cancers has been derived. A cost of £7,341.25 has been applied to patients without advanced stage cancer receiving treatment, and a cost of £15,484.91 is applied to those with advanced stage cancer.

2.3.4 Palliative care costs

The cost of palliative care at the end of life was estimated using values reported in 'Unit costs of health and social care 2021' by the Personal Social Services Research Unit (Jones & Burns 2021). The PSSRU reported the results of research carried out by the Nuffield Trust on behalf of the National End of Life Care Intelligence Network.

The total cost of care services received in the last twelve months of life were estimated for people with various medical conditions using data on health and social care service use patterns in seven local authorities. End of life costs for people diagnosed with cancer (n=19,934) were estimated from to be £11,242 and £1,655 for hospital care and social care, respectively. Thus, a total cost of £12,897 was applied for people dying of disease specific causes in the model, in additional to chemotherapy costs of £6,069.

A limitation of this approach is that it relies upon a cost that is generic to all cancers rather than a specific cost for palliative care in head and neck cancer. However, in the absence of more robust data, it has been assumed that palliative care costs in head and neck cancer would not differ substantially to such costs in other cancer.

2.3.5 Scenario analysis

A scenario analysis explored the impact of applying cost per resource use rather than applying a single cost per procedure. This method was applied in the SHTG (SHTG 2018) BIM, and the same methods and assumptions have been applied in this scenario.

Additional costs associated with OLB in the scenario analysis are provided in Table 6. Each biopsy is expected to take 15 minutes of a consultant's time, priced at £2.03 per minute, resulting in total staff cost of £31.13 per procedure when an additional nurse cost is also considered.

Under the scenario analysis, each complication as defined in Table 3, is associated with a number of additional bed days, provided in Table 6.

Table 6. Model inputs: Additional costs applied in scenario analysis

Resource	Mean	Source
Additional staff member cost per procedure	£0.68	PSSRU; band 5 nurse (Jones & Burns 2021)
Cost per minute of consultant time	£2.03	PSSRU; surgical consultant (Jones & Burns 2021)
Working channel forceps per procedure	£6.49	(NHS Supply Chain 2022)
Decontamination per procedure	£24.44	(SHTG 2018)
Topical anaesthesia per procedure	£9.26	BNF (Joint Formulary Committee 2022)
Additional bed days per minor complication	1	(SHTG 2018)
Additional bed days per major complication	6	(SHTG 2018)

The costs applied per type of visit are as in Table 5, with an additional cost of £1,392.42 applied per additional bed day for an inpatient stay. As in the base case analysis, all patients are assumed to undergo an initial outpatient visit.

2.4 Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of QALYs. These are estimated by combining life year estimates with a baseline utility value of 0.913, sourced from NICE Guideline 36 (NICE 2016).

Patients treated for head and neck cancer will be subject to a utility decrement associated with treatment. Utility values have been derived from NICE Guideline 36 (NICE 2016) where a weighted average of utility decrement associated with treatment per stage of various head and neck cancers has been derived. A utility decrement of 0.09 has been applied to account for patients receiving treatment for non-advanced stage cancer, and a decrement of 0.23 has been applied to patients receiving treatment for advanced stage cancer.

3. Results

3.1 Base case results

The base case health economic results of the analysis are provided in Table 7. The results show that using OLB as the diagnostic tool for head and neck cancer is expected to reduce costs by £816 per patient compared with OTB; however, due to the potential for misdiagnosis of patients, it is also associated with 0.04 fewer QALYs per patient, resulting in a corresponding ICER of £21,011 per QALY. Note the interpretation of the ICER changes in scenarios where an intervention is less effective and less costly, with values above the threshold considered cost effective because higher values indicate greater savings for each QALY lost. Since this saving is greater than the threshold of £20,000 per QALY, OLB is considered to be cost effective.

Table 7. Base case health economic results

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Operating theatre biopsy (OTB)	£7,718	-	9.24	-	-
Outpatient pharyngolaryngeal biopsy (OLB)	£6,902	-816	9.21	-0.04	£21,011
*Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year					

The base-case analysis predicted that diagnosing patients with OLB results in 1,417 operating theatre biopsies being avoided in a total of 2,183 patients. Avoiding OTB procedures reduces demand on operating theatre time, thereby providing benefit to other patients in the healthcare system. However, this diagnostic strategy resulted in 92 positive cases of head and neck cancer being missed and 27 patients misdiagnosed as a positive case, 2 of whom would go on to receive unnecessary treatment.

Table 8 provides a cost breakdown for both diagnostic strategies at a cohort-level (2,183 patients). The high upfront costs of additional equipment are offset by the long-term cost-savings from less treatment costs and fewer daycase visits and inpatient stays at hospital.

Table 8. Base case results: cost breakdown at a cohort-level (per 2,183 patients)

Diagnostic strategy	Outpatient pharyngolaryngeal biopsy (OLB)	Operating theatre biopsy (OTB)	Incremental
Treatment	£13,659,142	£14,139,401	-£480,259
Additional equipment	£160,489	£0	£160,489
Outpatient visits	£295,993	£0	£295,993
Daycase visits	£685,367	£1,952,257	-£1,266,890
Inpatient visits	£265,747	£756,976	-£491,229
Total	**£15,066,739**	**£16,848,635**	**-£1,781,896**

3.1.1 Scenario analyses

There are a number of key assumptions in the analysis which have been explored in additional sensitivity analysis:

- Scenario 1: No patients undergo OTB following a negative diagnosis from OLB.

- Scenario 2: All patients undergo OTB following a negative diagnosis from OLB.
- Scenario 3: False negative patents are detected within 2 months.
- Scenario 4: Costs and resource use evaluated separately.
- Scenario 5: Equivalent complication rates between the two strategies.

The health economic results of these analyses are presented in Table 9, with additional results on the diagnostic accuracy of the OLB presented in Table 10 for scenario 1 and 2.

Table 9. Scenario analyses: health economic results

Scenario	Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
		Total	Incremental	Total	Incremental	
1	OTB	£7,718	-	9.24	-	-
	OLB	£6,516	-£1,202	9.19	-0.06	£20,873
2	OTB	£7,718	-	9.24	-	-
	OLB	£7,674	-£44	9.24	0.00	£33,098
3	OTB	£7,718	-	9.24	-	-
	OLB	£7,119	-£599	9.24	0.00	£287,288
4	OTB	£7,958	-	9.24	-	-
	OLB	£7,060	-£898	9.21	-0.04	£23,105
5	OTB	£7,718	-	9.24	-	-
	OLB	£6,965	-£754	9.21	-0.04	£20,660

*Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Table 10. Scenario analyses: additional results

Scenario	Additional results of OLB	Total
Base case	Positive results missed	92
	Patients with a false positive	27
	Unnecessary treatments	2
	Avoided operating theatre biopsies	1,417
1	Positive results missed	138
	Patients with a false positive	27
	Unnecessary treatments	2
	Avoided operating theatre biopsies	1,890
2	Positive results missed	0
	Patients with a false positive	27
	Unnecessary treatments	2
	Avoided operating theatre biopsies	468

Across all modelled scenarios, OLB remains a cost-effective diagnostic strategy.

Although scenario 1 is associated with fewer incremental QALYs than in the base case analysis, there are higher cost savings associated with this approach from avoided procedures. However, despite avoiding 473 more OTB than in the base case analysis, an additional 46 patients will not be correctly diagnosed as positive under this approach.

When all patients who test negative are assumed to undergo additional OTB, OLB remains cost-effective as the removal of false negative patients results in minimal differences in QALYs between diagnostic arms. Costs are still lower than OTB alone, however, the difference between the strategies is much smaller as 949 more patients undergo additional OTB than in the base case analysis.

When all patients who are incorrectly given a negative result from the OLB are diagnosed within two months, there are minimal QALY differences between the two procedures. However, due to the large cost savings under this approach, OLB becomes highly cost-effective under this scenario.

Minimal differences are seen when costs and resource use are evaluated separately as opposed to resource use being captured in the cost of the procedure, and when complication rates are assumed equal between strategies. This supports the base case approach.

3.1.2 Threshold analysis

A threshold analysis was conducted to assess the impact of adjusting the proportion of patients who are incorrectly identified as having cancer during OLB and go on to receive treatment unnecessarily.

Within the model, all patients who are diagnosed with advanced stage cancer undergo a PET-CT scan and any false positive diagnoses are assumed to be detected. Those who are not diagnosed with advanced stage disease undergo conventional staging, where 20% of false positive cases are missed under base case settings.

Results of the threshold analysis are presented in Figure 2, and show that when this value goes above 42%, OLB is no longer considered a cost-effective strategy. This is due to the long-lasting quality of life implications for these patients, as well as the unnecessary costs for treatment.

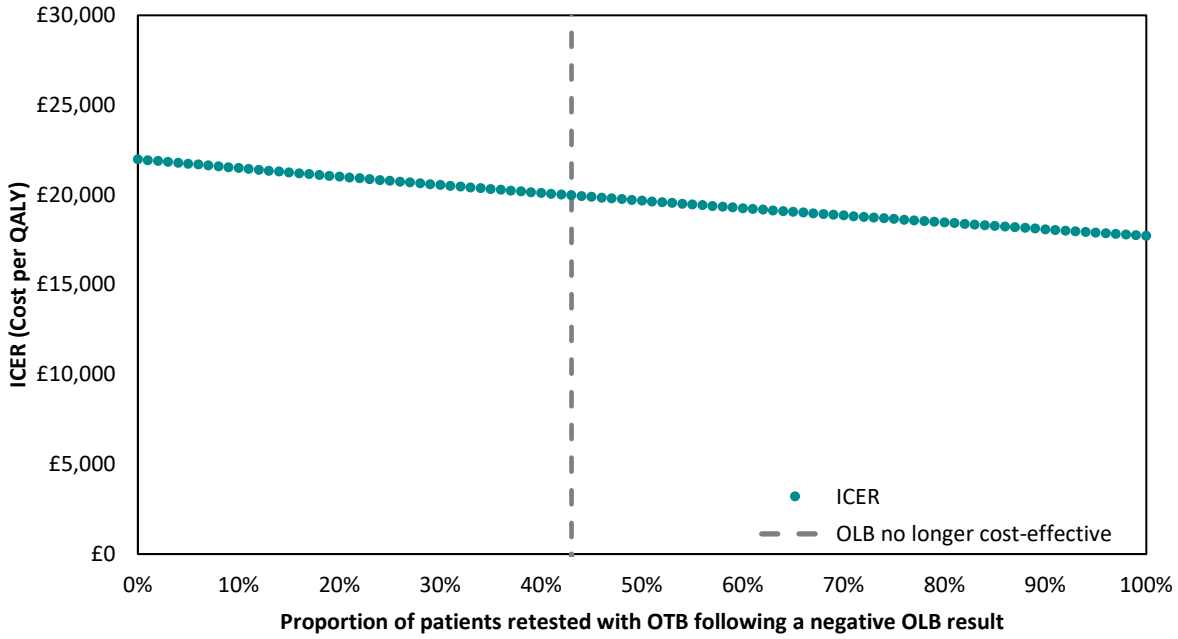


Figure 2. Analysis of the proportion of patients receiving unnecessary treatment

3.2 Deterministic sensitivity analysis results

A series of deterministic sensitivity analyses (DSA) were conducted, whereby an input parameter is changed, the model is re-run, and the new cost-effectiveness result is recorded. This is a useful way of estimating uncertainty and determining the key drivers of the model result. The amount that each input is varied by is provided in Table 11.

Table 11. Deterministic sensitivity: Input values

Modelled scenario	Mean Value	Lower bound	Upper bound
Model Settings			
Time horizon	40	5	50
Discount rates - benefits	3.5%	0.0%	6.0%
Discount rates - costs	3.5%	0.0%	6.0%
Proportion of population male	72.5%	58.0%	87.0%
Baseline age	65.8	52	79
Population inputs			
Patients with suspicious lesions	2,183	1,746	2,620
Probability of disease being present	30.6%	24.5%	36.7%
Sensitivity (Probability of True Positive)	76.1%	60.9%	91.3%
Specificity (Probability of True Negative)	97.9%	78.3%	100.0%
Patients with advanced disease at diagnosis	54.0%	43.2%	64.8%
Proportion of negatives that are suspected false negatives	33.3%	26.6%	40.0%
Hazard ratio for survival in patients not receiving treatment	1.06	0.85	1.27
Hazard ratio for survival in patients with advanced disease	2.00	1.60	2.40
Proportion of false positives undetected	20.0%	0.0%	100.0%
Patients able to tolerate a PET-CT scan	95.3%	76.3%	100.0%
Complication inputs			
Probability of outpatient biopsy complications	0.9%	0.72%	1.08%
Probability of outpatient biopsy intolerance	12.5%	10.0%	15.0%
Probability of outpatient biopsy complications/intolerance	13.4%	10.72%	16.08%
Probability of major daycase complications	2.7%	2.16%	3.24%
Probability of minor daycase complications	1.0%	0.8%	1.2%
Probability of overnight stay due to patient circumstances	15.0%	12.0%	18.0%
Resource use inputs			
Time to pay off imaging stack plus peripherals	5	3	10
Time to pay off equipment laryngoscope	5	3	10
Number of laryngoscopes needed per board	2	1	5
Additional minutes required to perform outpatient biopsy	15	0	45

Modelled scenario	Mean Value	Lower bound	Upper bound
Number of years of maintenance for laryngoscope	5	3	10
Number of years of maintenance for imaging stack	5	3	10
Cost inputs			
Average cost per outpatient visit	£136	£108	£163
Average cost per daycase visit	£1,100	£880	£1,320
Cost per inpatient visit	£1,854	£1,483	£2,225
Average annual treatment cost – non-advanced	£7,341	£5,873	£8,819
Average annual treatment cost – advanced	£15,485	£12,388	£18,582
End-of-life treatment	£6,069	£4,855	£7,283
Palliative care costs	£12,897	£10,318	£15,476
PET-CT scan costs	£668	£534	£801
Costs of conventional imaging	£46	£37	£55
Utility and life expectancy inputs			
Baseline utility	0.91	0.73	1.00
Treatment decrement: non-advanced	0.09	0.07	0.11
Treatment decrement: non-advanced	0.23	0.19	0.28
*Abbreviations: QALYs: quality adjusted life years			

The results of the 30 most influential parameters on the ICER are presented in Figure 3. All results of the DSA remain in the south-west quadrant of the cost-effectiveness plane, meaning that an ICER of over £20,000 per QALY would be deemed cost-effective. The analysis shows that there are thirteen situations whereby OLB is no longer cost-effective.

The choice of time horizon is the most influential parameter. Increasing the time horizon makes minimal difference to modelled results as there will be no mortality impact, however, when running the model over the shorter time horizon of five years, OLB becomes a highly cost-effective strategy. This is due to very similar life years and QALYs between the two strategies over this time horizon.

Parameter changes which impact cost-effective conclusions are:

- Decreasing the discount rate of benefits
- Decreasing baseline age
- Increasing the prevalence of disease
- Decreasing sensitivity and specificity
- Decreasing the proportion of patients with advanced stage disease at diagnosis
- Increasing the mortality hazard ratio in patients not receiving treatment
- Decreasing the mortality hazard ratio in patients with advanced disease
- Increasing the number of laryngoscopes required per health board
- Decreasing the average cost per daycase visit
- Decreasing the average cost per inpatient visit
- Increasing the baseline utility.

Decreasing the baseline age of patients in the model means that costs are higher across both strategies due to treating patients for a longer amount of time. This leads to reduced incremental

costs between arms and thus a lower ICER for OLB. Similarly, when patients with advanced stage cancer are closer in survival to those with non-advanced stage cancer, or when there are less patients with advanced stage disease at diagnosis, patients are treated for longer and incremental costs between arms is decreased.

When the prevalence of disease in the population is increased, more patients are subject to being misdiagnosed by OLB, resulting in results no longer being cost-effective.

When the sensitivity of OLB is decreased there are a much higher number of positive patients missed, resulting in worse quality of life for patients undergoing the procedure. Similarly, lowering specificity results in more patients being misdiagnosed and a greater difference in quality of life between diagnostic methods. Likewise, when patients not receiving treatment are subject to a worse survival rate, the OLB procedure becomes less cost-effective as survival becomes worse compared to OTB.

If more laryngoscopes were needed to be purchased per health board, the costs of the OLB procedure would be increased, making the procedure less cost-effective. Similarly, if treatment costs were greater, there would be greater incremental costs between arms, with OLB becoming a more cost-saving strategy, meaning that cost-effectiveness would increase.

On the other hand, if costs associated with inpatient and daycase visits were reduced, the overall costs of OTB would be less, and so there would be less cost-savings with the OLB procedure.

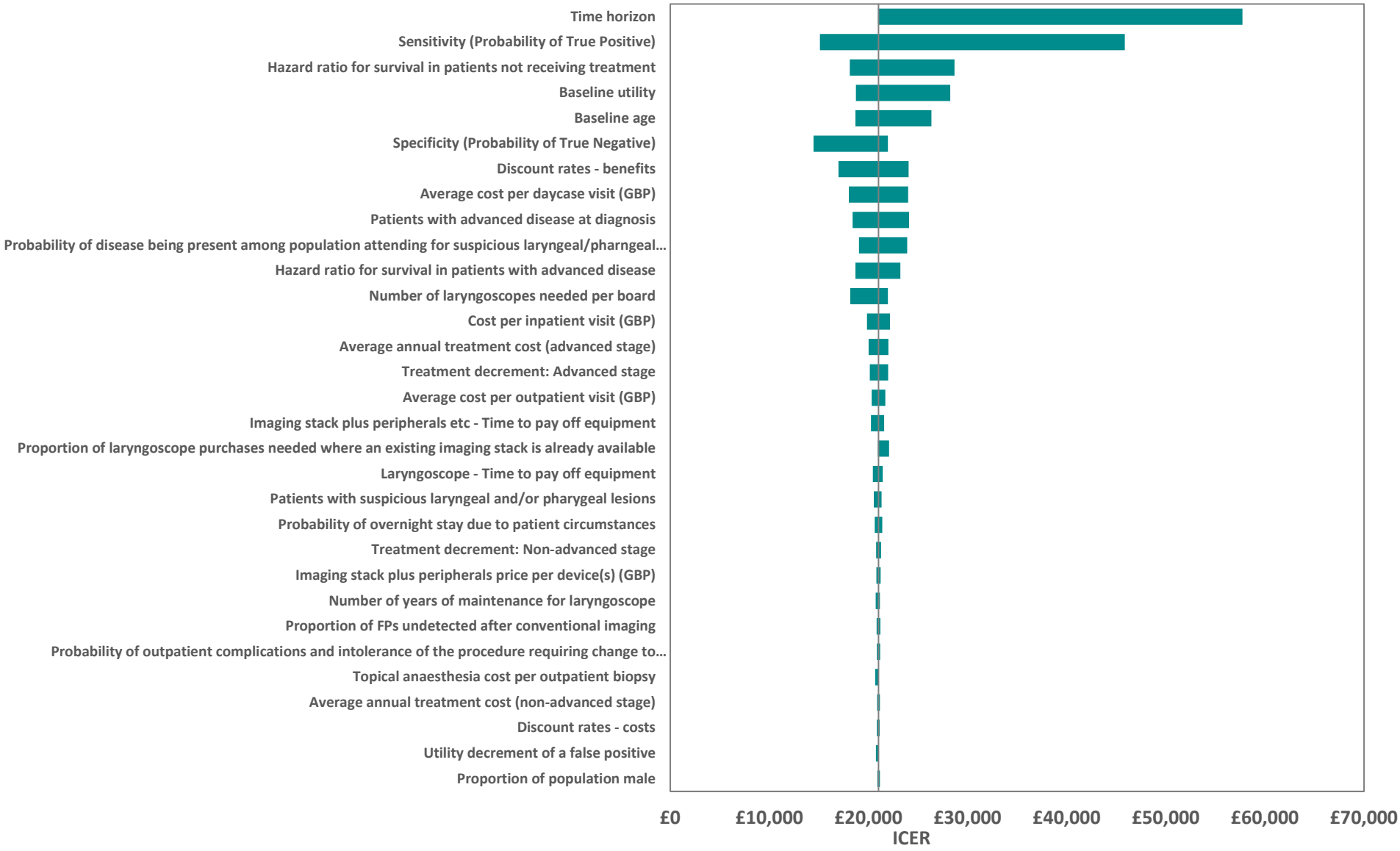


Figure 3. Results of the deterministic sensitivity analysis

3.3 Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case were replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are presented using ICER scatterplots and cost-effectiveness acceptability curves (CEACs). The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graphs show the probability of OLB being considered cost effective at the various cost-effectiveness thresholds on the x-axis.

Table 12 presents the health economic results from the PSA. Under this analysis, OLB is a cost-effective strategy with an ICER of £39,385 per QALY, and a 96.77% chance of being cost-effective.

Table 12. Probabilistic sensitivity analysis: health economic results

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Operating theatre biopsy (OTB)	£7,659	-	8.82	-	-
Outpatient pharyngolaryngeal biopsy (OLB)	£6,971	-£688	8.81	-0.02	£39,385
*Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year					

Figure 4 shows the ICER scatterplot for the PSA. All points reside in the bottom half of the graph, indicating that OLB is less costly than OTB, and with the exception of one point, they are entirely concentrated in the south-west quadrant, meaning that QALYs are also fewer under this strategy. The results of the analysis are more skewed to the cost-effective side of the willingness-to-pay threshold, indicating that OLB is likely to be a cost-effective strategy.

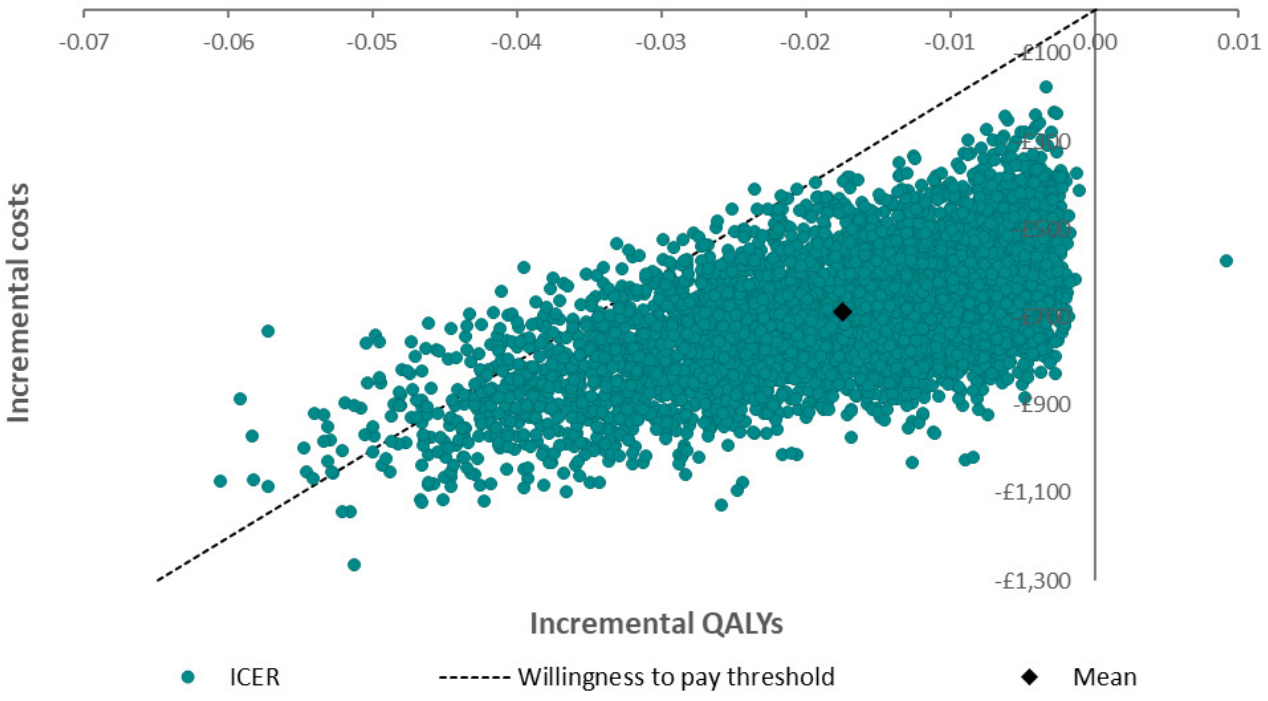


Figure 4. Cost-effectiveness plane from PSA

Figure 5 presents the probability of OLB being considered cost-effective at various cost-effectiveness thresholds. Due to the ICERs residing in the south-west quadrant, the probability that OLB are cost effective decreases as the willingness-to-pay threshold increases. At a threshold of £20,000 per QALY, there is a 96.77% probability that the strategy would be cost-effective, decreasing to 73.22% as the threshold reaches £30,000.

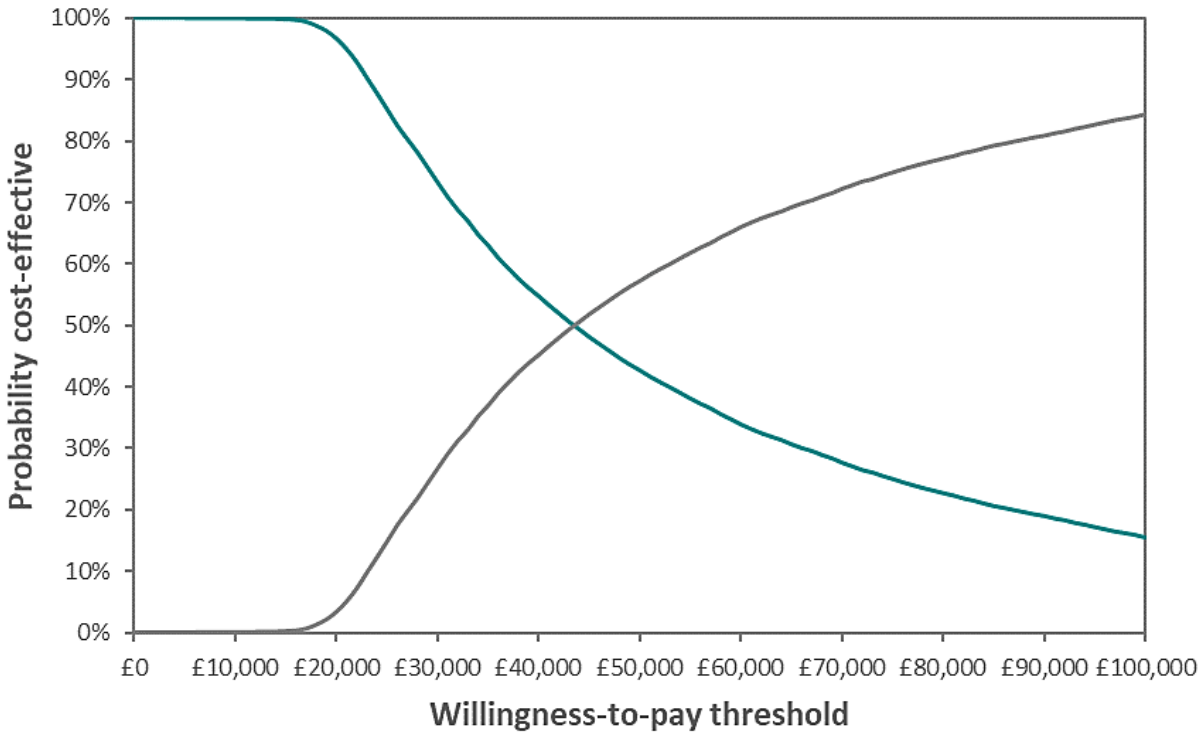


Figure 5. Cost-effectiveness acceptability curve