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The role of local anaesthetic biopsy in the head and neck cancer diagnostic pathways

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Lim AE, Douglas CM, Montgomery J. An open structure questionnaire on reasons for delay in presentation: a study of patients attending clinic with red flag symptoms of head and neck cancer. Eur Arch Otorhinolaryngol. 2020;277(6):1801-1806.

Article 2 [2]

Lim AE, Zahra B, Moen CM, Montgomery J. The impact of local anaesthetic biopsy in head and neck cancer on cancer pathway waiting times. The Annals of the Royal College of Surgeons of England. 2023;105(4):331-335.

Article 3 [3]

Lim AE, Moen CM, Montgomery J. National survey sampling exercise on current practice in channelled local anaesthetic biopsy in suspected head and neck cancer. The Journal of Laryngology and Otology. 2024;138(3):338-340.

Article 4 [4]

Lim AE, Rogers ADG, Owusu-Ayim M, Ranjan S, Manickavasagam J, Montgomery J. A systematic review: impact of in-office biopsy on safety and waiting times in head and neck cancer. The Journal of Laryngology and Otology. 2022;136(10):909-916.

Article 5 [5]

Lim AE, Rogers ADG, Montgomery J. Prospective cohort study assessing patient satisfaction and diagnostic accuracy in channelled endoscope local anaesthetic biopsy in the investigation of head and neck cancer. Head Neck. 2024;46(1):15-22.

Article 6 [6]

Lim AE, McKeegan E, Townsley RB, Montgomery J. Changing rates of synchronous upper aerodigestive tract malignancy in head and neck cancer- why are we still using panendoscopy? The Journal of Laryngology and Otology. 2024:1-16.

Article 7 [7]

Lim AE, Williamson A, Green F, Ying LK, Li L, Moen, C, Vasanthan R, Wharf O, Wong J, Paleri V, INTEGRATE. Clinical Factors Influencing the Compliance With National Head and Neck Cancer Targets in the United Kingdom: Results From a National Cohort Study. Clinical Otolaryngology. 2025;50(4):739-750.

Acronyms

Allied health professional	AHP
Artificial intelligence	AI
Computed tomography	CT
Ear, nose and throat	ENT
Fine needle aspirate	FNA
Flexible nasoendoscopy	FNE
General anaesthetic	GA
General practitioner	GP
Human papilloma virus	HPV
Head and neck cancer	HNC
Local Anaesthetic	LA
Machine Learning	ML
Multidisciplinary Team	MDT
Magnetic Resonance Imaging	MRI
Narrow band imaging	NBI
National health service	NHS
National Institute for Health and Care Excellence	NICE
Positron Emission Tomography-Computed Tomography	PET-CT
Squamous cell carcinoma	SCC
Speech and Language Therapist	SLT
Synchronous primary cancer	SPC
Upper aerodigestive tract	UADT

United Kingdom	UK
Ultrasound	US
Urgent Suspicion of Cancer	USoC

Summary

The incidence of head and neck cancer (HNC) is rising in the United Kingdom (UK), leading to growing pressures on HNC services. Cancer Research UK estimates that cancer referrals will rise by 21% in the next 5 years, with 300,000 patients experiencing delays in cancer treatment[8,9]. HNC pathways are saturated with referrals, resulting in prolonged waits to diagnose HNC and subsequent delays in initiating cancer treatment. This thesis explores existing problems in the diagnostic pathway for HNC in the UK and offers novel solutions, focusing on improving pathway efficiency through the use of local anaesthetic (LA) biopsy.

To initiate referral into the HNC pathway, a patient must recognise red flag symptoms and present to a healthcare professional. Patients with HNC often present with advanced stage disease, which contributes to poor morbidity and mortality outcomes[10] . Article 1 represents the first investigation into the patient-related factors that contribute to the late presentation seen in HNC. Crucially, it was identified that cancer patients take longer to present with symptoms in comparison to patients with benign disease. Presentation delay was most often a consequence of the patient not recognising concerning symptoms. This highlights the urgent need to educate patients about red flag symptoms, through public health campaigning and targeting high risk groups by health promotion during routine healthcare interactions.

The National Health Service (NHS) recommends 95% of patients should have their cancer treatment started within 62 days of referral[11]. Article 2 offers original insight into the impact of LA biopsy on pathway times in the UK. In an observational cohort, LA biopsy was associated with significantly shorter times to biopsy and multidisciplinary team (MDT)

discussion in comparison to general anaesthetic (GA) biopsy. Integration of LA biopsy into outpatient services may offer a solution to extended diagnostic waiting times, with the potential to lead to earlier and more effective treatment.

Despite the exciting potential of LA biopsy, its routine use in the UK is limited. Although there have been anecdotal reports, real-world clinical utilisation of LA biopsy has not previously been quantified in the UK. This knowledge gap is addressed by Article 3, a UK-wide survey regarding utilisation of LA biopsy in current clinical practice. Few clinicians employ LA biopsy, with less than half (48%) reporting use of endoscopic and oral LA biopsy. Reasons for not using LA biopsy included concerns about clinic over-running, complications, missing a synchronous primary cancer (SPC) and poor patient tolerance. Regardless of the potential benefits of LA biopsy, it seems that at the individual clinician-level there are several barriers preventing its adoption into routine practice in the UK.

Given that many of the concerns raised in Article 3 lack a strong basis in the literature, Articles 4-6 seek to strengthen the evidence-base for potential benefits of LA biopsy and address the reservations. Article 4 is the first systematic literature review to investigate complications associated with HNC LA biopsy. Rates of minor and serious complications requiring intervention were both rare (<0.01%), comparable to GA biopsy rates. Article 5 addresses a gap in the literature by providing insight to patients' perspective and satisfaction after experiencing LA biopsy. Patients on LA and GA pathways were asked to complete questionnaires about their experience. A questionnaire specific to LA biopsy in HNC was not previously described, so the authors adapted from a validated gastrointestinal questionnaire to address this clinical question. There was no significant difference in patient-reported pain or discomfort scores and overall satisfaction was high. Article 6 investigated the rates of SPC in

a contemporary HNC population and the methods of SPC diagnosis. The rate of SPC was lower than previous reports (2.3%). With the rise of human papilloma virus (HPV)-related HNC, the incidence of SPC has likely decreased due to the reduced effect of 'field cancerisation' seen in smoking-related cancers[12]. The authors developed a new concept of 'comprehensive outpatient assessment', comprising of clinical examination with flexible nasoendoscopy (FNE) and cross-sectional imaging. It was hypothesised and proven that 'comprehensive outpatient assessment' is effective in identifying SPC, without the requirement of GA panendoscopy. These results provide evidence-based reassurance to clinicians that a GA can be avoided, if not otherwise indicated. Clinicians must combine an understanding of the shifting aetiology of HNC and the efficacy of contemporary high-resolution endoscopic and imaging technology, to rationalise investigations for HNC.

Article 7 is a collaborative research study that gathered real-world data on the clinical factors influencing HNC pathway times, at a national, multi-centre level. Routinely-collected waiting times data is published annually, but this study employed novel methodology to gain granular clinical data. There was poorer target compliance (34.6%) with targets than expected from national reports. Analysis of investigation pathways demonstrated that time to imaging, in particular Positron Emission Tomography-Computed Tomography (PET-CT), had prolonged delays (median 49 days). Clinical factors that improved compliance with pathway targets included referral through urgent cancer pathway, early tumour stage, avoidance of a GA biopsy and surgical treatment- highlighting areas specific to HNC that may guide future improvements to the service. Compliance with HNC targets did not have any significant impact on 2-year survival outcomes, demonstrating that assessment of service performance through generic targets may not reflect a true clinical benefit. Scrutiny of cancer-specific data

may help determine factors that can have a material, positive impact on patient morbidity and mortality.

This thesis explores deficiencies in the diagnostic pathway for HNC and challenges the traditional practice of investigating patients universally with panendoscopy. It provides novel evidence of the benefits of LA biopsy on cancer waiting times and demonstrates patient satisfaction and safety. LA biopsy has been incorporated in recent HNC guidelines[11] and in appropriate patients, should be offered as a first-line method of biopsy. Investment in outpatient services will be necessary to accommodate for increasing HNC referrals, and should include provision of equipment and staff for LA biopsy. Clinical data has demonstrated that compliance with pathway targets may not reflect clinical benefit, and a greater understanding of cancer-specific factors is needed to improve the service in a meaningful way to improve patient outcomes.

Introduction

Head and neck cancer

Head and neck cancer (HNC) encompasses cancer of the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, nasal cavity and sinuses, and salivary glands[13]. The most common cancer histology in the head and neck is squamous cell carcinoma (SCC) of the mucosal epithelium[14]. HNC is the 7th most common cancer in the United Kingdom (UK), with an incidence of up to 17.0 per 100,000[11,15,16]. In the last 30 years, HNC incidence in the UK has increased by over a third, with a 45% increase in females. Independent risk factors for HNC include smoking tobacco, drinking alcohol, Human Papilloma Virus (HPV) variants 16 and 18, deprivation and the use of illicit drugs[17]. Recent global trends have demonstrated a steep rise in the incidence of HPV-related malignancy, particularly in the oral cavity and oropharyngeal subsites[13]. This has contributed to a 34% increase in incidence of HNC in the UK, despite a reduction in prevalence of tobacco smoking[18]. The majority of patients with HNC present with advanced-stage disease[15], with 60-85% of patients having stage III or IV cancer at presentation[19,20]. Advanced stage at presentation has a significant negative impact on survival outcomes, with a 5-year overall survival of 34.8-39%[21,22]. Since the COVID-19 pandemic, there has been an increase in the rate of patients presenting with advanced disease and in the time taken to diagnose and treat HNC[23]. In the next 5 years, Cancer Research UK estimates that suspected cancer referrals will increase by 21% and 300,000 patients will experience delayed treatment for cancer[8,9].

Contextual framework

The Scottish Government recommends that treatment for cancer should be initiated within 62 days of referral to an Ear, Nose and Throat (ENT) specialist in 95% of cases[24]. From January to March 2025, only one of the fourteen National Health Service (NHS) Scotland health boards met this standard[25]. Delays to diagnosis and treatment negatively impact survival outcomes in HNC[26]. Diagnostic delays can occur at any point in the diagnostic pathway, and may be secondary to delayed referral from primary care, protracted waiting times for appointments and limited capacity for investigations. Traditionally, all patients with suspected HNC would receive a general anaesthetic (GA) panendoscopy. This would be used to assess the tumour, obtain histopathological diagnosis and evaluate for synchronous primary cancer (SPC). The body of work presented aims to contest the universal use of GA procedures in HNC patients, and explore the exciting potential of local anaesthetic (LA) biopsy and 'comprehensive outpatient assessment' as an alternative. The future of the HNC diagnostic pathway relies on modernisation of clinical practice and uptake of innovative processes, to accommodate the rising number of referrals and achieve superior clinical outcomes for patients.

Article 1:

An open structure questionnaire on reasons for delay in presentation: a study of patients attending clinic with red flag symptoms of head and neck cancer

The HNC pathway aims to fast-track patients with red flag symptoms and accelerate their cancer treatment. Red flag symptoms for HNC include neck lump, oral ulceration, oral leukoplakia or erythroplakia, hoarseness, throat pain or odynophagia. Red flag symptoms must be present and persistent for over 3 weeks[27]. Patients presenting with these symptoms are referred through an urgent suspicion of cancer pathway to undergo assessment by an ENT specialist. Biopsies and imaging are arranged to provide diagnosis and disease staging. In the UK, the gold standard is referral for multidisciplinary team (MDT) discussion[28], which is associated with improved survival in HNC[29]. Following this, the patient is counselled on the MDT outcome, and a patient-led treatment plan is created and initiated. UK guidelines recommend that 95% of patients complete this pathway within 62 days[25]. Article 1 introduces this thesis by investigating the initiation stage of the diagnostic pathway, when a patient develops symptoms and presents to primary care. It is well-established that the majority of patients with HNC present with late stage disease[15], though patient-related factors contributing to delayed presentation have yet to be explored. This article addresses a gap in current evidence and offers a unique insight into factors causing delayed presentation from the patient perspective through a questionnaire (Appendix 1).

Delays in patient presentation in the HNC pathway

Article 1 demonstrated that patients who were later found to have HNC waited months before presenting, whilst patients subsequently diagnosed with benign or no disease only waited a

number of weeks. The most common reason HNC patients reported for delayed presentation to their General Practitioner (GP), was simply not being worried about their symptoms. This is a noteworthy finding, which suggested a discordance in the symptoms that patients and healthcare professionals would regard as red flag signs for cancer. Discrepancies in knowledge between patient and healthcare provider contribute to extended delays in diagnosis, which may result in significant harms including progression and upstaging of cancer. It seems likely that addressing this divide would increase patient engagement with healthcare, encourage earlier presentation, and have a beneficial impact on treatment options and survival outcomes[30].

Socioeconomic characteristics of HNC patients may contribute to the delays in recognition of red flag symptoms which were observed in this study. Socioeconomic status encompasses the education, income and occupation of an individual, and is closely linked to health outcomes[31]. Most HNC patients are at risk of poor health literacy, which is associated with male gender, lower socioeconomic status and reduced access to education[32,33]. The link between HNC and low socioeconomic status, has a cause-and-effect relationship. Excess alcohol intake and tobacco smoking are established risk factors for HNC, but also associated with socioeconomic deprivation and low educational attainment[34]. Low socioeconomic populations concurrently have increased risk for HNC, reduced health literacy and poor engagement with healthcare, which compound to cause delays in presentation. HNC patients in lower socioeconomic groups have reduced overall survival[35].

Diagnostic delays have a knock-on effect on the initiation of treatment. Established associations between time-to-treatment and survival outcomes in HNC underpin the urgent need to shorten cancer pathway times. Rygalski et al[36] investigated the impact of timing of

surgical intervention in a retrospective cohort study of national cancer registry data including 37730 patients. They demonstrated a significant association between increased all-cause mortality and patients receiving surgical treatment greater than 67 days after diagnosis (Hazard Ratio 1.189). Liao et al[37] retrospectively reviewed outcomes in HNC patients and found increased rates of recurrence in patients with treatment initiated after 60 days.

Cancer referral rates

There is a disproportionately large number of referrals for suspected HNC, making up 9% of all suspected cancer referrals[11]. The number of referrals for suspected HNC is rising and the proportion of all Urgent Suspicion of Cancer (USoC) referrals that result in a HNC

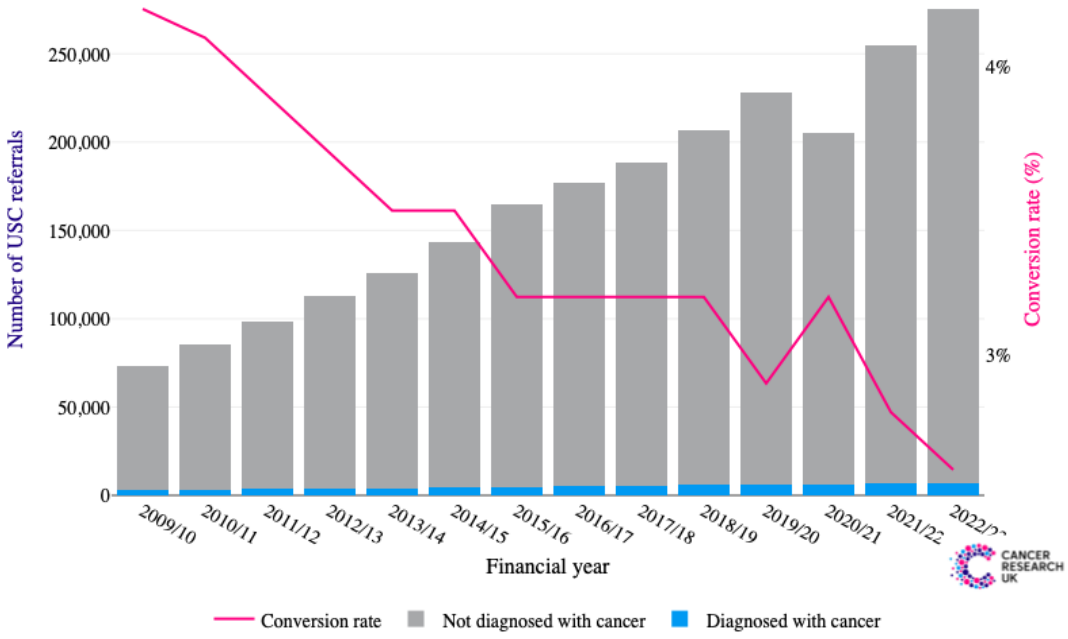


Figure 1. Graph demonstrating the number of USoC referrals with a cancer and non-cancer diagnosis, and the head and neck cancer conversion rate from 2009 to 2023 [8]

diagnosis, known as the conversion rate, is decreasing. Article 1 investigated cancer referral rates, HNC conversion rates and compliance with Scottish Referral Guidelines[27]. The conversion rate was 3% in this cohort and only 50% of referrals adhered to the Scottish

Referral Guidelines[27]. Poor referral compliance and increasing number of referrals may be contributing to the reduction in conversion rate[38] (Figure 1[8]). In the primary care setting, examination of the head and neck is limited to oral cavity examination and palpation of the neck. Complete assessment of the mucosal surfaces of the upper aerodigestive tract cannot be achieved without the use of specialist flexible nasoendoscopy (FNE). Challenges in diagnosis in the primary care setting may contribute to non-compliant urgent suspected cancer referrals[11].

Poor compliance with referral guidance may be improved by enhanced referral vetting using risk calculators. In oesophageal cancer, the Edinburgh Dysphagia Score (EDS) was used to risk stratify patients and down grade USoC referrals in low risk patients. This allowed for safe triaging of referrals, without downgrading any patients who had cancer[39]. Developing nurse-led triaging systems can help streamline the large volume of USoC referrals by identifying appropriate patients with red flag head and neck symptoms[40]. The EVEREST study has been approved as a clinical research project to assess the impact of a standardised diagnostic HNC pathway across the UK[41]. The referral system will integrate a validated Head and Neck Cancer Risk Calculator[42], to aid risk stratification and fast-track the high risk referrals.

Public health, health promotion and media campaigns

In areas of socioeconomic deprivation, patients are at high risk for developing HNC and have reduced access to healthcare and education. Health promotion campaigns in cancer awareness strive to educate the general public about red flag symptoms and promote earlier presentation. Media campaigns may be run on a national scale to reach large audiences,

through printed and digital media[43], and have the potential to enact change through direct and indirect means. Direct change is a result of influencing an individual's attitude, for example, through education about symptoms of cancer. Indirect change occurs when systemic societal changes lead to a shift in public opinion that has a secondary influence on an individual's actions[43]. Successful media campaigns have demonstrated positive changes in reducing tobacco and alcohol consumption[43,44]. However, in cancer awareness campaigning specific to HNC, there is limited evidence supporting long term behavioural change or impact on earlier disease presentation[45]. Sethi et al[46] carried out a 3 month public awareness campaign for laryngeal cancer, called the 'Croaky Voice' campaign. The campaign lead to limited improvement in public awareness, which returned to baseline following completion of the project.

There are several factors which make high risk populations for HNC challenging to target with health promotion. In lower socioeconomic groups, there can be limited access to internet, poor literacy and reduced healthcare engagement, all of which can limit the reach of media campaigns[47,48]. MacCarthy et al[49] carried out a questionnaire-based study during Mouth Cancer Awareness Day, in which patients were offered a free oral examination. The majority of patients were non-smokers and reported visiting a dentist at least once a year, which was higher than the national average. This suggested the Mouth Cancer Awareness Day mainly targeted patients who were low risk for cancer and likely to engage with dental check-ups regularly. Increased public awareness in this group may result in a swell in the number of referrals to the USoC pathway, without increasing the number of cancers being diagnosed. This phenomenon risks overwhelming tertiary care outpatient capacity, without improving outcomes amongst high-risk groups[50,51].

Health promotion can be carried out at an individual level during healthcare encounters. Bjorklund et al[52] carried out an interview-based study to explore factors that motivate HNC patients in their health decision making. Their results demonstrated that empowering individuals to make healthy choices requires buy-in from both the individual and healthcare professional[52]. Any healthcare interaction may be used to carry out health promotion. Regardless of benign or malignant diagnosis, the USoC appointment can be used to have a meaningful discussion with patients about making healthier lifestyle choices, including smoking cessation, reducing alcohol consumption, and improving red flag symptom awareness.

Screening programmes may be offered to patients with the aim of identifying early-stage cancer before a patient has presented with clinical symptoms. Globally, HNC screening initiatives have been run, predominantly using a simple oral cavity assessment as the screening tool. Gogarty et al[53] reviewed the HNC screening programmes reported in the literature. These demonstrated low rates of cancer detection, poor uptake in high risk populations, and a lack of cost-effectiveness[53]. In the UK, there is no screening programme for HNC. With the rise of HPV-positive oropharyngeal malignancy, HPV may be a target for future screening programmes. In Queensland, Australia, Tang et al[54] used polymerase chain reaction (PCR) testing of oral saliva for HPV-16 DNA in a cancer-free cohort. Follow-up of patients with persistently raised levels of HPV-16 resulted in early disease detection in two patients with malignant or dysplastic lesions. Serological testing for cell-free DNA-HPV has been used as part of surveillance for patients following treatment for oropharyngeal HPV-positive malignancy[55]. Recurrence was associated with persistently elevated high levels of cell-free DNA-HPV in the so-called ‘liquid biopsy’. This serological HPV detection tool has the potential to create a future screening programme for HNC[56,57].

Nevertheless, real-world application to screening would need to consider cost-effectiveness and limitations in HNC populations, as poor literacy and restricted access to travel may still reduce engagement.

Primary disease prevention and risk modification: Rose's theory

Primary disease prevention aims to reduce or mitigate risk factors before a patient develops the disease. Disease prevention aims to reduce the overall incidence of a disease, reduce the number referrals and improve capacity within the service. Primary disease prevention can be carried out by targeting individuals in 'high-risk' categories or through a population-based approach. Geoffrey Rose described the theory of population-based behavioural changes to target modifiable risk factors[58]. He hypothesised small changes in a large population may have a greater impact than large changes in a small population[59,60]. He suggested treating

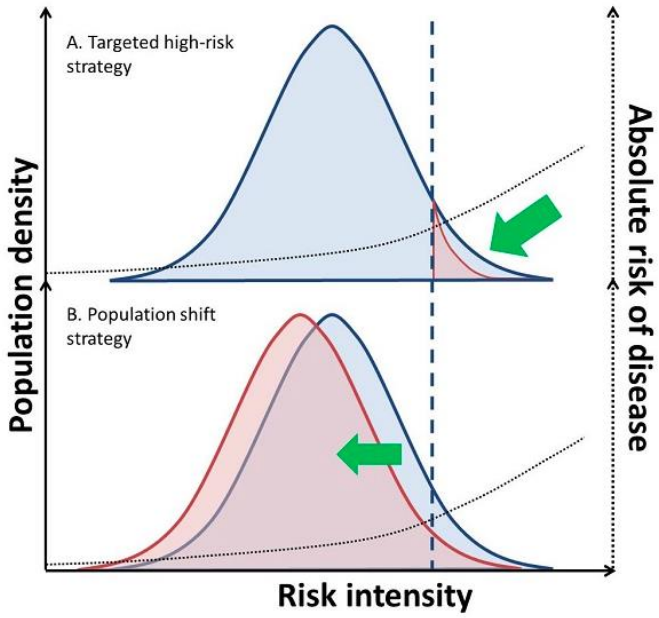


Figure 2. Rose's theory of population-based disease prevention, demonstrating risk reduction in targeted and population based strategies [61]

the population as an individual patient would result in a shift in the risk distribution curve, and thus have a greater impact on disease prevention overall (Figure 2) [61].

Primary disease prevention and risk modification : smoking

The UK has employed population-based and targeted approaches to reduce tobacco smoking and tackle high rates of smoking-related disease and mortality. In England, 1 in 7 adults smoke tobacco, and it is estimated that over half of these patients will die from smoking-related disease[62]. In 2006, Scotland became the first country in the UK to ban smoking in public spaces, and was followed in 2007 by England, Wales and Northern Ireland. Levy et al[63] assessed smoking rates between 1998 and 2009, a time during which several smoking policies were implemented to regulate smoking in the UK. During this period, rates of smoking reduced by 23% and it was estimated this would result in the prevention of 210,000 deaths by 2040. This demonstrates the impact population-based risk modification through legislation may have in preventing smoking-related disease. Between 2012 and 2015, the UK phased in a display ban on tobacco products, making it illegal for tobacco products to be displayed or promoted in the commercial setting. It was suggested that covering tobacco displays may reduce tobacco brand awareness and smoking susceptibility, which are factors that may influence a person to start smoking. Young adult and teenage populations have greater smoking susceptibility[64,65], and therefore a display ban may have a greater impact on this demographic. Ford et al[64] observed the impact of the tobacco product display ban in adolescents aged 11-16. To measure smoking susceptibility, respondents were surveyed about whether they were likely to smoke a cigarette in the next year or accept a cigarette if offered one by a friend. Smoking susceptibility was reduced following the display ban, compared to the pre-ban survey responses.

Despite the promising results from these disease prevention strategies, the impact on cancer incidence has varied. In lung cancer, the overall incidence has declined by 9% over the last 20 years, but risen in females (Figure 3)[8,66]. In HNC, the overall incidence has increased by 34% since 1993. HPV-related disease has increased in the last 20 years and become the leading risk factor for HNC, overtaking smoking and alcohol[67]. It is likely that any reduction in smoking-related cancer, has been masked by the steep rise in HPV-related oropharyngeal cancer.

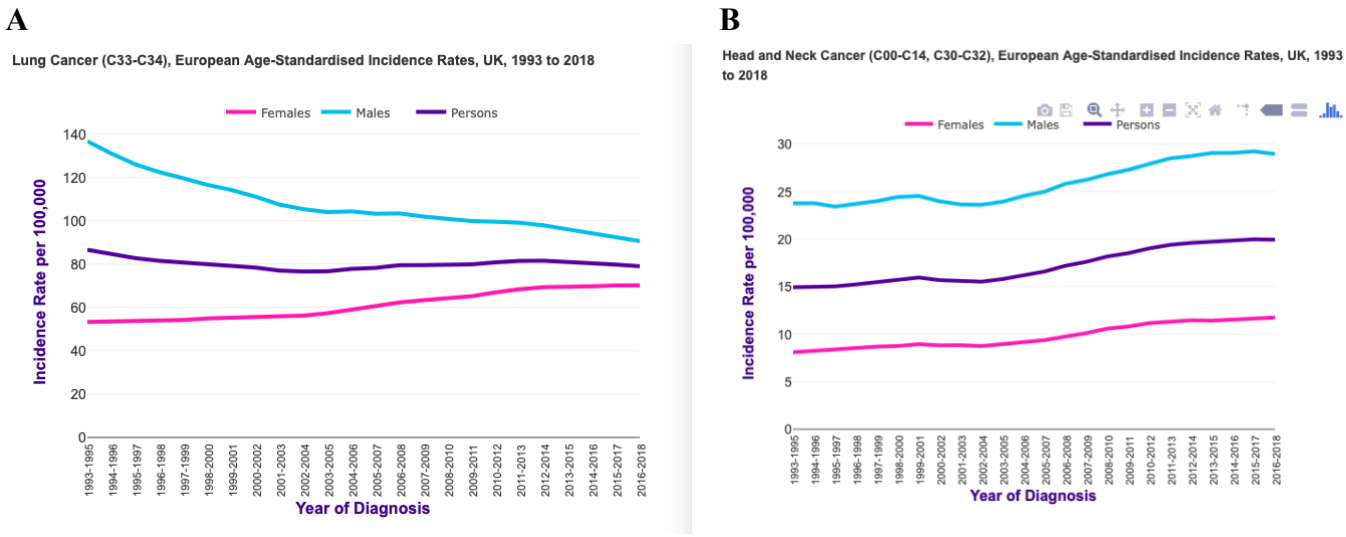


Figure 3. Incidence of lung cancer (A) and head and neck cancer (B) in the UK from 1993 to 2018 [8,66]. Figure modified from original reference.

Primary disease prevention and risk modification: human papillomavirus

Globally, there has been a rise in HNC related to HPV[68]. The virus inhibits tumour suppression, through proteins E6 and E7, causing rapid cell turn over. This unrestricted cell division leads to malignant tumour growth[69]. Vaccination programmes across the world have been introduced to target oncogenic subtypes of HPV associated with cervical and

oropharyngeal cancer. In 2008, the UK offered girls aged 12-13 a combined vaccine for HPV 16 and 18. The programme has been expanded to include all children and the current vaccine includes 9 subtypes of HPV[70,71]. Mehanna et al[70] investigated the impact of the HPV vaccine on detectable levels of HPV within the oral cavity and oropharynx. Identification of HPV was significantly lower in vaccinated females compared to those who were unvaccinated. In the UK, 10 years after the introduction of the HPV vaccination programme, a reduction in malignant and pre-malignant disease of the cervix has already been observed, with a relative reduction in cervical cancer incidence of 34%[72]. In oropharyngeal HPV-related malignancy, cancer usually develops several years or decades after initial infection with HPV. Currently the HPV vaccination programme has not resulted in a reduction in oropharyngeal incidence rates, and it is predicted this may take over 25 years to become evident[73].

Article 2:

The impact of local anaesthetic biopsy in head and neck cancer on cancer pathway waiting times

Following referral from primary care, the next step in the HNC pathway is assessment and diagnosis in a tertiary ENT service. Articles 2-5 will focus on the histopathological diagnosis of HNC, and specifically the use of LA biopsy as a technique for obtaining tissue samples. The synthesis of these articles provides a comprehensive overview of the role of LA biopsy in HNC investigation by exploring the impact on pathway times, patient and clinician experience, financial and environmental costs, and safety profile.

To improve time to diagnosis, modernising the approach to biopsy in HNC may offer a solution. In patients with suspicious lesions identified on examination, LA biopsy can be offered in clinic on the same day as initial specialist review. This can be carried out using direct transoral biopsy forceps, transoral biopsy under FNE guidance, or channelled endoscopic biopsy, where forceps are passed through the working channel of a fibreoptic endoscope. The advances in technology with channelled equipment and high quality fibreoptics, has expanded the use of LA biopsy in clinic. This can allow the user to biopsy lesions that may have previously been inaccessible in the awake patient, including the distal oropharynx, larynx and hypopharynx. Article 2 was the first article, to the authors knowledge, to assess the impact of LA on UK diagnostic pathway times in HNC. This novel research demonstrated that LA biopsy was superior to the traditional GA biopsy. The results found

Table 1. Pathway times for GA and LA biopsy patients [2]

Table 2 Pathway times USOC referral for LA- vs GA-biopsied patients

	GA	LA	*p*-value
Mean number of days			
From USOC referral to clinic	17.3	16.3	0.29
From clinic to biopsy	28.0	4.4	< 0.05
From clinic to treatment decision	44.2	19.4	< 0.05
From USOC referral to treatment decision	61.5	37.5	< 0.05

GA = general anaesthetic; LA = local anaesthetic; USOC, urgent suspicion of cancer

significantly shorter pathway times from clinic to biopsy ($p<0.05$) (Table 1)[2]. This faster diagnosis had a consequent impact on shortening the time to MDT decision, which was 37.5 days and 61.5 days in the LA and GA groups respectively ($p<0.05$). Additionally, in the LA A critique of Georffrey Rose's 'population strategy' for preventitive medicinebiopsy cohort, a larger proportion of patients were palliated after MDT (40% vs 18.3%). This likely reflects the patient selection for LA biopsy. Patients with advanced stage tumours may be unfit for a GA and the clinician may prefer to use a LA alternative. More advanced tumours may have a larger tumour bulk which might make it more amenable for identification and biopsy under LA. The authors identified that LA biopsy may offer a further benefit to palliative patients by reducing the number of invasive interventions, and allowing for swifter diagnosis and symptom management.

National cancer pathway guidance

There has been national interest in improving cancer outcomes in the UK. In the 'NHS Long Term Plan', a set of cancer targets has been released to improve outcomes throughout the UK. This aims to increase the number of patients surviving for five years or more after diagnosis of cancer, by 55,000 people and increase the proportion of cancer diagnosed at

early stage to 75%[74]. NHS England and Scotland have released updated diagnostic pathways, to help achieve these targets in HNC.

In NHS England, the HNC 28-day best practice timed pathway outlines the optimised cancer pathway for patients being referred from the community[11]. Recommendations suggest that patients have a specialist ENT clinical review by Day 10 following referral. At this appointment, biopsy can be performed if the lesion is accessible through LA technique. If the patient cannot have a LA biopsy, then it is performed under GA. Imaging modalities including ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography-CT (PET-CT) can be used for local, regional and whole-body imaging. Histopathological and imaging investigations must be completed before the patient can be discussed at the MDT. It is recommended that the patient is brought back to discuss treatment options following MDT discussion by Day 28.

In 2023, NHS Scotland updated their recommendations for USoC pathway targets (Figure 4 [75]). It is advised that the initial diagnostic tests, including US guided or LA biopsy, should be carried out in the first week after the referral has been vetted. By Day 21, cross-sectional imaging should be executed and reported, followed by MDT presentation by Day 30. In this updated recommendation, examination under GA is mentioned as a further diagnostic investigation, rather than standard for all patients.

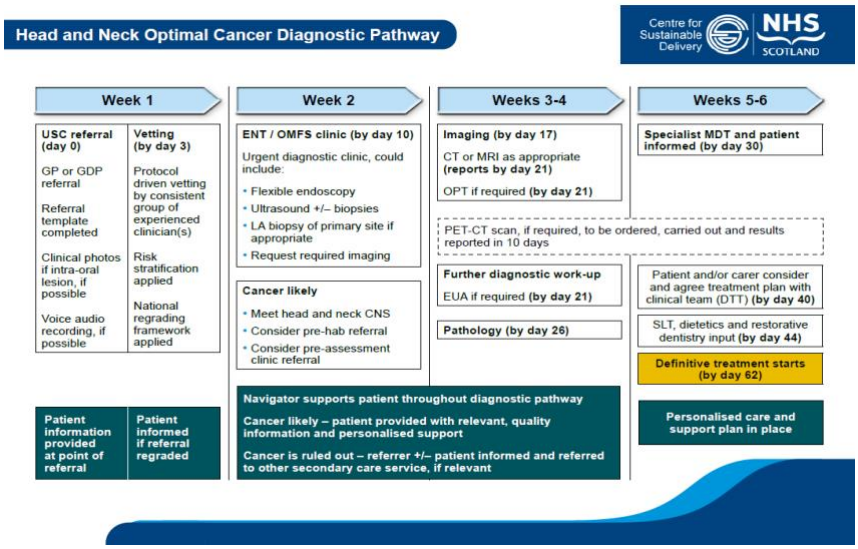


Figure 4: Head and Neck Optimal Cancer Pathway [74]

The pathway advantages of LA biopsy described in Article 2 have also been reflected in recently updated Head and Neck Cancer UK MDT Guidelines[76] released in 2024. In the latest phrasing of these recommendations, clinicians are encouraged to utilise the LA pathway in outpatient clinic in appropriate patients. It endorses the use of channelled flexible endoscopes, advising these can be safely used in an outpatient setting and may eliminate the requirement of GA biopsy in a large number of patients. The updated inclusion and emphasis on LA biopsy in national guidelines demonstrates the shift towards rationalising interventions and increasing capacity for investigations within the outpatient setting.

Statistical analysis clarifications

On composing this thesis, amendments that would improve the statistical analysis of this article have been identified. Unfortunately the original dataset is not available, but the following paragraph details the ways that this data could be developed.

Before analysing this data, the type of data must be established so that the correct analysis and display of data can be used. The data in Table 1 in this thesis (Table 2 within the article) displays the mean number of days from USoC referral to clinic, clinic to biopsy and USoC referral to treatment decision. This is a quantitative variable as it can be measured numerically. Quantitative data can be continuous or discrete- this data is continuous as the length of time can be given any value and is not limited to whole numbers.
In continuous quantitative data, the distribution must be calculated, which can be carried out by plotting the data on a stem and leaf plot. This is essential for determining the appropriate statistical analysis to perform. If the plotted data is a regular bell curve shape, this is normally distributed. If the plotted data does not fit this regular curved shape, due to steps, gaps or skewed configuration of the data, then it is non-normally distributed. If a visual display of the data distribution is to be included, a dot plot, histogram or bar chart can be used, depending on the data type.

In Article 2, it would be expected that in a pathway that has been designed with a target that is challenging but achievable, that a normally distributed bell curve would lie centred around the set target e.g. 62 days. In a cohort where the pathway times are shortened, for example in the LA biopsy cohort, this bell curve is likely to be skewed to the left, and may not be normally distributed[77]. To better this table, standard deviations (SDs) should be added for each mean value, to inform the reader of the scatter of data. Alternatively, the median could be displayed in this table as a way of demonstrating the data, especially in non-normally distributed data where the SD may be less informative due to skew of data. In this case, the interquartile range (IQR) could be provided for each median value, as an indicator of variation in the dataset[77].

Parametric tests are used in data that is normally distributed, whereas non-parametric tests are used in data that is non-normally distributed. If the presented data in Article 2 was normally distributed, then an unpaired t test would be used to assess if the difference between the means of the two groups was statistically significant. If the data was non-normally distributed, then a Mann-Whitney U test should be used as the non-parametric method of assessing significant difference between the ranked data points in each group[78].

Article 3:

National survey sampling exercise on current practice in channelled local anaesthetic biopsy in suspected head and neck cancer

Despite robust evidence that LA biopsy improves cancer pathway times and the reflection of these benefits in national guidelines, utilisation of LA biopsy has been limited in clinical practice[2,75,76]. Article 3 presents the results of a national survey (Appendix 2), that was carried out to understand the current investigative practice of ENT clinicians in the UK. The survey provided clinician-level data about the use of LA biopsy in current UK practice, that is lacking in high-level nationally collected audit data. Interestingly, only 48% of respondents reported using oral and endoscopic LA biopsy in clinic. Participants were asked about what they perceived as disadvantages of LA biopsy. In response, 29% of respondents thought carrying out a LA biopsy may make clinic run late and 24% were worried about complications such as bleeding. Other responses included 19% who were concerned about missing a synchronous primary malignancy, 14% thought it would be poorly tolerated by patients and 14% did not have an assistant to help perform the biopsy. When asked about barriers to using LA biopsy, 38% reported lack of access to channelled endoscopic equipment. When asked about changing practice, 43% of respondents who were not currently practicing LA biopsy with channelled endoscopy, stated that they would be interested in using this technique. This survey provided a unique insight into clinician concerns about LA biopsy and prompted the development of further studies in this body of research exploring the limited uptake of LA biopsy in the UK.

Clinic capacity for LA biopsy

The most common concern reported in Article 3, was the perceived risk of clinic running late. This concern is understandable, considering the mounting pressures on outpatient services and limited resources. A steep increase in the rate of USoC referrals for HNC has been seen in the last decade[79]. During the COVID-19 pandemic, a reduction in referrals was observed[80,81], which only led to a rebounding increase in referrals in the post-COVID era[82]. With the growing volume of referrals, ENT specialists have limited time and space in clinic to review and identify patients with HNC. Concern that clinic will run late, when many are already overbooked and time pressured, justifiably dissuades clinicians from carrying out an additional procedure in the outpatient clinic.

Dedicated diagnostic clinics may offer a solution by providing resource and staffing to enable LA biopsy. In 2004, the National Institute for Health and Care Excellence **(**NICE**)** published guidance on 'Improving Outcomes in Head and Neck Cancers'[83]. This described the features of an optimal rapid access neck lump clinic, which would include the provision of on-site head and neck pathologists and radiologists to provide same day diagnosis, based on the breast lump clinic model. It was estimated that the introduction of a weekly 'one-stop' clinic would cost roughly £2.2 million per year. Throughout the UK, hospitals have established neck lump clinics in response to this guidance. Al Hamarneh et al[84] published their experience of setting up a clinic based on the NICE guidelines. They reported that the majority of patients had benign or no evidence of disease, but amongst malignant neck lumps, they achieved a 74% rate of same-day diagnosis. One criticism of the NICE guidelines, was their restrictive nature in outlining such a specific clinic model, which may be dependent on local staffing and resources and not feasible to deliver universally. A systematic review reported minimal evidence in support of the NICE-recommended model and commented that alternative diagnostic clinic models may deliver similar results[85].

Whether it is integrated into the head and neck clinic or a separate 'one-stop' clinic, dedicated biopsy slots with longer time allocation can allow clinicians to perform LA biopsy without concerns of clinic running late. Resource allocation to restructure the clinic systems is essential to allow clinicians to incorporate LA biopsy into their practice without the risk of overwhelming services. Appropriate provision of nursing staff and equipment, including channelled endoscopes, is required to carry out LA biopsy. In Article 3, over a third of clinicians reported lack of access to this equipment and 14% reported they would not be able to carry out biopsies with channelled endoscopes because there was no assistant available in clinic. Some clinicians aspired to use LA biopsy, but were unable to incorporate it into their practice, due to the constraints of their current clinic set-up. Although initial investment in diagnostic clinics may be costly, there are financial savings to be made in the long term. Naidu et al[86] reported that the cost of a LA biopsy compared to a GA biopsy was $2053.91 versus $9024.47 per procedure. The cost comparison of between LA and GA biopsy is described further in Article 4.

Despite the potential savings that outpatient biopsy may provide, departments may be unable to deliver an outpatient biopsy service, if the initial investment into staffing and infrastructure is unavailable. For LA biopsy with channelled endoscopy, a department needs to have the funds for procurement, sterilisation, storage and maintenance of channelled endoscopes. If the department does not have capacity for channelled endoscopy, oral forceps used directly or under FNE guidance can be used to carry out LA biopsy in the outpatient setting, but the accessible subsites may be more limited. Channelled endoscopic biopsy also requires an assistant, for example a member of nursing or auxiliary staff, to open and close the biopsy forceps while the clinician directs the endoscope to the area of interest. Without appropriate

assistance the use of channelled endoscopic or FNE-guided oral forceps biopsy for HNC cannot be carried out.

Nurse and allied health professional led services

Through the establishment of a LA biopsy pathway, nurse or allied health professional (AHP) led clinics may further streamline the service and improve financial savings. Nurse-led nasoendoscopy clinics for low-risk patients have been successful in safely screening and triaging patients in the USoC referral pathway[87]. Metcalfe et al[88] created a nurse practitioner-led HNC screening clinic. From GP referrals, patients were risk stratified into high and low risk for HNC. A total of 660 low risk patients were assessed and examined with flexible nasoendoscopy by a nurse practitioner. There were no missed cancer diagnoses in this service, and it offered a cost-effective and faster diagnostic option to address the large volume of USoC referrals. Speech and Language Therapist (SLT)-led flexible nasoendoscopy clinics have also been successful in assessing patients referred with persistent dysphonia in the USoC pathway. Functional and benign diagnoses can be safely assessed and managed in SLT-led clinics[89]. In other cancer services, AHP-led procedural clinics are well-established. In the colorectal cancer service, nurse-led colonoscopy clinics have demonstrated excellent patient satisfaction and cost savings[90]. In colposcopy, consultants and nurse practitioners have similar levels of diagnostic accuracy in cervical biopsy[91]. With appropriate training, endoscopic LA biopsy of the head and neck could be carried out in a nurse-led outpatient setting. Dedicated outpatient biopsy teams would ensure the development of expertise and experience, which may further improve the diagnostic accuracy of the biopsies undertaken. This could ease time pressures associated with undertaking LA biopsy in busy outpatient clinics and ensure that appropriate equipment and staffing was available.

Carbon cost of GA and LA procedures

Promoting the use of LA biopsy and reducing the number of diagnostic GA procedures may limit the carbon footprint of the HNC pathway. The NHS contributes 40% of carbon emissions created in the UK public sector[92] and has pledged to become carbon neutral by 2050[93]. Surgery is associated with significant carbon costs, including the manufacturing, freight, sterilisation and disposal of surgical equipment, anaesthetic gases, and the ventilation and heating of operating rooms[93]. If LA biopsy is used to achieve histopathological diagnosis without theatre use, the overall pathway would be environmentally leaner. Such changes may generate improvements in economic and social sustainability in addition to environmental benefits, a phenomenon described as the 'triple bottom line'[94]. Avoiding a biopsy under GA protects the patient from risks associated with a GA, limits their travel time, and reduces time taken off work. Savings across the 'triple bottom line' have the potential to benefit the patient, NHS and planet. Volatile gases contribute to the carbon costs of general anaesthesia. Commonly used inhalational anaesthetic agents, such as desflurane and sevoflurane, became popularised in their use as rapid induction agents, and improved ability to control depth of anaesthesia[95]. After use, these gaseous agents take decades to break down, and while in the Earth's atmosphere, absorb energy and contribute to global warming. The environmental impact can be measured in carbon dioxide equivalent (CO2e) which compares the energy absorption of gases compared to CO2[96]. Desflurane has been identified as an agent with a particularly high global warming potential and CO2e. During a GA, one hour of minimum alveolar contraction for desflurane produces around 50 times the CO2e of sevoflurane (Figure 5[96]). Many initiatives have looked at eliminating the use of desflurane, and found a significant reduction in CO2e associated with their practice[97,98].

By utilising LA in the HNC pathway, the environmental impact of volatile agents is eliminated altogether.

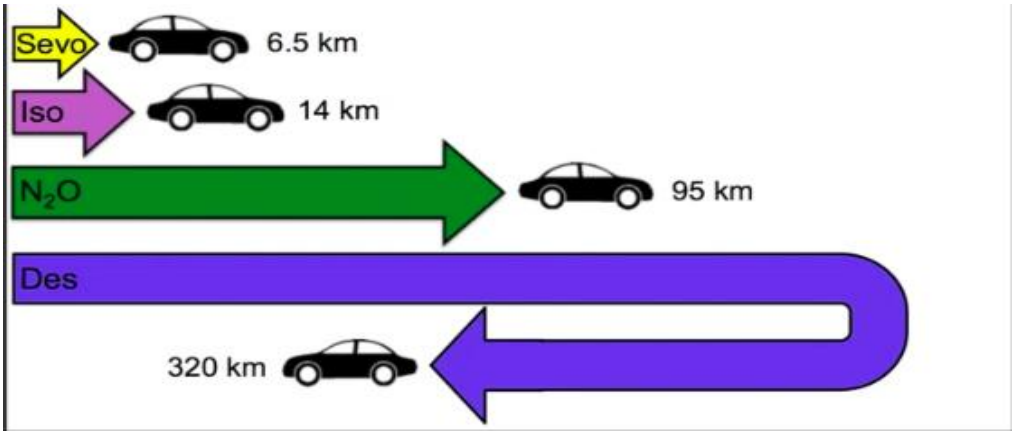


Figure 5- CO2e in kilometres driven for sevofluorane, isofluorane, nitrous oxide and desfluorane in 1 hour of general anaesthesia[93]. This figure has been modified from the original reference

Electrical energy use in surgical theatres, is a major contributor to the CO2 emissions of an operation. The majority of electrical energy consumption is derived from maintaining the heating, ventilation and air-conditioning in theatre suites[97,99]. Several studies have reported that electrical energy generation is the largest source of carbon emissions associated with surgical operations, representing up to 78% of overall carbon costs[99]. Electrical energy saving schemes, such as energy-efficient heating systems, motion sensitive lights and powering off at the end of the day, can improve sustainability in theatres. Carrying out procedures in the clinic environment, can have an even greater carbon saving by limiting the use of theatre suites, leading to reduced electricity consumption[93].

Carbon costs of LA procedures are predominantly associated with the required equipment. In LA biopsies of the larynx, a channelled endoscope can be used to visualise the larynx while taking a directed biopsy. Reusable and single-use fibreoptic scopes are available, with channelled and non-channelled options. During the COVID-19 pandemic, disposable

instruments were purchased with the intent to improve infection control. However, evidence suggests that reusable flexible nasoendoscopes can be successfully sterilised in centralised or clinic-based decontamination systems[100]. An independent cost analysis by Jegatheeswaran et al[101] found reusable fibre-optic nasoendoscopes cost 4.7% less than single-use nasoendoscopes, with a greater long term cost advantage. Concerns over the environmental impact of single-use instruments has been raised nationally by the Royal College of Surgeons of England, Glasgow, Edinburgh and Ireland. The Intercollegiate Green Theatres Checklist has been produced by these colleges, to encourage the surgical community to make environmentally friendly changes to its practice[102]. This document highlights the significant carbon cost of single-use equipment and encourages using reusable options over disposable instruments. In a systematic review, Spinos et al[103] reviewed the literature around reducing carbon cost of ENT services. This review identified areas that could be targeted to improve sustainability in ENT, including reducing theatre utility and single-use equipment, in particular, the need to move away from disposable flexible nasoendoscopy.

Article 4:

A systematic review: impact of in-office biopsy on safety and waiting times in head and neck cancer

Safety of LA biopsy

Article 4 is the first systematic review to examine safety, procedure tolerance, patient satisfaction and impact on waiting times of in-office biopsy in HNC. In the Article 3 survey, 24% of respondents were concerned about complications following LA biopsy. Article 4 sought to determine whether these concerns were founded on published evidence by examining the existing literature.

When carrying out a biopsy of the upper aerodigestive tract (UADT), complications that threaten the airway, such as bleeding or oedema, may be challenging to manage in the outpatient setting. In this review, nineteen articles were identified which commented on complications. Thirteen studies reported no complications or abandoned procedures. Complications that were reported from instrumentation of the UADT included bleeding, epistaxis, oedema, vasovagal, aspiration/choking and laryngospasm. Most complications were minor and self-limiting. A total of 2272 procedures were performed across all reporting studies and only 4 complications required intervention. The most significant complication was laryngeal oedema from a biopsy of a large glottic tumour, resulting in admission and a tracheostomy the following day[104]. The safety profile of LA biopsy was felt to be acceptable when compared with panendoscopy, that carries a 1.6% rate of unplanned tracheostomy[105].

This systematic review has contributed to answering previously unresolved questions about the safety profile of LA biopsy. It is clear that many clinicians' concerns about the safety profile of LA biopsy are not borne out in the literature, and that LA biopsy appears to be a safe alternative to GA biopsy

Local anaesthesia and patient tolerance

Poor patient tolerance was perceived by many clinicians as a potential disadvantage of LA biopsy. To anaesthetise the UADT, a LA agent, often lidocaine, can be applied topically or infiltrated. Topical application throughout the oral cavity can be administered by a spray, lozenge or gargle. In one randomised, double-blind study, level of patient discomfort was compared in patients receiving topical lidocaine spray and placebo prior to upper gastrointestinal endoscopy. Patients receiving topical lidocaine reported significantly less discomfort at the start of endoscopy and improved comfort throughout the procedure[106]. LA can be sprayed directly or through a catheter inserted into a nasendoscope working channel. This is particularly useful in areas that are challenging to reach with an oral spray such as the supraglottis and glottis, and allows for targeted LA delivery. Alternatively, this area can be anaesthetised by passing a needle through the cricothyroid membrane and spraying LA into the airway. The patient coughs to aerosolise the LA and distribute it throughout the upper airway. Often a combination of these approaches is used to maximise topical anaesthesia. Infiltration of LA around the superior laryngeal nerve to achieve a nerve block can be used to anaesthetise the larynx, but is rarely favoured as it is more invasive than topical application[107].

Intolerance of biopsy can result in poorer quality tissue being obtained and results being non-diagnostic, as the patient may move or stop the procedure[108]. Four articles in the literature were identified that provide data on the tolerability of LA biopsy (Table 2[4]). Patient tolerance was related to area of biopsy, with lower tolerability seen in vocal cord biopsy. Overall, <1% of procedures were abandoned due to poor patient tolerance. These findings should reassure clinicians that with effective LA administration, biopsy of the head and neck can be carried out with good patient tolerance, though some areas are more amenable to well-tolerated LA biopsy than others.

Table 2. Patient tolerance of outpatient HNC biopsy [4]

Author & year	Patients (*n*)	Not-tolerated/abandoned procedures (*n*)
Cohen *et al.*[15] 2014	117	6
Naidu *et al.*[11] 2012	12	1
Mohammed *et al.*[29] 2019	134	14
Lippert *et al.*[18] 2015	116	2

Cost comparison of LA and GA biopsy

Re-locating procedures from theatre to the outpatient setting is associated with financial savings. In ENT, innovations in equipment and practice have led to the ability to perform many procedures in an office setting, including vocal cord injections, transnasal laser surgery, transnasal oesophagoscopy and transnasal oesophageal balloon dilatation. A systematic review compared the costs of these in-office ENT surgical procedures with their theatre-based equivalents. Results found that all procedures performed in an outpatient setting led to financial savings compared with inpatient alternatives and could be up to 95% per

procedure[109]. All types of biopsy for investigating cancer have costs associated with equipment, staffing and clinical area utilisation. In GA cases, the cost of theatre staffing, heating and ventilation can generate significant costs per procedure that may be avoided by LA biopsy. When assessing cost differences, Article 4 concluded that the available evidence shows a lower cost associated with LA biopsy when compared to GA biopsy, saving up to £4984.89 per procedure (Table 3[4]). This vital information illustrates the substantial, long-term cost savings that LA biopsy can offer. The Scottish Health Technology Group produced an advice document on outpatient biopsy in laryngeal, pharyngeal and tongue base lesions[110]. This report estimated annual savings of LA biopsy would be over £400,000 per year in the Greater Glasgow and Clyde health board, after accounting for initial investment and expenditure. This analysis also factored in the assumption that patients with a negative LA biopsy would go on to have a GA biopsy. These compelling results should drive policy change at a local and national level and encourage investment in LA biopsy infrastructure to deliver long-term cost savings.

Table 3. Summary of papers in Article 4 systematic review discussing cost analysis [4]

Author & year	Country	In-office biopsy cost	Operating room biopsy cost	Savings per procedure per patient	In-office biopsy as percentage cost of operating room biopsy (%)
Naidu *et al.*,[11] 2012	USA	$2053.91 (£1482.43)	$9024.47 (£6513.51)	$6970.56 (£4984.89)	22.80
Marcus *et al.*,[26] 2019	USA	$7000 (£5003.18)	$11 000 (£7862.14)	$4000 (£2858.96)	63.60
Fang *et al.*,[18] 2015	Taiwan	NT$1264 (£32.58)	NT$10 913 (£281.32)	NT$9649 (£248.74)	11.60
Castillo-Farias *et al.*,[16] 2015	Spain	$65.44 (£47.23)	$1253.52 (£904.74)	$1188.08 (£853.04)	5.20
Saga *et al.*,[23] 2018	Spain	Data not provided	Data not provided	€1631 (£1420.20)	Data not provided
Schutte *et al.*,[24] 2018	Netherlands	€87.95 (£76.95)	€821.58 (£718.84)	€733.63 (£633.75)	10.7
Wellenstein *et al.*,[26] 2019	Netherlands	€583.54 (£507.65)	€1414.95 (£1232.07)	€831.41 (£720.12)	41.20

Article 5:

Prospective cohort study assessing patient satisfaction and diagnostic accuracy in channelled endoscope local anaesthetic biopsy in the investigation of head and neck cancer

Patient satisfaction

To the authors' knowledge, Article 5 is the first prospective study to look at patient satisfaction in endoscopic LA biopsy for HNC. Patient satisfaction is central to the success of the implementation of a new clinical pathway[111]. In other surgical specialties, the creation of rapid diagnostic pathways has been associated with high patient satisfaction[112,113]. The majority of patients referred through the USoC pathway report high level of personal concern on referral, regardless of whether they eventually have a benign or malignant diagnosis[114]. Throughout the cancer pathway, patients have increased rates of anxiety and depression[115]. LA biopsy offers a faster diagnosis and could reduce the time a patient spends anxiously waiting for diagnostic results. However, the authors also considered that patients may prefer a GA procedure. A one-stop clinic could be overwhelming and some individuals may prefer to return at a later date for their biopsy. For these reasons, patient satisfaction with GA biopsy was assessed for comparison. This article represents innovative research within the field by providing an insight into patients' perspectives, in contrast to the existing literature that is clinician-centred.

This study used a modified version of the Gastrointestinal Endoscopy Satisfaction Questionnaire (GESQ) (Appendix 3). No validated patient satisfaction questionnaire for endoscopic biopsy in ENT exists at the time of writing. The GESQ is a widely-accepted

patient satisfaction questionnaire in patients undergoing gastrointestinal endoscopy, with high internal validity[116]. A Modified version of the GESQ was created and given to patients undergoing LA endoscopic and GA biopsy for suspected HNC. Patients in the LA group had significantly greater satisfaction scores in the information, skills and hospital domains. There was no significant difference in pain and discomfort scores (Table 4[5]). All patients on both pathways were either 'very satisfied' or 'satisfied'. Data on pathway satisfaction could be shared with patients to contribute to the process of informed consent for a biopsy.

Table 4. Modified GESQ questionnaire results for LA and GA biopsy groups [5]

			Average questionnaire scores		
GESQ questions			**GA biopsy**	**LA biopsy**	***p*-value**
Questionnaire components	Information given before endoscopy		1.69	1.43	0.042
	Pain or discomfort before or after endoscopy		1.79	1.88	0.24
	Information given after endoscopy		1.81	1.57	0.008
	Skills and hospital		1.26	1.06	0.021
			Number of patient responses, *n* (%)		
If you were to have another biopsy, would you prefer LA or GA?		GA	17 (85%)	5 (17.9%)	
		LA	2 (10%)	20 (71.4%)	
		Not sure	1 (5%)	3 (10.7%)	

In the GA and LA cohorts, 20 and 28 patients respectively were included. A limitation of this study is the heterogeneity between the two groups. All patients were being investigated for suspected cancer, but the LA group included a greater number of cancers than the GA group. It is likely this discrepancy reflects clinical practice. If a clear cancer is seen in clinic and is accessible, a clinician will commonly attempt LA biopsy. If disease cannot be identified or if the pathology appears benign, clinicians may use GA biopsy as a means of ruling out malignancy. Patients with malignant and benign disease may have different expectations of the diagnostic pathway and varying levels of stress and anxiety may impact questionnaire scores. Another important difference between the two cohorts is the higher proportion of patients with palliative intent treatment in the LA biopsy group. This is a result of clinical

decision making, where clinicians favour a less invasive biopsy technique for patients with incurable disease. This could impact the results of the survey, as patients with palliative disease may have a different tolerance or perception of the biopsy pathway. The validity of the results may be impacted by these differences in the patient cohorts and may have contributed to differences seen in the questionnaire responses.

Diagnostic accuracy

Diagnostic accuracy is important in establishing the utility of a new biopsy technique and can help clinicians interpret pathology results. In Article 5, the sensitivity and specificity for LA biopsy was 68% and 100% respectively, comparable to rates reported in a systematic literature review[117]. Across sixteen included studies in this review, the median sensitivity of LA biopsy was 73% and median specificity rates were higher at 96.7%. The false negative rate was 13.6% for LA biopsy, and the false positive rate was 1.08%. In practical terms, if a LA biopsy result was positive, there was a high chance that this represented cancer. If the LA biopsy result was negative and there was a high clinical suspicion of malignancy, a repeat biopsy either under LA or GA would be recommended due to the considerable chance of a false negative.

Several factors may contribute to the false negative rate seen in LA biopsy. For endoscopic channelled biopsies, the size of the biopsy forceps is limited by the endoscope channel. Additionally, it can be challenging to take deep biopsies for submucosal lesions in an awake patient due to movement of the target area. The depth of biopsy may limit the ability for the pathology team to identify invasive features and confirm malignant diagnosis. The subsite of the biopsy may also influence diagnostic accuracy. Cha et al[118] found that true positive

rates in the subglottis and supraglottis were 100% and 86.8% respectively. Biopsy of the glottis had a lower rate of true positives at 73%. Taking biopsies of the glottis can be challenging in patients under LA, as the vocal cords will move if the patient coughs or speaks during the procedure. If the LA is not fully effective, the patient will cough during instrumentation of the glottis and may struggle to tolerate the procedure. Glottic cancers often present earlier than supraglottic cancers, so may be smaller in volume, which can make biopsy more technically challenging and reduce diagnostic yield.

Statistical analysis clarifications

On composing this thesis, amendments that would improve the statistical analysis of this article have been identified. Unfortunately the original dataset is not available, but the following paragraph details the ways that this data could be developed.
Before analysing this data, the type of data must be established so that the correct analysis and display of data can be used.

The GESQ uses 3 and 5-point Likert scales and binary questions. Although the Likert scale and binary responses are presented as ordinal, categorical data (e.g. ‘easy’, ‘fair’, ‘difficult’), the results are given a numerical rank (e.g. ‘1’, ‘2’, ‘3’) and therefore transformed into discrete, quantitative variables. The mean questionnaire scores for each component are displayed in Table 4 in this thesis (Table 3 within the article). However, this should be displayed as the median questionnaire score, as this is discrete data. To indicate the distribution of the data, IQR should also be provided. Typically data that is not continuous will not be normally distributed, but this could be confirmed by plotting this data on a bar chart. used for discrete or categorical data. For statistical analysis, assuming the data is non-

normally distributed, a Mann Whitney U test should have been conducted, as the outcome variable was quantitative, discrete data[77].

Article 6:

Changing rates of synchronous upper aerodigestive tract malignancy in head and neck cancer- why are we still using panendoscopy?

Comprehensive outpatient assessment

The data presented in Articles 2-5 demonstrate the benefits of LA biopsy. Despite these findings, there is still a low uptake of LA biopsy in clinical practice. A common reason for not using LA biopsy, reported in 19% of respondents in Article 3, was concern about missing a SPC of the UADT. Building on the earlier work in this thesis, Article 6 explores methods of identifying SPC, to determine whether avoidance of a GA panendoscopy would truly result in missed SPC diagnoses. This information is crucial to the potential utility of LA biopsy- if all patients were to require a GA panendoscopy to assess for SPC, then the pathway benefits of a biopsy under LA would be greatly diminished.

A second cancer diagnosis can be classified as a SPC, if the cancer is separate to the initial tumour and excluded as metastatic disease[119]. The rates of UADT SPC in HNC are reported in the literature to be as high as 19%[12,119–122]. Traditionally, panendoscopy including direct laryngoscopy and oesophagoscopy, was used to assess all mucosal surfaces for UADT SPC in patients under investigation for HNC[123,124]. Slaughter et al[12] introduced the concept of 'field cancerisation', describing the impact of carcinogens throughout the common mucosal lining of the UADT. Shared risk factors of tobacco smoking and alcohol drinking are thought to predispose patients to multiple malignancies within the UADT[122]. In recent years, decreasing incidence of SPC has been recognised, likely in relation to the rise in HPV-associated oropharyngeal cancer and reducing proportion

of smoking and alcohol related cancers[125]. In the data presented in Article 6, the rate of SPC was only 2.3%, considerably lower than historical rates[122]. Most patients in this study had a primary cancer originating from the oral cavity (13, 27.7%) or oropharynx (12, 25.5%). With the strong association of HPV with cancers in these areas, SPC related to 'field cancerisation' from carcinogens in tobacco and alcohol are less common[126]. It is vital that clinicians understand the changing aetiology of HNC and consequential reduction of SPC so that clinical pathways can be adapted to current disease trends.

Outpatient FNE has become a standard tool to assess patients presenting with suspected HNC. This has enabled clinicians to assess the mucosal surfaces of the nasal cavity, nasopharynx, oropharynx, larynx, and hypopharynx in the office setting. Suspicious mucosal changes can be identified by high quality views on FNE without the need for a general anaesthetic examination[127]. Narrow band imaging (NBI) filters white light so that only two wavelengths of light can be seen. The resultant image highlights bloods vessels and can illustrate pathological neo-angiogenesis[128]. NBI can be used with compatible FNE stacks in the outpatient clinic, to aid diagnosis of early stage disease[129]. NBI has been found to significantly improve the diagnosis of HNC compared to using white light endoscopy alone, with sensitivity of the assessment improving from 51.1% to 97.7% with the addition of NBI[130].

Patients under investigation for HNC undergo cross-sectional imaging to stage primary disease and detect SPC[131]. CT imaging of the thorax provides high resolution imaging of the mediastinal lymph nodes and lung parenchyma to assess for metastasis or SPC[132]. PET-CT is offered to patients with T4 cancer of the hypopharynx or nasopharynx, or N3 nodal disease[131]. Haerle et al[133] compared identification of SPC in HNC patients

examined with panendoscopy and PET-CT. In this study of 311 patients, PET-CT had a detection rate of 6.1% for SPC, compared to 4.5% for panendoscopy. An additional 5 cancers were picked up on PET-CT, that were within the assessment area for panendoscopy, and 6 cancers or pre-cancerous lesions were picked up outside the area covered by panendoscopy.

The authors of Article 6 aimed to understand whether panendoscopy has any additional benefit in the diagnosis of SPC compared to comprehensive outpatient assessment with cross-sectional imaging and FNE. This is a crucial question, which if answered, could act as a catalyst for change to ensure that the HNC diagnostic pathway remains fit for purpose in the modern era of HPV-associated disease. A retrospective cohort study was designed to investigate the means of investigation used to identify SPC in HNC. It was hypothesised that no further SPCs would be identified by panendoscopy, amongst patients who also underwent comprehensive outpatient investigations including FNE and appropriate imaging.

Amongst the 2325 included patients presented at the MDT for HNC, the panendoscopy rate was 63.8%. This may reflect opinions expressed in our national survey (Article 3)[3], which found that clinicians are hesitant to use the LA pathway alone due to concern of missing a SPC. In selected cases, panendoscopy under GA must be performed, for example if the tumour is challenging to access, the patient has poor tolerance of LA procedures or tumour mapping is required for surgical resection. In the present study, the majority of patients had a primary malignancy in the oral cavity or oropharynx; areas typically amenable to LA biopsy with a lower SPC rate. All patients with a comprehensive outpatient assessment had their SPC picked up on clinical examination, FNE, or cross-sectional imaging. The only SPC picked up solely at panendoscopy was in the tongue base, in a patient with a contralateral tongue base primary. The primary and secondary malignancies were detected on CT imaging,

but they were not reported as two separate cancers. This patient had incomplete outpatient assessment with no FNE was carried out in clinic and therefore, no examination of the tongue base was performed. The authors concluded that all patient with a comprehensive outpatient assessment had their SPC identified without a GA, and that panendoscopy should not be considered a routine investigation to screen for SPC. Clinicians can use this unique study as robust evidence to support their decision making to avoid GA in appropriate cases. Universal use of comprehensive outpatient assessment has the potential to reform and streamline the HNC diagnostic pathway.

Article 7

Clinical Factors Influencing the Compliance With National Head and Neck Cancer Targets in the United Kingdom: Results From a National Cohort Study

Delays to HNC target waiting times have been demonstrated through national reporting[75]. These data lack clinical context which is required to fully understand the underlying reasons for poor compliance with national standards. So far, this body of work has provided a detailed assessment of individual aspects of the diagnostic pathway and focussed on the application of LA biopsy. In this article, the final component of this thesis, the authors took a step back to provide an overview of the entire HNC pathway. Article 7 adopted a novel objective in this field of research, by seeking to gain multi-centre, national data with granular detail on clinical factors contributing to HNC pathway times. This study included 50 centres throughout the UK, contributing MDT data to INTEGRATE (The UK ENT Trainee Research Network), to create a snapshot of the real-world HNC pathway. It was demonstrated that compliance with HNC targets was worse than nationally reported, with a compliance rate of 35.7% with the 62-day target. The design of this study enabled a deeper exploration of individual factors contributing to poor pathway compliance that is not apparent in national statistics. Time to imaging contributed to delays, in particular, median time to PET-CT was 49 days (Figure 6 [7]). Patients undergoing LA biopsy achieved significantly faster time to diagnosis, decision to treat and initiation of treatment. Multivariate logistic regression analysis was used the examine the impact of clinical factors on target compliance. This demonstrated significantly better compliance with the 62-day target in patients referred through the USoC pathway, patients presenting with early T1-T2 stage disease, those not requiring a GA biopsy and those treated with surgery.

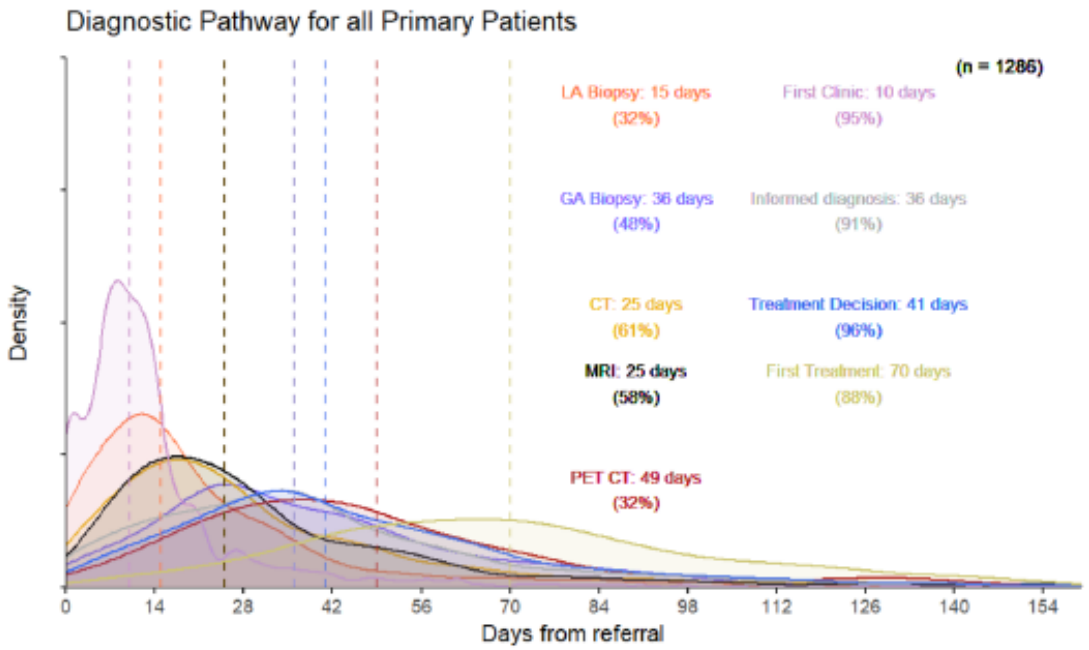


Figure 6. Median time from initial referral to investigations, diagnosis, decision and treatment. [7]

The utility of cancer waiting time targets in reflecting outcomes

Patients were stratified by 62-day target compliance, to examine the relationship with 2-year survival outcomes. Kaplan-Meier survival analysis demonstrated no significant difference in overall survival (Figure 7 [7]), disease free survival, disease specific survival or local recurrence free survival between those complying with and those missing the 62-day target. The natural history of HNC leads to progression and up-staging of cancer over time, which results in increasing morbidity of treatment and poorer survival[30]. The time taken for this progression to occur and have a significant impact on survival varies by tumour and patient factors. These results raise a fundamental question about whether the standards set out by the NHS are fit for purpose. Given that compliance with the 62-day target does not appear to be

associated with any clinical survival benefit, it is unclear whether these targets are useful in the practical and political assessment of cancer treatment in the UK.

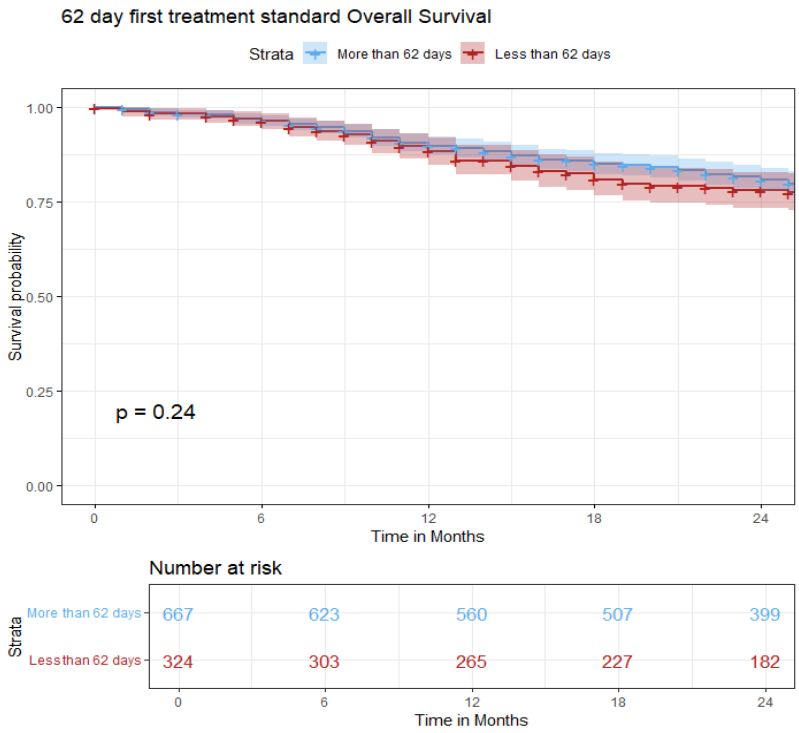


Figure 7. Overall survival in compliant and non-compliant patients with the 62 day target to initiate treatment. [7]

The Patient's Charter was created in 1991 and introduced three new rights of patients treated in the NHS, one of which was the right to access data on health services including waiting times[134]. Since then, targets have been introduced to different areas of the health service, in an attempt to reduce waiting times[135]. Disincentivisation schemes were introduced based on waiting time targets, so health boards may receive a monetary fine for each patient breaching the defined standard[136]. Additionally, these targets have been used as a benchmark system for assessing the condition of the NHS, which impacts public sector spending decisions. Given that our results suggest no significant relationship between survival and target compliance, one concern is that the current emphasis on targets risks drawing focus away from the specific needs of individual health boards[137]. Girolamo et al[138] used cancer registry data to investigate the association of cancer survival with cancer

waiting times compliance in colorectal, lung and ovarian cancer. The results demonstrated poorer survival at one year in the cohort of patients compliant with the pathway standards, compared to those who did not meet the targets. The authors suggested that this surprising result was likely due to confounding by the palliative cohort of patients who received expedited treatment but had a poor prognosis. Patients presenting with palliative HNC often require urgent admission at presentation and may require hospital treatment for airway emergencies, severe malnutrition, or end of life care. During this inpatient stay, diagnostic investigations may be carried out, creating a group of patients with fast cancer pathways but poor survival outcomes. In Article 7, 20.1% (254) of patients were treated with palliative intent. Analysis of all primary HNC patients, regardless of treatment intent, was used so the results could be compared with nationally reported data. However, the reasons for pathway compliance, including accelerated inpatient treatment, was not considered and may have been a confounding factor resulting in a poorer survival in the compliant population.

There is consensus in the literature that delay in treating cancer has a significant impact on mortality in HNC[139]. National cancer targets create a positive culture of prioritising timely investigation and treatment through urgent cancer pathways[11]. Alongside the nationally reported statistics, patient level data can give an insight into the nuanced differences in care for different cancer types. Slade et al[140] suggested that cancer waiting times should be cancer-specific and reflect the diagnostic and treatment challenges of each cancer type. Considering this in national policy and tailoring the waiting time standards for each cancer, may redirect the emphasis away from blanket targets, and focus on clinically significant aspects for each cancer pathway. Using cancer-specific data for each service would allow for allocation of resources to maximise clinical benefit. In Article 7, the median time for PET-CT from referral was 49 days. This exceeds the diagnostic pathway target time[11] that

recommends completion of all diagnostic investigations within 28 days of referral. This may reflect the lack of scan availability or the requirement for a specialist radiologist to report these scans. The rise in presentation with metastatic neck disease in unknown primary and oropharyngeal cancers, may also have resulted in greater demand for PET-CT. This is an example of how cancer-specific data is critical in truly understanding the factors underpinning pathway compliance. Integration of this information into future NHS guidance will allow for the creation of cancer-specific standards and clinically impactful resource management.

Survival in subgroups

The surprising results in Figure 7 may be influenced by the large number of patients in the overall cohort with early stage and HPV positive disease. These patients often have good survival outcomes, and if this population makes up the majority of included patients, it may mask any survival differences in other populations associated with target compliance. Further subgroup survival analysis has been performed in this study population[141] and demonstrated significantly better survival in early stage disease and p16 positive immunohistochemistry, which were also significant variables in multivariate analysis. Although it has not yet been performed, analysis of pathway compliance and survival in specific subgroups may reveal which populations are most affected by delays in pathways. It is hypothesised that subgroup analysis in p16 negative or advanced stage disease may demonstrate worse survival in non-compliant patients.

Global HNC pathways

This thesis has presented innovative ideas focused on improving the diagnostic HNC pathway in the UK's universal healthcare system. On the international stage, there are a variety of recommendations regarding diagnostic work-up and timings for HNC. The European Head and Neck Society (EHNS) have created recommendations for the assessment, diagnosis and management of HNC but do not specify pathway timings[142]. The World Health Organisation (WHO) recommends initiation of treatment within 90 days of presenting with cancer symptoms[143]. Although other countries often have their own national pathway recommendations[144], UK guidance is often cited as gold-standard in the literature[145,146]. In Spain, a fast-track head and neck cancer pathway (FTHNCP) was implemented in the Health Area of A Coruña and Cee[146]. This pathway introduced referral criteria, based on the NICE guidelines[131], that successfully reduced time from referral to specialist head and neck assessment. This demonstrated UK guidelines can be successfully implemented in comparable a European healthcare setting. UK guidelines may need adaptation to the specific healthcare resources, patient demographics and service challenges of a particular country. In Australia, investigations such as cross-sectional imaging, can be carried out before referral for ENT surgical consultation. Connell et al[145] found that patients with imaging prior to consultation had reduced time to treatment initiation. In this healthcare setting, the authors suggested that a 'cancer co-ordinator' could help optimise investigations prior to an ENT appointment and reduce delays. In low and middle income countries, the leading cause of cancer and cancer-related death is oral cavity cancer and barriers to making a diagnosis arise from limited and delayed access to healthcare[143]. In Botswana, a questionnaire was given to patients with oral cavity cancer, to understand the factors influencing delays in patient presentation and diagnosis[143]. Lack of formal education, high travel costs and lack of regular healthcare visits were among the factors that contributed to delays in patients seeking medical advice. Diagnostic delay was seen in female

patients and those with negative cancer beliefs. The authors advised improvement of cancer services in this country must focus on addressing access to health resources, patient education and cancer stigma.

This thesis has added significantly to the body of evidence favouring the use of LA biopsy in HNC diagnosis. It is hoped that these results will empower clinicians to modernise practice and optimise pathways internationally. Out-dated attitudes towards investigations for HNC are still present, even within contemporary European practice. For example, in the Netherlands it continues to be standard practice for all patients to undergo a GA staging panendoscopy [144]. The presented body of work supporting LA biopsy is most applicable to countries with similar demographic and resources to the UK, but the principles of LA biopsy can be applied globally, and may have added value in low and middle income countries, as it provides a cost-effective diagnostic solution.

Discussion

The NHS is currently overwhelmed by a lack of resource to meet growing demand on cancer services. Specifically in relation to HNC, the rise of HPV-related oropharyngeal malignancy has resulted in a marked increase in the incidence of HNC and number of urgent suspected cancer referrals. This thesis and body of published research has proposed a modern approach to HNC diagnosis, which focuses on addressing deficiencies in the current pathway with a view to improving service delivery and patient outcomes.

The benefit of LA biopsy in HNC investigation has been comprehensively demonstrated, and this has been reflected in recent HNC pathways[11]. This body of work has used a range of methodologies to gather clinically relevant data representative of current practice and give an insight into diagnostic barriers that exist in the UK. The use of a national survey yielded clinician-level data on factors preventing the widespread use of LA biopsy, which has not previously been understood. These results demonstrate that poor uptake of LA biopsy is not a local or individual problem, and instead reflects widespread concerns about safety, tolerability and practical applicability of LA biopsy, despite a lack of evidence supporting these concerns. This work sought to contest attitudes towards the complications and risks of LA biopsy by providing clinicians with robust evidence that LA biopsy could be effectively integrated into their practice. For HNC care to endure mounting service pressures, clinical practice must adapt and modernise.

With changing disease aetiology and falling incidence of SPC in HNC, the requirement for GA panendoscopy has been questioned in this thesis. It has been shown that GA procedures are still being undertaken in most cases, despite most cancers being amenable to LA

investigation. Outdated views on the necessity of panendoscopy must be disputed. This thesis has shown that the use of a 'comprehensive outpatient assessment' consisting of LA biopsy, high resolution imaging and fibre-optic FNE, can successfully achieve tissue diagnosis and screening for SPC without the need for a GA, in appropriate patients. The proposed concept would allow for shorter diagnostic times and reduced use of limited theatre resources.

The articles included in this thesis have used methodology focussed on gathering granular, patient-level data, rather than using statistics from national databases. These data have the benefit of providing specific and detailed information which cannot be matched by nationally-collected statistics. There are limitations, most obviously that patient numbers included are relatively low. Results from a single-centre study can also be subject to local discrepancies in practice that would not be representative of the whole of the UK. The final article in this thesis (Article 7) used innovative methodology to address this limitation, whilst continuing to collect high-fidelity data on individual patients. By creating a national-level, collaborative project, a greater number of sites and patients were included, to achieve a representative snapshot of UK practice. Interestingly, the results of Article 7 found no significant improvement in mortality amongst patients complying with pathway target times. This highlighted the limitations of relying on national cancer standards as a direct indicator of clinical benefit. Reflecting on this finding, future work should focus on how to quality-assess cancer services using metrics that correlate with actual improvements in morbidity and mortality for patients. The prioritisation of fast diagnosis and treatment is clinically important, but redesign of national guidelines must include cancer-specific data to see translation of targets to survival outcomes.

The future of diagnostics will be shaped by the integration of innovative technologies to streamline pathways, including artificial intelligence (AI) and machine learning (ML). ML is a type of AI in which an algorithm-based programme can learn to carry out a task through the input of task-related data. In early research, ML programmes have been used to aid HNC diagnosis in radiology and histology[147]. Extranodal extension (ENE) is a key factor in the staging for HNC, as it upgrades the regional lymph node stage and directly impacts the treatment offered to the patient[148]. Kann et al[149] created a ML model to assess CT imaged lymph nodes for ENE. The model had a sensitivity of 88% and specificity of 85%, which was higher than reported rates for clinician assessment for ENE in the literature. ML has also been applied to gathering and analysing data from histopathological whole-slide images (WSI)[147]. In a systematic review, 11 studies used ML algorithms to identify benign, dysplastic or malignant features in WSI in HNC. The diagnostic accuracy of ML algorithms was 79-100%[150]. The accuracy of ML appears similar to the accuracy of an operator using standard microscope evaluation, with the added benefit of a reduction in assessment time. Although there is currently limited evidence in which AI has been applied to HNC histology, the interest around the subject is growing. Collaboration between centres and leveraging of big datasets may contribute to training of ML algorithms in HNC histology, leading to improved accuracy. The integration of ML in future HNC pathway policy may allow for faster diagnosis, earlier initiation of treatment and improved cancer outcomes.

With the advent of AI integration in diagnostics, the research presented in this thesis lays the groundwork for the creation of an optimal HNC pathway. With the appropriate investment in outpatient resources and adoption of modern approaches to diagnostics, a one-stop outpatient clinic could provide same-day LA biopsy with AI-reported histology and cross-sectional imaging. This would revolutionise the diagnostic process for HNC and dramatically reduce

the time from initial referral to initiation of treatment. In theory, a patient could receive histopathological diagnosis and radiological staging at their first clinic appointment. To allow future innovations in practice, the first step must be the regular use of LA biopsy. If GA panendoscopy remains standard of care for all patients, the availability of theatres will remain the rate-limiting step in the diagnostic pathway and will prevent radical reductions in waiting times, regardless of the development of AI-led technology.

The role of panendoscopy

Panendoscopy or an examination under anaesthesia continues to have a vital role in the diagnostic work up and therapeutic treatment of HNC. If an airway is threatened, LA biopsy should not be attempted in the clinic setting, as trauma to the tumour can result in oedema of the tissue and deterioration of the airway. These patients should have their airway secured in an urgent, expedited basis in theatre, with appropriate anaesthetic support in case of a critical airway emergency. From a diagnostic point of view, biopsy must be performed under GA if the area is challenging to access or the patient has poor tolerance of LA procedures. Another key part of the diagnostic assessment of a cancer is considering the treatment that the patient may receive and gathering the information required for treatment pathway. Even if a biopsy can be performed as an outpatient, a GA may be required to understand the extent of the tumour and subsite involvement, to aid planning for oncological treatment, surgical resection and reconstruction. For example, in glottic tumours, it is essential to assess if there is involvement of the inferior aspect of the cord and subglottic extension, as this will determine whether the tumour is amenable to transoral laser microsurgery or if it is more appropriate for radiotherapy treatment.

Questionnaire and survey development

The questionnaire used in Article 1 and the survey used in Article 3 were created and tailored specifically for the research questions within these papers. The useability of these tools could have been enhanced by the integration of patient and public involvement and engagement (PPIE) and stakeholder input.

In PPIE, there are different levels of contribution that range from consultation, collaboration and co-development[151]. When appropriate, payment for PPIE should be considered following guidance from the National Institute for Health and Care[152]. In Article 1, an informal pilot study was carried out and this group of patients provided the authors with feedback about the questionnaire structure and wording. This process could have been more formalised and integrated into the research paper. In a questionnaire designed to understand the patient perspective, input from patients themselves into the construction of the questionnaire may have ensured the themes and questions were relevant and accessible to the patients. Involvement of professional stakeholders can also improve the performance of a questionnaire. In Article 1, the involvement of general practitioners in the development of the questionnaire may have helped provided useful feedback on causes for patient delay from a primary care perspective.

In Article 3, the survey was distributed through ENTUK, with the intention to understand the clinician perspective on the use of local anaesthetic biopsy. A limitation of this survey was the low response rate, with 58 respondents. This is a small proportion of the population of clinicians performing biopsies in HNC, and so may be liable to bias. Non-response bias describes the bias that occurs when there is a difference in the subjects who respond to the survey, compared to those who do not. Clinicians engaging with this survey may be

responding because of interest or strong opinion in the subject area, so answers may differ to those who did not respond to the survey and therefore may not be fully representative of the overall population[153]. If there had been a greater response from a wider network of clinicians, it may have helped reduce the non-response bias of the survey.

An alternative method of gaining expert opinion and consensus on a topic, would be through a Delphi study. This would involve a group of experts in the field responding to a series of surveys, known as 'Delphi rounds'. This is an anonymous process where the answers to the former survey dictate the content of the subsequent survey, and this process is repeated until a consensus is gained[154]. The repetitive nature of the Delphi methodology allows for feedback, debate and deliberation which may provide a more considered and robust output than a single on-off survey.

The development of a guidance document for LA biopsy

A clinical guidance document (Appendix 4) on the use of LA biopsy in HNC has been developed to aid clinicians in decision making. This document distils the most clinically relevant points from this thesis and summarises this information in a format designed to be easily accessible and clinically practical. To create this document, the NICE guidelines manual[155] was consulted. This manual outlines the optimal process of approaching and wording a set of guideline recommendations. A Decision Aid in the form of a flow chart was made as a way to help clinicians identify the appropriate method of biopsy for each individual patient. The document expands on these ideas and provides any available evidence from the literature. In particular, it is highlighted that even if a LA biopsy is possible, a GA procedure may be required for securing an airway or for oncological or surgical treatment planning. A section about training in LA biopsy was included, to outline the importance of the

technical and non-technical skills required to carry out LA biopsy in HNC and define a standardised set of competencies for practitioners training in this procedure.
The initial draft of this document was sent to stakeholders from the local Greater Glasgow and Clyde multidisciplinary team, including colleagues from oncology, radiology, pathology, anaesthetics, nursing and maxillofacial surgery. A stakeholder meeting was held to discuss this set of recommendations and an updated version of this document was generated incorporating the feedback from the MDT. Although this would not be a patient facing document, the authors felt it was important to consult patients about the information they felt was important for clinicians to know about regarding biopsy from a patient point of view. Patients who had previously had a LA biopsy for HNC were approached and agreed to review the document and the document was updated following this feedback.

This document has been sent to ENT UK and is currently under review for consideration of endorsement, in the hopes that this will be distributed through these channels and have a wider reach of clinicians across the UK.

Conclusion

This body of work demonstrates the growing need for faster diagnostic pathways and the benefits of utilising LA biopsy in HNC. Continuous scrutiny and reflection on current practice can help clinicians optimise pathways and redefine the 'gold standard'. This thesis has contributed to a growing body of evidence which supports the use of LA biopsy to diagnose HNC. Despite the integration of LA biopsy into the most recent national HNC pathway algorithms, this thesis has identified poor uptake of LA biopsy in real-world practice[11,75]. For these changes to materialise in clinical practice, efforts must focus on three main factors- future national guidelines, resource investment and clinician 'buy in'. Firstly, further updates of national HNC guidelines must further steer the direction of diagnostics to outpatient-led services. The presented thesis concludes that the LA biopsy pathway, in appropriate patients, is superior to GA biopsy. LA biopsy leads to faster pathway times, lower financial cost, lesser environmental impact and reduced theatre requirement, while maintaining comparable safety and efficacy profiles. Future iterations of standards must go further in emphasizing the superiority of LA biopsy and recommend it as the 'gold-standard' technique for diagnostics in HNC, particularly in the context of oral cavity and oropharyngeal malignancy. Secondly, resource management at a national and local level must aim to build a service with a greater emphasis on outpatient diagnostics by investing in staffing, infrastructure and equipment to support this pathway. Current spending in outpatient services will create the foundations to allow for future expansion and modernisation of diagnostics, including the application of AI and ML technology. Finally, at the clinician-level, ENT practitioners can use this thesis to provide a robust evidence base to guide their decision making in HNC investigation. Updated national recommendations will only have an impact if ENT clinicians support the use of LA biopsy and integrate it into their practice.

A potential focus of future research is investigation of cancer-specific clinical factors that could have a meaningful impact on patient care and outcomes. HPV-positive and HPV-negative cancers are discrete disease processes, with differences in presentation, progression and prognosis. Future national recommendations may need to consider these pathologies separately to effectively meet the needs of both groups of patients. Another area requiring investigation is diagnostics for patients requiring palliative management, given the current lack of specific recommendations in this group. For example, LA biopsy may have a greater role in this patient group, by avoiding the morbidity associated with a GA. Research to understand the pathway and perspective of the palliative population, may help drive investment in LA services. Further avenues of research may focus on improving symptom recognition in patients, as previous health campaigns and screening programmes have failed to impact rates of late presentation in HNC. Engaging high-risk HNC populations in research methodology may help to improve the effect of risk modification strategies in these groups. Finally, researching novel techniques, including serological testing for HPV and AI technology, may revolutionise the diagnostic process in HNC. This thesis has provided an essential evidence base for the use of LA biopsy to optimise diagnostic pathways, and lays the foundation for outpatient services to adapt to future technological advances that will continue to improve care for patients with HNC.

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Appendix 1.

Label

Questions for patients having been referred urgently

Are you MALE or FEMALE? _____

How old are you?_____

Who do you live with? LIVING WITH PARTNER/MARRIED LIVING ALONE

Do you work? YES NO STUDENT

What is your job? _____

Have you previously attended college or university? YES NO

Are you a smoker? YES NEVER SMOKED EX SMOKER

How much alcohol do you drink per week? LESS THAN 14 UNITS MORE THAN 14 UNITS

1. **What symptoms do you have? Please list below**

_____

_____

2. **Which of these symptoms, if any, cause you worry or concern?**

_____

3. **How long have you had your symptoms for (PLEASE CIRCLE)?**

   DAYS WEEKS MONTHS YEARS

4. **Do you feel you should have seen a doctor sooner (PLEASE CIRCLE)?**

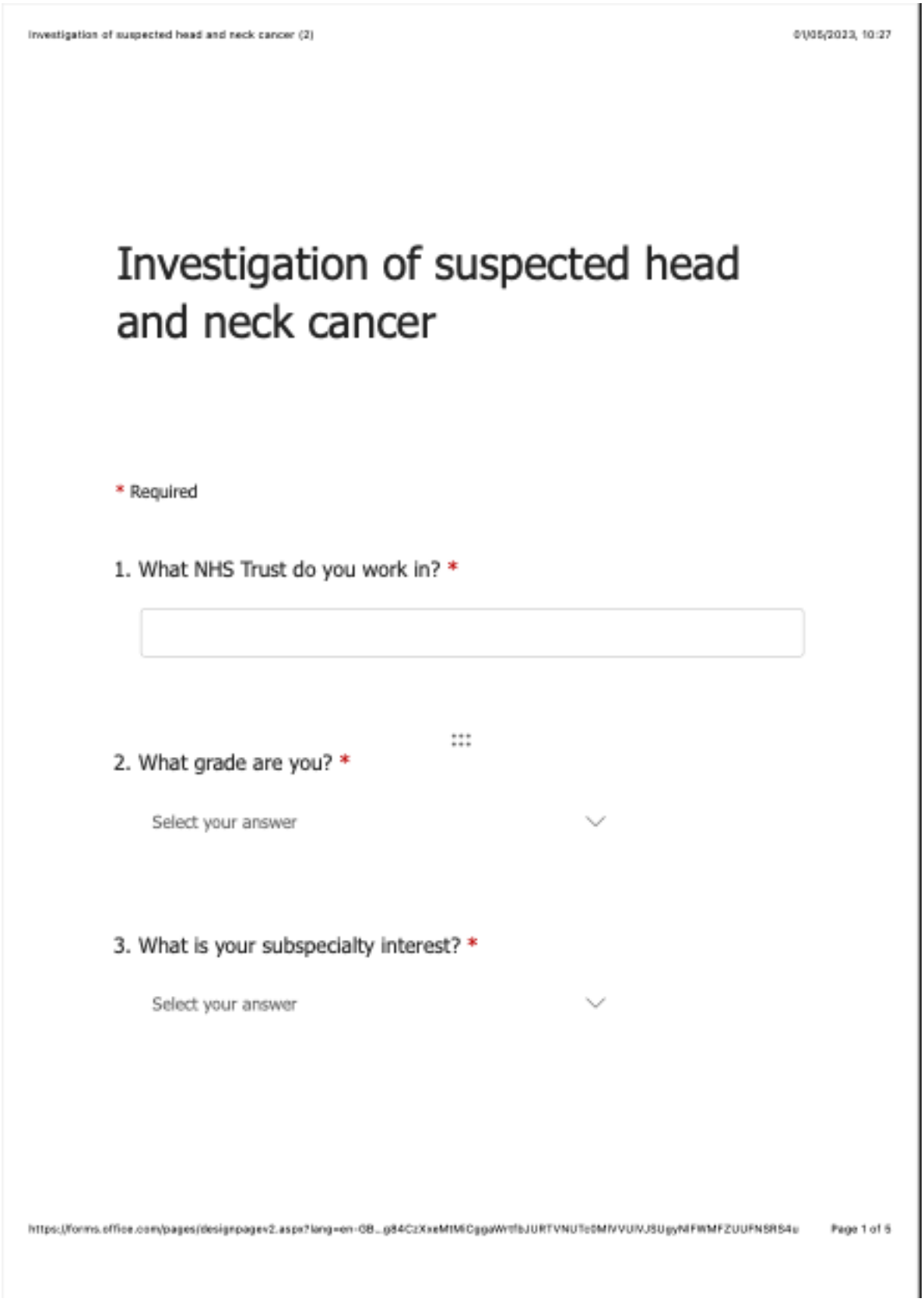
   YES NO

5. **Do you have any reasons for not seeing a doctor sooner?**

_____

Thank you, please hand questionnaire back to staff member

Appendix 2. Online Survey



Investigation of suspected head and neck cancer

* Required

1. What NHS Trust do you work in? *

2. What grade are you? *

Select your answer

3. What is your subspecialty interest? *

Select your answer

4. Do you perceive any diagnostic delay in cancer patients meeting their 31 day diagnostic target in your health board? *

- ◯ No – most patients are diagnosed within 31 days
- ◯ I don't know
- ◯ Yes – there are delays experienced by patients in my hospital

5. How do you gain histopathological samples when investigating a patient for suspected head and neck cancer? *

- ◯ GA biopsy only
- ◯ LA biopsy only
- ◯ GA and LA biopsy

6. If you use LA biopsy, what do you use? *

- ◯ LA biopsy with intra-oral forceps only
- ◯ LA biopsy with channeled endoscope with endoscopic forceps only
- ◯ Both LA biopsy with intra-oral forceps and channeled endoscope with endoscopic biopsy forceps
- ◯ Not applicable

7. What brand of endoscopic stack do you have at outpatients? *

Select your answer

8. What do you think the advantages are of taking LA biopsies – select all that apply *

- [ ] Faster cancer pathway
- [ ] Avoiding difficult intubations e.g. for large volume tongue base tumours
- [ ] Avoiding general anaesthetics e.g. for patients with poor performance scores
- [ ] A high diagnostic hit rate in the literature, comparable to GA biopsy
- [ ] It avoids panendoscopies on theatres lists that could create space for other procedures
- [ ] Other

9. What do you think the disadvantages are of taking LA biopsies? – select all that apply *

- [ ] I am worried about complications like bleeding
- [ ] I am worried that I might miss a synchronous primary cancer
- [ ] I don't have access to another doctor or nurse at clinic that could open and close the endoscopic biopsy forceps
- [ ] I worry it would make my clinic run late
- [ ] I don't think it is well tolerated by patients
- [ ] I don't see any major disadvantage
- [ ] Other

10. Do you see any barriers to taking LA biopsies? - select all that apply *

- [ ] I don't have access to channeled flexible laryngoscope in outpatients
- [ ] I would like to do this but feel I would need training
- [ ] Patients would find it uncomfortable
- [ ] I think it would be easy to do intra-oral biopsies, but would find endoscopic LA biopsies difficult to do
- [ ] No barriers with any LA biopsy
- [ ] Other

11. If you are do not currently use LA biopsy with channeled endoscope and endoscopic biopsy forceps, would you be interested in starting to use it? *

- ◯ Yes
- ◯ No
- ◯ N/A- already use it

12. Thank you so much for taking part in this survey!
Do you have any other comments about LA cancer biopsy?

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Microsoft Forms

Appendix 3. Modified Gastrointestinal Endoscopy Satisfaction Questionnaire (modified GESQ)

Patient name:

Patient CHI:

Gastrointestinal Endoscopy Satisfaction Questionnaire (Version 2)

This section has been developed with the aim of obtaining YOUR personal views based upon YOUR experience of having an endoscopy. There are no right or wrong answers to any of the questions: simply put a cross in the box that best describes how you think. Your answers will be treated in a confidential manner, and they will not affect your treatment in any way. The information provided will be used to find out how satisfied people are with their endoscopy, and to improve the endoscopy service.

1. How easy to understand was the information that was sent to you before your endoscopy?

Very easy	Easy	Fair	Difficult	Very difficult
☐	☐	☐	☐	☐

2. Was the information sent to you before your endoscopy appointment useful in answering your questions?

Very useful	Useful	Fair	Not very useful	Not at all useful
☐	☐	☐	☐	☐

3. Before you had your endoscopy, how much opportunity did you have to ask questions about the endoscopy procedure?

Plenty	A little	None
☐	☐	☐

4. How easy to understand was the explanation given to you before your endoscopy?

Very easy	Easy	Fair	Difficult	Very difficult
☐	☐	☐	☐	☐

5. Was the explanation given to you before your endoscopy useful in answering your questions?

Very useful	Useful	Fair	Not very useful	Not at all useful
☐	☐	☐	☐	☐

6. How would you rate the communication skills (eg. courtesy, respect, sensitivity, friendliness) of the person who performed your endoscopy?

Very poor	Poor	Fair	Good	Very good
☐	☐	☐	☐	☐

7. How would you rate the technical skills (eg. thoroughness, carefulness, competence) of the person who performed your endoscopy?

Very poor	Poor	Fair	Good	Very good
☐	☐	☐	☐	☐

8. How would you rate the communication skills (eg. courtesy, respect, sensitivity, friendliness) of the other staff in the endoscopy unit?

Very poor	Poor	Fair	Good	Very good
☐	☐	☐	☐	☐

9. How much discomfort did you experience during your endoscopy?

Very severe	Severe	Moderate	Mild	None
☐	☐	☐	☐	☐

10. How much pain did you experience during your endoscopy?

Very severe	Severe	Moderate	Mild	None
☐	☐	☐	☐	☐

11. How much discomfort did you experience after your endoscopy?

Very severe	Severe	Moderate	Mild	None
☐	☐	☐	☐	☐

12. How much pain did you experience after your endoscopy?

Very severe	Severe	Moderate	Mild	None
☐	☐	☐	☐	☐

13. After you had your endoscopy, how much opportunity did you have to ask questions about the findings?

Plenty	A little	None
☐	☐	☐

14. After you had your endoscopy, how much explanation of the findings did you receive?

Too much	About right	Not enough
☐	☐	☐

If you did not receive an explanation, then please go directly to question 18.

15. Did the person who performed your endoscopy give you the explanation?

Yes	No
☐	☐

16. How easy to understand was the explanation given to you after your endoscopy?

Very easy	Easy	Fair	Difficult	Very difficult
☐	☐	☐	☐	☐

17. Was the explanation given to you after your endoscopy useful in answering your questions?

Very useful	Useful	Fair	Not very useful	Not at all useful
☐	☐	☐	☐	☐

18. How would you rate the comfort of the recovery area in the endoscopy suite?

Very poor	Poor	Fair	Good	Very good
☐	☐	☐	☐	☐

19. Overall, how satisfied are you with your endoscopy?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied
☐	☐	☐	☐	☐

20. If, in the future, you have another endoscopy, how satisfied would you be to have it done by the same person?

Very satisfied	**Satisfied**	**Neither satisfied nor dissatisfied**	**Dissatisfied**	**Very dissatisfied**
☐	☐	☐	☐	☐

21. How would you rate the overall reputation of the hospital?

Very poor	**Poor**	**Fair**	**Good**	**Very good**
☐	☐	☐	☐	☐

22. Would you prefer to have your biopsy done on the same day under local anaesthetic (awake for procedure) in the clinic setting or wait a few weeks to have it done under general anaesthetic (asleep for the procedure) in the operating theatre?

Definitely under local anaesthetic	Probably under local anaesthetic	Not sure	Probably under general anaesthetic	Definitely under general anaesthetic
☐	☐	☐	☐	☐

Guidance document on local anaesthetic (LA) biopsy of the mucosal surfaces in head and neck cancer

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Introduction

Local anaesthetic (LA) biopsy is a safe and effective technique that can be used to gain tissue diagnosis of the mucosal surfaces of the aerodigestive tract when investigating for head and neck cancer (HNC). This can include the nasal cavity, oral cavity, pharynx and larynx. In appropriate patients, this can be used as a first line biopsy technique, and may result in a more efficient, cost-effective and sustainable pathway for the patient. However, careful patient selection is vital to ensure the correct biopsy method is being offered to each patient.

How to use this document

This guidance document has been designed to help clinicians make decisions about whether a biopsy should be carried out under local or general anaesthetic. The recommendations come from clinical experience and review of the current literature. It should be highlighted that currently the majority of research in this field is Level III and IV evidence. Therefore this guidance should be used as an adjunct to clinical judgement and shared decision making.

The benefits of local anaesthetic biopsy

LA biopsy can offer advantages over general anaesthetic (GA) biopsy in select patients. The benefits include avoidance of a GA, faster diagnostic pathway time and reducing financial and carbon costs.

A general anaesthetic carries risks of morbidity, including throat pain, dental damage, post-operative nausea and vomiting, anaphylaxis, thromboembolic events, cardiovascular and respiratory complications, and mortality. In patients with pre-existing medical conditions or a family history of general anaesthetic complications, the peri-operative risks of an anaesthetic may be greater[1]. Following a GA, patients require suitable carer supervision for 24 hours after the procedure, which may be at home or in the hospital. In some patients with HNC, a definitive airway such as tracheostomy, must be established in order for a general anaesthetic to be performed safely. The formation of a tracheostomy carries procedural risks but also may result in a prolonged hospital stay or in some social circumstances the patient may never be able to return to living independently.

Utilising outpatient services can improve the overall head and neck pathway. The time from clinic appointment to biopsy is significantly reduced in LA biopsy in comparison to GA biopsy (4.4 days vs 28 days), which has a consequential improvement in the overall pathway time[2]. Freeing up theatre space by moving diagnostic procedures to the clinic, may benefit patients requiring therapeutic surgical procedures by making theatre slots available.

In a literature review[3] comparing cost of LA and GA biopsy in HNC, all studies found cost savings in patients undergoing LA biopsy, with savings per patient per procedure ranging from £633.75 to £4984.89. The largest sources of carbon emission from operations is the anaesthetic gases and energy consumption, including heating, cooling, ventilation and lighting[4]. Consumables associated with anaesthesia, including glass ampoules, syringes and needles can be reduced in LA procedures. The financial cost and carbon footprint of the diagnostic process can be reduced if outpatient areas are used instead of theatres.

Safety of local anaesthetic biopsy

A literature review[3] including 22 articles with a total of 2272 procedures, investigated the safety profile of LA biopsy. Results found only 17 reported complications, with the majority being minor and self-limiting. Only 4 (0.002%) complications required intervention, including vasovagal reaction, epistaxis, laryngeal bleeding and laryngeal oedema. The case of laryngeal oedema was a biopsy of a large glottic tumour and the resultant oedema caused a deterioration in the airway and required a tracheostomy the following day[5]. The rate of unplanned tracheostomy in panendoscopy under GA are reported at 1.6%[6]. This highlights the requirement of a robust airway assessment and creation of an airway plan when a patient is undergoing a biopsy, regardless of whether this is under GA or LA. If there is any concern about the airway, procedures should be carried out in theatre with appropriate anaesthetic support.

A practitioner must consider the total dose of LA given to a patient, particularly in frail and low body weight patients who may be susceptible to toxicity. A commonly used local anaesthetic is lidocaine, which is the anaesthetic agent in co-phenylcaine and xylocaine. The maximum dose for lidocaine is 3mg/kg without adrenaline and 6mg/kg with adrenaline[7]. Local anaesthetic systemic toxicity (LAST) is a rare complication of systemic absorption of a LA agent, resulting in toxic levels that can cause adverse events and even mortality. A large

review of the US Food and Drug Administration's Adverse Events Reporting System from 1968 to 2023 has demonstrated that lidocaine is the top agent associated with mortality in LAST[8]. Different topical sprays have varying strengths of lidocaine, so care must be taken to calculate the maximum dose and how much is being delivered to the patient.

Performing channelled endoscopic biopsy

Channelled endoscopy has expanded the accessible areas for outpatient biopsy in HNC, to include the nasopharynx, distal oropharynx (tongue base) and supraglottis. When using a channelled endoscope, co-phenylcaine is applied intra-nasally for anaesthesia and vasoconstriction, to improve tolerability of the endoscope. To topicalise the target subsite, local anaesthesia, for example xylocaine 10%, can be applied through the oral cavity with an atomiser and/or down the working channel of the endoscope. Care must be taken to calculate the maximum dose of local anaesthesia (see above *Safety of local anaesthetic biopsy*). An assistant is required to open and close the jaws of the biopsy forceps, as the operator is holding the endoscope. Multiple biopsies may be required, as the samples in endoscopic biopsy are limited in size by the working channel diameter (2mm).

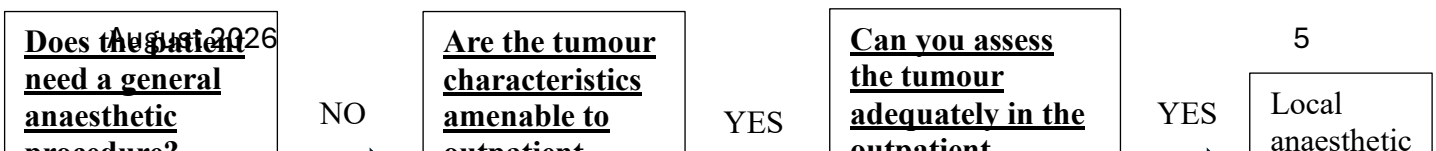
Patient perspective

Shared decision making and patient-centred care is fundamental in the cancer pathway. It is the practitioners responsibility to ensure the patient understands the biopsy options, and is informed of the risks and benefits of each technique specific to their personal clinical case.

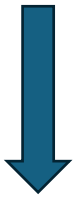
Interpreting biopsy results

A systematic review investigated the diagnostic accuracy of LA biopsy in HNC. The results found 73% sensitivity and 96.7% specificity in the 1572 cases that were included[9]. Translating these findings into clinical practice means if a biopsy result is negative, but there is high clinical suspicion of malignancy, then this result may be a false negative and a repeat biopsy would be advised. It is advised that all biopsy results are analysed in conjunction with clinical context.

Figure 1. Decision Aid: a flow chart to assess if a patient may be suitable for local anaesthetic biopsy of head and neck cancer



NO



Other considerations:

- Is the patient likely to be palliated?
- Is the patient fit for a general anaesthetic?
- Has the patient had imaging of the tumour prior to biopsy?
- Is the patient on anticoagulation or antiplatelet therapy?
- Has the patient had immunotherapy?

The topics raised in the Decision Aid (Figure 1) are discussed in further detail in the following pages.

Does the patient need a general anaesthetic procedure?

- Is the airway secure?

If the patient needs a definitive airway secured, this should be carried out in the theatre setting with appropriate airway support. Do not attempt a LA biopsy if the airway is threatened, as oedema post-biopsy can result in a critical deterioration of the airway. There is one case in the literature that describes the requirement of a tracheostomy the day after an outpatient biopsy, due to glottic oedema and airway obstruction post-biopsy[5].

- Can you fully assess the tumour?
  Assessment of the tumour extent and subsite involvement is critical when considering the treatment options that the patient may be offered, including oncological treatment and surgical resection/reconstruction (see page 12). For example, the depth and extension of vocal cord involvement in an early glottic tumour will impact the treatment decision making between transoral laser microsurgery (TLM) or radiotherapy[10]. If the tumour cannot be fully assessed in the outpatient setting, then a general anaesthetic procedure will be required to gain full understanding of the tumour.

- Is the patient unable to tolerate a LA procedure?

  Patients may be unable to tolerate a LA procedure for a number of reasons, including pain, gagging, anxiety or patient preference. There are limited reports of patient tolerability of LA biopsy in HNC in the literature. In a systematic review, four papers reported on tolerability, with only 23 cases identified of abandoned or not tolerated procedures, a rate of less than 1%[3]. If an attempted LA biopsy is not tolerated, it is recommended that a GA biopsy is carried out.

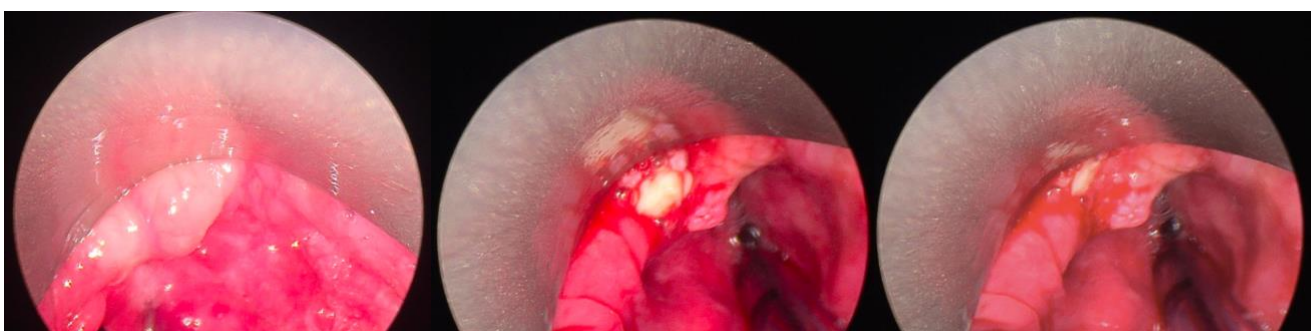
Are the tumour characteristics amenable to an outpatient biopsy?

- What is the tumour subsite?

- Tumours arising from the oral cavity, oropharynx, nasopharynx and supraglottis, are typically amenable to LA biopsy with oral forceps or channelled endoscopic biopsy[2,11].
- Tumours of the hypopharynx may be biopsied under LA if they are accessible, but will likely require a GA procedure to accurately assess their extent.
- It is recommended that glottic tumours are routinely biopsied under GA. This is because of the tumour location and the treatment decision making in these tumours. If the tumour is small volume, the biopsy procedure can be technically challenging as the vocal cords can move in the outpatient setting and may be difficult for patients to tolerate. If the tumour is large volume, there is a risk of post-procedure oedema that could result in airway deterioration. If being treated curatively, tumours of the glottis require assessment of the inferior extent of the tumour, to determine whether it is amenable to TLM and this should be carried out under GA.
- It is recommended that subglottic tumours are routinely biopsied under GA as they are challenging to access in the outpatient setting and may be poorly tolerated by the patient.
- Exceptions to these recommendations may be appropriate in selected clinical cases.

- Is the tumour necrotic?

  Necrotic tumours can be biopsied under LA, but attention must be paid to the tissue quality that is being obtained. If the tissue appears necrotic, this may not be diagnostic of malignant disease. This tissue should still be sent for pathological assessment, but additional samples are recommended to increase the likelihood of a diagnostic result. Figure 2 illustrates a necrotic tumour of the epiglottis with sloughy superficial tissue, requiring deep biopsy under general anaesthetic to gain representative tissue samples to confirm invasive malignancy.



- Is the tumour submucosal?

  Exophytic tumours are typically amenable to LA biopsy. Submucosal tumours can be biopsied under LA, but it may be more challenging to obtain results diagnostic of malignant invasion as this requires deep tissue biopsies. When sampling a submucosal tumour, multiple biopsies from the same site are essential to ensure the biopsy is representative of the tumour rather than the overlying mucosa. Figure 3 and Figure 4 demonstrate a challenging deep, right tongue base tumour that is predominantly submucosal with a small area of ulceration. Despite the accessible subsite, biopsy of this tumour required a general anaesthetic for adequate visualisation to ensure representative tissue samples were taken.

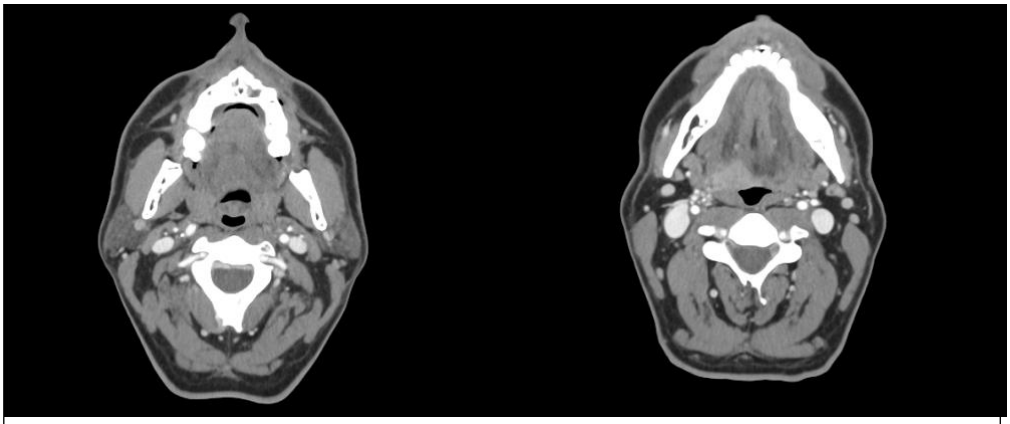


Figure 3. Axial computed tomography demonstrating (A) tongue base clear of tumour superiorly and (B) deep right tongue base tumour, challenging to visualise from the mucosal surface.

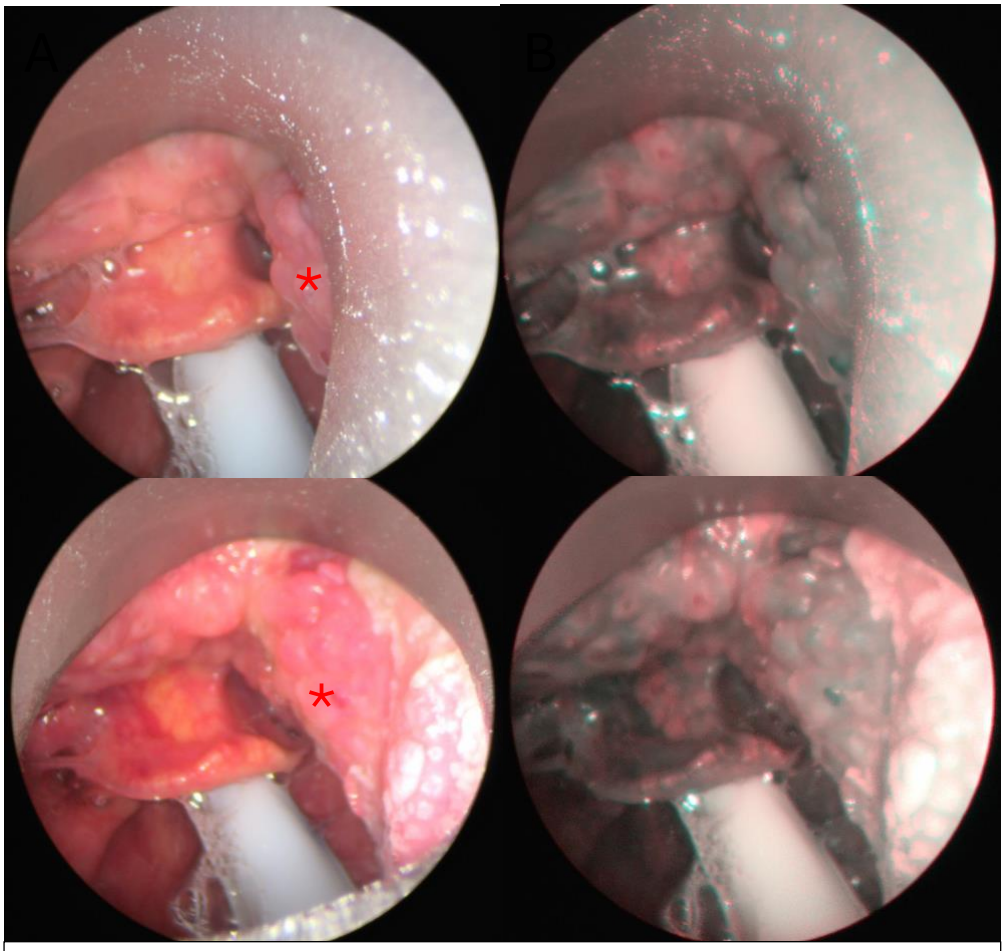


Figure 4. Submucosal tongue base tumour in white light (A) and narrow band imaging (B) views in panendoscopy under general anaesthetic. Red asterix (*) highlighting tumour site.

- Is the lesion ulcerated?

  If a lesion is ulcerated, biopsy from the centre of the ulcerated lesion may be taken. However, surface epithelium may be required for diagnosis, such as in HPV-associated sinonasal tumours. In this case, additional biopsy of intact epithelium should be taken, so a biopsy of non-ulcerated tumour should be taken if possible.

- Will the tumour require PDL-1 or molecular testing?

  If supplementary testing may be required, pathology specimens need to be large enough for testing. Molecular testing may be required in unusual tumours, such as salivary tumours, sarcoma or sinonasal undifferentiated carcinoma (SNUC). If imaging or initial clinical assessment suggests the tumour may be of an unusual aetiology, then a GA biopsy is recommended to ensure a large volume of tissue can be sent for the specimen.

What information to provide in pathology request:

Specify if P16/HPV is required

Relevant PMH including if patient has had radiotherapy or immunotherapy

If the patient is a part of a trial (additional samples may be required)

Can you assess the tumour adequately in the outpatient setting, for treatment planning?

- Do you have enough information if that patient is treated with radiotherapy?

Delineation of the primary tumour Gross Tumour Volume (GTV), is required to determine the Clinical Target Volume (CTV) for treatment with radiotherapy[12]. To adequately identify the GTV, a detailed knowledge of extent of the tumour and subsite involvement is required. It is the responsibility of the investigating clinicians to ensure that this information is gathered during the diagnostic process, and if this cannot be adequately assessed in the outpatient setting, an examination under GA may be required.

Information required by Oncology for treatment planning:
Description of staging
Anatomic organs and key structures that are involved
Explicit lateralisation
Mobility of tumour
AND (if available)
Photographs with orientation can be useful in addition to description including narrow band imaging endoscopy if available

- Do you have enough information if that patient is treated with surgery?

  Surgical resection and reconstruction requires full understanding of the extent of the tumour and subsite involvement. If this cannot be adequately assessed in the outpatient setting, an examination under GA may be required.

Other considerations:

- Is the patient likely to be palliated?

LA biopsy plays an important role in the care of palliative patients and can reduce the number of invasive procedures required for these patients[2].

- Is the patient fit for a general anaesthetic?
  When considering a GA procedure, the patients fitness for a GA should be assessed and if required a high risk anaesthetic assessment should be carried out where appropriate counselling about the risks of anaesthesia can be given and it may be determined that further investigations are required. Patients may have a higher general anaesthetic risk if they are frail or have pre-existing cardio-respiratory co-morbidities[1]. If the patient is not fit to undergo a GA, LA may offer a means for histopathological diagnosis. If a patient is unfit for a GA, it is unlikely that they will not be fit for radiotherapy and this may influence whether treatment intent is curative or palliative.

- Has the patient had imaging of the tumour prior to biopsy?
  There is limited evidence in the literature about the impact of post-biopsy changes affecting the clinical staging of tumours on cross-sectional imaging. Inflammation has been demonstrated in tumours following biopsy during histopathological assessment[13]. However, the degree of inflammation is unclear in mucosal head and neck biopsy which uses small forceps, particularly endoscopic biopsy which is limited to the 2mm diameter of the endoscope channel. The authors can find no evidence in the literature regarding upstaging of tumours following biopsy of the mucosa in the larynx, pharynx or nasal cavity. There is a retrospective cohort study investigating oral cancer, that compared the upstaging of patients with MRI before or after incisional biopsy of tongue cancers[14]. The results found no significant difference in the number patients who were up-staged, down-staged or remained the same stage, in comparing the groups with MRI before or after biopsy. The results did find a significant delay in the diagnostic pathway of patients with MRI carried out before biopsy. Given the lack of evidence, this guidance concludes that ideally imaging would be carried out before biopsy, but in the current NHS climate of pathway delays and resources limitations, histopathological diagnosis should not be delayed for imaging in most cases. An exception to this would be in the case of thin oral cavity cancers, where the depth of invasion may determine whether a patient is treated with a

neck dissection or sentinel lymph node biopsy. In these cases clinicians may choose to carry out imaging before biopsy, but this is determined on an individual case basis.

- Is the patient on anticoagulation or antiplatelet therapy?
  Anticoagulation or antiplatelet use is not a contraindication for LA biopsy and rarely need to be withheld for this procedure[3,5,15]. Clinicians should use clinical judgement to assess the patient's medications and if there are any concerns, consult the appropriate responsible physician or if unavailable, the on-call Haematology or Cardiology teams. Guidance for patients requiring dental extractions on anticoagulants or antiplatelet medications provides a detailed recommendation for managing these therapies[16].

- Has the patient had immunotherapy?
  Following the results of the KEYNOTE-689 trial, biopsy results are not recommended in assessing the response of a tumour following immunotherapy treatment. Given the low rate of major pathological response (9.4% with pembrolizumab), current practice is to proceed with resection and adjuvant therapy without biopsy and regardless of macroscopic response[17].

Training

It is recommended that training clinicians or allied health professionals in LA biopsy follows a standardised program and that all practitioners of LA biopsy maintain up to date knowledge and technical skills for this procedure in continued professional development.

The following section outlines the key areas required in a training program for LA biopsy in HNC:

Decision making

- Trainee demonstrates understanding of risks and benefits of LA biopsy in HNC
- Trainee demonstrates understanding of risks and benefits of GA biopsy in HNC
- Trainee applies knowledge to clinical situation to select appropriate patient for LA biopsy

Patient counselling

- Trainee carries out informed consent for local anaesthetic biopsy, outlining the procedure, risks/benefits and post-procedure advice
- Trainee answers patient's questions relating to biopsy technique
- Trainee demonstrates patient-centred care with shared decision making process

Technical skill

- Trainee selects appropriate patient for LA biopsy (can use Decision Aid)
- Trainee selects appropriate LA biopsy technique for tumour subsite
- Trainee applies local anaesthetic through appropriate method of delivery (e.g. oral spray/atomiser, endoscopic channel)
- Trainee uses channelled endoscopic biopsy forceps to gain representative tissue sample of tumour
- Trainee uses directly visualised or endoscopically-guided oral forceps to gain representative tissue sample of tumour
- Trainee deals with any complication or side effect, if applicable

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