SURGEON-LED MULTI-CENTRE COLLABORATIVE RESEARCH IN HEAD & NECK CANCER:

Studies in Remote Triage, Transoral Robotic Surgery for Recurrent Disease and Consensus Management in Unknown Primary Disease

A clinical thesis which responded to the challenges and opportunities presented during the COVID-19 pandemic.

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Thesis submitted for the degree of Doctor of Philosophy

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DECLARATIONS

I declare that this thesis has been composed by myself and that this work has not been submitted, in whole or in part, for any other degree or professional qualification.

Parts of this thesis have been prepared for dissemination in scientific journals as peer-reviewed publications. I played the principal, or a major role, in the conceptualisation and delivery of the included studies, the analysis and interpretation of the resulting data, as well as the preparation and drafting of the manuscripts.

The work contained herein is my own except where explicitly stated and appropriate credit has been given to the contributions of others. Due references have been provided for all supporting literatures and resources.

John Charles Hardman

ABSTRACT [300 words]

Head and neck cancer (HNC) is newly diagnosed in around 1.5 million people each year, making it the sixth most common type of cancer worldwide. Some elements of HNC care are common and can be adequately investigated in a single institution setting and in a reasonable timeframe. However, for rarer aspects, single institutions may not allow timely identification and recruitment of eligible patients, and so will struggle to be generalisable to the wider healthcare system. For these reasons, multi-centre studies are superior.

Additionally, surgeons are often best placed to identify and recruit research subjects, as well as report on their clinical course. Firstly, they have an intimate understanding of the patients under their care and so are ideally placed to understand the suitability of each subject to the research question at hand. Secondly, they understand their healthcare service and so the capacities and capabilities of the system they work within. Thirdly, they are on the front-line of healthcare delivery and so are more likely to encounter potentially eligible patients than research personnel working at a distance.

This thesis explores the use of surgeon-led multi-centre collaborative research across three areas of HNC, tracking the patient journey: from referral as a suspected cancer; to diagnosis and management of unknown primary disease; and onto treatment with salvage surgery for recurrence. Presented over three parts and seven chapters, the included studies have engaged with every head and neck unit in the UK, with input from over 380 healthcare professionals. These works have culminated in the production of national guidelines, to meaningfully impact patient care, have secured over £3 million in funding for a future randomised trial of over 100,000 patients (the largest multi-centre study of HNC patients to date) and have reset the treatment paradigm for a subset of patients with recurrent HNC.

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contributors are acknowledged at the start of each chapter, and all collaborators are named in the relevant appendices.

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List of Abbreviations

Abbreviation	Expansion
ACE-27	Adult Co-Morbidity Evaluation
AEBCD	Accelerated Experience-Based Co-Design
AI	Artificial Intelligence
AJCC	American Joint Committee on Cancer
AOT	Association of Otolaryngologists in Training
API	Application Programming Interface
ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
AZ	Arizona
BAETS	British Association of Endocrine and Thyroid Surgeons
BAHNO	British Association of Head and Neck Oncologists
BAOMS	British Association of Oral and Maxillofacial Surgeons
BAPRAS	British Association of Plastic, Reconstructive and Aesthetic Surgeons
BCT	Behaviour Change Technique
BRC	Biomedical Research Centre
CENTRAL	(Cochrane Central Register of Controlled Trials)
CEO	Chief Executive Officer
CH	Conventional Histology
CI	Confidence Intervals
CI	Chief Investigator
CIO	Chief Information Officer
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	COronaVIrus Disease 2019
CQC	Care Quality Commission
CRN	Cancer Research Network
CRT	Chemoradiotherapy
CT	Computed Tomography
CTU	Clinical Trials Unit
CWT	National Cancer Waiting Times Monitoring Data Set
DASS	Depression Anxiety and Stress Scale

Abbreviation	Expansion
DFS	Disease-Free Survival
DMC	Data Monitoring and Ethics Committee
DNA	DeoxyriboNucleic acid
DSS	Disease-Specific Survival
EBCD	Experience-Based Co-Design
EBV	Epstein-Barr Virus
ECOG	Eastern Cooperative Oncology Group
EDI	Equality, Diversity and Inclusivity
EHNS	European Head and Neck Society
ENE	Extranodal Extension
ENT	Ear Nose and Throat (surgery)
ENT UK	British Association of Otorhinolaryngology - Head and Neck Surgery
EP	Expert Presentation
EPR	Electronic Patient Record
EQ-5D-5L	Euro-QoL group five-Dimension five-Level health-related quality of life questionnaire
ES	Effect Size
ESMO	European Society for Medical Oncology
ESTRO	European SocieTy for Radiotherapy and Oncology
EVEREST	EVolution of a patiEnt-REported symptom-based risk stratification sySTem to redesign the suspected Head and Neck cancer referral pathway
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin Fixed Paraffin Embedded
FIND	Finding/Identifying primaries with Neck Disease
FNAC	Fine Needle Aspiration Cytology
FOSIT	Feeling Of Something In the Throat
FOSS	Functional Outcome Swallowing Scale
GP	General Practitioner
GRADE	Grading of Recommendations Assessment Development and Evaluation
H&N	Head and Neck
HaNC-RC-v2	Head and Neck Cancer Risk Calculator version 2
HANCUK	Head And Neck Cancer United Kingdom (patient advocacy group)
HES	Hospital Episode Statistics
HN	Head and Neck

Abbreviation	Expansion
HNC	Head and Neck Cancer
HNCTT	Head and Neck Cancer Telephone Triage
HNSCC	Head and Neck Squamous Cell Carcinoma
HNSCCUP	Head and Neck Squamous Cell Carcinoma of Unknown Primary
HPV	Human Papillomavirus
HR	Hazard Ratio
HRA	Health Research Authority
HRQOL	Health-Related Quality Of Life
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
IMRT	Intensity-Modulated Radiation Therapy
INTEGRATE	(The UK ENT Trainee Research Network)
IP	Intellectual Property
IPD	Individual Patient Data
IQR	Interquartile Range
ISRCTN	International Standard Randomised Controlled Trial Number
IT	Information Technology
KM	Kaplan Meier
LASSO	Least Absolute Shrinkage and Selection Operator
LLC	Limited Liability Company
LRFS	Local Recurrence-free Survival
LSHTM	London School of Hygiene and Tropical Medicine
LSOA	Lower Layer Super Output Area
MA	Massachusetts
MALT	Mucosa-Associated Lymphoid Tissue
MDADI	MD Anderson Dysphagia Inventory
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MINORS	Methodological Index for NOn-Randomized Studies
MOA	Mechanisms of Action
MOSES	MucOsectomy and Step sErial Sectioning
MRI	Magnetic Resonance Imaging

Abbreviation	Expansion
NA	Non Applicable
NASSS	Non-adoption, Abandonment, Scale-up, Spread, Sustainability
NBI	Narrow Band Imaging
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Analysis and Registration Service
NCRD	National Cancer Registration Dataset
NCRI	National Cancer Research Institute
ND	Neck Dissection
NHS	National Health Service
NHSE	National Health Service England
NHSX	National Health Service user eXperience unit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPT	Normalisation Process Theory
NPV	Negative Predictive Value
OGD	Oesophago-gastro-duodenoscopy
OPSCC	Oropharyngeal Squamous Cell Carcinoma
OS	Overall Survival
PBC	Public Benefit Corporation
PCTU	Pragmatic Clinical Trials Unit
PET-CT	Positron emission tomography/Computed tomography
PH	Proportional Hazards
PI	Principal Investigator
PMT	Project Management Team
PPI	Patient and Public Involvement
PPV	Positive Predictive Value
PREM	Patient Reported Experience Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient Reported Outcome Measure
PROSPERO	(International database of prospectively registered systematic reviews in health and social care)
PSC	Programme Steering Committee
PSM	Propensity Score Matching

Abbreviation	Expansion
PSS	Performance Status Scale
QALY	Quality-Adjusted Life-Year
QMUL	Queen Mary University of London
QR	Quick Response (code)
R&D	Research and Development
RAP	Rapid Qualitative Analysis
RCPath	Royal College of Pathologists
RCR	Royal College of Radiologists
RCS	Royal College of Surgeons
RCSLT	Royal College of Speech and Language Therapists
RCT	Randomised Controlled Trial
RECUT	REcurrent Cancers of the Upper aerodigestive Tract
RM	Royal Marsden
ROC	Receiver Operator Characteristics
RT	Radiotherapy
RTDS	Radiotherapy Dataset
RTOG	Radiation Therapy Oncology Group
SACT	Systemic Anti-Cancer Therapy
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SLT	Speech and Language Therapy
SMS	Short Message Service (text message)
SNOMED	Systemized NOmenclature of MEDicine (clinical terms)
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SR	Systematic Review
SSS	Step Serial Sectioning
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
SUS	System Usability Scale
TBM	Tongue Base Mucosectomy
TDF	Theoretical Domains Framework
TFA	Theoretical Framework of Acceptability
TLM	Transoral Laser Microsurgery

Abbreviation	Expansion
TMG	Trial Management Group
TOEC	TransOral Endoscopic eleCtrosurgery
TORS	Transoral Robotic Surgery
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
US	UltraSound
USA	United States of America
WP	Work Package

THESIS STATISTICS AND OUTPUTS

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Peer reviewed publications, submitted manuscripts and outputs

1. Hardman JC, Tikka T, Paleri V, ENT UK, BAHNO and INTEGRATE (The UK ENT Trainee Research Network). Remote triage incorporating symptom-based risk stratification for suspected head and neck cancer referrals: A prospective population-based study. Cancer. 2021;127(22):4177-4189. https://doi.org/grst
2. Zhang H*, Hardman JC*, Tikka T, et al. Symptom-based remote assessment in post treatment head and neck cancer surveillance: a prospective national study. Clin Otolaryngol. Published online May 30, 2022. http://doi.org/gp86hm. **Joint first authors*
3. Paleri V, Patterson J, Hardman J, et al. EVolution of a patiEnt-REported symptom-based risk stratification sySTem to redesign the suspected Head and Neck cancer referral pathway (EVEREST-HN). NIHR Programme Grant for Applied Research. Start date September 2022. https://fundingawards.nihr.ac.uk/award/NIHR202862
5. Hardman JC, Harrington K, Brady GC, Roe JWG, O'Leary B, Paleri V. Step Serial Sectioning of Oropharyngeal Tissue for Head and Neck Squamous Cell Carcinoma of Unknown Primary (MOSES). Submitted to Clinical Otolaryngology (HNSCCUP Supplement) December 2022.
6. INTEGRATE (The UK ENT Trainee Research Network). Investigations for Suspected Head and Neck Squamous Cell Carcinoma of Unknown Primary (HNSCCUP): A National Cohort Study. Submitted to Clinical Otolaryngology (HNSCCUP Supplement) December 2022.
7. INTEGRATE (The UK ENT Trainee Research Network). Survival Outcomes in Head and Neck Squamous Cell Carcinoma of Unknown Primary (HNSCCUP): A National Cohort Study. Submitted to Clinical Otolaryngology (HNSCCUP Supplement) December 2022.
8. Hardman JC, Harrington K, Roques T, et al. Methodology for the development of National Multidisciplinary Management Recommendations using a multi-stage meta-consensus initiative. BMC Med Res Methodol. 2022;22(1):189. https://doi.org/h4s3
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THESIS INTRODUCTION

Precis

This thesis considers three areas of head and neck cancer care over seven chapters, following the patient journey from referral to diagnosis and onto treatment for recurrence. Cumulatively, it demonstrates that surgeon-led multi-centre collaborative research is an effective methodology for investigating head and neck cancer. The included studies have engaged every head and neck unit in the UK, with input from over 380 professionals and have led to successful funding for a randomised trial of more than 100,000 patients.

Overview of thesis structure

This thesis investigates three topic areas within HNC using surgeon-led multi-centre collaborative methodology. HNC is newly diagnosed in around 1.5 million people each year, making it the sixth most common type of cancer worldwide.[1] In the UK, the patient journey commonly starts with presentation to the General Practitioner (GP), before referral into secondary care for review, followed by diagnostic investigations and treatment, as appropriate. For some unfortunate patients, primary treatment does not lead to long-term cure, and they may undergo treatment for residual or recurrent disease.

Some elements of head and neck cancer (HNC) care are common and can be adequately investigated in single institution setting in a reasonable timeframe. For example, most head and neck centres have a reasonable number of patients under post-treatment surveillance who could be cross-sectionally sampled for their attitudes towards follow-up practices or research the efficacy of emerging techniques like circulating tumour DNA. However, for rarer aspects of HNC care, a single institution may not allow timely identification and recruitment of eligible patients and, by its nature, will struggle to be generalisable across the wider healthcare system. For example, investigating the management of uncommon tumour types, like adenoid cystic carcinoma, or outcomes from specific treatments that are not applicable to all cancers, like the effectiveness of salivary bypass tubes in salvage laryngectomy. For these reasons, multi-centre studies can be superior.

Surgeons are often best placed to identify and recruit research subjects, as well as report on their clinical history. This may be for a number of reasons. Firstly, they have an intimate understanding of the patients under their care and so are ideally placed to understand the suitability of each subject to the research question at hand. Secondly, they understand their healthcare service and so, particularly for studies looking to set-up at short notice, they understand the capacities and capabilities of the system they work within. Thirdly, they are on the front-line of healthcare delivery and so, for some conditions (particularly emergency conditions), are more likely to encounter potentially eligible patients in a timely manner than research personnel working at a distance. However, this does not undermine the importance of non-clinical researchers. Instead, it highlights the benefits

including surgeons as part of a heterogeneous research group to ensure the spectrum of research skills are represented to optimise the chance of a project's success.

The related parts of this thesis together demonstrate successful applications of surgeon-led multi-centre collaborative research methodology across different aspects of the HNC patient's care: **PART 1** explores secondary care-based remote triage, specifically its implementation during the pandemic for suspected HNC referrals from general practice, as well as for surveillance following treatment within secondary care, and culminates in the description of a successful Programme Grant for Applied Research application to further investigate this over the next six years;[2–4] **PART 2** explores the diagnosis and management of patients with head and neck squamous cell carcinoma who present with unknown primary disease, culminating in the production of National Consensus Management Guidelines;[5] and **PART 3** considers the application of transoral robotic surgery (TORS) for residual, recurrent and new primary HNC in previously irradiated fields, culminating in an award-winning international cohort study.[6–8]

Surgeons and centres have been engaged in a variety of ways throughout these three parts and across the various chapters with some notable similarities. The two studies in **PART 1** and the National Audit project in **PART 2** were set-up and deployed rapidly as a service evaluation and clinical audit, respectively, using clinician-completed standardised Excel Data Tools to collate anonymised standard-of-care clinical care. This successfully avoided the extra regulatory hurdles attracted by research projects registered through Research and Development (R&D) departments which may use personally identifiable or non-standard-of-care data. In **PART 3**, a similar clinician-completed Data Tool was used but the core study went through formal R&D channels to ensure appropriate legal oversight where contributions from international centres were essential. **PART 2** similarly includes a study that also went through R&D channels but relied on the prospective identification of eligible patients by front-line surgeons to ensure appropriate recruitment. **PART 2** further used practising surgeons to access every head and neck multidisciplinary team (MDT) in the United Kingdom to gauge consensus opinion to develop a clinical practice guideline using a national Delphi exercise.

Layout

This multi-part thesis includes three topic areas covering the initial presentation with HNC, attempts to diagnose primary HNC, and management of residual or recurrent HNC. Although all three parts relate to HNC care individually, they consider three quite distinct aspects of that care. As a result, for clarity, the relevant literature will be explored in dedicated introductions to each part. This will give the reader appropriate context for the forthcoming methods and results which are presented sequentially for each study as separate chapters. The context and impact of each part will then be considered with three dedicated discussions at the end of each part.

Context to the parts of this thesis

The following text gives context to the circumstances from which each part of this thesis, and the individual studies, arose:

PART 1: Remote triage for head and neck cancer

PART 1 of this thesis was catalysed by the onset of the COVID-19 pandemic. At a time when many research activities unrelated to the pandemic were being suspended, including the projects that constitute **PART 2** and **PART 3**, routine care in the NHS was having to adapt rapidly to the anticipated disruption.[9] From early 2020, non-emergency healthcare in particular was being curtailed to divert resources to acute and intensive care where the majority of the COVID-19 burden would be felt.[10,11] Cancer services, although relatively protected, were not immune to disturbance as behaviours from both the patient side and the health service side sought to change established practices surrounding referral and review.[12,13] Face-to-face appointments were discouraged wherever possible, as was examination or instrumentation of the upper aerodigestive tract, so as not to increase potential exposure to a virus that was presumed to reside, at least partially, in the pharynx.[13,14] Consequently, many essential appointments began taking place remotely, and predominantly via telephone, rather than via video link.[11,15,16] This was the case in primary as well as secondary care and so there were at least three levels at which a suspected HNC referral could differ at this period compared to pre-pandemic times: firstly, the patients' change in consulting behaviour, where they were more reluctant to engage with healthcare services; secondly; GPs had shifted to routinely arranging remote consultations as the first point of contact, and so foregoing examination; and thirdly, specialist services had also adopted this practice, with examination including flexible nasendoscopy being discouraged unless felt essential.

In March 2020, the first 'lockdown' was announced in the UK to start on the 23rd day of that month. The author and their primary supervisor liaised remotely on 21 March 2020 and felt this offered a unique opportunity both to assist HN specialists in assessing patients remotely and to study this shift in practice. A national service evaluation was envisaged which was rapidly developed and delivered over multiple UK centres using surgeon-led distribution and collaboration. This national service evaluation encompassed both new suspected HNC referrals undergoing telephone triage (**The HNCTT Study for suspected HNC**) and post-treatment HNC patients under surveillance undergoing telephone triage (**The HNCTT Study for post-treatment surveillance**). Although labelled as Service Evaluation to facilitate roll out and take-up, the resultant data lend themselves to analysis as prospective observational cohort studies. Inspired by this work, the author and primary supervisor developed The EVEREST-HN Programme to further research remote triage in the suspected HNC population, which was awarded funding in August 2021 and launched formally in September 2022.

PART 2: National Consensus for head and neck SCC of unknown primary

Head and neck squamous cell carcinoma of unknown primary (HNSCCUP) was the topic that began this PhD effort, by way of **The MOSES Study**. However, as a prospective clinical study, its conduct was hampered by the COVID-19 pandemic, leading to the study growing in ambition and scope. Its major outputs will be realised after the submission of this thesis once the 5-year follow-up data matures. **PART 2** starts with the core work stemming from **The MOSES Study**, reporting the outcomes from examining the diagnostic oropharyngeal specimens obtained in the search for the unknown primary origin of cervical metastasis.

The MOSES Study recruited patients with unknown primary HNC at the time of undergoing a diagnostic procedure, namely Tongue Base Mucosectomy (TBM). However, not all patients presenting with unknown

primary disease will undergo a TBM: the primary disease may be identified before it is appropriate to offer TBM, for example through imaging investigations and/or other diagnostic surgeries; the centre may not be able to offer TBM due to local preferences or resource constraints; or TBM may contraindicated due to patient factors that would mean the procedure is too morbid. Consequently, to understand better the full diagnostic journey of more patients presenting with head and neck squamous cell carcinoma of unknown primary (HNSCCUP), **The HNSCCUP National Audit 2021** was developed to investigate earlier aspects of the patient pathway further using surgeon-led collaborative network.

Both these studies increased our knowledge of the management of HNSCCUP and moved the field forward. To consolidate this new knowledge, and to maximise the potential impact on patient care, a multi-stage meta-consensus initiative was developed and delivered: **The HNSCCUP Consensus Exercise**. This culminated in the production of new National Consensus Guidelines for management of HNSCCUP that will be incorporated in the 6th edition of the 'United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer' and, at time of writing, are due imminent publication by the Journal of Laryngology and Otology with Professor Stuart Winter and Professor Jarrod Homer as guideline editors. An expanded version of the guidelines will also be published in a dedicated supplement in Clinical Otolaryngology (the official journal of ENT UK), for which the author and supervisors are guest editors.

PART 3: Transoral robotic surgery for recurrent head and neck cancer

Setting up a multi-centre prospective clinical study, such as **The MOSES Study**, takes time. Even after the scientific aspects of the study have been decided upon, the process of drafting the required documents and obtaining sponsor and regulatory approvals takes months. As a result, the studies in **PART 3** were instigated in tandem to maximise productivity in the early stages of the doctoral placement. Transoral robotic surgery (TORS) is being increasingly adopted in the management of HNC though, to date, this has principally been in the primary disease setting. Evidence for its use in the recurrent setting has been lacking, chiefly as clinical experience in individual centres is slow to accrue as TORS for recurrence falls outside of accepted regulatory approvals.[17] As a result, **The RECUT Study** was developed to pool the collective experience of some of the world's leading hospitals across three continents using a surgeon-led international collaborative to deliver a multi-centre observational cohort study. **The RECUT Review** is a systematic review and meta-analysis that was conducted prior to **The RECUT Study** to understand the knowledge-base in this field and help identify potential units for inclusion in the planned cohort study.

A note to the reader

This work embodies the author's passion for surgeon-led collaborative research applied to the field of head and neck cancer. Cumulatively, the chapters demonstrate what can be achieved remotely by surgeons working collaboratively across multiple centres; achievements that, it is argued, would be impossible to obtain in a practical timeframe from a single surgeon or single institution or even single country. It is hoped the reader enjoys digesting this thesis as much as the author has enjoyed conducting the research and preparing the work herein.

Hypothesis

An overarching hypothesis is presented to appropriately link the three parts of this thesis:

- Surgeon-led multi-centre collaboration is an effective methodology to research head and neck cancer.

PART 1 REMOTE TRIAGE FOR HNC

Precis of studies contributing to **PART 1**

- **The HNCTT Study for suspected HNC** assessed the implementation of a symptom-based remote triage system for suspected HNC referrals across 41 UK centres.
- **The HNCTT Study for post-treatment surveillance** assessed remote consultations in post-treatment HNC patients in 16 UK centres.

Introduction to **PART 1**

The emergence of COVID-19 in early 2020 led to significant changes in the normal practices for diagnosis and management of cancer.[11,18,19] This was especially pronounced in specialties such as Ear Nose and Throat (ENT) surgery, head and neck (HN) surgery and oral surgery, where aerosol generating procedures were more commonly performed.[20,21] Patients and healthcare services alike had an interest in avoiding hospital attendance to reduce the potential for spreading infection and to preserve resources for the pandemic response.[13] Part of the shift in practice included a sharp uplift in the use of telemedicine in place of face-to-face outpatient appointments.[15,22]

Suspected HNC referrals

Patients referred from primary care to secondary care with suspected Head and Neck Cancer (HNC) are at particular risk of harm from changes to the standard-of-care diagnostic pathway. In normal times, physical examination combined with flexible transnasal endoscopy of the upper aerodigestive tract, where indicated, are considered essential facets of the new patient evaluation. Remote assessment necessarily forgoes these facets and relies on the patient history and the referral information provided by the primary care physician alone. However, it may also facilitate earlier patient contact, may use fewer outpatient resources and may allow a more efficient route to targeted investigations in selected patients.[23,24] Patients with cancer may be diagnosed faster and those without cancer may be reassured more efficiently; giving potential benefits to patients and healthcare services alike. However, at the time it was widely adopted remote triage was novel to most clinicians and the safety of this practice had not been established in these patients. It is likely an increase in telemedicine will remain to some degree in post-pandemic times and so it is necessary to review its safety in this population.[25]

Members of the present study team had previously developed and validated a risk calculator (HaNC-RC-v2) based on the symptom and demographic data of around 10,000 new patient referrals with suspected HNC.[26] This was disseminated just prior to the worst of the disruption brought about by the initial peak of COVID-19 in the UK and is freely available online (http://www.orlhealth.com/risk-calculator-2.html). Communicating and understanding risk is an important element of shared decision making between patients and clinicians in healthcare.[27] The use of a standardised triage system can further help the understanding of the decision making

process and the role of clinical judgement for each patient. As the pandemic resources strained by the pandemic recover, and society re-focuses on the importance of valuing all lives equally, effective risk stratification may have a prominent role in addressing the back-log of referrals to cancer services.[28]

In the UK, since 2005, guidance from the National Institute for Health and Care Excellence (NICE) has recommended that patients presenting to their primary care physicians with symptoms in the head and neck region suggestive of cancer be referred to secondary care via a rapid access pathway to be assessed within two weeks.[29] This pathway covers all cancers affecting the head and neck region, including: pharyngeal; laryngeal; oral cavity/lip; thyroid; cutaneous; salivary gland; nasal cavity/sinus; and cancers affecting the ear. A number of other non-HNC malignancies may also inevitably be identified on this pathway if they present with symptoms in the head and neck, for example: thoracic lesions causing swallowing obstruction or hoarseness from injury to the recurrent laryngeal nerve; and non-HNC metastasising to cervical lymph nodes or lymphomas presenting as neck lumps.

Post-treatment HNC surveillance

Face-to-face appointments are the standard-of-care after treatment for HNC. These encounters allow many of the complex needs of these patients to be met, including the detection of recurrent disease, monitoring for treatment related toxicity, addressing rehabilitation and nutritional needs, and tailored patient support through the survivorship phases.[30] The development of a relationship between this group of patients with the clinical team is fundamental in the holistic approach to their care, which should include psychological support, patient education and addiction counselling.[31] Though guidelines exist for follow-up intervals in post-treatment HNC patients, these are based on expert recommendations and there is a paucity of evidence to support its efficacy.[30,31]

A recent national audit of current UK practice for post-treatment HNC patients showed significantly higher detection rates of disease in patients who had expedited appointments, compared with routine follow-up, suggesting potential benefits from a patient-initiated model.[32]

Since the emergence of COVID-19 in early 2020, a shift towards telemedicine has formed a fundamental part of NHS practice. Minimising person-to-person contact to reduce the spread of infection and preserve resources during the pandemic has influenced many aspects of healthcare,[21,33] including outpatient services in ENT and head and neck surgery.[13] Whilst there was reluctance to perform routine per oral examination or flexible nasendoscopy, the additional risk of attending hospital in person for follow-up seemed excessive, and so a remote model to allow symptom assessment could be justified. In the new patient setting, remote assessment may allow triage directly to imaging investigations for the highest risk patients, and even avoid hospital attendance entirely for the lowest risk for whom clinical examination may add little diagnostic value.[2] This not only increases efficiency and resource management, but may also improve patient compliance and satisfaction by eliminating travel and wait times. Unfortunately, this surveillance cohort does not have a validated risk calculator to support decision making, but national audit data may still be able to provide useful context for the patients being assessed.[26,32]

And so to **PART 1**...

In consultation with ENT UK (British Association of Otorhinolaryngology - Head and Neck Surgery) and BAHNO (British Association of Head and Neck Oncologists), and through collaboration with INTEGRATE (The UK ENT Trainee Research Network), a National Service Evaluation was rapidly developed and implemented to monitor this unique shift in practice towards head and neck cancer telephone triage (HNCTT) consultations in both the suspected HNC (**1.1**) and post-treatment HNC populations (**1.2**).[34] Stemming from this work, a comprehensive research programme was developed and has secured funding to further investigate this in a multi-centre surgeon-led collaborative setting over the next six years (The EVEREST-HN Programme).

1.1 The HNCTT Study for suspected HNC

1.1.1 Full title

Remote triage incorporating symptom-based risk stratification for suspected head and neck cancer referrals: A prospective population-based study.

1.1.2 Contributions

Under supervision, the author led this study from conceptualisation, through protocol development, data collection, assimilation, analysis, visualisation and interpretation. Further, the author led on writing, reviewing and editing the text contained herein, which has also been published in the journal **Cancer**.[2]

The author is grateful to the following individuals for their contributions towards the delivery of this study and its write-up:

- Theofano Tikka, who developed the risk stratification algorithm that this study was based on and helped give early feedback on its deployment in the Excel Data Tool. She also reviewed and edited the manuscript, which benefitted from her insight as a senior head and neck surgical trainee.
- The numerous Consultant Leads and Trainee Site Leads (named in the **Appendix 3**) who facilitated the registration of the study at their institutions and the submission of anonymised patient data to the Project Management Team, as per the study protocol.
- Further thanks are given to the innumerable uncredited clinicians around the country who collected data as part of the National Service Evaluation that formed the core of this work.
- Vinidh Paleri, who supervised the work from conceptualisation to production and approval of the final report.

1.1.3 Abstract *[250 words]*

Background

Remote triage for suspected head and neck cancer (HNC) referrals was adopted by many institutions during the initial peak of the COVID-19 pandemic. Its safety in this population has not been established.

Methods

A 16-week prospective multi-centre national service evaluation was conducted starting 23 March 2020. Suspected HNC referrals undergoing remote triage in UK secondary care centres were identified and followed up for 6 months minimum to record cancer status. Triage was supported by risk stratification using a validated calculator.

Results

Data for 4,568 cases were submitted by 41 centres serving a population of approximately 26 million. These represented 14.1% of the predicted maximum referrals for this population outside of pandemic times, giving the study a margin of error of 1.34% at 95% confidence. Completed 6-month follow-up data were available for 99.8% with an overall cancer rate of 5.6% (n=254/4,557).

Rates of triage were: 25.4% urgent imaging investigation (n=1,156); 27.8% urgent face-to-face review (n=1,268); 30.3% deferred assessment (n=1,382); and 16.4% discharged (n=749). Corresponding missed cancers rates were: 0.5%; 0.3%; 0.9%; and 0.9% (n=5/1,048; 3/1,149; 12/1,382; and 7/747, p=0.15). The negative predictive value for a non-urgent triage outcome and no cancer diagnosis was 99.1%. Overall harm was reported in 0.24% (n=11/4,557) and was highest for deferred assessments (0.58%, n=8/1,382).

Conclusions

Remote triage, incorporating risk stratification, may facilitate targeted investigations for higher risk patients and avoid unnecessary hospital attendance for lower risk patients. The risk of harm was low and may be reduced further with appropriate safety netting of deferred appointments.

1.1.4 Aim

This study aims to report the findings of this 16-week prospective service evaluation of remote triage of suspected HNC referrals, conducted during the initial peak of COVID-19 pandemic in the UK.

1.1.5 Methods

The protocol for this study was published in advance at https://entintegrate.co.uk. This study report has been prepared with reference to the STROBE checklist for cohort studies.[35]

1.1.5.1 Ethical considerations

The Health Research Authority decision tool determined the study design to fall under the remit of service evaluation, and so no ethical approval was required (available at: http://hra-decisiontools.org.uk/research/).

1.1.5.2 Study design and setting

A national prospective service evaluation was conducted, supported by ENT UK (the British Association of Otorhinolaryngology - Head and Neck Surgery) and BAHNO (the British Association of Head and Neck Oncologists), and delivered using INTEGRATE (The UK ENT Trainee Research network). All UK ENT departments were invited to participate via social media and mailouts from the supporting organisations. Sites could open at any point during the prospective data collection period. Registration as per local governance guidelines was required to participate.

1.1.5.3 Participants

Patients referred on the suspected HNC pathway to secondary care, who were prospectively identified and completed remote triage over a telephone consultation, were eligible for inclusion. These patients have been referred by primary care physicians to secondary care HNC specialists for further assessment, without any upfront requirement for imaging, procedures or biopsies prior to this assessment.

1.1.5.4 Data collection

Cases were identified over a 16-week period between 23 March and 13 July 2020. Final submission of data was accepted after a minimum 6-month follow-up. This timeframe was chosen to be a pragmatic compromise between allowing a long enough interval for a missed cancer to re-present and short enough to be able to give timely feedback to the ENT community about the safety of the shift in practice.

To be eligible for inclusion, cases were required to have complete demographic and symptom data with no null data points in these fields. To facilitate this, a standardised electronic case report form was created using Excel software (Microsoft Corporation, Washington, USA) (**Figure 1-1**, available at https://entintegrate.co.uk) which incentivised completion of data by displaying a risk stratification result from the HaNC-RC-v2 only if all relevant triage fields were accurately filled out.[9] Data were held offline at each centre until the follow-up period had passed for all patients, whereupon the patient record was checked by the local team for a diagnosis of cancer at any time since their initial triage, classed as either on the urgent assessment pathway or 'late' if at any time thereafter.

The following data were collected: patient demographics; smoking and alcohol history; symptoms as per the HaNC-RC-v2;[26] triage outcome; clinician and patient preference for review/investigation; cancer diagnosis timing; and the primary site of the cancer, if identified. Data were not collected on the specific type of investigation requested, the grade of the clinicians completing the triage consultation or the stage of cancer at time of diagnosis as there was no immediate intention to use these data in the analysis and so as not to overburden the participating clinicians who would be collecting the information.

The Project Management Team (PMT) handled only anonymised data, with all identifiable information removed prior to submission by the local teams. Where missing or ambiguous data were identified by the PMT, a query was raised with the local site to clarify each data point. Where missing data could not be resolved, that record was excluded from relevant analysis.

A user guide was produced to support the clinicians in registering the project locally and to guide data collection (**Appendix 1**). Certificates were produced as evidence of participation for all Consultant leads, Trainee site leads and local collaborators (**Appendix 2**). Collaborative authorship was also offered to all Consultant leads and Trainee site leads for any subsequent publications, as per the protocol (protocol available at https://entintegrate.co.uk/entuk2wwtt). Sites were requested not to submit data until local data governance requirements had been satisfied.

1.1.5.4.1 Using the data tool with in-built risk stratification

Risk stratification was performed using the HaNC-RC-v2 which is open license and freely available online at http://orlhealth.com/risk-calculator-2.html. This tool was validated in a population undergoing face-to-face assessment with suspected HNC. It was incorporated in the Excel Data Tool as a decision aid, to assist experienced healthcare professionals in assessing patients following a rapid shift in practice towards remote triage as part of the COVID-19 pandemic response. The algorithm for the calculator had been developed to deliver a negative predictive value of 98.6% for those classed as low risk. Clinicians were instructed to consider both the clinical history and the outcome of the risk stratification in proposing their management plan.

1.1.5.5 Data analysis

The primary outcome was the diagnosis of cancer after a minimum of 6 months follow-up. Cancers identified incidentally, whether from investigations arising from the index referral but not relating to the referral symptoms, or cancers identified in the follow-up period which were not linked to the index referral, were not included in the analysis. This was intended to ensure the referral symptoms themselves could be relied upon as prognosticators of any subsequent cancer diagnosis and, as such, was indiscriminate as to the ultimate site/type of cancer diagnosed.

No *a priori* sample size calculation was performed. Categorical variables were compared using the Chi squared test with Yates' correction, with a two-tailed p value of 0.05 taken as significant. Analysis was performed using R statistical software (R Foundation, Vienna, Austria).

1.1.5.6 Interim reports

After 8 weeks, interim data were requested from participating centres and a report was produced to allow rapid feedback of preliminary findings to the UK ENT community. The interim report was disseminated electronically via an ENT UK mailout on 3 June 2020 and was hosted online at https://entuk.org and https://entintegrate.co.uk (**Appendix 4**).

1.1.6 Results

1.1.6.1 Centres and submissions

Final data were submitted by 41 of 47 UK centres who registered interest in taking part (32 in England, 6 in Scotland, 2 in Wales and 1 in Northern Ireland) with 4,568 cases eligible for analysis with complete demographic and symptom data (median cases per centre: 99; range 10 to 337; interquartile range (IQR) 40 to 157). The median age for referrals was 58 (range 1 to 98 years; IQR 46 to 69 years) and 57.1% were female (n=2,608).

The 41 centres serve a population of approximately 26 million people (**Table 1-4**). Our data therefore represent 14.1% of the predicted maximum referrals for this population and time period, based on activity outside of pandemic conditions (referral rate 404.5 per 100,000; 2019/20),[36] allowing for a margin of error of 1.34% at a 95% confidence level for the study.

1.1.6.1.1 Data completeness

The cancer status at 6 months minimum follow-up was provided in 99.8% of cases (n=4,557) with 11 records having incorrect patient identifiers recorded at the initial triage, precluding local follow-up. The triage outcome was provided for 99.7% of cases (n=4,555) and the clinician advice for management was provided in 98.5% of cases (n=4,501).

1.1.6.2 Symptoms

Table 1-1 summarises the incidence of presenting symptoms, smoking history and alcohol history, alongside their positive predictive value (PPV) for cancer at any time and their triage outcomes. The non-negative responses to these factors are presented with clinically interesting pairings in **Figure 1-2** and **Figure 1-3**. **Figure 1-2** contrasts the incidence (inner) with the PPV (outer) for each factor. **Figure 1-3** contrasts the discharge rate (inner) with rate of triage directly to an investigation (outer) for each factor.

1.1.6.3 Diagnosis of cancer

Table 1-2 summarises the cancer status by: triage outcome; clinician advice for assessment; and risk stratification with HaNC-RC-v2. The overall rate of a cancer related to the referral symptoms in this population was 5.6% (n=254/4,557), with a 5.0% rate on the urgent pathway (n=227/4,568) and a 0.6% rate in the follow-up period (n=27/4,330).

1.1.6.3.1 Triage outcome

Triage outcome indicates the decision made by the clinician using the information from the remote assessment and the risk stratification from HaNC-RC-v2. This was classed as either urgent assessment (a face-to-face clinical assessment and/or investigation; 53.2%) or non-urgent (deferred reviews or investigations and discharges; 46.8%). Triage outcome (urgent vs non-urgent) and cancer at any time were significantly associated (9.7% vs 0.9%, p=<0.0001). The sensitivity, specificity, PPV and NPV for being triaged to urgent assessment and having a related cancer diagnosed at any time were 92.5%, 49.1%, 9.7% and 99.1%, respectively.

Late cancers identified at any point after the initial urgent diagnostic assessment pathway were reported in 0.9% of those triaged as non-urgent and 0.4% of those assessed urgently. (n=19/2,129 and 8/2,197, respectively, p=0.0439).

A more detailed breakdown by triage outcome is given in **Table 1-2**. Rates of triage were: 25.4% to urgent imaging investigation (n=1,156); 27.8% to urgent face-to-face review (n=1,268); 30.3% to deferred assessment (n=1,382); and 16.4% were discharged (n=749). Corresponding late cancers rates were: 0.5%; 0.3%; 0.9%; and 0.9% (n=5/1,048; 3/1,149; 12/1,382; and 7/747). These rates were not significantly different (p=0.15).

It should be noted that patients classed as non-urgent (deferred reviews or investigations and discharges) could not, by this definition, have cancers recorded as being found on the urgent pathway in this analysis.

1.1.6.3.2 Clinician advice for assessment

Clinician advice for assessment with either a review/investigation was recorded as either yes (69.7%) or no (30.3%). Clinician advice for assessment and cancer at any time were significantly associated (7.3% vs 1.5%, p=<0.0001). The sensitivity, specificity, PPV and NPV for preference for review/investigation and having a related cancer diagnosed at any time were 91.6%, 31.5%, 7.3% and 98.5%, respectively.

Late cancers were reported in 0.5% of those who were advised by their clinician for a review or investigation and 0.7% of those not advised for further assessment. (n=16/2,925 and 10/1,349, respectively, p=0.5840).

It should be noted that 72.2% of the group who clinicians advised for assessment were seen urgently, compared with 10.0% of those not advised for further assessment (n=2,265/3,139 vs n=136/1,362), limiting the potential for reporting of urgent cancers in the latter group.

1.1.6.3.3 Risk stratification

Risk was stratified as either high (31.3%) or low (68.7%), as determined by HaNC-RC-v2. Stratification to high risk and a cancer at any time were significantly associated (13.0% vs 2.2%, p=<0.0001), with the following diagnostic parameters: sensitivity, specificity, PPV and NPV were 73.2%, 71.1%, 13.0% and 97.8%, respectively.

Late cancers were reported in 0.6% of the high risk group compared with 0.6% of the low risk group (n=7/1,249 vs n=20/3,081, p=0.9023).

It should be noted that 91.5% of the high risk group were seen and/or assessed urgently compared with 35.7% of the low risk group (n=1,306/1,427 vs n=1,118/3,128), limiting the potential for reporting of urgent cancers in the low risk group.

1.1.6.4 Primary cancer site

Table 1-3 shows the primary site of the 254 cancers reported in the study period that were related to the referral symptoms. The median age for patients with cancer was 65.5 years (range 21 to 94 years, IQR 57 to 73 years) and 34.6% were female (n=88/254).

The most common cancers were oropharyngeal (25.6%, n=65), lymphoma (17.7%, n=45) and laryngeal (12.2%, n=31). **Figure 1-4** shows the distribution of cancers by age compared with the referral cohort as a whole.

Lymphoma, lung and oesophageal were the most common non-HNCs in the cohort. Non-HNCs represented 33.9% of cancers identified from these patients referred on the suspected HNC pathway (n=86/254).

1.1.6.5 Late cancers and harm

Of the 27 cases who had cancer identified late, 8 had undergone urgent assessment, of whom 4 were classed as low risk, compared to 19 cases not urgently assessed, of whom 17 were classed as low risk (**Table 1-5**). The treating clinicians were contacted to obtain details of factors which may have contributed to the late diagnosis and any perceived harm from the delay (defined as either worse prognosis or escalated treatment). It was felt that harm had resulted from the late diagnosis in 0.24% of patients triaged (n=11/4,557; 7 HNC and 4 non-HNC), with the highest relative rate amongst deferred appointments at 0.58% (n=8/1,382), with lower rates in those discharged (0.13%, n=1/749), triaged to urgent investigation (0.09%, n=1/1,156) and triaged to urgent face-to-face review (0.08%, n=1/1,268). The sites of the primary cancer for those coming to harm are identified in **Table 1-3**.

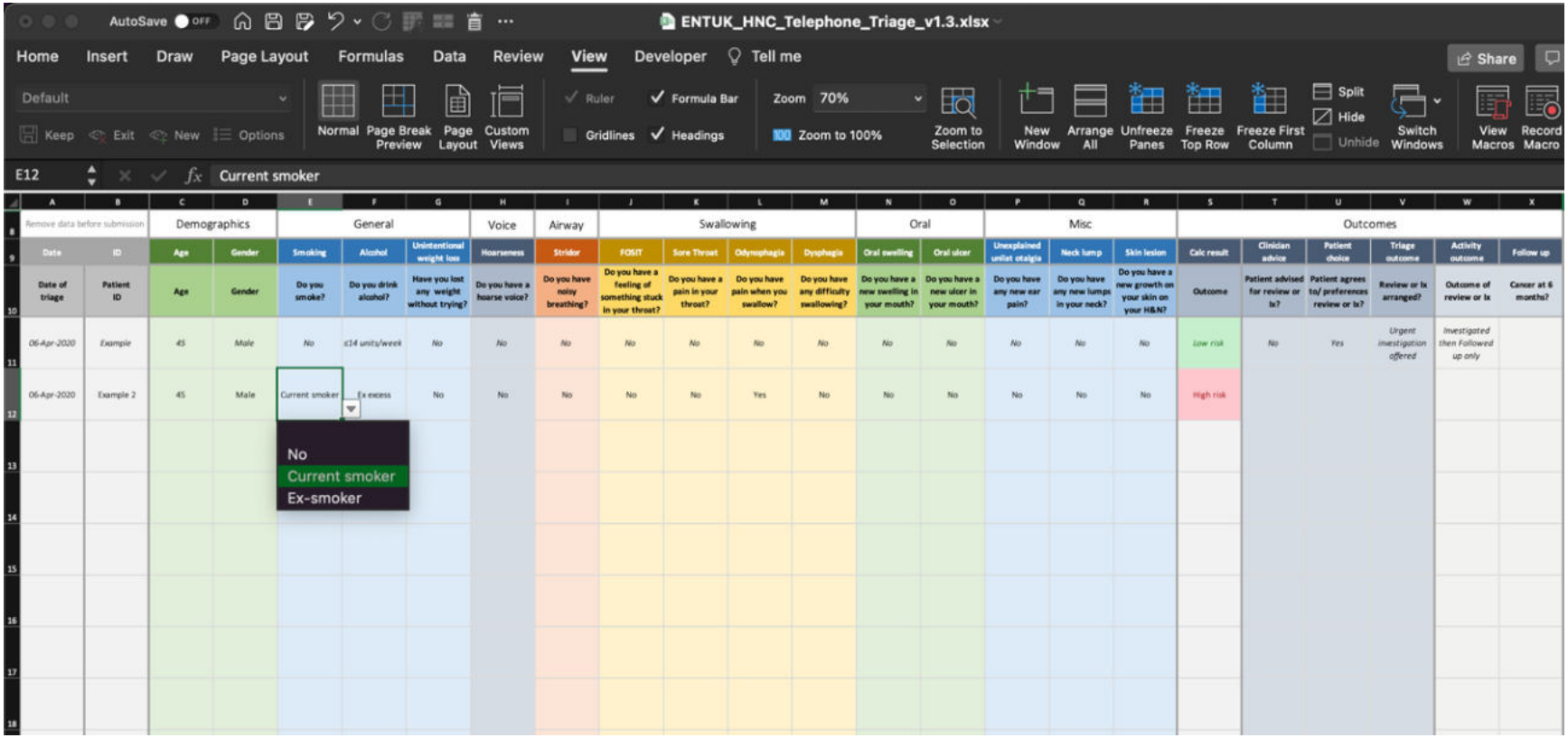


Figure 1-1: Screenshot of the Excel Data Tool in the HNCTT Study. Drop down menus and data validation were used to ensure data integrity. The 'Calc result'/'Outcome' column auto populates based on the parameters chosen for each case.

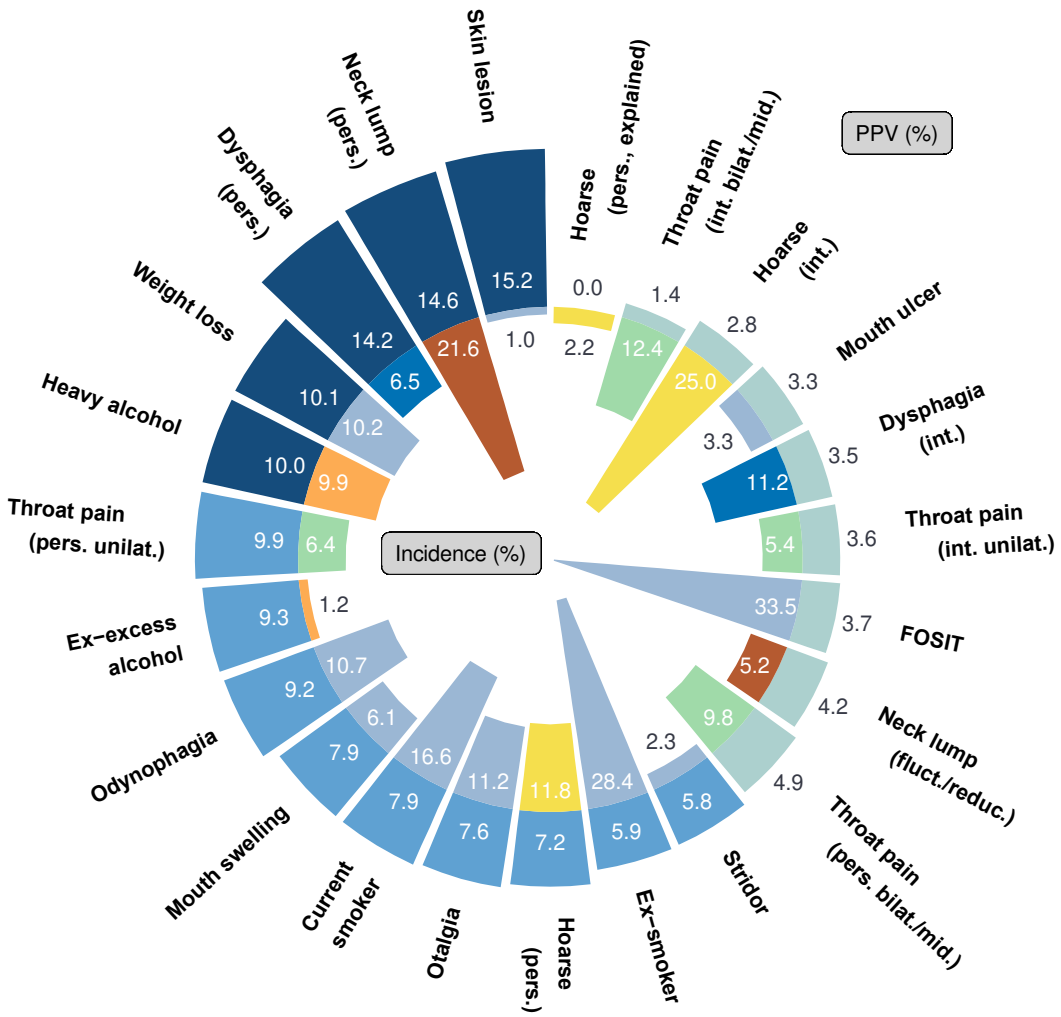


Figure 1-2: *The incidence of symptoms and their PPV for the HNCTT Study. The outer ring displays the PPVs of the nonnegative responses to symptom, smoking, and alcohol triage questions, which are contrasted against the incidences of these responses on the inner ring.*
Colours besides blue in the inner-ring group together responses with more than 2 tiers that would compete with each other.
bilat indicates bilateral; fluct./reduc., fluctuating/reducing; FOSIT, feeling of something in the throat; int., intermittent; mid., midline; pers., persistent; PPV, positive predictive value; unilat.; unilateral.

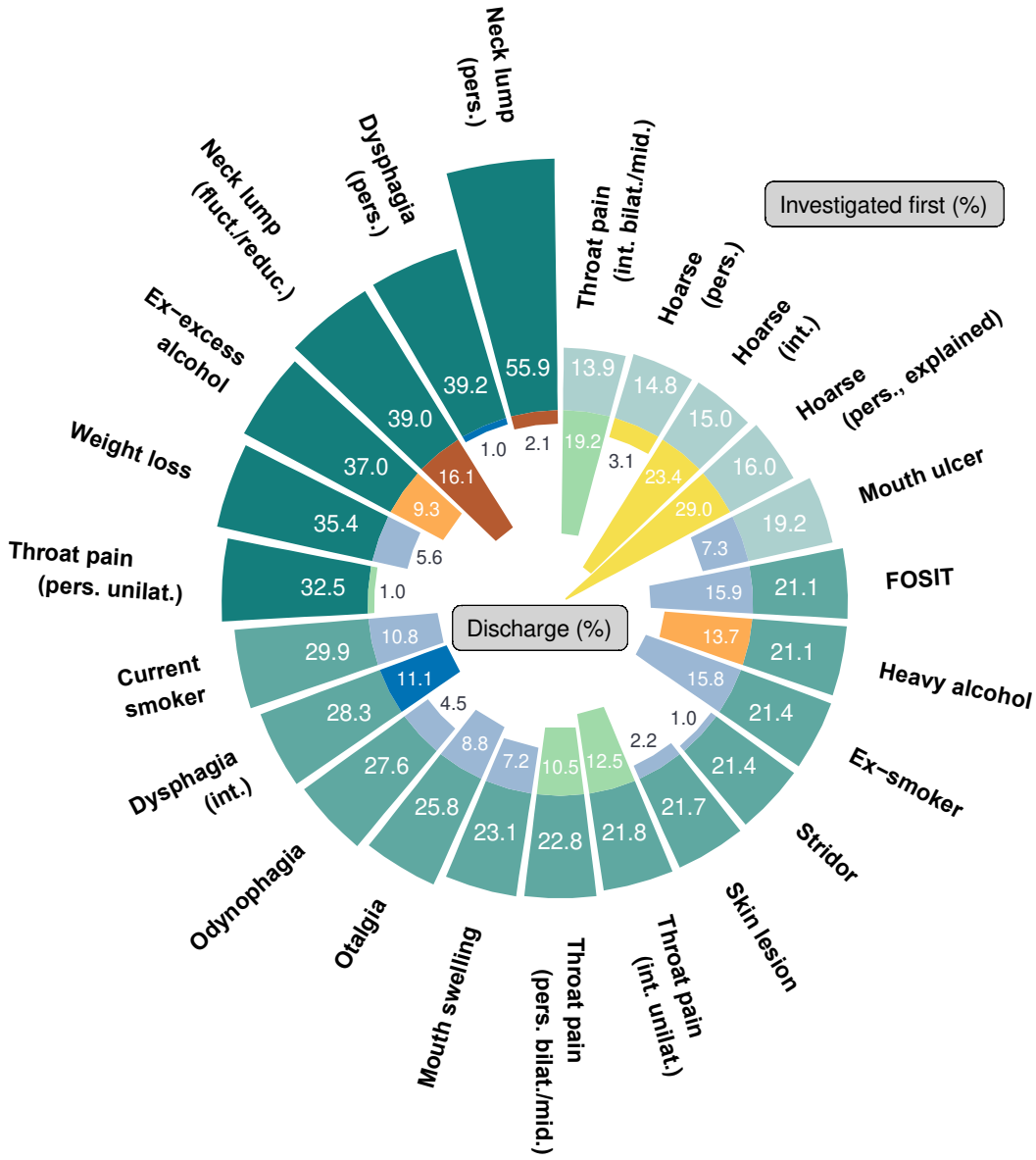


Figure 1-3: *The triage outcomes for symptoms in the HNCTT Study. The outer ring displays the rates of triage directly to an urgent investigation for the nonnegative responses to symptom, smoking, and alcohol triage questions, which are contrasted against the rates of direct discharge for these responses on the inner ring.*
Colours besides blue in the inner-ring group together responses with more than 2 tiers that would compete with each other.
bilat indicates bilateral; fluct./reduc., fluctuating/reducing; FOSIT, feeling of something in the throat; int., intermittent; mid., midline; pers., persistent; unilat.; unilateral.

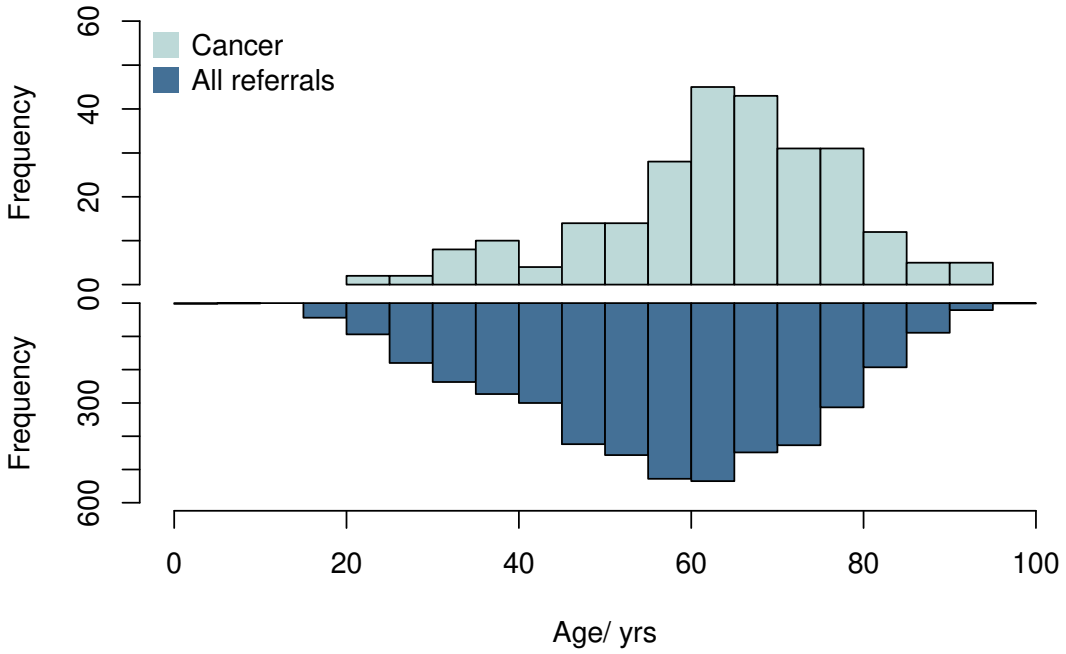


Figure 1-4: Age distribution in the HNCTT Study for (top) patients with cancer and (bottom) all suspected head and neck cancer referrals. Note that the scales differ by a factor of 10.

Table 1-1: Responses to standardised triage questions for the HNCTT Study (based on HaNC-RC-v2), with positive predictive value (PPV) for cancer found at any time and response rate by triage outcome. Clinicians were asked the outcome of the remote consultation. If the patient underwent imaging or a diagnostic procedure then 'investigation' was chosen. If the patient underwent a face-to-face review then 'Review' was chosen. Where 'first' is specified, this was the initial activity following remote triage. Where 'at any time' is specified, the activity took place at some point in the patients' diagnostic workup. Responses in italic show the specific positive response to that question that are surmised in the 'yes' row above.

						Urgent								Non-urgent			
				Cancer		Investigation				Review				Deferred		Discharged	
		All responses		PPV and true positives		Investigation first		Investigation at any time		Review first		Review at any time					
		%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n
	Overall		4568	5.6	254	25.3	1156	37.4	1707	27.8	1268	37.3	1703	30.3	1382	16.4	749
General	Do you smoke?																
	No	55.0	2513	4.7	117	25.9	652	36.0	905	23.1	580	32.3	811	32.2	809	18.4	462
	Current smoker	16.6	757	7.9	60	29.9	226	48.1	364	35.1	266	47.3	358	24.0	182	10.8	82
	Ex-smoker	28.4	1298	5.9	77	21.4	278	33.7	438	32.5	422	41.1	534	30.1	391	15.8	205
	Do you drink alcohol?																
	≤14 units/week	88.9	4063	5.0	204	25.6	1041	37.0	1505	26.5	1078	35.8	1456	30.8	1250	16.8	682
	>14 units/week	9.9	451	10.0	45	21.1	95	38.8	175	38.8	175	49.9	225	26.2	118	13.7	62
	Ex excess	1.2	54	9.3	5	37.0	20	50.0	27	27.8	15	40.7	22	25.9	14	9.3	5
	Have you lost any weight without trying?																
	No	89.8	4102	5.0	207	24.2	991	35.1	1440	26.1	1071	35.0	1435	31.8	1304	17.6	723
	Yes	10.2	466	10.1	47	35.4	165	57.3	267	42.3	197	57.5	268	16.7	78	5.6	26
Voice and airway	Do you have a hoarse voice?																
	No	61.0	2785	6.6	183	31.9	889	43.8	1221	24.2	674	35.9	1001	27.9	776	15.7	436
	Yes	39.0	1783	4.0	71	15.0	267	27.3	486	33.3	594	39.4	702	34.0	606	17.6	313
	Persistent	*11.8*	*541*	*7.2*	*39*	*14.8*	*80*	*37.7*	*204*	*57.3*	*310*	*63.0*	*341*	*24.8*	*134*	*3.1*	*17*
	Intermittent	*25.0*	*1142*	*2.8*	*32*	*15.0*	*171*	*22.9*	*261*	*23.1*	*264*	*29.1*	*332*	*38.3*	*437*	*23.4*	*267*
	Persistent but explained	*2.2*	*100*	*0.0*	*0*	*16.0*	*16*	*21.0*	*21*	*20.0*	*20*	*29.0*	*29*	*35.0*	*35*	*29.0*	*29*
	Do you have noisy breathing?																
	No	97.7	4465	5.6	248	25.4	1134	37.2	1660	26.8	1198	36.3	1620	30.8	1373	16.8	748
	Yes	2.3	103	5.8	6	21.4	22	45.6	47	68.0	70	80.6	83	8.7	9	1.0	1
Swallowing	Do you have a feeling of something stuck in your throat?																

	No	66.5	3036	6.5	197	27.4	833	39.7	1206	27.1	822	37.2	1128	28.6	868	16.6	505
	Yes	33.5	1532	3.7	57	21.1	323	32.7	501	29.1	446	37.5	575	33.6	514	15.9	244
	Do you have a pain in your throat?																
	No	66.0	3013	6.2	186	27.4	826	38.5	1161	23.9	719	34.3	1032	29.8	898	18.6	559
	Yes	34.0	1555	4.4	68	21.2	330	35.1	546	35.3	549	43.2	671	31.1	484	12.2	190
	Persistent bilateral/ midline	*9.8*	*448*	*4.9*	*22*	*22.8*	*102*	*38.8*	*174*	*41.5*	*186*	*49.3*	*221*	*25.2*	*113*	*10.5*	*47*
	Persistent unilateral	*6.4*	*292*	*9.9*	*29*	*32.5*	*95*	*58.9*	*172*	*57.5*	*168*	*69.2*	*202*	*8.6*	*25*	*1.0*	*3*
	Intermittent bilateral/ midline	*12.4*	*567*	*1.4*	*8*	*13.9*	*79*	*20.6*	*117*	*19.2*	*109*	*25.0*	*142*	*47.4*	*269*	*19.2*	*109*
	Intermittent unilateral	*5.4*	*248*	*3.6*	*9*	*21.8*	*54*	*33.5*	*83*	*34.7*	*86*	*42.7*	*106*	*31.0*	*77*	*12.5*	*31*
	Do you have pain when you swallow?																
	No	89.3	4078	5.1	209	25.0	1021	35.4	1444	24.6	1004	33.9	1383	32.2	1313	17.8	727
	Yes	10.7	490	9.2	45	27.6	135	53.7	263	53.9	264	65.3	320	14.1	69	4.5	22
	Do you have any difficulty swallowing?																
	No	82.3	3759	5.2	194	23.8	895	34.8	1307	25.9	973	34.9	1313	31.6	1189	18.3	689
	Yes	17.7	809	7.4	60	32.3	261	49.4	400	36.5	295	48.2	390	30.7	248	29.0	235
	Persistent	*6.5*	*296*	*14.2*	*42*	*39.2*	*116*	*66.2*	*196*	*48.6*	*144*	*64.2*	*190*	*11.1*	*33*	*1.0*	*3*
	Intermittent	*11.2*	*513*	*3.5*	*18*	*28.3*	*145*	*39.8*	*204*	*29.4*	*151*	*39.0*	*200*	*31.2*	*160*	*11.1*	*57*
Oral	Do you have a new swelling in your mouth?																
	No	93.9	4291	5.4	232	25.4	1092	36.5	1565	26.1	1122	35.6	1527	31.1	1335	17.0	729
	Yes	6.1	277	7.9	22	23.1	64	51.3	142	52.7	146	63.5	176	17.0	47	7.2	20
	Do you have a new ulcer in your mouth?																
	No	96.7	4417	5.6	249	25.5	1127	37.3	1649	26.6	1174	36.2	1597	30.9	1365	16.7	738
	Yes	3.3	151	3.3	5	19.2	29	38.4	58	62.3	94	70.2	106	11.3	17	7.3	11
Miscellaneous	Do you have any new ear pain?		4568														
	No	88.8	4057	5.3	215	25.2	1024	36.0	1460	25.6	1038	35.0	1419	31.6	1280	17.4	704
	Yes	11.2	511	7.6	39	25.8	132	48.3	247	45.0	230	55.6	284	20.0	102	8.8	45
	Do you have any new lumps in your neck?																
	No	73.2	3346	3.0	100	15.3	513	25.4	850	27.7	926	33.6	1125	36.0	1205	20.6	690
	Yes	26.8	1222	12.6	154	52.6	643	70.1	857	28.0	342	47.3	578	14.5	177	4.8	59
	Persistent	*21.6*	*986*	*14.6*	*144*	*55.9*	*551*	*75.6*	*745*	*30.6*	*302*	*51.3*	*506*	*11.3*	*111*	*2.1*	*21*
	Fluctuating/ reducing	*5.2*	*236*	*4.2*	*10*	*39.0*	*92*	*47.5*	*112*	*16.9*	*40*	*30.5*	*72*	*28.0*	*66*	*16.1*	*38*
	Do you have a new growth on your skin on your head and neck?																

	No	99.0	4522	5.5	247	25.3	1146	37.1	1679	27.4	1241	37.0	1674	30.4	1374	16.5	748
	Yes	1.0	46	15.2	7	21.7	10	60.9	28	58.7	27	63.0	29	17.4	8	2.2	1

Table 1-2: Cancers by time of diagnosis in the HNCTT Study, alongside: triage outcome; clinician advice for assessment; and results of risk stratification. Rows in italic provide further information but are not part of the breakdown for the above row totals. .

		Cancers								
		Urgent			Late			Any time		
	% of all cases	%	Cancers	Total	%	Cancers	Total	%	Cancers	Total
By triage outcome				4555			4326			4553
Urgent assessment	**53.2**	**9.4**	**227**	**2424**	**0.4**	**8**	**2197**	**9.7**	**235**	**2424**
Investigation first	25.4	9.3	108	1156	0.5	5	1048	9.8	113	1156
Investigation at any time	*37.5*	*13.1*	*224*	*1707*	*0.5*	*8*	*1483*	*13.6*	*232*	*1707*
Review first	27.8	9.4	119	1268	0.3	3	1149	9.6	122	1268
Review at any time	*37.4*	*12.7*	*217*	*1703*	*0.3*	*5*	*1486*	*13.0*	*222*	*1703*
Non-urgent	**46.8**	**0.0**	**0**	**2131**	**0.9**	**19**	**2129**	**0.9**	**19**	**2129**
Deferred	30.3	0.0	0	1382	0.9	12	1382	0.9	12	1382
Discharged	16.4	0.0	0	749	0.9	7	747	0.9	7	747
By clinician advice				4501			4274			4499
Clinician advised for assessment	**69.7**	**6.8**	**214**	**3139**	**0.5**	**16**	**2925**	**7.3**	**230**	**3139**
Clinician NOT advised assessment	**30.3**	**0.8**	**11**	**1362**	**0.7**	**10**	**1349**	**1.5**	**21**	**1360**
By risk stratification				4568			4330			4557
High risk	**31.3**	**12.5**	**179**	**1429**	**0.6**	**7**	**1249**	**13.0**	**186**	**1428**
Low risk	**68.7**	**1.5**	**48**	**3139**	**0.6**	**20**	**3081**	**2.2**	**68**	**3129**
OVERALL	100	5.0	227	4568	0.6	27	4330	5.6	254	4557

Table 1-3: Site of primary cancer by time of diagnosis in the HNCTT Study, alongside: proportion found late; and number identified as coming to harm. Yellow highlighted rows are head and neck cancers.

	Cancers							
	Urgent		Late		Any time		Proportion found late	Number coming to harm
Site of primary cancer	%	n	%	n	%	n	%	n
Oropharynx	27.3	62	11.1	3	25.6	65	4.6	1
Lymphoma	18.5	42	11.1	3	17.7	45	6.7	-
Larynx	10.6	24	25.9	7	12.2	31	22.6	5
Thyroid	9.3	21	11.1	3	9.4	24	12.5	-
Lung	4.8	11	18.5	5	6.3	16	31.3	1
Oesophageal	4.4	10	11.1	3	5.1	13	23.1	2
Unknown primary	4.0	9	0.0	0	3.5	9	0.0	-
Hypopharynx	3.5	8	0.0	0	3.1	8	0.0	-
Oral cavity	3.5	8	0.0	0	3.1	8	0.0	-
Salivary	3.5	8	0.0	0	3.1	8	0.0	-
Skin	3.1	7	0.0	0	2.8	7	0.0	-
Breast	1.8	4	0.0	0	1.6	4	0.0	-
Nasal cavity	1.3	3	3.7	1	1.6	4	25.0	1
Nasopharynx	1.3	3	3.7	1	1.6	4	25.0	-
Leukaemia	0.9	2	0.0	0	0.8	2	0.0	-
Ovarian	0.9	2	0.0	0	0.8	2	0.0	-
Colorectal	0.4	1	0.0	0	0.4	1	0.0	-
Liver	0.0	0	3.7	1	0.4	1	100.0	1
Prostate	0.4	1	0.0	0	0.4	1	0.0	-
Renal	0.4	1	0.0	0	0.4	1	0.0	-
TOTAL	89.4	227	10.6	27	100.0	254	10.6	11

Table 1-4: Populations served as declared by trusts submitting data to the HNCTT Study. As available from organisation Annual Reports, public websites or National Health Service trust information at www.nhs.uk.

Centre	Trust	Trust population served (March 2021)	Population served source
Aberdeen Royal Infirmary	NHS Grampian	500000	https://www.nhsgrampian.org/about-us/about-nhs-grampian/
Aintree University Hospital	Liverpool University Hospitals NHS Foundation Trust	630000	https://www.liverpoolft.nhs.uk/about-us/
Antrim Area Hospital	Northern Health and Social Care Trust	470000	https://www.northerntrust.hscni.net/
Birmingham City Hospital	Sandwell and West Birmingham Hospitals NHS Trust	500000	https://www.cqc.org.uk/provider/RXK/reports
Blackpool Victoria Hospital	Blackpool Teaching Hospitals NHS Foundation Trust	330000	https://www.nhs.uk/Services/Trusts/Overview/DefaultView.aspx?id=2096
Broomfield Hospital, Chelmsford	Mid Essex Hospital Services NHS Trust	1200000	https://www.meht.nhs.uk/
Charing Cross Hospital, London	Imperial College Healthcare NHS Trust	1500000	https://www.cqc.org.uk/sites/default/files/new_reports/AAAH1330.pdf
Chase Farm Hospital, London	Royal Free London NHS Foundation Trust	1600000	http://s3-eu-west-1.amazonaws.com/files.royalfree.nhs.uk/Annual_report/Annual_Report_2019-20_final.pdf
Countess of Chester Hospital	Countess of Chester NHS Foundation Trust	250000	https://www.nhs.uk/Services/Trusts/Overview/DefaultView.aspx
Cumberland Infirmary, Carlisle	North Cumbria University Hospitals NHS Trust	340000	http://www.wnecumbria.nhs.uk/wp-content/uploads/2016/09/CQC-NCUH-NHS-Trust-Report-Sept-2015.pdf
East Surrey Hospital, Redhill	Surrey and Sussex Healthcare NHS Trust	535000	https://www.nhs.uk/Services/Trusts/Overview/DefaultView.aspx?id=1120
Glangwili General Hospital, Carmarthen	Hywel Dda University Health Board	387284	https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/Local-Health-Boards/populationestimates-by-lhb-age
Glasgow Royal Infirmary	NHS Greater Glasgow and Clyde	1200000	https://www.scot.nhs.uk/organisations/greater-glasgow-clyde/
Guy's Hospital	Guy's and St Thomas' NHS Foundation Trust	Unavailable	
Hinchingbrooke Hospital, Huntingdon	North West Anglia NHS Foundation Trust	700000	https://www.nwangliaft.nhs.uk/about-us/
Kent & Canterbury Hospital	East Kent Hospitals University NHS Foundation Trust	695000	https://www.ekhuft.nhs.uk/patients-and-visitors/about-us/
Manchester Royal Infirmary (MRI)	Manchester University NHS Foundation Trust	750000	https://mft.nhs.uk/the-trust/
Milton Keynes University Hospital	Milton Keynes University Hospital NHS Foundation Trust	252000	https://www.cqc.org.uk/location/RD816/reports

Ninewells Hospital, Dundee	NHS Tayside	416,090	http://www.nhstaysidecdn.scot.nhs.uk/NHSTaysideWeb/idcplg
Northampton General Hospital	Northampton General Hospital NHS Trust	880,000	https://www.northamptongeneral.nhs.uk/About/Our-Organisation/About-the-Organisation.aspx
Northwick Park Hospital, London	London North West University Healthcare NHS Trust	1,000,000	https://www.nhs.uk/Services/Trusts/Overview/DefaultView.aspx?id=104613
Pinderfields Hospital, Wakefield	The Mid Yorkshire Hospitals NHS Trust	530,000	https://www.midyorks.nhs.uk/download/doc/docm93jijm4n4980.pdf
Princess Alexandra Hospital, Harlow	Princess Alexandra Hospital NHS Trust	350,000	https://www.pah.nhs.uk/about-us/
Queen Elizabeth Hospital Birmingham	University Hospitals Birmingham NHS Foundation Trust	800,000	https://www.birminghamhealthpartners.co.uk/partner-organisations/university-hospitals-birmingham-nhs-foundation-trust-uhb/
Royal Albert Edward Infirmary, Wigan	Wrightington, Wigan and Leigh NHS Foundation Trust	326,000	https://www.nhs.uk/Services/Trusts/Overview/DefaultView.aspx?id=901
Royal Blackburn Hospital	East Lancashire Hospitals NHS Trust	521,000	https://www.cqc.org.uk/provider/RXR/reports
Royal Preston Hospital	Lancashire Teaching Hospitals NHS Foundation Trust	1,500,000	https://www.lancsteachinghospitals.nhs.uk/research-industry/
St John's Hospital, Livingston	NHS Lothian	800,000	https://www.scot.nhs.uk/organisations/lothian/
Stepping Hill Hospital, Greater Manchester	Stockport NHS Foundation Trust	350,000	https://www.stockport.nhs.uk/
Sunderland Royal Hospital	South Tyneside and Sunderland Foundation NHS Trust	430,000	https://www.stsft.nhs.uk/about-us/welcome-stsft
The Royal Liverpool University Hospital	Liverpool University Hospitals NHS Foundation Trust	630,000	https://www.liverpoolft.nhs.uk/about-us/
The Royal Marsden Hospital	The Royal Marsden NHS Foundation Trust	196,000	https://www.cqc.org.uk/location/RPY01/reports
University College London Hospital	University College London Hospitals NHS Foundation Trust	1,300,000	https://www.uclh.nhs.uk/download_file/force/3268/702
University Hospital Coventry and Warwickshire (UHCW)	University Hospitals Coventry and Warwickshire NHS Trust	1,000,000	https://www.cqc.org.uk/provider/RKB/reports
University Hospital Crosshouse, Kilmarnock	NHS Ayrshire & Arran	367,000	https://www.scot.nhs.uk/organisations/ayrshire-arran/
University Hospital Monklands, Airdrie	NHS Lanarkshire	655,000	https://www.nhslanarkshire.scot.nhs.uk/about-us/
University Hospital of Wales (UHW), Cardiff	Cardiff & Vale University Health Board	500,490	https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/Local-Health-Boards/populationestimates-by-lhb-age
Walsall Manor Hospital	Walsall Healthcare NHS Trust	260,000	https://www.nhs.uk/Services/Trusts/Overview/DefaultView.aspx?id=654

Warrington Hospital	Warrington and Halton Teaching Hospitals NHS Foundation Trust	330,000	https://whh.nhs.uk/about-us/our-hospitals
West Suffolk Hospital, Bury St Edmunds	West Suffolk NHS Foundation Trust	280,000	https://www.wsh.nhs.uk/Join-our-team/Why-West-Suffolk.aspx
Wythenshawe Hospital, Greater Manchester	South Manchester NHS Foundation Trust	750,000	https://mft.nhs.uk/the-trust/

Table 1-5: Late cancers being identified as coming to harm in the HNCTT Study.

Demographics	Primary cancer site	Triage outcome	Risk stratification	Harm from worse prognosis?	Harm from escalated treatment?
77M	Larynx	Deferred	Low	No	No
87M	Lung	Deferred	Low	No	No
72F	Lymphoma	Deferred	Low	No	No
81M	Lymphoma	Deferred	Low	No	No
63F	Oesophageal	Deferred	High	No	No
72F	Larynx	Discharged	Low	No	No
72M	Lung	Discharged	Low	No	No
82M	Lung	Discharged	Low	No	No
32M	Nasopharynx	Discharged	Low	No	No
38M	Oropharynx	Discharged	Low	No	No
32F	Lymphoma	Urgent Ix	Low	No	No
30F	Thyroid	Urgent Ix	High	No	No
37M	Thyroid	Urgent Ix	High	No	No
40F	Thyroid	Urgent Ix	Low	No	No
59F	Lung	Urgent Rv	Low	No	No
59M	Oropharynx	Urgent Rv	High	No	No
66M	Larynx	Deferred	Low	No	Yes
77M	Nasal cavity	Deferred	Low	No	Yes
68F	Larynx	Deferred	Low	Yes	No
74F	Lung	Deferred	High	Yes	No
56M	Oropharynx	Deferred	Low	Yes	No
76M	Larynx	Deferred	Low	Yes	Yes
86M	Liver	Deferred	Low	Yes	Yes
76M	Larynx	Discharged	Low	Yes	Yes
70F	Oesophageal	Discharged	Low	Yes	Yes
73M	Oesophageal	Urgent Ix	High	Yes	Yes
40F	Larynx	Urgent Rv	Low	Yes	Yes

1.2 The HNCTT Study for post-treatment surveillance

1.2.1 Full title

Symptom-based remote assessment in post-treatment head and neck cancer surveillance: a prospective national study.

1.2.2 Contributions

Under supervision, the author led this study from conceptualisation, through protocol development, data collection, assimilation, analysis, visualisation and interpretation. Further, the author led on writing, reviewing and editing the text contained herein, which has also been submitted for publication and, at time of writing, is undergoing peer-review.

The author is grateful to the following individuals for their contributions towards the delivery of this study and its write-up:

- Henry Zhang, who helped draft, review and edit the final manuscript, which benefitted from his insight as a senior head and neck surgical trainee.
- Hisham Mehanna and Paul Nankivell, who reviewed and edited the manuscript, which benefitted from their insights as senior head and neck surgeons.
- The numerous Consultant Leads and Trainee Site Leads (named in **Appendix 5**) who facilitated the registration of the study at their institutions and the submission of anonymised patient data to the Project Management Team, as per the study protocol.
- Further thanks is given to the innumerable uncredited clinicians around the country who collected data as part of the National Service Evaluation that formed the core of this work.
- Vinidh Paleri, who supervised the work from conceptualisation to production and approval of the final report.

1.2.3 Abstract *[250 words]*

Objectives

To report the incidence of locoregional recurrence in HNC patients under surveillance following treatment undergoing symptom-based remote assessment.

Design and setting

A 16-week multi-centre prospective cohort study in UK ENT departments.

Participants

HNC patients under surveillance following treatment undergoing symptom-based telephone assessment.

Main outcome measures

Incidence of locoregional recurrent HNC after minimum 6-month follow-up.

Results

Data for 1,078 cases were submitted by 16 centres, with follow-up data completed in 98.9% (n=1,066). Following telephone consultation, 83.7% of referrals had their face-to-face appointments deferred (n=897/1,072). New symptoms were reported by 11.6% (n=124/1072) at telephone assessment; 72.6% (n=90/124) of this group were called for urgent assessments, of whom 48.9% (n=44/90) came directly for imaging without preceding clinical review.

The sensitivity and specificity for new symptoms as an indicator of cancer recurrence were 35.3% and 89.4%, respectively, with a negative predictive value of 99.7% (p=0.002). Locoregional cancer identification rates after a minimum of 6 months of further monitoring, when correlated with time since treatment, were: 6.0% (n=14/233) <1 year; 2.1% (n=16/747) between 1 and 5 years; and 4.3% (n=4/92) for those >5 years since treatment.

Conclusions

Telephone assessment, using patient-reported symptoms, to identify recurrent locoregional HNC was widely adopted during the initial peak of the COVID-19 pandemic in the UK. The majority of patients had no face-to-face reviews or investigations. New symptoms were significantly associated with the identification of locoregional recurrent cancers with a high specificity, but a low sensitivity may limit symptom assessment being used as the sole surveillance method.

1.2.4 Aim

The primary aim of this study was to understand the incidence of locoregional recurrence in HNC patients under post-treatment surveillance undergoing symptom-based remote assessment during the initial peak of COVID-19 in the UK.

1.2.5 Methods

The protocol for this study was published in advance at https://entintegrate.co.uk. This study report has been prepared with reference to the STROBE checklist for cohort studies.

1.2.5.1 Ethical considerations

The Health Research Authority decision tool determined the study design to fall under the remit of service evaluation, and so no ethical approval was required (available at: http://hra-decisiontools.org.uk/research/).

1.2.5.2 Study design and setting

A national prospective service evaluation was conducted, supported by ENT UK (the British Association of Otorhinolaryngology - Head and Neck Surgery) and BAHNO (the British Association of Head and Neck Oncologists), and delivered using INTEGRATE (The UK ENT Trainee Research network). All UK ENT departments were invited to participate via social media and mailouts from the supporting organisations. Sites could open at any point during the prospective data collection period. Registration as per local governance guidelines was required to participate.

1.2.5.3 Participants

Patients were eligible for inclusion if they were under surveillance following treatment for HNC in secondary care, and were undergoing telephone consultation as part of routine follow-up. Patients with known residual/recurrent disease were excluded.

1.2.5.4 Data collection

Cases were identified over a 16 week period, between 23 March and 13 July 2020. Final submission of data was accepted after a minimum 6-month follow-up period for all patients. To be eligible for inclusion, cases had to have complete demographic and symptom data with no null data points. To facilitate this, a standardised electronic case report form was created using Excel software (Microsoft Corporation, Washington, USA) and made available online (**Figure 1-5**, https://entintegrate.co.uk).

Two bespoke results, derived from the 2018 INTEGRATE/BAHNO National Audit of Post-Treatment HNC surveillance,[32] were displayed by the tool for each patient, which were based on the patient characteristics and symptom data entered (**Figure 1-6**). To promote the submission of complete and valid data, these results were only displayed if all relevant fields were completed by the clinician. Firstly, the clinician was presented with the overall rate of cancer diagnosis related to the time since completion of treatment and the presence of new symptoms. Secondly, the tool presented the highest PPV for any relevant symptom that was reported.

Data were held offline at each centre until the follow-up period had passed for all patients, whereupon the patient record was checked by the local team for a diagnosis of cancer at any time since their initial telephone consultation.

The following data were collected: patient demographics; smoking and alcohol history; a symptom inventory comprising 17 locoregional and three general symptoms (based on the HaNC-RC-v2 and United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer 2016);[26,37] subsequent management, including face-to-face reviews and investigations; clinician and patient preference for review/investigation; diagnosis of cancer; time since completion of treatment; and the site of the primary cancer for which they were under surveillance.

Clinicians were asked to record if the patient had experienced '*any new symptoms since your last appointment?*'. Only if answered 'yes' were further symptom questions revealed through conditional formatting.

The Project Management Team (PMT) handled only anonymised data, with all identifiable information removed prior to submission by the local teams. Where missing or ambiguous data were identified by the PMT, a query was raised with the local site to clarify each data point. Where missing data could not be resolved, that record was excluded from relevant analysis.

A user guide was produced to support the clinicians in registering the project locally and to guide data collection (**Appendix 1**). Certificates were produced as evidence of participation for all Consultant leads, Trainee site leads and local collaborators (**Appendix 2**). Collaborative authorship was also offered to all Consultant leads and Trainee site leads for any subsequent publications, as per the protocol (available at https://entintegrate.co.uk/entuk2wwtt). Sites were requested not to submit data until local data governance requirements had been satisfied.

1.2.5.5 Data analysis

The primary outcome was the diagnosis of residual/recurrent/new primary locoregional cancer after a minimum of 6 months follow-up. Distant metastases only were not included.

No *a priori* sample size calculation was performed. Categorical variables were compared using the Fisher's exact test, with a two-tailed p value of 0.05 taken as significant. Analysis was performed using R statistical software (R Foundation, Vienna, Austria).

Results will be presented in tables displaying the entire cohort of patients in view of reported symptoms, to show the association of symptoms to further cancer in the context of time since initial presentation and cancer subsite.

1.2.5.6 Interim report

After 8 weeks, interim data were requested from participating centres and a report was produced to allow rapid feedback of preliminary findings to the UK ENT community. This report was disseminated electronically via an ENTUK mailout on 3 June 2020 and was hosted online at https://entuk.org and https://entintegrate.co.uk (**Appendix 4**).

1.2.6 Results

1.2.6.1 Centres and submissions

Final data were submitted by 16 UK centres who registered to take part (13 in England, 2 in Scotland, 1 in Wales) with 1,078 cases eligible for analysis with complete demographic and symptom data (median 60.5 cases per centre; range 2 to 218; interquartile range (IQR) 8 to 94). A valid outcome from the remote assessment was recorded in 99.4% (n=1,072/1,078) and valid 6-month follow-up was reported in 98.9% (n=1,066/1,078).

The median age for all subjects was 65 (range 19 to 93 years; IQR 56 to 72 years) and 71.9% were male (n=775).

1.2.6.2 New symptoms and management outcome

Table 1-6 shows the identification of locoregional cancer for patients reporting new symptoms, further divided by assessment outcome. The overall incidence of newly identified cancer after 6-month minimum follow-up was 3.2% (n=34/1,066).

At the time of telephone assessment, 14.5% (175/1072) patients were given an urgent appointment, with 69.1% (n=121/175) attending directly for a face-to-face clinic appointment and 30.9% (n=54/175) coming straight to an imaging investigation without prior face-to-face clinical review. For the subset of patients reporting new symptoms, the rate of direct to imaging investigations was significantly higher (48.9% vs 11.8%, n=44/90 vs 10/85; p<0.001)

Following telephone consultation, 11.6% (124/1,072) patients reported new symptoms and 83.7% of referrals had their face-to-face appointments deferred (n=897/1,072). There were 34 patients (3.2%) who reported new symptoms and also had their appointments deferred, none of whom developed locoregional recurrence in the subsequent surveillance period. In those being urgently assessed, the incidence of new locoregional disease was significantly higher in those with new symptoms (13.3% vs 1.2%, n=12/90 vs 1/85; p=0.0026).

Overall, the sensitivity and specificity for the association between new symptoms and new locoregional cancer by the end of the 6-month minimum surveillance period were 35.3% and 89.4% (positive predictive value (PPV) 9.8%; negative predictive value (NPV) 97.7%; p=0.0002).

1.2.6.3 Time since completion of treatment

Locoregional cancer identification rates in the study follow-up period, related to time since completion of treatment, were as follows: 6.0% (n=14/233) within 1 year; 2.1% (n=16/747) between 1 and 5 years; and 4.3% (n=4/92) of those still under follow-up after 5 years (**Table 1-7**). There was a significant association between new symptoms and further cancer for all three cohorts. The lowest specificity was amongst patients more than five years out from treatment (81.8%), highlighting this group as the most at risk of not reporting new symptoms but then developing further cancer during the surveillance period. It should be noted that standard practice in the UK is to follow HNC patients for a period of 5 years, therefore patients in this cohort still under follow up after this time are unlikely to be representative of all patients treated for HNC.

1.2.6.4 Cancer subsite

Table 1-8 shows the distribution of head and neck cancers under post-treatment follow-up by anatomical site. The commonest sites were oropharynx (39.7%; n=426) and larynx (28.2%; n=302), comprising 67.9% of all patients. The rates of reporting new symptoms at telephone assessment are also presented, alongside the locoregional cancer identified by the end of the 6-month minimum surveillance period. Associations between these two factors are explored for each primary site.

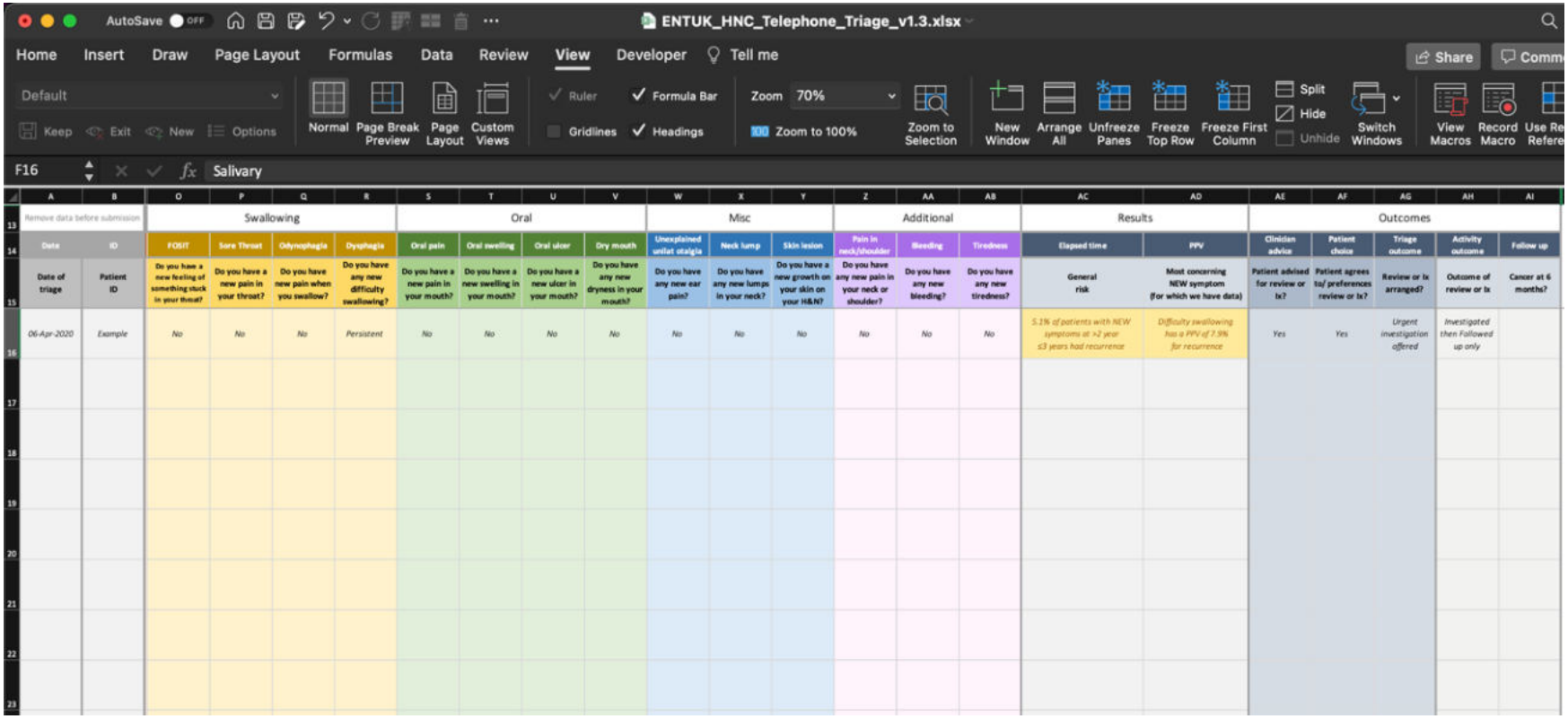


Figure 1-5: Screenshot of the Excel Data Tool used in the HNCTT Surveillance Study. 'Results' columns were only populated if all parameters were completed for each case.

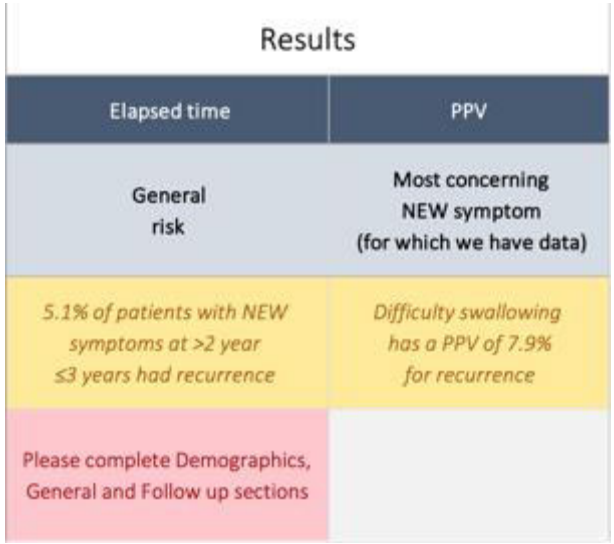


Figure 1-6: Result from the Excel Data Tool in the HNCTT Surveillance Study showing an example of the bespoke output offered to clinicians following completion of relevant data. PPV is positive predictive value.

Table 1-6: New symptoms, assessment outcome and locoregional recurrence in the HNCTT Surveillance Study.

		Further locoregional cancer identified					
		At time of assessment			By end of 6-month minimum surveillance period		
	% of all cases	Cancers	Total	%	Cancers	Total	%
New symptoms	**11.6**	**12**	**124**	**9.7**	**12**	**122**	**9.8**
Urgent assessment	72.6	12	90	13.3	12	89	13.5
Non-urgent	27.4	0	34	0.0	0	33	0.0
No new symptoms	**88.4**	**1**	**948**	**0.1**	**22**	**944**	**2.3**
Urgent assessment	9.0	1	85	1.2	2	85	2.4
Non-urgent	91.0	0	863	0.0	20	859	2.3
TOTAL	**100.0**	**13**	**1072**	**1.2**	**34**	**1066**	**3.2**

Table 1-7: New symptoms, time since completion of treatment and locoregional recurrence in the HNCTT Surveillance Study.
NPV is negative predictive value, PPV is positive predictive value, Sens is sensitivity, Spec is specificity.

	Overall		**New symptoms reported at telephone assessment**		**Further locoregional cancer identified by end of 6-month minimum surveillance period**		**Association between new symptoms and further cancer**	**NPV**	**PPV**	**Sens**	**Spec**
Time since completion of treatment	n	%	n	%	n	%	p	%	%	%	%
≤1 year	233	21.7	37	15.9	14	6.0	0.0467	95.4	13.9	35.7	85.8
>1 year ≤5 years	747	69.7	68	9.1	16	2.1	0.0471	98.2	6.0	25.0	91.4
>5 years	92	8.6	19	20.7	4	4.3	0.0267	98.6	15.8	75.0	81.8
TOTAL	**1072**	**100**	**124**	**11.6**	**34**	**3.2**	**0.0002**	**97.7**	**9.8**	**35.3**	**89.4**

Note: sub-groups with lower specificity are at greater risk of presenting with no symptoms but then developing further cancer.

Table 1-8: New symptoms, site of primary cancer and locoregional recurrence in the HNCTT Surveillance Study.
NPV is negative predictive value, PPV is positive predictive value, Sens is sensitivity, Spec is specificity.

	Overall		New symptoms reported at telephone assessment		Further locoregional cancer identified by end of 6-month minimum surveillance period		Association between new symptoms and further cancer	NPV	PPV	Sens	Spec
Site of primary cancer	n	%	n	%	n	%	p	%	%	%	%
Oropharynx	426	39.7	51	12.0	8	1.9	0.0008	99.2	10.0	62.5	89.2
Larynx	302	28.2	42	13.9	16	5.3	0.0503	95.8	12.2	31.3	87.4
Thyroid	61	5.7	6	9.8	2	3.3	0.1885	98.2	16.7	50.0	91.5
Hypopharynx	55	5.1	6	10.9	2	3.6	1.0000	95.9	0.0	0.0	88.7
Oral cavity	50	4.7	8	16.0	1	2.0	0.1600	100	12.5	100	85.7
Unknown primary	48	4.5	4	8.3	0	0.0	1.0000	100	0.0	-	91.7
Other	37	3.5	3	8.1	1	2.7	1.0000	97.1	0.0	0.0	91.7
Nasopharynx	30	2.8	1	3.3	1	3.3	1.0000	96.6	0.0	0.0	96.6
Salivary	26	2.4	1	3.8	1	3.8	1.0000	96.0	0.0	0.0	96.0
Nasal cavity	23	2.1	1	4.3	1	4.3	1.0000	95.5	0.0	0.0	95.5
Skin	14	1.3	1	7.1	1	7.1	1.0000	92.3	0.0	0.0	92.3
TOTAL	1072	100	124	11.6	34	3.2	0.0002	97.7	9.8	35.3	89.4

Note: sub-groups with lower specificity are at greater risk of presenting with no symptoms but then developing further cancer.

PART 1 Discussion

Remote triage for suspected HNC referrals

The HNCTT Study for suspected HNC was the first multi-centre study to report the effectiveness of remote triage incorporating risk stratification in patients referred to secondary care with suspected HNC.[38] It was also the first study of suspected HNC patients to report medium-term outcomes to identify cancers that may have been missed by current diagnostic practices. This prospective multi-centre study was uniquely placed to learn lessons from the changes in practice brought about by the initial peak of the COVID-19 pandemic in the UK, and offers significant insight into a real world use of a remote triage system, incorporating risk stratification, in suspected HNC referrals. The robust prospectively collected patient-level data allowed direct linkage of the referral symptoms to diagnosis of a related cancer, removing potentially distracting incidental cancers that may contaminate similar studies relying on retrospective database queries.[39]

Despite the pressures on hospitals and clinicians during the initial peak of the COVID-19 pandemic, there was widespread and meaningful engagement with 41 centres contributing data and near complete 6-month outcomes at 99.8%. This has demonstrated stakeholder support to the use of a standardised symptom inventory to record the assessment of suspected HNC patients and is a testament to surgeon-led multi-centre collaborative research in the UK.

A small proportion of patients who were assessed urgently and were discharged from the urgent pathway were diagnosed with cancers at a later time (0.4%). Although this rate was lower than for those triaged as non-urgent (0.9%), it has still highlighted the need for suspected cancer diagnostic services to be judged on medium-term outcomes to allow for delayed re-presentation, and not to use the point of discharge as the definitive endpoint of pathway performance. Given the natural history of HNC, it was felt that six months was an appropriate timescale for a patient to re-present or have had their deferred assessment expedited and receive a cancer diagnosis linked to their referral symptoms. It is acknowledged that the standard 'urgent' pathway for suspected HNC referrals would have had some disruption for those included in **The HNCTT Study for suspected HNC** due to the COVID-19 pandemic.

The sensitivity and specificity of the HaNC-RC-v2 in this population were lower than recorded in the validation work that produced the algorithm, though the negative predictive value of 97.8% remained high.[26,40,41] A number of factors may have influenced this difference in algorithm performance: the symptom landscape of patients presenting to their primary care physicians may have been impacted by the pandemic; the referral practices of primary care physicians may have been affected by fewer patients undergoing face-to-face assessment in primary care;[4] the population differed slightly as this service evaluation included only those referred from primary care on the suspected HNC referral pathway, not routine HN patients who also contributed to the HaNC-RC-v2; the primary outcome for the present study was cancer at six months minimum, thereby also taking into account late diagnoses; the overall incidence of cancer in this study was lower; patients contributing to HaNC-RC-v2 were also examined which may have influenced how symptoms were recorded by clinicians;[42,43] and this multi-centre national study involved a greater number of clinicians

over a wider geographical area than used to generate the HaNC-RC-v2. Further analysis of the data collected in this study will help inform future risk stratification algorithms for suspected HNC referrals undergoing remote triage.

The overall cancer incidence of 5.6% identified in **The HNCTT Study for suspected HNC** is consistent with rates reported in the literature and by national datasets, which vary between 3.6% and 11.8%, and also corresponds with a national trend towards lower incidence rates in this population over time.[26,39,44–46] As the number of suspected cancer referrals to secondary care increases, risk stratification may become even more important for appropriate use of hospital resource allocation and identification of cancers which represent a diminishing proportion of the referrals coming in. However, burdening primary care physicians with collecting and recording symptom data for risk stratification is unlikely to be appropriate. Firstly, the referral to secondary care, in part, helps to allay patient anxieties as they feel they are getting specialist input. Secondly, accurate and consistent recording of symptom data may rely on clinical experience from a specialist. Indeed, encouraging more referrals from primary care is desirable in order to identify cancers at an earlier stage in the hope of improving prognosis and/or reducing treatment intensity.[47] Appropriate risk stratification could be part of the strategy to handle higher volumes of referrals to deliver on these goals in the future and is a central facet to The EVEREST-HN Programme.

The majority of patients who were felt to have come to harm were observed in the deferred group (n=8/11) who did not undergo any urgent assessment and who were not discharged back to primary care. Clinicians may choose to monitor a patients' symptoms, to give opportunity to resolve with conservative management or a 'trial of time', but this should not be at the expense of appropriate examination and/or investigations in higher risk patients. It should be noted that the practice of deferring appointments was likely exacerbated by the pandemic, reflecting prevailing public health advice at that time to reduce hospital visits. Certain symptoms and practices were identified by this service evaluation as being at particular risk of late diagnosis and HN clinicians should be particularly mindful of thoracic pathology manifesting with HN symptoms (**Table 1-1** and **Table 1-3**). A history of Intermittent hoarseness may be indicative of a weak vocal cord from a palsied recurrent laryngeal nerve, brought on by a lung lesion or mediastinal mass, and so should prompt direct visualisation or appropriate cross-sectional imaging. Reports of dysphagia in the presence of normal upper aerodigestive tract examination should prompt urgent oesophageal endoscopy to rule out more distal lesions.[48] **The HNCTT Study for suspected HNC** confirmed the finding of a third of cancers on the suspected HNC referral pathway being non-HN cancers, corroborating previous reports.[45]

*Limitations to **The HNCTT Study for suspected HNC***

The following limitations are acknowledged: the use of only local data may have missed patients who subsequently presented to other units; it is not possible to assert that consecutive patients were included from all centres or submitted by each clinician; local practices may have included pre-screening of suspected HNC appointments to ensure they were suitable for remote triage; no data were received by the study management team on patients in whom the remote triage and risk stratification process was incomplete; and, the rate of oral cancer was lower than anticipated, reflecting low engagement from oral surgery and maxillofacial specialties.

Future study of remote triage in suspected HNC referrals

The EVEREST-HN Programme is ideally placed to continue to investigate remote triage for suspected HNC referrals using surgeon-led multi-centre collaborative research. Remote triage, involving live and contemporaneous dialogue with the patient, such as telephone or video call, allows symptom data to be obtained but still requires both the patient and clinician to be available at the same time and, most commonly, during normal working hours. Shifting to electronic data capture, with symptoms reported directly by the patient outside of a synchronous consultation, also allows for processing of the referral at any time of day, and allows for up-front processing of the information, including risk stratification, before the referral is reviewed by a clinician.

The most notable limitation anticipated from The EVEREST-HN Programme is the applicability of the risk stratification algorithm itself. Owing to the relatively low incidence of cancer in the suspected HNC referral population (around 5%), an accurate algorithm must necessarily see many thousands of patients to be useful. In order to generate a useable algorithm within the available time and resources of a PGfAR grant, this algorithm will be based on around 5,000 patients. Additionally, when considering the full gamut of cancers that may present following a suspected HNC referral (**Table 1-3**), a single algorithm will be biased towards the cancers with the highest incidence, namely oropharyngeal and laryngeal.

The full benefit of the programme will likely be realised following its completion when symptom data from 52,000 suspected HNC referrals and their cancer statuses will be available. At this point, it is anticipated that multiple algorithms may be developed to consider risks for rarer symptom clusters and rarer cancers. Additionally, regional variations in practice and cancer incidence may be explored.

It is hoped that, even with an algorithm that will have a known 'miss rate' (in that its sensitivity will fall short of 100%) the complex intervention and change in triage behaviours that define The EVEREST-HN Programme, will be shown to be overall worthwhile. Firstly, in patient experience; secondly, in clinician experience; and thirdly, to the efficiency of the healthcare service as a whole.

Conclusions for remote triage for suspected HNC referrals

Remote triage, augmented by risk stratification, was widely adopted in the care of suspected HNC referrals in response to the initial peak of the COVID-19 pandemic. Appropriately implemented, **The HNCTT Study for suspected HNC** has shown it may facilitate more targeted investigations for high-risk patients and help avoid unnecessary hospital attendance for the lowest risk patients. Deferring appointments, without appropriate escalation to urgent assessment or discharge with safety netting, may be associated with particular risk of harm. Further study is needed and will be explored through the comprehensive ground-up research programme delivered by the author and the supervising team over the next six years (The EVEREST-HN Programme).

Remote triage in post-treatment HNC surveillance

The HNCTT Study for post-treatment surveillance was a prospective multi-centre cohort study that was uniquely placed to investigate a major shift in practice in HNC surveillance, catalysed by the COVID-19 pandemic in the UK. The findings corroborate those of previous retrospective studies, showing symptoms to be an effective method for identifying residual, recurrent or new primary disease in this group of patients, but which may have been confounded by face-to-face clinical examination.[32,49,50]

Nearly three-quarters of the 11.6% of patients who reported new symptoms at telephone assessment were offered an urgent face-to-face appointment or imaging investigation. Additionally, the rate of locoregional recurrence was significantly higher in those who reported new symptoms (9.8%) compared to those who were symptom free at time of telephone assessment (2.3%; p=0.0002, **Table 1-6**). This association suggests that using patient-reported symptoms as a predictor of disease may be an appropriate initial assessment tool in similar contexts. Current practice relies heavily on scheduled outpatient reviews but it is possible that focusing resources on patients who report new symptoms could lead to earlier identification of locoregional recurrent disease, as well as save resources on potentially superfluous outpatient appointments.

However, caution must be exercised, as the relatively low sensitivity of 35.3% indicates a reasonable number of patients were found to have further locoregional disease who may not present with specific symptoms. The high specificity (89.4%) reflects the low incidence of cancer in those patients who did not report new symptoms. These findings were consistent even when stratifying for time since completion of treatment and by cancer subsite, showing agreement across a wide spectrum of patients. A small number of patients (22) were identified to have further cancer during the surveillance period, and this is reflected in the groups with lower specificity. No particular group was identified to be at a markedly higher risk of developing further cancer having reported no new symptoms, as shown by the relatively high specificities (time since treatment: 81.8% to 91.4%, cancer subsite: 85.7% to 96.6%). These findings may offer further impetus for adoption of a patient-initiated, symptom-based follow-up model, as previously proposed,[32] but in conjunction with additional elements given the low sensitivity.

Symptom-based remote assessment was not shown to be equally effective in all subgroups investigated in **The HNCTT Study for post-treatment surveillance**. New symptoms in patients over five years since initial treatment did not correlate well with the development of new cancers (specificity 81.8%). It was also observed that the rate of further cancers in this group was higher than for patients one to five years post treatment. As such, this cohort is unlikely to be representative of all HNC patients and caution should be observed for remote review, especially for HNC subtypes like laryngeal cancer, which have previously been shown to recur later than oropharyngeal and hypopharyngeal subtypes.[51]

It should be noted that many aspects of the standard-of-care pathway for post-treatment HNC patients were disrupted by the Covid-19 pandemic. Most notably, the shift to remote consultations precluded any chance of physical examination at the time of assessment. As such, symptoms could not be linked to clinical signs, and incidental examination findings in otherwise asymptomatic patients would never be investigated. Clinicians should be mindful when conducting remote assessments that early post-treatment symptoms can mimic those of residual or recurrent disease, and as such, have a low threshold for investigating patients further.[52]

During this initial period of the COVID-19 pandemic, instrumentation of the upper aerodigestive tract was discouraged over fears of contamination and aerosol generation.[14] This shift in practice was at odds to the current practice of HNC surveillance in the UK, where routine scheduled clinical review including flexible nasendoscopy is gold standard.[37] The PET-NECK trial showed a scheduled FDG-PET-CT at three months resulted in lower morbidity and costs than routine neck dissections following chemoradiotherapy for head and neck squamous cell carcinoma.[53] Other studies have suggested a role for FDG-PET-CT for detection of further disease at the primary site.[52,54,55] It is possible that wider adoption of scheduled post-treatment imaging, used alongside a patient-reported symptom-based model, may facilitate earlier detection of recurrence and be more responsive to patients' needs. The PET-NECK-2 trial may go some way towards answering this question, though results are still some way off.[56]

*Limitations to **The HNCTT Study for post-treatment surveillance***

The following limitations are acknowledged: the use of only local data may have missed patients who subsequently presented to other units; it is not possible to assert that consecutive patients were included from all centres or submitted by each clinician; local practices may have included pre-screening of suspected HNC appointments to ensure they were suitable for telephone assessment; and the rate of oral cancer was lower than anticipated, reflecting low engagement from oral surgery and maxillofacial specialties.

Finally, asking about 'any new symptoms since your last appointment' may have been interpreted differently by individual clinicians. For example, the recurrence of a symptom from the primary disease presentation, or a worsening of an already prevalent symptom, may not have been interpreted as truly 'new', influencing the recording.

Conclusions for remote triage in post-treatment HNC surveillance

Telephone assessment, using patient-reported symptoms, to identify new locoregional disease in post-treatment HNC patients was widely adopted during the initial peak of the COVID-19 pandemic in the UK. The majority of patients had no face-to-face reviews or investigations as a result.

In **The HNCTT Study for post-treatment surveillance**, new symptoms were significantly associated with the identification of locoregional recurrent cancers with a high specificity, but a low sensitivity may limit symptoms alone being used as the sole surveillance method.

However, patient-reported symptoms, in combination with other surveillance strategies, may be acceptable to patients and facilitate a more appropriate use of healthcare resources.

PART 2 NATIONAL CONSENSUS FOR HNSCCUP CARE

Precis of studies contributing to **PART 2**

- **The MOSES Study** prospectively recruited head and neck squamous cell carcinoma of unknown primary (HNSCCUP) patients undergoing tongue base mucosectomy (TBM) and subjected their diagnostic oropharyngeal specimens to step serial section (SSS) histopathological processing.
- **The HNSCCUP National Audit 2021** assessed the management and outcomes in HNSCCUP patients undergoing diagnostic PET-CT over a 5-year period in the UK.
- **The HNSCCUP Consensus Exercise** used a National Consensus Day and Delphi methodology to generate consensus recommendations for the management of HNSCCUP in the UK.

Introduction to **PART 2**

This introduction sets out the background to the initial presentation and management of HNSCCUP to setup the rationale for the projects contained within **PART 2**.

Background to the presentation and initial management of Head and Neck SCC of Unknown Primary (HNSCCUP)

The management of de novo neck masses is part of routine clinical practice for the head and neck cancer clinician. The differential diagnosis is broad and varies from transient benign lesions to manifestations of advanced and aggressive malignancies. A principal role of the managing clinician is to arrive at a diagnosis. The work-up should seek to obtain the most clinically relevant information possible, as quickly as reasonably practicable, whilst minimising any unnecessary delay, exposure to harmful radiation or morbidity from diagnostic biopsies and procedures.

'Unknown primary' head and neck cancer is far from a single entity. Indeed, the purpose of the diagnostic work-up is to remove this label from as many patients as possible, in order to offer the highest-quality patient-centred care, tailored to the individual patients' disease. Regardless, at the end of this diagnostic process, a subset of patients will persist with regional or distant metastatic disease without an identifiable primary tumour site. Indeed, those whose primary site is identified along the way will be treated according to their specific tumour management algorithms.

Squamous cell carcinoma (SCC) is the most common histopathological subtype in the unknown primary head and neck cancer. Whilst other cell types may be encountered in small numbers in clinical practice, a different array of putative sites may be considered. As a result, diagnostic imaging, diagnostic surgery and therapeutic options will differ.

Classification and Epidemiology of HNSCCUP

A definitive rate for the occurrence of unknown primary cancer in the head and neck is difficult to establish from the published literature for a number of reasons. Firstly, as technologies like PET-CT and tongue base mucosectomy emerge, the detection rate of previously evasive primaries is increasing.[57,58] Secondly, the disease profile for head and neck SCC has changed over the past decades, with an increased prevalence of high-risk human papillomavirus (HPV) associated disease which is heavily associated with head and neck SCC of unknown primary (HNSCCUP).[59] Thirdly, as mentioned previously, the classification of what constitutes an unknown primary changes as the patient progress through their diagnostic pathway. Consequently, the medical literature uses the term 'unknown primary' to apply to a spectrum of clinical entities, applied at any point from presentation with a neck lump to starting treatment for a metastatic deposit without a confirmed primary site of origin.

Proposed classifications

Patients who present with a neck lump may be classed as having **clinically suspected metastatic cancer from an unknown primary** but should only acquire that label following a comprehensive clinical assessment, including FNE, and only if the neck lump is presumed to be metastatic from an epithelial site in the upper aerodigestive tract (UADT). Once cyto-pathological sampling has been performed, either from fine needle aspiration, core biopsy or open biopsy, and this has confirmed SCC, then the patient may be said to have a **clinically suspected HNSCCUP**. Cross-sectional and/or functional imaging is commonly the next step in the diagnostic pathway (see below) and if this returns negative for a primary site, the patient may be classed as being a **clinico-radiological HNSCCUP**. In most instances, after imaging, diagnostic surgeries are performed and if the primary site remains elusive, the patient may be said to be a **histopathological HNSCCUP**. Finally, following exhaustion of the diagnostic pathway, as determined by the managing team, the patient may be referred to as a **treated HNSCCUP**, even if management is only palliative.

Epidemiology

Perhaps the most consistent cohort of 'unknown primaries' to comment on is those treated as HNSCCUPs, as for tracking outcomes, these patients will have consistently started their post-treatment surveillance period with this label. Incidence rates quoted in the literature vary and are not always well referenced but historically appear to be around 2%.[60] **The HNCTT Study for suspected HNC** (found in **PART 1** of this thesis) looked at 4,568 suspected HNC referrals from primary to secondary care in the UK and identified a slightly higher rate of 3.5% (n=9/254) of the identified cancers who were **treated HNSCCUP**s.[2] However, these statistics are not overly helpful to clinicians on the frontline managing suspected HNC patients as these values represent patients at the end of their diagnostic journey, not the start of it. It would perhaps be more useful to consider patients at each stage of the diagnostic pathway; to understand the pick-up rates from clinical examination, diagnostic imaging and diagnostic surgery. However, robust data in these areas are not yet forthcoming, largely owing to the difficulty of studying the pathway of a condition that is relatively rare and where the working diagnosis is frequently changing.

Histopathology

Again, the concept of what is considered an 'unknown primary' must be confronted. Before clinical assessment and cytopathological sampling has been completed, the full gamut of benign and malignant, primary and secondary lesions, must be under consideration for the patient presenting with a neck lump. A not insignificant number of patients in this group will be found to have reactive lymphadenopathy, negating the need for any further diagnostic investigations. Some will resolve to be primary malignant disease, such as lymphomas, and so will continue down their respective management pathways. However, some will be shown to be metastatic deposits and, in these instances, the specific cellular subtype (and other markers) will give clues as to the origin of the primary disease.

The most common metastatic cell type in the head and neck region is SCC.[61] Identification of different biomarkers, in addition to the cell type, can help to point to specific primary sites: the presence of Epstein-Barr virus-encoded RNAs (EBERs) on *in situ* hybridisation points toward a nasopharyngeal origin;[62,63] and, the overexpression of the tumour suppressor gene p16 may be seen with HPV cancers, strongly associated with oropharyngeal primaries in the modern era.[59] However, p16 overexpression is also seen in cutaneous malignancies.[64,65] In such cases, the pattern of cervical nodal involvement may be key to directing further work-up. Cutaneous lesions may not necessarily involve the deep cervical chain (levels II-IV) and may be more likely to involve supraclavicular, parotid or perifacial nodes, even in isolation.[66] Confirmation of HPV infection may also help point towards a mucosal origin either through in situ hybridisation for HPV DNA or reverse transcriptase polymerase chain reaction (RT-PCR) for mRNA showing transcriptionally active HPV infection.[67] Where nodal involvement is isolated to the supraclavicular nodes (level V) and SCC is confirmed, epithelial sites outside of the head and neck must be given due consideration, with the lung and oesophagus being amongst the most common primary locations.[68,69]

Cell types other than SCC may also present a diagnostic uncertainty. Adenocarcinoma may originate from minor salivary glands of the head and neck or from many other sites in the body, including the oesophagus, stomach, intestines, pancreas, lung, breast, cervix, ovary and prostate.[70,71] Ancillary testing with immunostaining may identify proteins specific to a primary site, narrowing the search considerably.[72] Melanoma is also known to present with metastatic disease without obvious primary site and may have mucosal origins in the nasal cavity or sinuses in addition to the more commonly seen cutaneous source.[73]

Non-surgical diagnostic work-up to become a clinico-radiological HNSCCUP

Clinic-based assessment

History

Symptoms related to the full spectrum of head and neck primary sites must be explored at the initial presentation, alongside further system reviews if non-head and neck sites are suspected. Particular attention should be paid to a history of previous cancer and these sites should be assumed to be responsible for any newly presenting neck masses until recurrent disease is ruled out. Otalgia deserves a special mention as the clinician should be cognisant it may represent irritation of the glossopharyngeal nerve supplying the pharynx referring pain to the tympanic cavity (tympanic plexus via Jacobson's nerve). Additionally, supraclavicular pain,

not attributable to nodal disease, may relate to diaphragmatic irritation (of the phrenic nerve) referring to cutaneous branches of the cervical plexus (via the supraclavicular nerves). Unusually, cough may relate to ear canal pathology (via Arnold's nerve, a branch of the vagus). Reports of central lower neck or throat pain or difficulty swallowing may relate to oesophageal pathology. In most other sites, disease would commonly manifest with local symptoms.

It is also worth mentioning that synchronous primaries are common in HNC patients.[74] As such, investigations should be continued for further primary sites if the nodal pattern or sidedness of the metastatic disease is not as expected.

Direct clinical examination

Cytopathological confirmation that the neck lump is a metastatic deposit is not normally available at the time of initial presentation. Regardless, a comprehensive clinical evaluation of potentially putative primary sites should be part of the standard work-up. The principal level of nodal involvement may direct the examination to the most probable primary sites: e.g., for submental or submandibular nodes the oral mucosa should be scrutinised; for parotid or superficial nodes sun exposed skin should be surveyed; and for supraclavicular nodes the scalp and nasopharynx should be closely examined. The clinician should remove dentures and should use spatulas to allow for comprehensive visual assessment of the oral cavity. Additionally, an otoscope should be used to examine the external auditory canal and tympanic membrane when a cutaneous primary is considered.

Endoscopy with or without Virtual ChromoEndoscopy (VCE)

Comprehensive visual assessment of the mucosa of the upper aerodigestive tract should include flexible nasendoscopic (FNE) assessment of the nasal cavities, pharynx and larynx in the office setting before being labelled a clinically-suspected unknown primary. If a primary site is not immediately obvious on FNE then the patient may be asked to perform specific manoeuvres to expose more troublesome subsites: the head may be turned to the side to open the contralateral piriform fossa; the jaw may be protruded to open the laryngeal inlet and view the laryngeal surface of the epiglottis; and the tongue may be protruded to expose the valleculae.

Modern endoscopic equipment may incorporate non-white light technologies, broadly termed 'virtual chromoendoscopy' (VCE), to improve the contrast between the mucosal surface and its related vasculature, without the use of topical or intravenous dyes.[75] The increased vascularity seen in malignant tissues may allow primary site identification under VCE, that would not be apparent under white light alone, in as many as 35% of cases.[76]

Cyto-pathological confirmation

Cytology and core biopsy

The gold standard for achieving a cyto-pathological biopsy is ultrasound-guided needle sampling.[77] Characterisation of the lesion with ultrasound allows benign appearing lesions to be appropriately left undisturbed compared to free-hand sampling. For those appearing malignant, fine needle aspiration cytology (FNAC) can be used to obtain cells, or groups of cells, which may be analysed to determine the site of origin of the lesion where a metastatic deposit is suspected. In the majority of cases cytology is sufficient for

diagnosis.[78] However, in some cases, core biopsy may be necessary offering two main advantages: firstly, it allows the specimen to undergo histological evaluation, meaning the cells can be appreciated in the context of the tissue, not just in isolation; and secondly, in many centres, phenotyping for HPV and EBV are more easily performed on the blocks of tissue obtained from a core than on the individual cells available through FNAC, which may require techniques like 'cell blocking' to allow immunohistochemistry to be performed.

Diagnostic imaging

Ideally, to minimise the potential for confounding from post-procedure inflammatory changes, all diagnostic imaging should be completed before any diagnostic biopsies are performed.[79] Additionally, with up to 10% of clinico-radiologically unknown primary cases being found to have synchronous primary disease following diagnostic biopsies, radiologists should consider identifying multiple possible primary targets when reviewing any imaging to ensure no potentially viable lesions are overlooked.[80–82]

CT and MRI

Contrast-enhanced CT and/or MRI of the neck are the modalities of choice for assessing primary sites in the head and neck. When no primary site is clinically evident, these investigations may still be arranged in an attempt to detect submucosal disease. Research into the use of investigations of unknown primary disease is challenging: prospective studies are not common owing to the relative rarity of the disease; and retrospective studies struggle with patient identification and classification of 'unknown primary' disease early in the pathway, as covered earlier. As such, estimation of the number of suspected HNSCCUP who have a primary site correctly identified with imaging investigations is not straight-forward and this is particularly applicable to CT and MRI which may be arranged early in the diagnostic pathway where true numbers are very much unknown. This selection bias may lead to published rates of primary lesion identification being lower than experienced in routine clinical practice but this is already fairly high as around 79%, suggesting CT and MRI are effective in the majority of cases of clinically suspected HNSCCUP disease.[83]

PET-CT

18F-Fluorodeoxyglucose-PET-CT has been shown to be effective in the evaluation of HNSCCUP, with primary tumours detected in around a third of patients.[84–86] PET-CT is commonly performed as a second line investigation, after conventional contrast-enhanced CT and/or MRI have failed to identify a probable primary site. However, arranging first-line concurrent MRI and PET-CT for all patients with suspected HNSCCUP may optimise the chances of identifying elusive primary lesions in a timely manner through combination of three modalities, thereby avoiding progression to speculative diagnostic surgeries and reducing the time to starting definitive treatment.

Surgical diagnostic work-up to become a clinico-radiological HNSCCUP

In a minority of patients, the primary site remains clinically and radiologically occult despite comprehensive clinical and radiological work-up.[87] In these patients, speculative diagnostic surgery of putative primary sites is commonly advocated in a final attempt to identify a culpable cancer before definitive treatment is undertaken.[88]

The rationale for oropharyngeal diagnostic surgery

Over recent years, there has been an increasing recognition of the role of HPV infection in HNCs[61,89] and this association has also been observed in unknown primary disease.[90] In parallel, tongue base mucosectomy (TBM) has been increasingly adopted in clinico-radiologically occult primary disease, where the oropharyngeal lymphoepithelial tissue is likely to be the origin of the majority of HPV-related cases.[91,92] However, a number of fundamental issues remain with the rationale for performing this speculative diagnostic surgery. Firstly and most fundamentally, identification of a primary site has not been definitively linked to improved oncological outcomes. Secondly, the biological and clinical behaviour of these tumours has not been shown to be similar to their clinically or radiologically evident oropharyngeal tumours. And thirdly, the occurrence of multifocal disease means that incomplete oropharyngeal sampling may be falsely reassuring even after a single primary has been identified.[74,93] Regardless, in spite of extensive diagnostic work-up including speculative diagnostic surgery, a number of patients will go on to start treatment as HNSCCUP.[87] Accepting that current practice may include palatine tonsillectomy and TBM, it may then be asked if there is any more that could be done with the resultant specimens to improve identification rates?

PART 2.1: Understanding the histopathological processing of tissues after surgical removal for HNSCCUP

Once diagnostic tissue samples have been obtained from putative primary sites, they undergo histopathological processing including fixation into tissue blocks, commonly measuring around three millimetres in depth. Conventional histology (CH) techniques obtain a representative section from each block which is subjected to microscopic analysis by a qualified pathologist. Theoretically, small clinico-radiologically occult primary cancers could reside within this tissue block and be overlooked using these standard techniques. A histopathological processing technique called step serial sectioning (SSS) has been used to examine tissue specimens with greater fidelity by sampling the entire tissue block at regular intervals, reducing the chance of missing small tumours that may otherwise be overlooked. The use of this technique has previously been reported in head and neck cancer[94–97] but it has not been applied to diagnostic specimens in this interesting subset of challenging patients with unknown primary disease. In **PART 2**, **The MOSES Study** will use SSS to help answer this question.

PART 2.2: Understanding the diagnostic pathway and impact of treatment on survival in HNSCCUP

Understanding the diagnostic pathway in HNSCCUP

An ideal pathway to investigate a patient with suspected HNSCCUP starts with clinical examination, including flexible nasendoscopy, in search of a primary site. Confirmation of regionally metastatic disease with FNAC and/or core biopsy should follow urgently and ideally be conducted with ultrasound guidance. Urgent cross-sectional imaging (CT and/or MRI) should be obtained for staging and to search for the clinically occult primary site, with the addition of 18F-FDG-PET-CT.[98] However, anecdotally, this patient group experiences significant variation across the UK, and globally, in their diagnostic evaluations before being pronounced an HNSCCUP and starting definitive treatment. In the absence of a standardised diagnostic pathway, patients with HNSCCUP

experience protracted investigation and are unlikely to meet the NHS' 28-Day faster diagnosis standard (FDS) or the first definitive treatment (FDT) for new cancer diagnoses.[99–101]

Numerous clinical practice guidelines exist for the management of HNSCCUP, largely based on evidence from single-institution retrospective studies.[102,103] However, with the advent of high-yield diagnostic techniques such as modern cross-sectional imaging, PET-CT, and tongue base mucosectomy (TBM), historical management strategies and clinical outcomes are becoming increasingly outdated. Furthermore, the increase in HPV related HNC has changed the disease profile of HNSCCUP, influencing the pattern of distribution of putative primary sites, diagnostic surgeries, and prognosis.[104,105] Understanding current HNSCCUP diagnostic pathways is an important step toward improving the experience and outcomes for these patients, whilst improving diagnostic efficiency.

Understanding the impact of treatment on survival in HNSCCUP

For the multitude of reasons already discussed, the published 5-year overall survival rates range widely in the literature from 49-73% across case series.[87,106–108] One variable that may have significant impact on outcomes is the relative combinations of surgery and radiotherapy. The 2016 UK MDT HNC guidelines recommended patients with N1 disease without extranodal extension (ENE) should be treated with single modality surgery.[109] The 2020 ASCO guidelines go further, advocating the possibility of surgical management alone for small-volume unilateral neck disease, irrespective of ENE, and for small-volume bilateral neck disease with no clinical ENE.[103] However, surgical treatment alone risks leaving putative primary sites unaddressed as, even if bilateral tonsillectomy and tongue base mucosectomy has been performed to remove the oropharyngeal lymphoepithelial tissue, this cannot hope to cover every potential epithelial site of origin for a HNSCCUP. Without the administration of radiation therapy or systemic anticancer therapy, neck dissection alone may risk primary emergence or development of clinically occult micrometastases outside of the resected nodal neck levels. Understanding and critiquing the contemporary management of patients treated for regionally metastatic head and neck SCC without an identified primary site is key to improving the experience and outcomes for these patients.

In **PART 2**, **The HNSCCUP National Audit 2021** will investigate the diagnostic pathway and oncological management of HNSCCUP in the UK.

PART 2.3: Developing guidelines to influence patient care

National guidelines are an effective tool to attempt to standardise care and improve patient outcomes. Various methods have been employed to generate national guideline recommendations.[110–112] The management of HNSCCUP has been the subject of a number of these methods which have been used to produce the most widely referenced recommendations.[88,98,102,103,109,113] However, the successful adoption of new guidance into standard practice is not just dependent on assimilation of the best available evidence, but also relies on buy-in from the clinicians delivering day-to-day patient care. Guidelines must be considerate of existing resource constraints, as well as being aspirational in their scope. Current strategies to generate guidelines may involve meetings behind 'closed doors' and/or rely on a handful of 'experts' not familiar with the full gamut of practice preferences and limitations across the healthcare system.[98,109,111,112]

The Delphi process is often used in scenarios where refining a group opinion is desired and has previously been successfully implemented in head and neck oncology.[114–116] It relies on anonymised responses, to reduce bias from dominant individuals, and iterative feedback, to provide group pressure towards conformity.[117] A Delphi exercise may be used to allow a wider range of stakeholders to review a set of draft recommendations before adoption, even if the recommendations have been generated using robust procedures and based on the best available evidence with little equipoise. This may have two benefits: firstly, it allows for a greater number of individuals to input into the process than may be able to attend a time-constrained event such as a consensus day, and secondly, it may help to consolidate more universal buy-in to the resultant output as more stakeholders have been included in production.

Multidisciplinary team (MDT) meetings in healthcare are already set up to consider relevant evidence and deliver consensus opinions. They are mindful of patient wishes and requirements, and of their own local practice capabilities.[118] As such, they are well placed to consider the impact of clinical recommendations on the healthcare they can deliver. Whilst individual MDTs may have particular biases towards more dominant specialties therein, an exercise that seeks to include all MDTs in a given field would be able to mitigate much of this local variation to maximise the suitability of any consensus guidelines agreed upon.

Additionally, funding is not always available to support the development of clinical practice guidelines. This may be a particular issue for rarer conditions (such as HNSCCUP) that may struggle to attract similar funding compared to more common diseases that can attract more attention. Consequently, methodologies that can utilise voluntary effort and can delegate the workload to multiple stakeholders, may be desirable.

And so to **PART 2**...

PART 2 includes three linked projects to further our understanding of HNSCCUP management. Evidence from **The MOSES Study** and **The HNSCCUP National Audit 2021** was presented at a National Consensus Day as part of **The HNSCCUP Consensus Exercise**, ultimately leading to production of the **Final HNSCCUP MDT Consensus Guidelines**. Appreciating the full impact of this body of work will be possible in years to come but the conduct of these multi-centre surgeon-led collaborative projects has already engaged a multitude of clinicians from a variety of backgrounds across the country.

2.1 The MOSES Study

2.1.1 Full title

Evaluation of the role of tongue base MucOsectomy and Step sErial Sectioning in the management of the unknown primary squamous cell cancer in the head and neck.

2.1.2 Contributions

The initial funding for this study had been secured prior to the author starting the Clinical Research Fellow post around which this Doctoral thesis is centred (**Appendix 9**). However, the study protocol was developed by the author alongside the primary and backup supervisors. As a result of this development, a further grant application was submitted (and successfully awarded) in order to recognise the increased scope of the study (**Appendix 10**).

At the appointment of the author into post, there was no established HN surgical research infrastructure at The Royal Marsden NHS Foundation Trust. As such, all sponsor and site trial management responsibilities were initially undertaken by the author, including multi-centre study setup, recruitment, data collection and assimilation. Over time, the department has grown and these responsibilities have been taken over by appropriate research and development staff. However, the experience gave the author invaluable insight into the requirements of establishing and running multi-centre surgical trials.

The author has further led on writing, reviewing and editing the text contained herein, which at time of writing, is being prepared submission for peer-review and publication.

The author is grateful to the following individuals for their contributions towards the delivery of this study and its write-up:

- The HN surgery research and development department at The Royal Marsden, with particular mention to Amy O'Reilly.
- The various Principal Investigators outlined in **Appendix 11** who have been integral in establishing the MOSES study at their centres and recruiting patients.
- Vinidh Paleri and Kevin Harrington, who supervised the work from conceptualisation (VP), through to protocol development, and then to production and approval of the final report.

2.1.3 Abstract *[265 words]*

Objectives

In patients presenting with suspected head and neck squamous cell carcinoma of unknown primary (HNSCCUP), tonsillectomy and tongue base mucosectomy (TBM) are used to help identify clinico-radiologically occult primary disease.

This study aimed to establish the effectiveness of a step serial section (SSS) histopathological technique over conventional histology (CH) when analysing these diagnostic tissue specimens.

Materials and Methods

Adults with clinico-radiologically occult HNSCCUP undergoing TBM were recruited to the multi-centre MOSES study (ClinicalTrials.gov: NCT04151134). Tissues underwent CH at participating centres and then SSS at a central laboratory.

Results

Tissue from 58 eligible patients was analysed (median age 58, range 47-82; 17.2% female), with 20,480 sections cut in the laboratory and 4,096 sections examined by a pathologist (median 64 per patient, range 28-135). The most common diagnostic scenarios and their outcomes were: TBM following historic tonsillectomy (incidence 36.2%; primary found in 57.1%, 95% CI 36.5-75.5); TBM after negative bilateral tonsillectomy (incidence 25.9%; primary found in 42.9%, 95% CI 21.4-67.4); and TBM with bilateral tonsillectomy (incidence 24.1%; primary found in 46.7%, 95% CI 24.8-69.9).

CH techniques at central review identified two undiagnosed primary tumours and revised the diagnosis of two cases, down staging the patients' disease. SSS identified a single additional tumour: an ipsilateral synchronous tongue base tumour where a contralateral tumour had been identified on CH. Multifocal disease was seen in 8.6%; all were HPV-related and in the tongue base.

Conclusions

In a prospectively identified multi-centre cohort of patients undergoing TBM for HNSCCUP, SSS added a considerable histopathological workload with minimal additional diagnostic benefit. A second opinion using conventional histological techniques may be more beneficial.

2.1.4 Aim

This study aimed to establish the effectiveness of conventional techniques and step serial sectioning histopathological processing in analysing diagnostic oropharyngeal tissue samples in a prospectively identified multi-centre cohort undergoing tongue base mucosectomy for head and neck squamous cell carcinoma of unknown primary.

2.1.5 Methods

2.1.5.1 Ethical considerations and regulatory approvals

The study protocol was reviewed and approved by the study sponsor (The Royal Marsden NHS Foundation Trust), London - Riverside Research Ethics Committee (19/LO/1101) and the Health Research Authority (IRAS256047). The Study was registered at clinicaltrials.gov (NCT04151134).

2.1.5.2 Study design and setting

A prospective multi-centre non-interventional cohort study was conducted in UK secondary care head and neck departments. The primary endpoint was diagnosis of cancer on oropharyngeal tissue specimens on histopathological processing.

2.1.5.3 Participant eligibility criteria

Patients 16 years old and over, with cytologically or pathologically confirmed cervical metastatic SCC, undergoing TBM for identification of primary site, were included. Patients with a history of previous HNC or history of radiation to the head and neck region, or undergoing targeted biopsies, were excluded.

2.1.5.4 Participant identification

Patients were identified at the multidisciplinary team (MDT) meetings of participating centres at any time in their diagnostic pathway prior to undergoing TBM.

2.1.5.5 Standard of care practice

Inclusion in the study did not influence indications for surgery, or the technical aspects of the surgery itself. Choice of method of TBM remained with the participating centre. Following resection of the lingual tonsil tissue via TBM, routine histopathological processing was conducted locally, according to their usual practices and procedures, with anatomically orientated specimens fixed in 10% neutral buffered formalin and cut into 2-3 mm parallel pieces and then processed to paraffin wax. Four micrometre sections were cut and stained with haematoxylin and eosin stain (H&E) and then examined by a pathologist for evidence of SCC. This conventional histopathological assessment was confirmed as the standard operating procedure at the participating sites and contributed to the MDT recommended management plan.

2.1.5.6 Step serial sectioning histopathology

The lingual tonsil obtained via TBM, along with any palatine tonsillar tissue removed as part of the patients' diagnostic work up to identify a primary tumour, were subsequently transferred to the study sponsor for step serial sectioning (SSS).

Five 4 μm serial sections were cut every 500 μm through the formalin fixed paraffin embedded (FFPE) blocks until the tissue was depleted. At each 'step', section three was stained with H&E. If an SCC was identified then serial sections two and four were submitted for HPV testing (p16 immunohistochemistry and high-risk

HPV DNA in situ hybridisation (HR-HPV-ISH)). Serial sections one and five were retained for repeat tests, as required. Interval sections between the 'steps' were discarded. **Figure 2-1** demonstrates the additional diagnostic advantage afforded by SSS.

2.1.5.7 Data collection

Data were recorded on patient demographics, medical and surgical history, relevant investigations, peri-operative outcomes, conventional histology results, the initial planned definitive treatment and oncological status up to 12 months. Patients also completed questionnaires on pain and swallowing function using the MD Anderson Dysphagia Index (MDADI). The oncological and functional outcomes do not form the focus of this report.

The first phase of the study opened to recruitment in November 2019. A second phase of the study will extend the recruitment from 60 to 100 patients with reporting of oncological and functional follow-up to 5 years, although these additional participants will not have SSS performed on their oropharyngeal tissues.

2.1.5.8 Statistical analysis

No a priori sample size calculation was conducted as recruitment was limited by funding to 60 patients' specimens. Descriptive statistics are presented with 95% confidence intervals (CI) using the Wilson score, where appropriate. Sub-groups were defined by the timing of tonsillectomy with relation to TBM as this affects the probable pick-up rates. Loss of follow-up was not applicable as the endpoint was contemporaneous. Missing or ambiguous data were clarified with the participating sites and persistently missing data points were excluded from relevant analyses.

2.1.6 Results

2.1.6.1 Centres and patients

Between November 2019 and December 2021, 60 patients from 19 centres across the United Kingdom were recruited and underwent TBM (median 3 cases per centre; range 1 to 9). Two patients were subsequently withdrawn prior to their oropharyngeal tissue undergoing SSS (reclassification as salivary gland cancer and a patient withdrawal) but recruitment was paused to allow interim analysis, giving 58 complete cases. Following interim analysis, the Study Management Team agreed not to recruit further patients for step serial sectioning as part of the ongoing study. The median age for all included patients was 58 (range 47-82) and 17.2% were female (n=10).

2.1.6.2 TBM technique and timing

Techniques for TBM were: transoral robotic surgery (TORS) in 75.9% (n=44/58), transoral electrocautery (TOEC) in 19.0% (n=11/58), and transoral laser microsurgery (TLM) in 5.2% (n=3/58). **Table 2-1** gives further breakdown by subgroup.

TBM was most commonly performed following an historic tonsillectomy (36.2%, n=21/58). It was performed as a staged procedure after negative palatine tonsillectomy in 25.9% (n=15/58) and concurrently with tonsillectomy in 24.1% (n=14/58). Other combinations of timings of TBM surgery and completeness of palatine and lingual lymphoepithelial resection accounted for 13.8% (n=8/58; **Table 2-2**).

2.1.6.3 Conventional histology

At central review with conventional histology techniques (including original slides), two cases were 'upgraded' and two were 'downgraded'. The upgraded cases had new ipsilateral tongue base primaries identified that had not been diagnosed by the participating site. The downgraded cases included a case where the diagnosis of squamous cell carcinoma was changed to inflammatory ulceration and necrotising sialometaplasia and another case where the tumour had been diagnosed as a single large tumour, but was two separate, smaller synchronous tumours. There was a single case of *carcinoma in situ* identified in the contralateral base of tongue lymphoepithelial tissue.

2.1.6.4 Step serial sectioning histopathology

A total of 20,480 sections were cut in the laboratory with 4,096 sections directly examined by the pathologist (median 64 per patient, range 28 to 135; **Table 2-1**). SSS identified a single additional synchronous tumour: an HPV-positive ipsilateral tongue base tumour in a patient who had had a contralateral tongue base primary identified on CH (**Figure 2-2**). The additional tumour was contained entirely within the tissue block (dimensions on the section 5.8 mm x 3.0 mm and estimated to measure 2.0 mm within the block). Review of the original sections from the participating site confirmed the tumour was not evident.

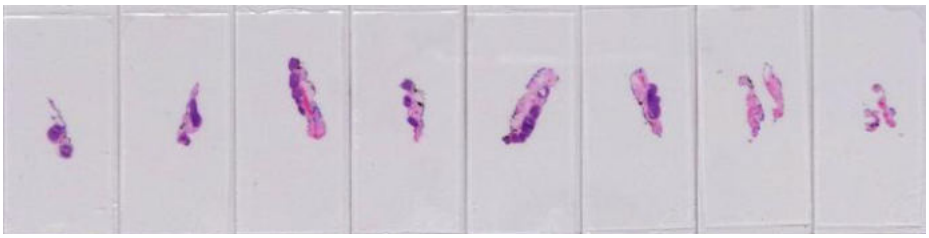
Overall, 8.6% (95% CI 3.7 to 18.6, n=5/58) of TBM patients in this cohort had multifocal disease, all found bilaterally in the tongue base. Notably, 20% (95% CI 7.0 to 45.2, n=3/15) of those having tonsillectomy and

TBM in a single theatre episode had synchronous disease. All primary cancers identified on central laboratory testing were HPV-related SCCs.

2.1.6.5 TBM identification rates

The overall identification rate for TBM following SSS according to study protocol was 48.3% (95% CI 35.9 to 60.8). By subgroup, the rates were: when performed following a negative bilateral tonsillectomy 42.9% (95% CI 21.4 to 67.4); when performed at the same time as bilateral tonsillectomy 46.7% (95% CI 24.8 to 69.9); and when performed in the context of an historic tonsillectomy 57.1% (95% CI 36.5 to 75.5).

A. Conventional sections



B. Step sections

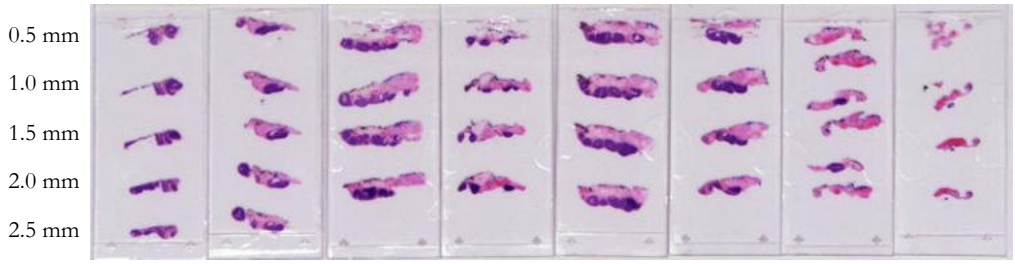


Figure 2-1: Comparison of the fidelity of step serial sectioning with conventional histology for palatine tonsillar specimens in the MOSES Study. Conventional sections from 8 blocks stained with haematoxylin and eosin (A). Step sections taken at 500μm intervals through the block generates a further 33 sections for examination (B).

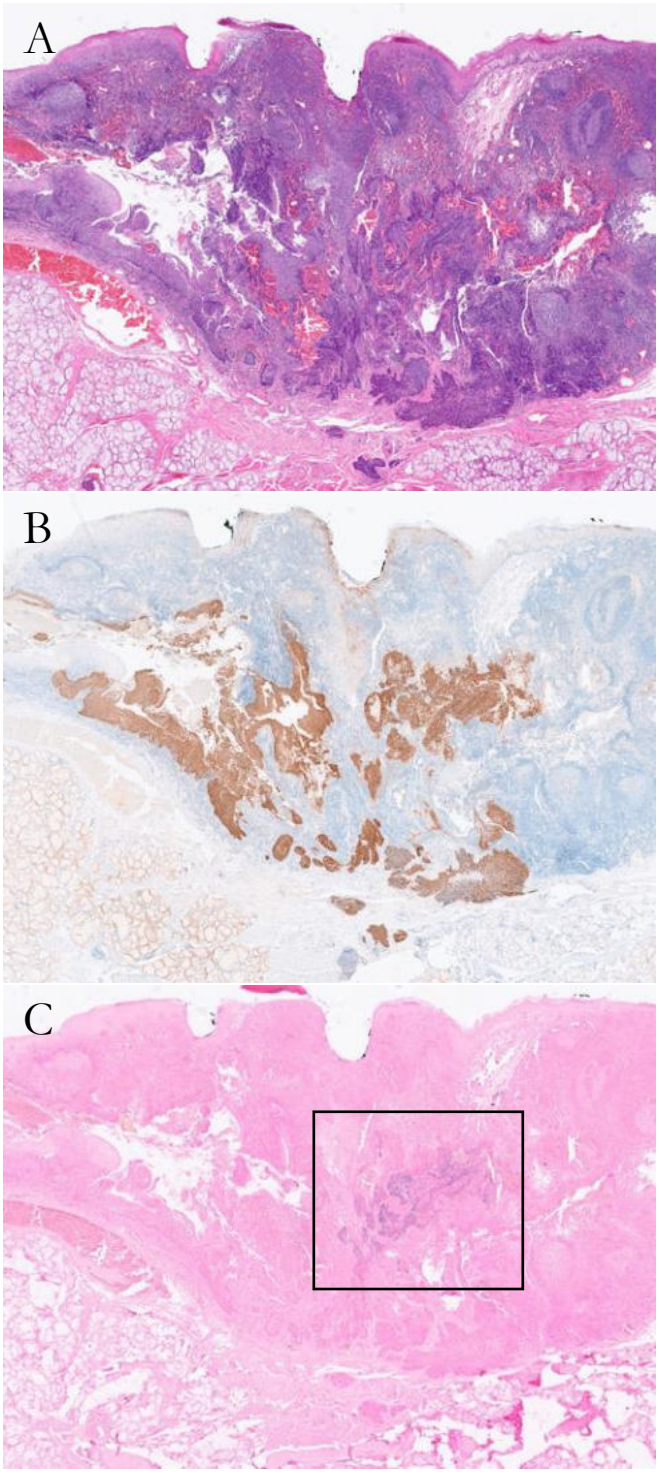


Figure 2-2: *Right tongue base HPV-associated squamous cell carcinoma discovered by serial step sections in the MOSES Study. Haematoxylin and eosin (A), p16 immunohistochemistry (B) and high-risk human papillomavirus DNA in situ hybridisation (C), black box highlights patch of positive staining (Magnification x2.5).*

Table 2-1: Clinicopathological features for all patients and for the most common diagnostic surgical scenarios in the MOSES Study.
TBM is tongue base mucosectomy.
HPV-ISH is human papillomavirus in situ hybridisation.
EBER-ISH is Epstein-Barr encoding region in situ hybridisation.
CT is computed tomography,
MRI is magnetic resonance imaging.
PET-CT is 18F- Fluorodeoxyglucose- Positron emission tomography-computerised tomography.
†final histopathological status.
^size given for largest focus of primary site disease in cases of multifocal disease.
**closest of any margins in cases of multifocal disease.*
#taking account of final HPV status by p16 immunohistochemistry.

		All patients (N=58)	Bilateral tonsillectomy and bilateral TBM (N=15)	Bilateral tonsillectomy then bilateral TBM (N=14)	Bilateral TBM (historic tonsillectomy) (N=21)	
Variable	**Classification**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**p**
Age	**Data available**	58 (100)	15 (100)	14 (100)	21 (100)	0.122
	Median, years	58	53	57	61	
	Minimum, years	47	47	51	52	
	Maximum, years	82	70	78	82	
	Mean, years	59.7	55.8	59.5	63.3	
	Standard deviation, years	8	6.5	8	8.4	
Sex	**Data available**	58 (100)	15 (100)	14 (100)	21 (100)	0.378
	Female	10 (17.2)	1 (6.7)	1 (7.1)	5 (23.8)	
	Male	48 (82.8)	14 (93.3)	13 (92.9)	16 (76.2)	
Smoking history	**Data available**	58 (100)	15 (100)	14 (100)	21 (100)	0.87
	Never smoker	22 (37.9)	7 (46.7)	5 (35.7)	7 (33.3)	
	Ex-smoker	28 (48.3)	7 (46.7)	7 (50)	10 (47.6)	
	Current smoker	8 (13.8)	1 (6.7)	2 (14.3)	4 (19)	
Alcohol history	**Data available**	58 (100)	15 (100)	14 (100)	21 (100)	0.080
	Never	5 (8.6)	1 (6.7)	3 (21.4)	1 (4.8)	
	Occasional	25 (43.1)	9 (60)	7 (50)	6 (28.6)	
	Moderate	20 (34.5)	2 (13.3)	4 (28.6)	10 (47.6)	
	Heavy	8 (13.8)	3 (20)	0	4 (19)	
p16 status†	**Data available**	56 (96.6)	15 (100)	14 (100)	19 (90.5)	0.501
	Negative	9 (16.1)	1 (6.7)	3 (21.4)	4 (21.1)	
	Positive	47 (83.9)	14 (93.3)	11 (78.6)	15 (78.9)	
HPV-ISH status†	**Data available**	19 (32.8)	8 (53.3)	2 (14.3)	6 (28.6)	0.233
	Negative	2 (10.5)	0	0	2 (33.3)	
	Positive	17 (89.5)	8 (100)	2 (100)	4 (66.7)	
EBER-ISH status†	**Data available**	12 (20.7)	3 (20)	5 (35.7)	4 (19)	0.045
	Negative	10 (83.3)	1 (33.3)	5 (100)	4 (100)	
	Positive	2 (16.7)	2 (66.7)	0	0	
CT neck	**Data available**	31 (53.4)	5 (33.3)	10 (71.4)	12 (57.1)	0.126
	Yes	31 (53.4)	5 (33.3)	10 (71.4)	12 (57.1)	
	No	0	0	0	0	

MRI neck	**Data available**	58 (100)	15 (100)	14 (100)	21 (100)	0.184
	Yes	51 (87.9)	15 (100)	11 (78.6)	18 (85.7)	
	No	7 (12.1)	0	3 (21.4)	3 (14.3)	
PET-CT	**Data available**	58 (100)	15 (100)	14 (100)	21 (100)	1
	Yes	57 (98.3)	15 (100)	14 (100)	20 (95.2)	
	No	1 (1.7)	0	0	1 (4.8)	
Clinical nodal status (TNM8)#	**Data available**	58 (98.3)	14 (93.3)	14 (100)	21 (100)	0.292
	cN1	49 (84.5)	13 (86.7)	12 (85.7)	18 (85.7)	
	cN2 (HPV-positive)	1 (1.7)	1 (6.7)	0	0	
	cN2a	2 (3.4)	0	1 (7.1)	0	
	cN2b	5 (8.6)	1 (6.7)	1 (7.1)	3 (14.3)	
	cN3b	1 (1.7)	0	0	0	
TBM method	**Data available**	58 (100)	15 (100)	14 (100)	21 (100)	0.628
	TORS	44 (75.9)	10 (66.7)	10 (71.4)	16 (76.2)	
	TLM	3 (5.2)	2 (13.3)	1 (7.1)	0	
	TOEC	11 (19)	3 (20)	3 (21.4)	5 (23.8)	
Maximum tumour size^	**Data available**	33 (97.1)	10 (90.9)	6 (100)	13 (100)	0.562
	Median, mm	8	7.25	10.75	8	
	Minimum, mm	2	2	4	2	
	Maximum, mm	26	26	18	17	
Tumour margin*	**Data available**	33 (97.1)	11 (100)	6 (100)	12 (92.3)	0.252
	Positive (<1mm)	18 (54.5)	7 (63.6)	2 (33.3)	7 (58.3)	
	Close (1-3mm)	9 (27.3)	2 (18.2)	2 (33.3)	5 (41.7)	
	Clear (>3mm)	6 (18.2)	2 (18.2)	2 (33.3)	0	
Step serial sectioning result	**Total sections**	4096	1300	1175	1188	0.031
	Median sections	64	90	92	52	
	Minimum sections	28	35	39	31	
	Maximum sections	135	135	128	107	
	Mean sections	70.6	86.7	83.9	56.6	
	Additional primary	1 (1.7)	1 (6.7)	0	0	
	No additional primary	57 (98.3)	14 (93.3)	14 (100)	21 (100)	
Final pathology	**Data available**	58 (100)	15 (100)	14 (100)	21 (100)	<0.001
	No foci	23 (39.7)	3 (20)	8 (57.1)	9 (42.9)	
	Single foci	30 (51.7)	9 (60.0)	5 (35.7)	11 (52.4)	
	Multiple foci	5 (8.6)	3 (20)	1 (7.1)	1 (4.8)	

Table 2-2: Locations of primary tumours for all diagnostic surgical scenarios in the MOSES Study. TBM is tongue base mucosectomy.

Diagnostic surgical scenario	N (%)	Location of primary disease					Rates	
		No foci n (%)	Ipsilateral tonsil n (%)	Ipsilateral tongue base, >1cm from midline n (%)	Tongue base within 1 cm of midline n (%)	Bilateral synchronous tongue base n (%)	Tongue base cancer % (95% CI)	Any OP cancer % (95% CI)
Bilateral tonsillectomy and bilateral TBM	15 (25.9)	3 (20)	5 (33.3)	4 (27.7)	0	3 (20)	20.0 (7.0, 45.2)	80.0 (54.8, 93.0)
Bilateral tonsillectomy then bilateral TBM	14 (24.1)	8 (57.1)	0	5 (35.7)	0	1 (7.1)	7.1 (1.3, 31.5)	42.9 (21.4, 67.4)
Bilateral TBM (historic tonsillectomy)	21 (36.2)	9 (42.9)	0	3 (14.3)	8 (38.1)	1 (4.8)	42.9 (24.5, 63.5)	57.1 (36.5, 75.5)
Ipsilateral tonsillectomy and bilateral TBM	5 (8.6)	2 (40.0)	2 (40.0)	0	1 (20.0)	0	20.0 (3.6, 62.4)	60.0 (23.1, 88.2)
Ipsilateral tonsillectomy and ipsilateral TBM	1 (1.7)	0	0	0	1 (100)	0	100 (20.7, 100)	100 (20.7, 100)
Ipsilateral tonsillectomy, then contralateral tonsillectomy and TBM	2 (3.4)	1 (50.0)	0	1 (50.0)	0	0	0 (0, 65.8)	50.0 (9.5, 90.5)
Overall	58 (100)	23 (39.7)	7 (12.1)	13 (22.4)	10 (17.2)	5 (8.6)	25.9 (16.3, 38.4)	60.3 (47.5, 71.9)

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2.2 The HNSCCUP National Audit 2021

2.2.1 Full title

Investigations and Survival Outcomes in Head and Neck Squamous Cell Carcinoma of Unknown Primary (HNSCCUP): a National Cohort Study.

2.2.2 Contributions

The author is Chair of INTEGRATE, the UK ENT Trainee Research Network. In this capacity he has overseen the development and delivery of this study, from conceptualisation through protocol development, data collection, assimilation, analysis, visualisation and interpretation. The author has further led on writing, reviewing and editing the text contained herein, which at time of writing, is being prepared for submission for peer-review and publication.

The author is grateful to the following individuals for their contributions towards the delivery of this study and its write-up (full delineation of roles and affiliations available in **Appendix 15**):

- The INTEGRATE Head and Neck sub-specialty committee of trainees, who have contributed at every step of the study: Andrew Williamson, Sian Dobbs, Shivun Khosla, Kristijonas Milinis, Chris Hogan, James Constable, Ben Tudor-Green and Kate Hulse.
- ENT UK Head & Neck Society Council, who supported the project. Of note, Sanjai Sood, who endorsed a letter of support.
- The ENT UK Foundation Research Grants Programme who awarded the project a grant (**Appendix 20**).
- Vinidh Paleri, who supervised the work from conceptualisation to production and approval of the final report in his role as Executive Oversight.

2.2.3 Abstract *[430 words]*

Objectives

Head and neck squamous cell carcinoma from an unknown primary (HNSCCUP) is a rare and challenging condition to investigate and treat. This study aimed to investigate the diagnostic pathways of suspected HNSCCUP patients managed in the UK and describe the influence of HPV and differing treatments on survival.

Design

A retrospective observational cohort study was conducted in UK ENT centres of adults who underwent 18F-Fluorodeoxyglucose-PET-CT (PET-CT) within three months of diagnosis with metastatic cervical squamous cell carcinoma, over five years from 1 January 2015. Patients with no primary site on examination and no history of previous head and neck cancer were eligible. Survival outcomes are presented for patients who started treatment for HNSCCUP.

Results

Data were received from 57 centres for 965 patients; 68.5% with HPV-related disease. For patients referred without prior imaging, three cycles of investigations were observed with ultrasound, cross-sectional imaging (MRI or CT) and PET-CT, occurring at medians of 17, 29.5, and 46 days from referral. Of patients with no primary on PET-CT (50.1%, n=479/960), ipsilateral tonsillectomy had the highest diagnostic yield (18.7% cancers in 74.5% undergoing procedure, n=52/278/373), followed by tongue base mucosectomy (15.4% in 21.7%, n=16/104/479) and contralateral tonsillectomy (0.9% in 62.9%, n=2/234/372). PET-CT with concurrent MRI was associated with higher primary site detection than concurrent CT (p=0.003). A minority of patients undergoing treatment with curative intent received their first-definitive-treatment within 62 days of referral (15.2%, n=77/505, median 92 days, IQR:71-117).

482 patients started treatment for HNSCCUP (65.7% HPV-positive, n=282/429). HPV-negative disease was associated with increased age, smoking, alcohol consumption, and performance status (p<.0001). Five-year overall survival (OS) for HPV-positive patients was 85.0% (95% CI:78.4-92.3) and 43.5% (95% CI:32.9-57.5) for HPV-negative. HPV-negative status was associated with worse OS, disease-free (DFS), and disease-specific (DSS) survival (p<.0001). Unilateral HPV-positive disease treated with surgery alone exhibited worse 5-year DFS (24.9%, 95% CI:8.5-73.1) and local control (LC) (41.8%, 95% CI:21.5-81.4) compared to radiotherapy (DFS 82.3%, 95% CI:74.7-90.6; LC 98.8%, 95% CI:96.5-100) or combined modalities (DFS 94.3%, 95% CI:89.0-99.9; LC 98.6%, 95% CI:95.9-100)(p<.0001). LC was again worse in unilateral HPV-negative patients treated with surgery alone compared to radiotherapy or combined treatments (p=0.017).

Conclusions

The majority of patients experienced a protracted diagnostic pathway and waited over three months for definitive treatment. Earlier PET-CT with concurrent MRI may expedite diagnosis. TBM may be more productive than contralateral tonsillectomy for primary site detection. HPV-positive HNSCCUP patients exhibited fewer comorbidities and improved survival. In HPV-positive and HPV-negative patients, radiotherapy alone or in combination with neck dissection was associated with improved disease control compared to single modality surgery. The impact of diagnostic surgery on primary site emergence and survival remains unestablished.

2.2.4 Aim

This study aimed to investigate the diagnostic pathways of suspected HNSCCUP patients managed in the UK and to describe the influence of HPV and differing treatment regimens on survival.

2.2.5 Methods

The protocol for this study was published in advance at https://entintegrate.co.uk. This study report has been prepared with reference to the STROBE checklist (STrengthening the Reporting of OBservational studies in Epidemiology).[35]

2.2.5.1 Ethical considerations

This project reported on routinely collected and anonymised data. The Health Resource Authority decision tool (available at: http://www.hra-decisiontools.org.uk/research/) classified it as a clinical audit. Therefore, patient consent and ethical approval was not required.

2.2.5.2 Study design and setting

A retrospective multi-centre audit was conducted as part of a National Consensus Initiative in HNSCCUP. All UK secondary care ENT departments were invited to participate via adverts from ENT UK and the Association of Otolaryngologists in Training (AOT).

2.2.5.3 Participant eligibility criteria

Consecutive patients managed by ENT departments undergoing PET-CT within three months of histopathologically diagnosed metastatic cervical squamous cell carcinoma (SCC) between 1 January 2015 and 1 January 2020, with no apparent primary tumour site on initial outpatient examination (including clinic-based endoscopy), were included. Patients with a history of previous HNC, previous radiotherapy to the head and neck region, or in whom the PET-CT was not performed to investigate a clinically occult primary tumour site, were excluded.

2.2.5.4 Participant identification

Participating centres were advised to identify potentially eligible subjects by searching local informatics records (using appropriate SNOMED II/CT histopathology codes, provided in the study protocol) or searching head and neck MDT records. Patients' clinical records were then screened by the local team and eligibility criteria applied.

2.2.5.5 Data collection

Study-relevant data were recorded onto a standardised electronic data tool, created using Excel software (**Figure 2-3**, Microsoft Corporation, Washington, USA). Restricted data fields and data validation were used to improve data completeness and homogeneity. Anonymised Data Tools were submitted to the project management team (INTEGRATE) and combined for pooled analysis. Following central data integrity checks, missing or ambiguous data were clarified with the local teams through multiple bespoke auto generated emails that read data from the master spreadsheet (**Appendix 16**). Persistently missing data points were nullified and excluded from relevant analyses.

Patient risk factors were reported according to local clinical records including smoking (current/ex-smoker/never smoker/unknown) and alcohol consumption status (none/light/heavy/unknown). Performance status was reported using the Eastern Cooperative Oncology Group (ECOG) performance status scale.[119] HPV status was reported as per local procedures and records (positive/negative/not performed).

A step-by-step guide was produced to support the clinicians in registering the project locally and to guide data collection (available at https://entintegrate.co.uk/hnsccup). A dedicated document surmising the Audit Standards from four relevant publications was also provided to aid local registration (**Appendix 17**). Sites were requested not to submit data until local data governance requirements had been satisfied. Certificates were produced as evidence of participation for all Consultant leads, Trainee site leads and local collaborators (**Appendix 19**). Collaborative authorship was also offered to all Consultant leads and Trainee site leads for any subsequent publications, as per the protocol (available at https://entintegrate.co.uk/hnsccup).

2.2.5.6 Data analysis

No a priori sample size calculation was performed. Categorical variables were compared using the Fisher's exact test and continuous variables using the Wilcoxon test. Time-to-event outcomes [overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS) and local control (LC)] were estimated using the Kaplan-Meier (KM) method, with subgroups compared using log-rank tests. Endpoints were as follows: death from any cause for OS; diagnosis of residual or recurrent regional or distant disease, or new primary site disease, or death from any cause for DFS; death from residual or recurrent disease, or death from new primary site disease for DSS; and diagnosis of new primary site disease for LC.

Prognostic factors for time-to-event outcomes were assessed using Cox proportional hazards regression analysis. The proportional hazards assumption was assessed using Schoenfeld residuals and visual assessment of the KM curves. Time-varying coefficients were further assessed using a log(time) interaction, which was adopted if returning a statistically significant, or close to statistically significant, result. The multivariable model was constructed using a backward stepwise elimination process. The initial model was built with variables found to be statistically significant on univariable analysis. At each stage, the least statistically significant variable above the threshold was eliminated until only statistically significant variables remained. A P value threshold of less than .05 was used throughout to denote statistical significance. Analyses used the 'survival' and 'survminer' packages in R statistical software (R Foundation, Vienna, Austria).

2.2.5.7 Interim reports

Interim data were presented at the HNSCCUP National Consensus Day to allow rapid feedback of preliminary findings to the HNC community. Presentations were given to cover three stages following the patient journey, from presentation to post-treatment surveillance, and pre-recorded for delivery on the day (**Appendix 18**).

2.2.6 Results

2.2.6.1 Centres and patients

Data was received from 57 UK centres for 965 patients identified during the study period, of whom 78.5% (n=739) were referred via the urgent referral pathway for suspected HNC (**Table 2-3**). Median age was 59 years and 74.1% (n=702) of patients were male. The majority had an ECOG status of 0 (74.0%, n=692) and the predominant presenting nodal level was level II (79.3%, n=751).

A primary site was not identified in 482 patients who commenced treatment as HNSCCUP with a median age of 60.5 years and 75.7% were male (**Table 2-4**). The median follow-up was 33.9 months for survivors (range = 0-74.3; IQR = 21.7-48.4) and 29.1 months for all patients (range = 0-77.7; IQR = 14.8-44.5).

2.2.6.2 Investigations before diagnostic surgery

Of patients on the urgent referral pathway, 60.6% (n=585) had no prior investigations at the point of initial consultation. Within this group, the median days from referral to the following secondary care pathway events were: FNE 13; FNAC 14; ultrasound neck 17; core biopsy 28; MRI neck 28; CT chest 29, CT neck 30; PET-CT 46; examination under anaesthesia (EUA) 56; FDT 92 (**Figure 2-4** and **Figure 2-5**). Comparison of these pathway events shows that 12 days elapsed between FNAC and the earliest cross-sectional imaging (MRI Neck) and 25 days elapsed between FNAC and PET-CT (median times, **Figure 2-5**). Of the patients on the urgent referral pathway without prior investigations who were then treated with curative intent, 15.2% (n=77/505) met the NHS 62-day target for FDT (median 92 days, IQR = 71-117).

PET-CT

All patients underwent PET-CT as a criterion for inclusion in this study. A 'clear primary site' was reported on PET-CT in 26.9% (n=258/960), 'no clear primary site' in 50.1% (n=478/960) and an 'equivocal' result in 23.2% (n=224/960). Following diagnostic biopsies, a primary tumour site was confirmed in 89.5% (n=230/257), 24.6% (n=117/476) and 56.8% (n=126/222) of these PET-CT result classifications, respectively. The locations of the clinico-radiologically occult primary sites, that were ultimately identified following diagnostic biopsies, are presented in **Table 2-5** with **Figure 2-6** depicting the subset of oropharyngeal sites identified.

Patients undergoing a 'concurrent' (within 10 days) MRI and PET-CT had a statistically higher chance of a histologically confirmed primary site being identified compared to those who underwent concurrent CT and PET-CT (62.5%, n=95/152 vs 40.5%, n=30/74; p=0.003). The mode of concurrent imaging was the only factor demonstrating a statistically significant difference on primary site identification on univariable analysis and so multivariable analysis was not required (**Table 2-6**).

2.2.6.3 Diagnostic surgery for HNSCCUP with no clear primary on PET-CT

Of patients with HNSCCUP with no clear primary site on PET-CT, 69.1% (n=331/479) underwent a single diagnostic theatre episode with 19.4% (n=93/479) undergoing more than one **Table 2-4**. Rates for diagnostic

yield and proportion undergoing the following oropharyngeal procedures were: ipsilateral tonsillectomy 18.7% in 74.5% (n=52/278/373), contralateral tonsillectomy 0.9% in 62.9% (n=2/234/372) and TBM 15.4% in 21.7% (n=16/104/479) (not including glossotonsillar sulcus or multifocal diagnoses).

Full clearance of oropharyngeal lymphoid tissues (bilateral TBM with bilateral tonsillectomy, if tonsils present) was reported in 26.3% (n=19/72) with a history of previous tonsillectomy and 12.8% (n=45/351) without previous tonsillectomy. The majority of bilateral TBMs were performed concurrently with bilateral tonsillectomy (62.2%; n=28/45).

Of the TBM group, the following techniques were employed: Transoral Robotic Surgery with diathermy (29.8%, n=31); Transoral Laser Microsurgery (8.7%, n=9); Transoral Endoscopic Electrocautery (25.0%, n=26); direct vision with diathermy (26.0%, n=27) and other combinations in 10.6% (n=11). The diagnostic yield of the relative techniques employed for TBM are displayed in **Figure 2-10**.

Untargeted biopsies (no clinical or radiological suspicion of malignancy at biopsy site) were performed in 57.4% (n=201/418) of patients who underwent at least one diagnostic theatre episode. The following diagnostic yields were reported: tonsil 6.5% (n=2/31) (not otherwise undergoing tonsillectomy), tongue base 4.1% (n=6/146) (not otherwise undergoing TBM), hypopharynx 0% (n=0/43), nasopharynx 0% (n=0/94).

2.2.6.4 Outcomes by HPV status

Individual treatments for all HNSCCUP, with stratification by HPV status, are presented in **Table 2-4** which shows significant differences between groups in patient characteristics and management strategies. HPV-positive patients (65.7%, n=282/429) were more likely to undergo diagnostic oropharyngeal surgery but less likely to undergo neck dissection, with rates of radiation therapy also seen to be higher in this cohort. Marked differences were seen in both groups for OS, DFS and DSS with no significant difference in LC (**Figure 2-7** and **Table 2-10**), which was confirmed on multivariable regression analysis (**Table 2-11**). The 5-year OS for HPV-positive disease was 85.0% (95% CI 78.4 to 92.3) and 43.5% (95% CI 32.9 to 57.5) for HPV-negative disease.

2.2.6.5 Outcomes from management of unilateral neck disease

For subgroup comparisons, the HPV cohorts were restricted to patients with unilateral neck disease (cN1, cN2a and cN2b by TNM 7 and cN1 by TNM 8) who underwent treatment with curative intent, and then stratified into three groups as to whether they underwent ipsilateral neck dissection, ipsilateral neck radiotherapy or both (**Table 2-8**). Survival outcomes for these groups are presented in **Figure 2-8** and **Figure 2-9** and summarised in **Table 2-10**.

For HPV-positive disease (**Figure 2-8**), little difference is seen between OS and DSS for the three treatment groups. For DFS and LC (primary emergence) there was a highly statistically significant difference in outcomes. Notably, the surgery only cohort fared worst for local control with 41.8% (95% CI 21.5 to 81.4) at 5 years, compared to 98.6% (95% CI 95.9 to 100) for both modalities and 98.8% (95% CI 96.5 to 100) for radiation therapy alone (p <.0001). Similarly, DFS was worse in patients managed by neck dissection alone, with 5-year

rates of 24.9% (95% CI 8.5 to 73.1) compared to 82.3% (95% CI 74.7 to 90.6) for radiotherapy monotherapy and 94.3% (95% CI 98 to 99.9) for combined modality treatment (p<.0001).

For HPV-negative disease (**Figure 2-9**), overall numbers were lower but a similar trend was seen with statistically worse LC (primary emergence) in the surgery only cohort. Again, the surgery-only cohort fare worst but there is overlap in 95% confidence intervals between the groups (p = 0.017).

The sites of primary emergence in these unilateral neck disease patients were: ipsilateral tongue base (n=6), midline tongue base (n=1), ipsilateral tonsil (n=2), cervical oesophagus (n=1), ipsilateral parotid (n=1), larynx (n=1), hypopharynx (n=1), oral cavity (n=1), not specified (n=4).

2.2.6.5.1 Prognosticators of time-to-event outcomes

Results from univariable analysis are shown in **Table 2-12** and multivariable analysis in **Table 2-11**. Following multivariable analysis, HPV-related disease was associated with improved outcomes in OS, DFS and DSS; chemotherapy was associated with improved DFS; contralateral TBM was associated with poorer DFS; and ipsilateral neck radiation therapy was associated with improved LC.

2.2.6.6 Outcomes from management of bilateral neck disease

In HNSCCUP patients with known HPV status, only 17 HPV-positive and 10 HPV-negative patients were recorded as having bilateral neck metastases (cN2c by TNM 7) and were treated with curative intent. All these patients underwent radiation therapy with two HPV-positive and one HPV-negative patient also undergoing bilateral neck dissections. Further commentary on the oncological outcomes were not explored due to low numbers.

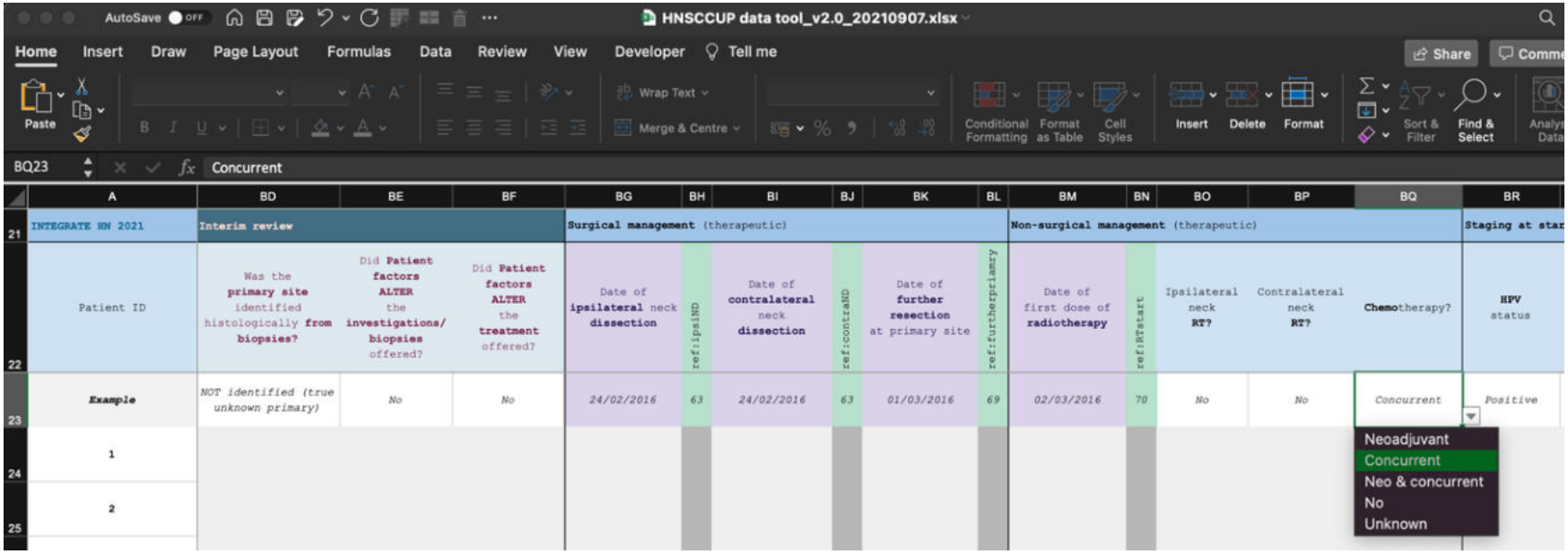


Figure 2-3: Screenshot of the Excel Data Tool used in the HNSCCUP National Audit. Dates of birth and of key events were used to generate durations which were then removed prior to submission to ensure anonymisation.

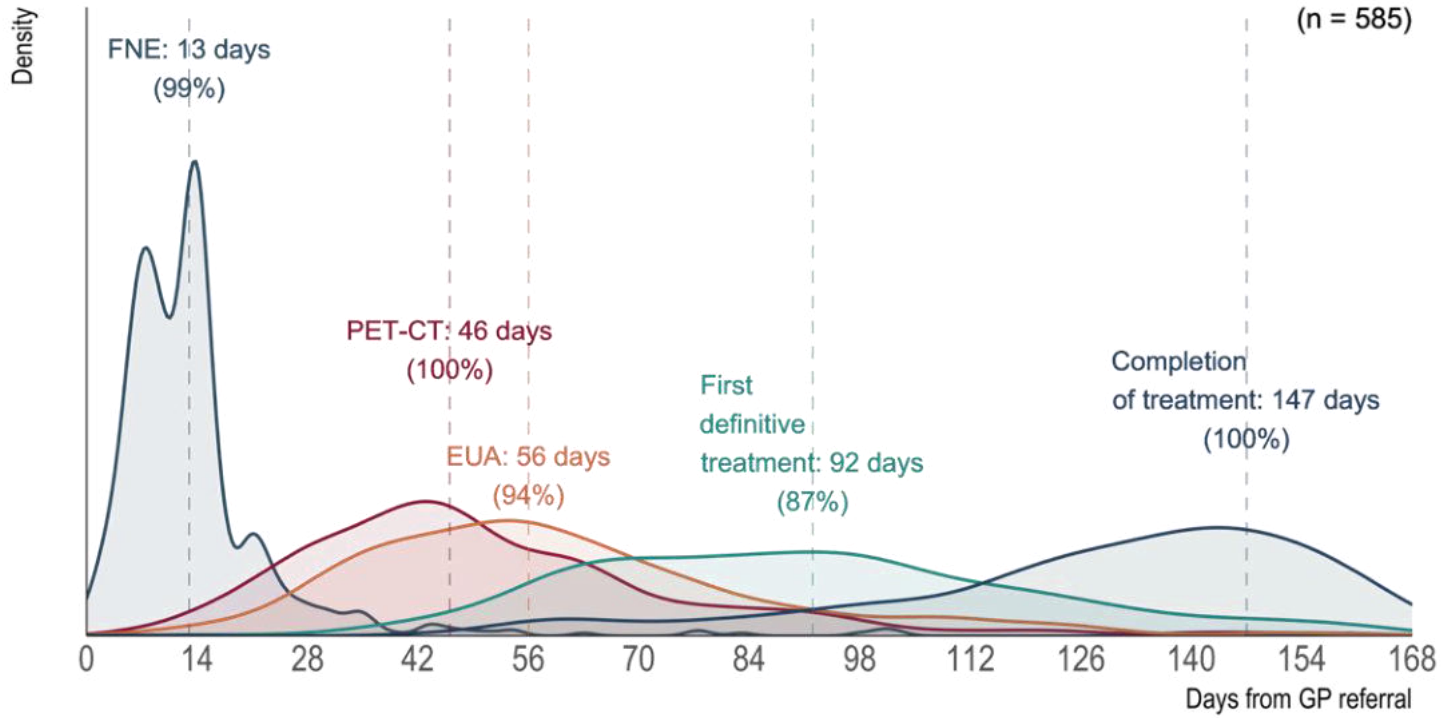


Figure 2-4: Density chart of days until key events in the overall pathway for patients referred on the suspected head and neck cancer pathway without prior investigations in the HNSCCUP National Audit. Dashed lines indicate median durations and percentages indicate the proportion of the cohort with relevant data.

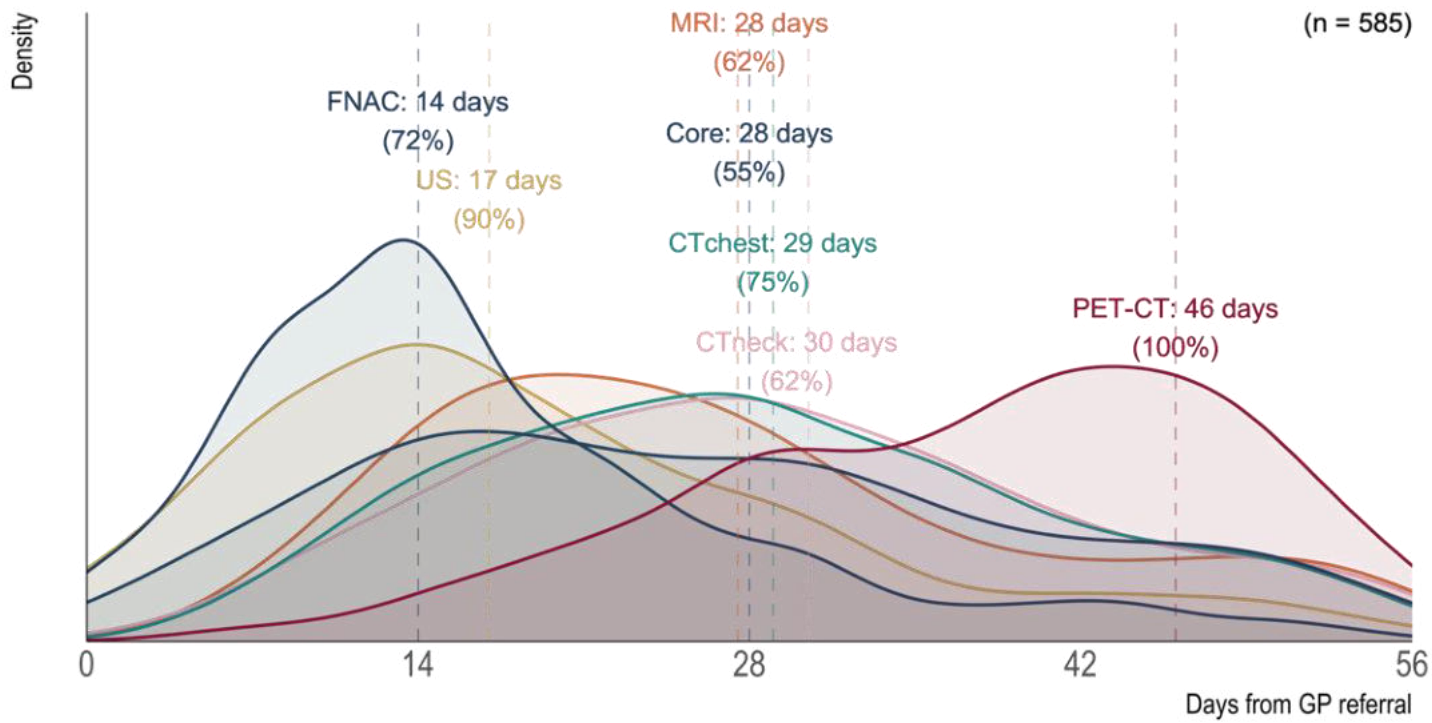


Figure 2-5: Density chart of days until investigations before diagnostic surgery for patients referred on the suspected head and neck cancer pathway without prior investigations in the HNSCCUP National Audit. Dashed lines indicate median durations and percentages indicate the proportion of the cohort with relevant data.

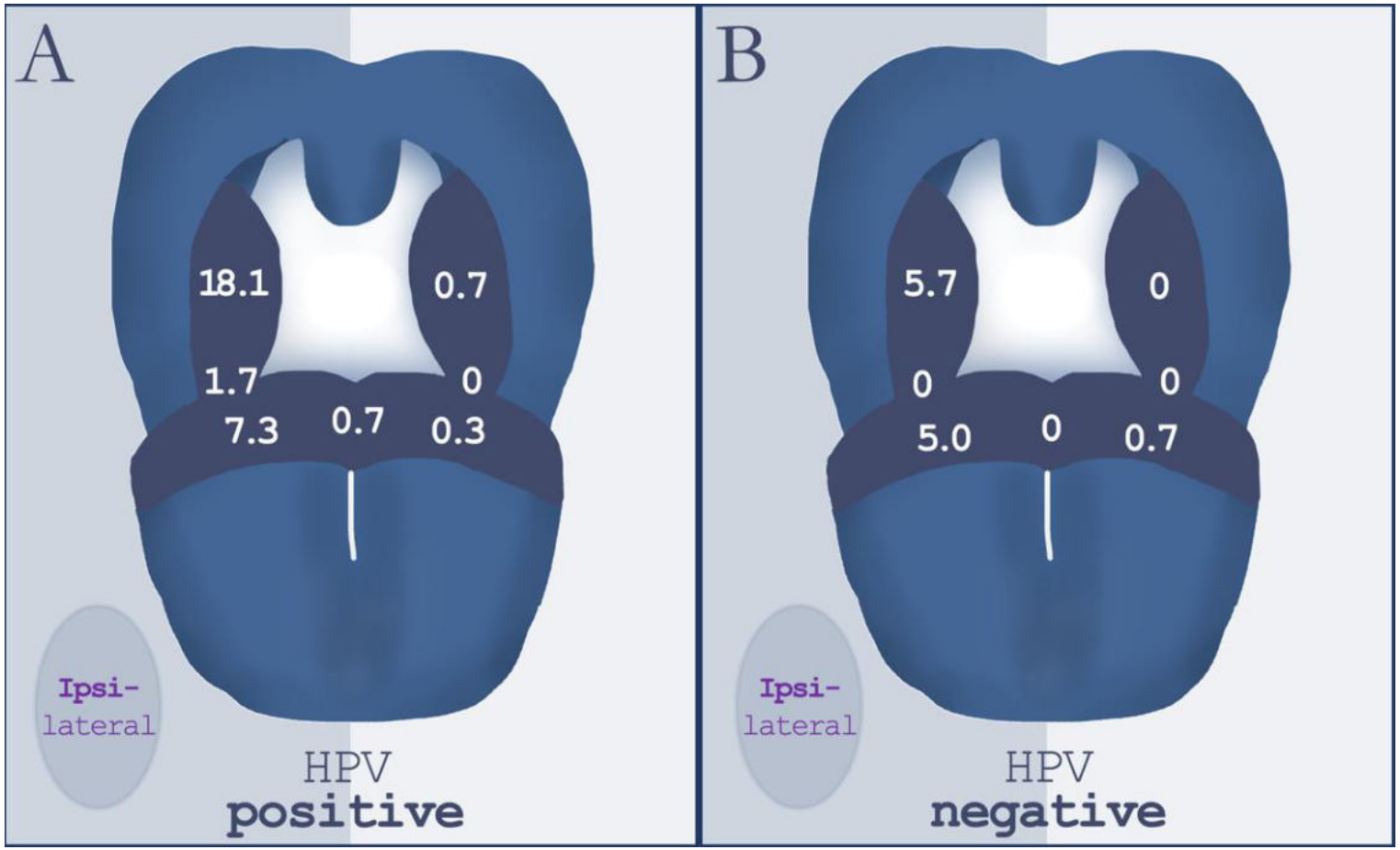


Figure 2-6: Final histological oropharyngeal primary sites with 'no clear primary' on PET-CT in the HNSCCUP National Audit. (A) HPV-positive patients, and (B) HPV-negative patients. Figures in percentages. Please note, primary site identification rates will be influenced by incidence of diagnostic oropharyngeal surgery which is listed alongside full primary site data stratified by HPV in ***Table 2-7****.*

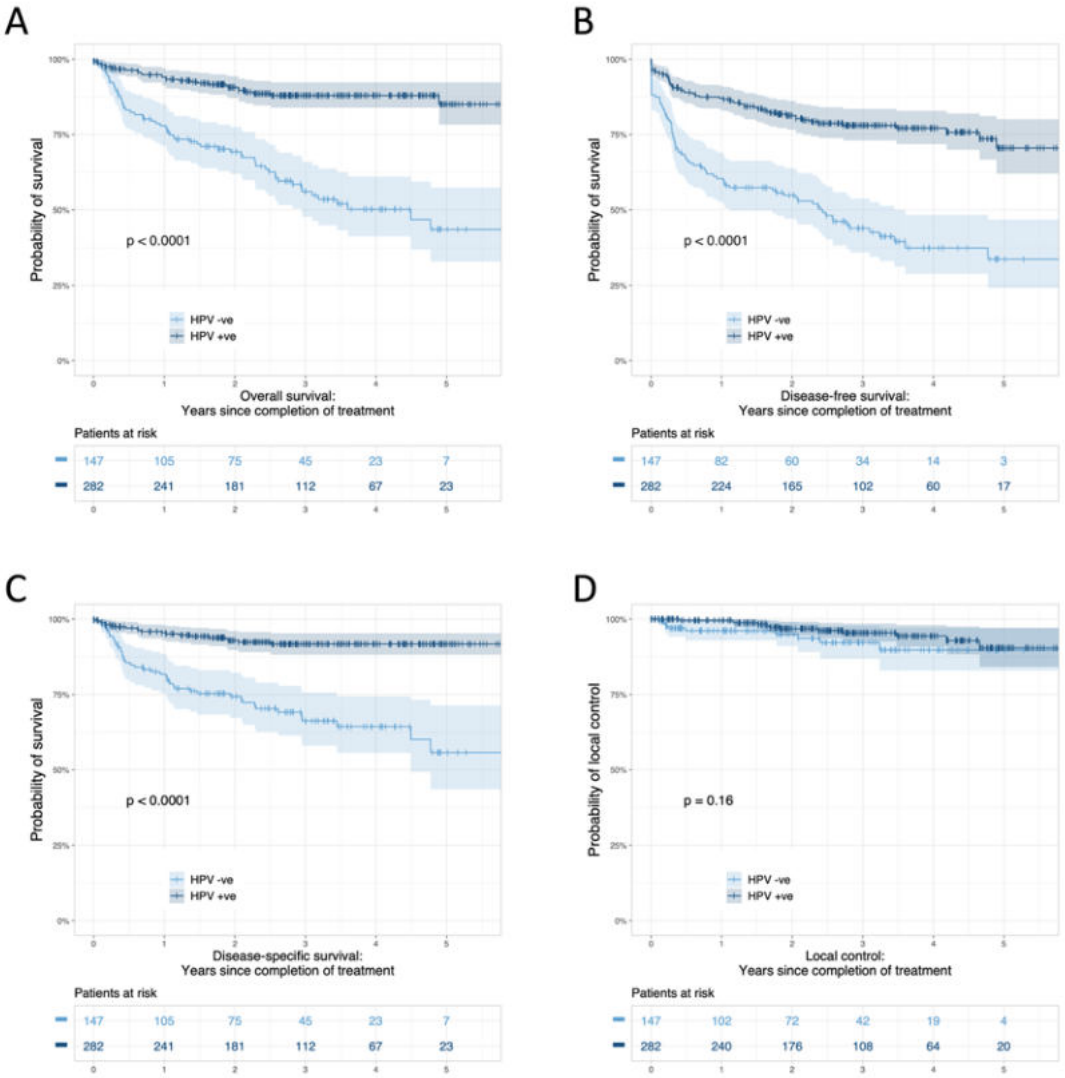


Figure 2-7: Kaplan-Meier survival estimates stratified by HPV status in the HNSCCUP National Audit.
(A) overall survival; (B) disease-free survival; (C) disease-specific survival; (D) local control.

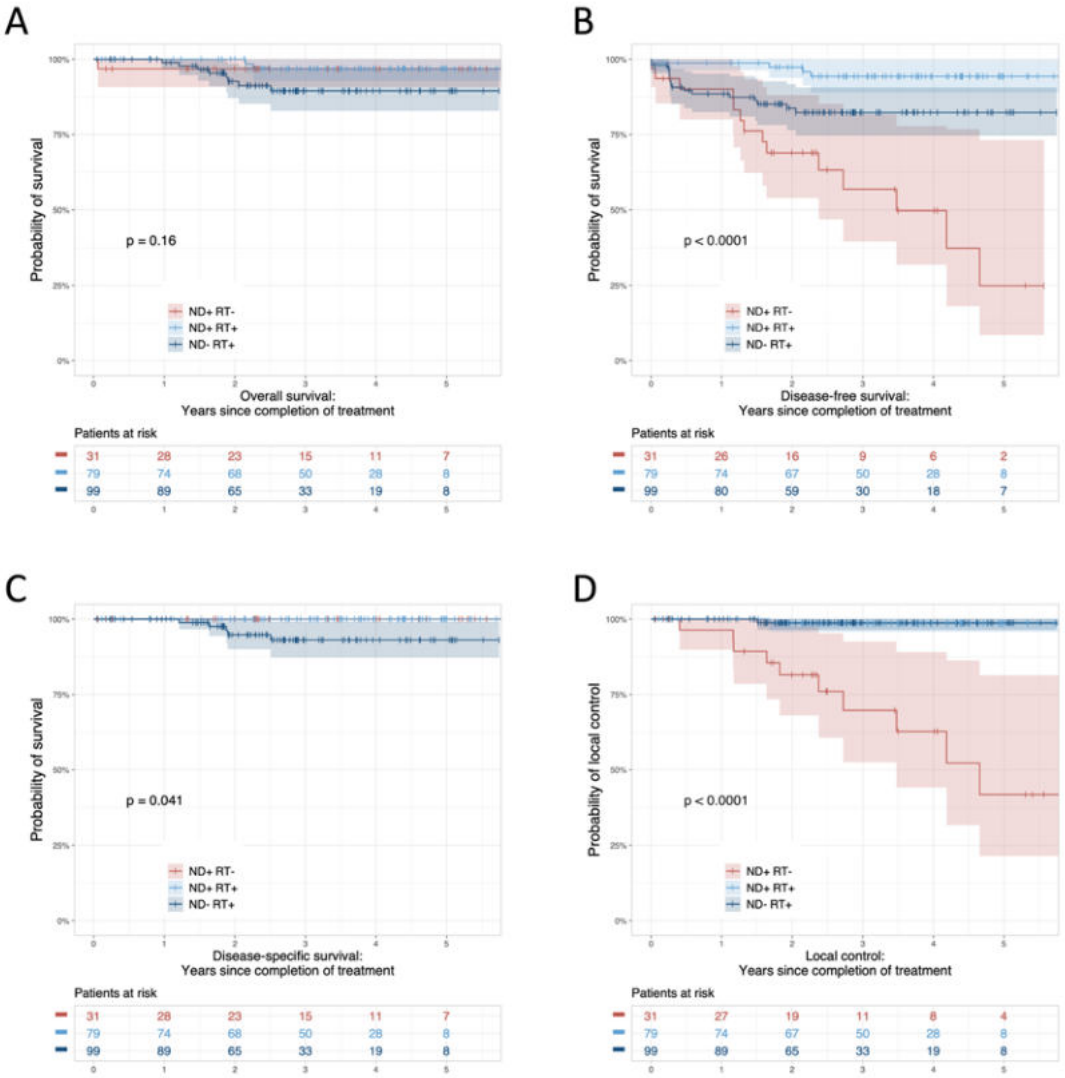


Figure 2-8: Kaplan-Meier survival estimates for HPV-positive patients with unilateral neck disease undergoing treatment with curative intent stratified by treatment category in the HNSCCUP National Audit.
(A) overall survival; (B) disease-free survival; (C) disease-specific survival; (D) local control.
ND+ RT- is ipsilateral neck dissection without ipsilateral neck radiotherapy.
ND+ RT+ is ipsilateral neck dissection and ipsilateral neck radiotherapy.
ND- RT+ is ipsilateral neck radiotherapy without ipsilateral neck dissection.

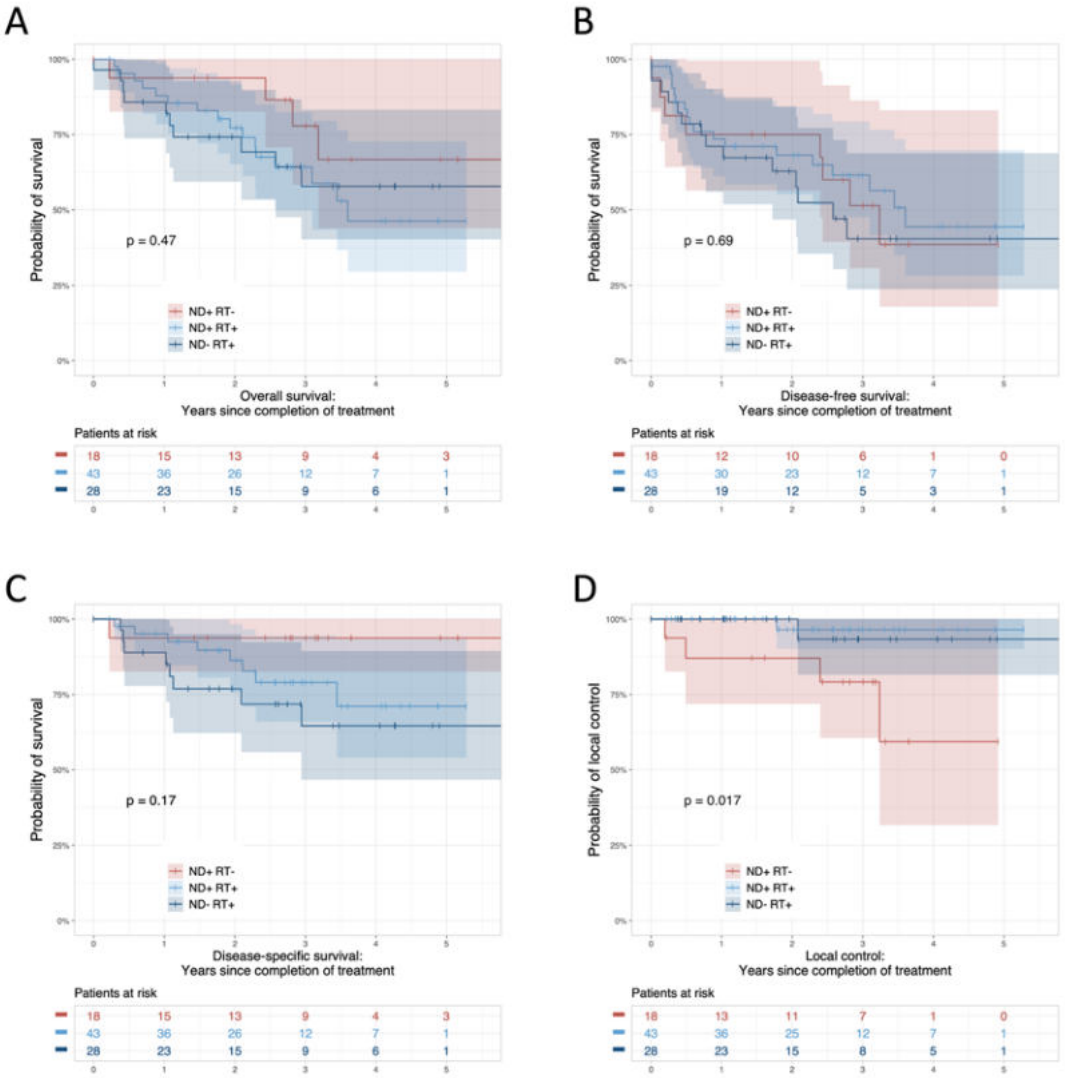


Figure 2-9: Kaplan-Meier survival estimates for HPV-negative patients with unilateral neck disease undergoing treatment with curative intent in the HNSCCUP National Audit.
(A) overall survival; (B) disease-free survival; (C) disease-specific survival; (D) local control.
ND+ RT- is ipsilateral neck dissection without ipsilateral neck radiotherapy.
ND+ RT+ is ipsilateral neck dissection and ipsilateral neck radiotherapy.
ND- RT+ is ipsilateral neck radiotherapy without ipsilateral neck dissection.

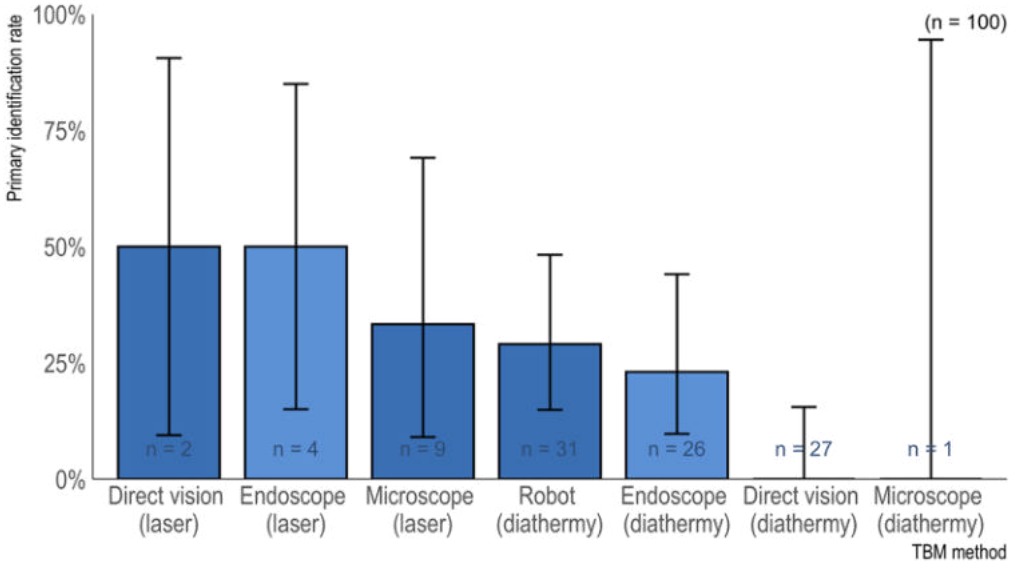


Figure 2-10: Bar chart of relative identification rates from TBM in the HNSCCUP National Audit.
Error bars represent 95% confidence intervals.
TBM is tongue base mucosectomy.

Table 2-3: Clinico-pathological characteristics for all patients and for suspected HNSCCUP referrals without prior investigations in the HNSCCUP National Audit.
HNSCCUP is head and neck squamous cell carcinoma of unknown primary, ECOG is Eastern Cooperative Oncology Group, GP is general practitioner, HNC is head and neck cancer, NBI is narrow band imaging.

		All patients (n 965)	Suspected HNSCCUP without prior investigations (n 585)
Variable	**Classification**	**n (%)**	**n (%)**
Age	**Median, years**	59	58
	Minimum, years	26	26
	Maximum, years	89	87
	Mean, years	59.7	59
	Standard deviation, years	9.8	9.7
Sex	**Data available**	571 (97.6)	98.1 (571)
	Female	245 (25.9)	25.9 (136)
	Male	702 (74.1)	74.1 (435)
Smoking status	**Data available**	883 (91.5)	91.5 (540)
	Never smoker	291 (33)	33 (174)
	Ex-smoker	314 (35.6)	35.6 (191)
	Current smoker	278 (31.5)	31.5 (175)
Alcohol status	**Data available**	781 (80.9)	80.9 (483)
	No alcohol	148 (19)	19 (79)
	Light alcohol	450 (57.6)	57.6 (295)
	Heavy alcohol	183 (23.4)	23.4 (109)
ECOG performance status	**Data available**	935 (96.9)	96.9 (575)
	0	692 (74)	74 (446)
	1	175 (18.7)	18.7 (103)
	2	56 (6)	6 (21)
	3	12 (1.3)	1.3 (5)
Referral source	**Data available**	942 (97.6)	97.6 (585)
	GP: suspected HNC pathway	739 (78.5)	78.5 (585)
	GP: other priority	71 (7.5)	7.5 (0)
	Other source	132 (14)	14 (0)
Outpatient NBI	**Data available**	783 (81.1)	81.1 (486)
	Yes	13 (1.7)	1.7 (8)
	No	770 (98.3)	98.3 (478)
Principal nodal level at presentation	**Data available**	947 (98.1)	98.1 (579)
	1	45 (4.8)	4.8 (28)
	2	751 (79.3)	79.3 (451)
	3	105 (11.1)	11.1 (74)
	4	21 (2.2)	2.2 (12)
	5	25 (2.6)	2.6 (14)

Table 2-4: Clinicopathological factors and treatments for all treated HNSCCUP patients and by HPV status intent in the HNSCCUP National Audit.
HNSCCUP is head and neck squamous cell carcinoma from an unknown primary, ECOG is Eastern Cooperative Oncology Group, PET-CT is 18F-Fluorodeoxyglucose- Positron emission tomography- computerised tomography, TBM is tongue base mucosectomy, HPV is human papillomavirus, EBV is Epstein-Barr virus, NOS is not otherwise specified.

		Treated HNSCCUP (n=482)	Treated HNSCCUP with HPV-positive disease (n=282)	Treated HNSCCUP with HPV-negative disease (n=147)	
Variable	**Classification**	**n (%)**	**n (%)**	**n (%)**	**p**
Age	**Median, years**	60.5	58	64	<0.001
	Minimum, years	26	26	34	
	Maximum, years	88	86	88	
	Mean, years	61.4	59.1	63.9	
	Standard deviation, years	9.9	9.4	9.3	
Sex	**Data available**	465 (96.5)	274 (97.2)	143 (97.3)	0.861
	Female	113 (24.3)	66 (24.1)	34 (23.8)	
	Male	352 (75.7)	208 (75.9)	109 (76.2)	
Smoking	**Data available**	447 (92.7)	259 (91.8)	139 (94.6)	<0.001
	Never smoker	132 (29.5)	99 (38.2)	24 (17.3)	
	Ex-smoker	167 (37.4)	101 (39)	44 (31.7)	
	Current smoker	148 (33.1)	59 (22.8)	71 (51.1)	
Alcohol	**Data available**	401 (83.2)	225 (79.8)	130 (88.4)	<0.001
	No alcohol	82 (20.4)	45 (20)	28 (21.5)	
	Light alcohol	225 (56.1)	144 (64)	58 (44.6)	
	Heavy alcohol	94 (23.4)	36 (16)	44 (33.8)	
ECOG performance status	**Data available**	464 (96.3)	272 (96.5)	139 (94.6)	<0.001
	0	318 (68.5)	212 (77.9)	71 (51.1)	
	1	103 (22.2)	45 (16.5)	48 (34.5)	
	2	35 (7.5)	13 (4.8)	16 (11.5)	
	3	8 (1.7)	2 (0.7)	4 (2.9)	
Principal nodal level at presentation	**Data available**	475 (98.5)	280 (99.3)	146 (99.3)	0.006
	1	33 (6.9)	11 (3.9)	17 (11.6)	
	2	356 (74.9)	218 (77.9)	104 (71.2)	
	3	56 (11.8)	32 (11.4)	18 (12.3)	
	4	15 (3.2)	11 (3.9)	3 (2.1)	
	5	15 (3.2)	8 (2.9)	4 (2.7)	
Did patient factors alter the investigations/ biopsies offered?	**Data available**	459 (95.2)	269 (95.4)	139 (94.6)	0.001
	No	414 (90.2)	251 (93.3)	120 (86.3)	
	Patient choice	13 (2.8)	6 (2.2)	5 (3.6)	
	Patient fitness	28 (6.1)	11 (4.1)	11 (7.9)	
	Patient choice & fitness	4 (0.9)	1 (0.4)	3 (2.2)	
Primary site on PET-CT	**Data available**	481 (99.8)	281 (99.6)	147 (100)	<0.001
	No clear primary seen	358 (74.4)	200 (71.2)	121 (82.3)	
	Equivocal	96 (20)	65 (23.1)	19 (12.9)	
	Clear primary seen	27 (5.6)	16 (5.7)	7 (4.8)	

HPV status	**Data available**	429 (89)	282 (100)	147 (100)	-
	Positive	282 (65.7)	282 (100)	0 (0)	
	Negative	147 (34.3)	0 (0)	147 (100)	
	Not performed	40 ()	0 ()	0 ()	
EBV status	**Data available**	341 (70.7)	195 (69.1)	107 (72.8)	0.520
	Positive	5 (1.5)	5 (2.6)	0 (0)	
	Negative	116 (34)	63 (32.3)	49 (45.8)	
	Not performed	220 (64.5)	127 (65.1)	58 (54.2)	
Clinical N classification (as per TNM 7)	**Data available**	450 (93.4)	263 (93.3)	138 (93.9)	0.002
	cN1	115 (25.6)	70 (26.6)	34 (24.6)	
	cN2 (NOS)	2 (0.4)	2 (0.8)	0 (0)	
	cN2a	96 (21.3)	63 (24)	23 (16.7)	
	cN2b	175 (38.9)	101 (38.4)	54 (39.1)	
	cN2c	32 (7.1)	17 (6.5)	13 (9.4)	
	cN3 (NOS)	5 (1.1)	5 (1.9)	0 (0)	
	cN3a	12 (2.7)	4 (1.5)	6 (4.3)	
	cN3b	13 (2.9)	1 (0.4)	8 (5.8)	
M classification	**Data available**	469 (97.3)	274 (97.2)	143 (97.3)	<0.001
	M0	448 (95.5)	270 (98.5)	133 (93)	
	M1	21 (4.5)	4 (1.5)	10 (7)	
Prior tonsillectomy	**Data available**	429 (89)	254 (90.1)	126 (85.7)	0.035
	Yes	91 (21.2)	67 (26.4)	18 (14.3)	
	No	338 (78.8)	187 (73.6)	108 (85.7)	
Ipsilateral tonsillectomy	**Data available**	458 (95)	271 (96.1)	137 (93.2)	0.022
	Yes (including remnant)	265 (72.2)	157 (77)	80 (67.2)	
	No (excluding prior tonsillectomy)	102 (27.8)	47 (23)	39 (32.8)	
Contralateral tonsillectomy	**Data available**	454 (94.2)	267 (94.7)	137 (93.2)	0.440
	Yes (including remnant)	225 (62)	130 (65)	72 (60.5)	
	No (excluding prior tonsillectomy)	138 (38)	70 (35)	47 (39.5)	
Ipsilateral TBM	**Data available**	482 (100)	282 (100)	147 (100)	0.106
	Yes	86 (17.8)	61 (21.6)	23 (15.6)	
	No	396 (82.2)	221 (78.4)	124 (84.4)	
Contralateral TBM	**Data available**	482 (100)	282 (100)	147 (100)	0.125
	Yes	65 (13.5)	46 (16.3)	17 (11.6)	
	No	417 (86.5)	236 (83.7)	130 (88.4)	
Did patient factors alter the treatment offered?	**Data available**	461 (95.6)	269 (95.4)	140 (95.2)	<0.001
	No	369 (80)	228 (84.8)	102 (72.9)	
	Patient choice	35 (7.6)	23 (8.6)	9 (6.4)	
	Patient fitness	51 (11.1)	16 (5.9)	25 (17.9)	
	Patient choice & fitness	6 (1.3)	2 (0.7)	4 (2.9)	
Ipsilateral neck dissection	**Data available**	481 (99.8)	281 (99.6)	147 (100)	0.008
	Yes	247 (51.4)	135 (48)	85 (57.8)	
	No	234 (48.6)	146 (52)	62 (42.2)	
Contralateral neck dissection	**Data available**	482 (100)	282 (100)	147 (100)	0.332
	Yes	14 (2.9)	6 (2.1)	4 (2.7)	

	No	468 (97.1)	276 (97.9)	143 (97.3)	
Ipsilateral neck radiotherapy	**Data available**	469 (97.3)	271 (96.1)	147 (100)	0.001
	Yes	377 (80.4)	226 (83.4)	113 (76.9)	
	No	92 (19.6)	45 (16.6)	34 (23.1)	
Contralateral neck radiotherapy	**Data available**	438 (90.9)	247 (87.6)	142 (96.6)	0.002
	Yes	137 (31.3)	93 (37.7)	37 (26.1)	
	No	301 (68.7)	154 (62.3)	105 (73.9)	
Chemotherapy	**Data available**	466 (96.7)	272 (96.5)	144 (98)	<0.001
	Neoadjuvant	15 (3.2)	5 (1.8)	6 (4.2)	
	Concurrent	225 (48.3)	154 (56.6)	55 (38.2)	
	Neoadjuvant & concurrent	9 (1.9)	5 (1.8)	3 (2.1)	
	No	217 (46.6)	108 (39.7)	80 (55.6)	
Post-treatment PET-CT	**Data available**	480 (99.6)	281 (99.6)	146 (99.3)	0.770
	Yes	249 (51.9)	164 (58.4)	69 (47.3)	
	No	231 (48.1)	117 (41.6)	77 (52.7)	

Table 2-5: Histopathological findings for all patients and for HNSCCUP with no clear primary on PET-CT in the HNSCCUP National Audit.
HNSCCUP is head and neck squamous cell carcinoma from an unknown primary, HPV is human papillomavirus, EBV is Epstein-Barr virus, NOS is not otherwise specified.

		All patients (n 965)	HNSCCUP with no clear primary on PET-CT (n 479)
Variable	**Classification**	**n (%)**	**n (%)**
HPV status	**Data available**	936 (97)	466 (97.3)
	Positive	641 (68.5)	289 (62)
	Negative	236 (25.2)	144 (30.9)
	Not performed	59 (6.3)	33 (7.1)
EBV status	**Data available**	667 (69.1)	334 (69.7)
	Positive	12 (1.8)	5 (1.5)
	Negative	202 (30.3)	103 (30.8)
	Not performed	453 (67.9)	226 (67.7)
Clinical N classification (TNM 7)	**Data available**	798 (82.7)	401 (83.7)
	cN1	204 (25.6)	115 (28.7)
	cN2 (NOS)	1 (0.1)	0 (0)
	cN2a	159 (19.9)	84 (20.9)
	cN2b	330 (41.4)	153 (38.2)
	cN2c	69 (8.6)	27 (6.7)
	cN3 (NOS)	6 (0.8)	3 (0.7)
	cN3a	11 (1.4)	8 (2)
	cN3b	18 (2.3)	11 (2.7)
Clinical M classification (TNM 7)	**Data available**	929 (96.3)	464 (96.9)
	M0	886 (95.4)	447 (96.3)
	M1	43 (4.6)	17 (3.7)
Histologically confirmed primary site	**Data available**	954 (98.9)	473 (98.7)
	No primary site	482 (50.5)	359 (75.9)
	Ipsilateral tonsil	230 (24.1)	64 (13.5)
	Contralateral tonsil	2 (0.2)	2 (0.4)
	Ipsilateral glossotonsillar sulcus	17 (1.8)	5 (1.1)
	Contralateral glossotonsillar sulcus	0 (0)	0 (0)
	Ipsilateral tongue base	135 (14.2)	29 (6.1)
	Midline Tongue base, within 1 cm of midline	6 (0.6)	2 (0.4)
	Contralateral tongue base	4 (0.4)	2 (0.4)
	Soft Palate	1 (0.1)	0 (0)
	Vallecula	2 (0.2)	0 (0)
	Multiple foci (unilateral, all >1cm from midline)	7 (0.7)	3 (0.6)
	Multiple foci (bilateral, contralateral or any foci within 1 cm of midline)	6 (0.6)	1 (0.2)
	Oral cavity	6 (0.6)	1 (0.2)
	Nasopharynx	15 (1.6)	0 (0)
	Hypopharynx (NOS)	19 (2)	0 (0)
	Posterior pharyngeal wall	3 (0.3)	0 (0)

	Post cricoid region	4 (0.4)	2 (0.4)
	Supraglottis	5 (0.5)	0 (0)
	Glottis	2 (0.2)	1 (0.2)
	Subglottis	1 (0.1)	0 (0)
	Cervical oesophagus	3 (0.3)	0 (0)
	Parotid	3 (0.3)	1 (0.2)
	Submandibular gland	1 (0.1)	1 (0.2)

Table 2-6: Univariable analysis of CT versus MRI performed concurrently with PET-CT (within 10 days) in the HNSCCUP National Audit.
HNSCCUP is head and neck squamous cell carcinoma from an unknown primary, NOS is not otherwise specified, HPV is human papillomavirus, ECOG is Eastern Cooperative Oncology Group, PET-CT is 18F-Fluorodeoxyglucose-Positron emission tomography- computerised tomography.

		Concurrent PET-CT and CT only (n 74)	Concurrent PET-CT and MRI only (n 152)	
Variable	**Classification**	**n (%)**	**n (%)**	**p**
Age	**Median, years**	57.5	59	0.395
	Minimum, years	35	40	
	Maximum, years	89	86	
	Mean, years	58.7	59.6	
	StDev, years	10.6	9.3	
Sex	**Data available**	74 (100)	152 (100)	0.247
	Female	14 (18.9)	41 (27)	
	Male	60 (81.1)	111 (73)	
Smoking	**Data available**	70 (94.6)	132 (86.8)	0.167
	Never smoker	20 (28.6)	45 (34.1)	
	Ex-smoker	24 (34.3)	55 (41.7)	
	Current smoker	26 (37.1)	32 (24.2)	
Alcohol	**Data available**	58 (78.4)	114 (75)	0.117
	No alcohol	15 (25.9)	18 (15.8)	
	Light alcohol	27 (46.6)	71 (62.3)	
	Heavy alcohol	16 (27.6)	25 (21.9)	
ECOG performance status	**Data available**	69 (93.2)	148 (97.4)	0.362
	0	56 (81.2)	108 (73)	
	1	8 (11.6)	30 (20.3)	
	2	4 (5.8)	9 (6.1)	
	3	1 (1.4)	1 (0.7)	
	4	0 (0)	0 (0)	
Principal nodal level at presentation	**Data available**	71 (95.9)	148 (97.4)	0.833
	1	2 (2.8)	6 (4.1)	
	2	59 (83.1)	113 (76.4)	
	3	8 (11.3)	21 (14.2)	
	4	0 (0)	3 (2)	
	5	2 (2.8)	5 (3.4)	
HPV status	**Data available**	71 (95.9)	139 (91.4)	0.743
	Positive	51 (71.8)	103 (74.1)	
	Negative	20 (28.2)	36 (25.9)	
Histologically confirmed primary site	**Data available**	74 (100)	152 (100)	0.003
	Yes	30 (40.5)	95 (62.5)	
	No	44 (59.5)	57 (37.5)	
Prior tonsillectomy	**Data available**	69 (93.2)	139 (91.4)	1
	Yes	12 (17.4)	23 (16.5)	
	No	57 (82.6)	116 (83.5)	
	Data available	70 (94.6)	144 (94.7)	0.816

Clinical N classification (as per TNM 7)	**cNx**	0 (0)	0 (0)	
	cN0	0 (0)	0 (0)	
	cN1	14 (20)	22 (15.3)	
	cN2 (NOS)	0 (0)	1 (0.7)	
	cN2a	15 (21.4)	33 (22.9)	
	cN2b	32 (45.7)	67 (46.5)	
	cN2c	7 (10)	15 (10.4)	
	cN3 (NOS)	1 (1.4)	0 (0)	
	cN3a	0 (0)	2 (1.4)	
	cN3b	1 (1.4)	4 (2.8)	
M classification	**Data available**	72 (97.3)	146 (96.1)	1
	M0	70 (97.2)	142 (97.3)	
	M1	2 (2.8)	4 (2.7)	

Table 2-7: Diagnostic surgeries for all patients and for HNSCCUP with no clear primary on PET-CT in the HNSCCUP National Audit.
HNSCCUP is head and neck squamous cell carcinoma from an unknown primary. NOS is not otherwise specified, UADT is Upper Aero-Digestive Tract, TBM is tongue base mucosectomy.
^of those undergoing at least one diagnostic theatre episode.
**targeted based on any radiological or clinical suspicion at time of surgery.*

		All patients (n 965)	No clear primary site on PET-CT (n 479)
Variable	**Classification**	**n (%)**	**n (%)**
Total diagnostic theatre episodes	**Data available**	909 (94.2)	455 (95)
	0	80 (8.8)	31 (6.8)
	1	652 (71.7)	331 (72.7)
	2	164 (18)	88 (19.3)
	3 or more	13 (1.4)	5 (1.1)
Prior tonsillectomy	**Data available**	873 (90.5)	433 (90.4)
	Yes	138 (15.8)	82 (18.9)
	No	735 (84.2)	351 (81.1)
Ipsilateral tonsillectomy	**Data available**	914 (94.7)	455 (95)
	Yes (including remnant)	512 (66)	278 (74.5)
	No (excluding prior tonsillectomy)	264 (34)	95 (25.5)
Contralateral tonsillectomy	**Data available**	907 (94)	454 (94.8)
	Yes (including remnant)	396 (51.5)	234 (62.9)
	No (excluding prior tonsillectomy)	373 (48.5)	138 (37.1)
Ipsilateral TBM	**Data available**	965 (100)	479 (100)
	Yes	156 (16.2)	104 (21.7)
	No	809 (83.8)	375 (78.3)
Contralateral TBM	**Data available**	965 (100)	479 (100)
	Yes	108 (11.2)	82 (17.1)
	No	857 (88.8)	397 (82.9)
Any untargeted UADT biopsy^	**Data available**	820 (92.7)	418 (93.3)
	Yes	296 (36.1)	201 (48.1)
	No	524 (63.9)	217 (51.9)
Forceps biopsies of Nasopharynx^	**Data available**	789 (89.2)	401 (89.5)
	Nil	612 (77.6)	284 (70.8)
	Targeted	59 (7.5)	23 (5.7)
	Untargeted	118 (15)	94 (23.4)
Forceps biopsies of Tonsils^	**Data available**	797 (90.1)	408 (91.1)
	Nil	501 (62.9)	261 (64)
	Targeted	182 (22.8)	58 (14.2)
	Untargeted	114 (14.3)	89 (21.8)
Forceps biopsies of Tongue base^	**Data available**	787 (88.9)	395 (88.2)
	Nil	284 (36.1)	133 (33.7)
	Targeted	260 (33)	86 (21.8)
	Untargeted	243 (30.9)	176 (44.6)
Forceps biopsies of Hypopharynx^	**Data available**	795 (89.8)	410 (91.5)
	Nil	684 (86)	348 (84.9)
	Targeted	50 (6.3)	19 (4.6)

	Untargeted	61 (7.7)	43 (10.5)
Forceps biopsies of Other sites^	**Data available**	690 (78)	354 (79)
	No	599 (86.8)	306 (86.4)
	Yes	91 (13.2)	48 (13.6)
Intraoperative Frozen biopsy^	**Data available**	703 (79.4)	360 (80.4)
	Yes	23 (3.3)	8 (2.2)
	No	680 (96.7)	352 (97.8)
Intraoperative Narrow band imaging^	**Data available**	646 (73)	325 (72.5)
	Yes	21 (3.3)	11 (3.4)
	No	625 (96.7)	314 (96.6)
Intraoperative Ultrasound^	**Data available**	690 (78)	350 (78.1)
	Yes	4 (0.6)	1 (0.3)
	No	686 (99.4)	349 (99.7)

Table 2-8: Comparison of patient and treatment factors between HNSCCUP with unilateral nodal disease treated with curative intent, stratified by treatment groups intent in the HNSCCUP National Audit.
HNSCCUP is head and neck squamous cell carcinoma from an unknown primary, ECOG is Eastern Cooperative Oncology Group, TBM is tongue base mucosectomy, HPV is human papillomavirus, NOS is not otherwise specified.

		HPV-positive HNSCCUP with unilateral neck disease treated with ipsilateral neck dissection but with no ipsilateral radiotherapy (n=31)	HPV-positive HNSCCUP with unilateral neck disease treated with ipsilateral neck dissection and with ipsilateral radiotherapy (n=79)	HPV-positive HNSCCUP with unilateral neck disease treated with no ipsilateral neck dissection but with ipsilateral radiotherapy (n=99)		HPV-negative HNSCCUP with unilateral neck disease treated with ipsilateral neck dissection but no ipsilateral radiotherapy (n=18)	HPV-negative HNSCCUP with unilateral neck disease treated with ipsilateral neck dissection and ipsilateral radiotherapy (n=43)	HPV-negative HNSCCUP with unilateral neck disease treated with no ipsilateral neck dissection but with ipsilateral radiotherapy (n=28)	
Variable	**Classification**	**n (%)**	**n (%)**	**n (%)**	**p**	**n (%)**	**n (%)**	**n (%)**	**p**
Age	**Median, years**	61.5	58	57	0.265	67.5	63	61.5	0.632
	Minimum, years	32	31	26		50	46	34	
	Maximum, years	86	79	77		81	88	75	
	Mean, years	60.5	58.4	57.3		66.5	62.9	60.7	
	Standard deviation, years	10.9	9.6	8.3		8.7	9	8.5	
Sex	**Data available**	31 (100)	76 (96.2)	94 (94.9)	0.062	18 (100)	42 (97.7)	28 (100)	0.450
	Female	8 (25.8)	13 (17.1)	31 (33)		3 (16.7)	7 (16.7)	8 (28.6)	
	Male	23 (74.2)	63 (82.9)	63 (67)		15 (83.3)	35 (83.3)	20 (71.4)	
Smoking	**Data available**	31 (100)	67 (84.8)	92 (92.9)	0.525	16 (88.9)	43 (100)	27 (96.4)	0.993
	Never smoker	13 (41.9)	25 (37.3)	41 (44.6)		3 (18.8)	8 (18.6)	5 (18.5)	
	Ex-smoker	10 (32.3)	28 (41.8)	38 (41.3)		4 (25)	13 (30.2)	7 (25.9)	
	Current smoker	8 (25.8)	14 (20.9)	13 (14.1)		9 (56.3)	22 (51.2)	15 (55.6)	
Alcohol	**Data available**	26 (83.9)	59 (74.7)	78 (78.8)	0.090	16 (88.9)	42 (97.7)	24 (85.7)	0.446
	No alcohol	7 (26.9)	11 (18.6)	12 (15.4)		5 (31.3)	7 (16.7)	5 (20.8)	
	Light alcohol	12 (46.2)	37 (62.7)	58 (74.4)		4 (25)	21 (50)	12 (50)	
	Heavy alcohol	7 (26.9)	11 (18.6)	8 (10.3)		7 (43.8)	14 (33.3)	7 (29.2)	
ECOG performance status	**Data available**	30 (96.8)	75 (94.9)	94 (94.9)	0.450	17 (94.4)	42 (97.7)	26 (92.9)	0.495
	0	25 (83.3)	61 (81.3)	79 (84)		8 (47.1)	27 (64.3)	14 (53.8)	

	1	4 (13.3)	11 (14.7)	14 (14.9)		8 (47.1)	10 (23.8)	11 (42.3)	
	2	0 (0)	3 (4)	1 (1.1)		1 (5.9)	4 (9.5)	1 (3.8)	
	3	1 (3.3)	0 (0)	0 (0)		0 (0)	1 (2.4)	0 (0)	
Principal nodal level at presentation	**Data available**	31 (100)	78 (98.7)	99 (100)	0.364	18 (100)	43 (100)	28 (100)	0.132
	1	3 (9.7)	2 (2.6)	3 (3)		5 (27.8)	3 (7)	4 (14.3)	
	2	22 (71)	68 (87.2)	76 (76.8)		11 (61.1)	35 (81.4)	16 (57.1)	
	3	4 (12.9)	6 (7.7)	11 (11.1)		2 (11.1)	4 (9.3)	6 (21.4)	
	4	1 (3.2)	1 (1.3)	6 (6.1)		0 (0)	0 (0)	0 (0)	
	5	1 (3.2)	1 (1.3)	3 (3)		0 (0)	1 (2.3)	2 (7.1)	
Clinical N classification (as per TNM 7)	**Data available**	31 (100)	78 (98.7)	99 (100)	0.001	18 (100)	40 (93)	28 (100)	<0.001
	cN1	15 (48.4)	13 (16.7)	34 (34.3)		14 (77.8)	12 (30)	4 (14.3)	
	cN2a	10 (32.3)	26 (33.3)	20 (20.2)		3 (16.7)	9 (22.5)	6 (21.4)	
	cN2b	6 (19.4)	39 (50)	45 (45.5)		1 (5.6)	19 (47.5)	18 (64.3)	
Prior tonsillectomy	**Data available**	29 (93.5)	71 (89.9)	90 (90.9)	0.679	15 (83.3)	36 (83.7)	27 (96.4)	0.796
	Yes	7 (24.1)	20 (28.2)	29 (32.2)		2 (13.3)	6 (16.7)	6 (22.2)	
	No	22 (75.9)	51 (71.8)	61 (67.8)		13 (86.7)	30 (83.3)	21 (77.8)	
Ipsilateral tonsillectomy	**Data available**	31 (100)	76 (96.2)	96 (97)	0.421	17 (94.4)	40 (93)	27 (96.4)	0.020
	Yes (including remnant)	19 (76)	48 (85.7)	51 (76.1)		10 (66.7)	31 (91.2)	11 (52.4)	
	No (excluding prior tonsillectomy)	6 (24)	8 (14.3)	16 (23.9)		5 (33.3)	3 (8.8)	10 (47.6)	
Contralateral tonsillectomy	**Data available**	31 (100)	74 (93.7)	94 (94.9)	0.847	17 (94.4)	40 (93)	27 (96.4)	0.011
	Yes (including remnant)	13 (52)	38 (70.4)	46 (70.8)		9 (60)	28 (82.4)	8 (38.1)	
	No (excluding prior tonsillectomy)	12 (48)	16 (29.6)	19 (29.2)		6 (40)	6 (17.6)	13 (61.9)	
Ipsilateral TBM	**Data available**	31 (100)	79 (100)	99 (100)	0.014	18 (100)	43 (100)	28 (100)	0.388
	Yes	11 (35.5)	20 (25.3)	13 (13.1)		6 (33.3)	8 (18.6)	5 (17.9)	
	No	20 (64.5)	59 (74.7)	86 (86.9)		12 (66.7)	35 (81.4)	23 (82.1)	
Contralateral TBM	**Data available**	31 (100)	79 (100)	99 (100)	0.048	18 (100)	43 (100)	28 (100)	0.304
	Yes	8 (25.8)	13 (16.5)	9 (9.1)		5 (27.8)	6 (14)	3 (10.7)	

	No	23 (74.2)	66 (83.5)	90 (90.9)		13 (72.2)	37 (86)	25 (89.3)	
Did patient factors alter the treatment offered?	**Data available**	31 (100)	75 (94.9)	96 (97)	0.409	16 (88.9)	39 (90.7)	27 (96.4)	0.879
	No	29 (93.5)	73 (97.3)	89 (92.7)		15 (93.8)	36 (92.3)	24 (88.9)	
	Patient choice	2 (6.5)	2 (2.7)	3 (3.1)		1 (6.3)	0 (0)	1 (3.7)	
	Patient fitness	0 (0)	0 (0)	4 (4.2)		0 (0)	3 (7.7)	2 (7.4)	
	Patient choice & fitness	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
Contralateral neck dissection	**Data available**	31 (100)	79 (100)	99 (100)	1	18 (100)	43 (100)	28 (100)	0.300
	Yes	0 (0)	1 (1.3)	1 (1)		0 (0)	3 (7)	0 (0)	
	No	31 (100)	78 (98.7)	98 (99)		18 (100)	40 (93)	28 (100)	
Contralateral neck radiotherapy	**Data available**	26 (83.9)	72 (91.1)	86 (86.9)	<0.001	18 (100)	42 (97.7)	26 (92.9)	0.004
	Yes	0 (0)	27 (37.5)	39 (45.3)		0 (0)	10 (23.8)	11 (42.3)	
	No	26 (100)	45 (62.5)	47 (54.7)		18 (100)	32 (76.2)	15 (57.7)	
Chemotherapy	**Data available**	27 (87.1)	78 (98.7)	96 (97)	<0.001	18 (100)	42 (97.7)	28 (100)	<0.001
	Neoadjuvant	0 (0)	1 (1.3)	3 (3.1)		0 (0)	2 (4.8)	1 (3.6)	
	Concurrent	0 (0)	41 (52.6)	82 (85.4)		1 (5.6)	18 (42.9)	18 (64.3)	
	Neoadjuvant & concurrent	0 (0)	0 (0)	1 (1)		0 (0)	0 (0)	2 (7.1)	
	No	27 (100)	36 (46.2)	10 (10.4)		17 (94.4)	22 (52.4)	7 (25)	

*Table 2-9: Diagnostic surgeries for all patients and for HNSCCUP with no clear primary on PET-CT in the HNSCCUP National Audit. HNSCCUP is head and neck squamous cell carcinoma from an unknown primary, HPV is human papillomavirus, ECOG is Eastern Cooperative Oncology Group, NOS is not otherwise specified, UADT is Upper Aero-Digestive Tract, TBM is tongue base mucosectomy. ^of those undergoing at least one diagnostic theatre episode. *targeted based on any radiological or clinical suspicion at time of surgery*

		No clear primary site on PET-CT	
		HPV-positive (n=289)	**HPV-negative (n=144)**
Variable	**Classification**	n (%)	n (%)
Age	**Median, years**	57	64
	Minimum, years	26	41
	Maximum, years	86	89
	Mean, years	58.1	64.8
	StDev, years	9.4	9.5
Sex	**Data available**	284 (98.3)	140 (97.2)
	Female	74 (26.1)	33 (23.6)
	Male	210 (73.9)	107 (76.4)
Smoking	**Data available**	267 (92.4)	136 (94.4)
	Never smoker	93 (34.8)	26 (19.1)
	Ex-smoker	102 (38.2)	45 (33.1)
	Current smoker	72 (27)	65 (47.8)
Alcohol	**Data available**	228 (78.9)	125 (86.8)
	No alcohol	42 (18.4)	29 (23.2)
	Light alcohol	145 (63.6)	58 (46.4)
	Heavy alcohol	41 (18)	38 (30.4)
ECOG performance status	**Data available**	280 (96.9)	136 (94.4)
	0	220 (78.6)	79 (58.1)
	1	45 (16.1)	38 (27.9)
	2	13 (4.6)	16 (11.8)
	3	2 (0.7)	3 (2.2)

Clinical N classification (TNM 7)	**Data available**	239 (82.7)	122 (84.7)
	cN1	71 (29.7)	35 (28.7)
	cN2a	53 (22.2)	21 (17.2)
	cN2b	91 (38.1)	44 (36.1)
	cN2c	17 (7.1)	9 (7.4)
	cN3 NOS	3 (1.3)	0
	cN3a	1 (0.4)	6 (4.9)
	cN3b	3 (1.3)	7 (5.7)
M classification	**Data available**	278 (96.2)	141 (97.9)
	M0	274 (98.6)	133 (94.3)
	M1	4 (1.4)	8 (5.7)
Total diagnostic trips to theatre	**Data available**	277 (95.8)	134 (93.1)
	0	8 (2.9)	18 (13.4)
	1	208 (75.1)	91 (67.9)
	2	57 (20.6)	24 (17.9)
	3 or more	4 (1.4)	1 (0.7)
Prior tonsillectomy	**Data available**	269 (93.1)	121 (84)
	Yes	59 (21.9)	18 (14.9)
	No	210 (78.1)	103 (85.1)
Ipsilateral tonsillectomy	**Data available**	280 (96.9)	132 (91.7)
	Yes (including remnant)	178 (80.5)	75 (65.8)
	No (excluding prior tonsillectomy)	43 (19.5)	39 (34.2)
Contralateral tonsillectomy	**Data available**	279 (96.5)	132 (91.7)
	Yes (inc. remnant)	152 (69.1)	62 (54.4)
	No (exc. prior tonsillectomy)	68 (30.9)	52 (45.6)
Ipsilateral TBM	**Data available**	289 (100)	144 (100)
	Yes	75 (26)	26 (18.1)
	No	214 (74)	118 (81.9)
Contralateral TBM	**Data available**	289 (100)	144 (100)

	Yes	62 (21.5)	18 (12.5)
	No	227 (78.5)	126 (87.5)
Any untargeted biopsy^	**Data available**	265 (94.3)	116 (92.1)
	Yes	116 (43.8)	63 (54.3)
	No	149 (56.2)	53 (45.7)
Forceps biopsies of Nasopharynx^	**Data available**	253 (90)	113 (89.7)
	No	183 (72.3)	78 (69)
	Targeted*	19 (7.5)	4 (3.5)
	Untargeted/ random	51 (20.2)	31 (27.4)
Forceps biopsies of Tonsils^	**Data available**	258 (91.8)	113 (89.7)
	No	172 (66.7)	72 (63.7)
	Targeted*	39 (15.1)	11 (9.7)
	Untargeted/ random	47 (18.2)	30 (26.5)
Forceps biopsies of Tongue base^	**Data available**	251 (89.3)	109 (86.5)
	No	89 (35.5)	34 (31.2)
	Targeted*	60 (23.9)	19 (17.4)
	Untargeted/ random	102 (40.6)	56 (51.4)
Forceps biopsies of Hypopharynx^	**Data available**	261 (92.9)	114 (90.5)
	No	222 (85.1)	100 (87.7)
	Targeted*	14 (5.4)	2 (1.8)
	Untargeted/ random	25 (9.6)	12 (10.5)
Forceps biopsies of Other sites^	**Data available**	217 (77.2)	100 (79.4)
	No	194 (89.4)	85 (85)
	Yes	23 (10.6)	15 (15)
Intraoperative Frozen biopsy^	**Data available**	231 (82.2)	97 (77)
	Yes	2 (0.9)	2 (2.1)

	No	229 (99.1)	95 (97.9)
Intraoperative Narrow band imaging^	**Data available**	205 (73)	93 (73.8)
	Yes	8 (3.9)	3 (3.2)
	No	197 (96.1)	90 (96.8)
Intraoperative Ultrasound^	**Data available**	223 (79.4)	98 (77.8)
	Yes	1 (0.4)	0
	No	222 (99.6)	98 (100)
Histologically confirmed primary site	**Data available**	288 (99.7)	141 (97.9)
	NOT identified (true unknown primary)	201 (79.4)	121 (107.1)
	Ipsilateral tonsil	52 (20.6)	8 (7.1)
	Contralateral tonsil	2 (0.8)	0
	Ipsilateral glossotonsillar sulcus	5 (2)	0
	Contralateral glossotonsillar sulcus	0	0
	Ipsilateral tongue base	21 (8.3)	7 (6.2)
	Midline Tongue base, within 1 cm of midline	2 (0.8)	0
	Contralateral tongue base	1 (0.4)	1 (0.9)
	Multiple foci (unilateral, all >1cm from midline)	3 (1.2)	0
	Multiple foci (bilateral, contralateral or any foci within 1 cm of midline)	1 (0.4)	0
	Oral cavity	0	1 (0.9)
	Post cricoid region	0	1 (0.9)
	Parotid	0	1 (0.9)
	Submandibular gland SCC	0	1 (0.9)

Table 2-10: Oncological outcomes for all patients and by subgroups intent in the HNSCCUP National Audit. HNSCCUP is head and neck squamous cell carcinoma from an unknown primary, HPV is human papillomavirus, CI is confidence interval, OS is overall survival, DFS is disease-free survival, DSS is disease-specific survival, LC is local control.

Oncological status	All treated HNSCCUP % (95% CI)	HPV-positive treated HNSCCUP % (95% CI)	HPV-negative treated HNSCCUP % (95% CI)	HPV-positive HNSCCUP treated with neck dissection and without radiotherapy % (95% CI)	HPV-positive HNSCCUP treated with neck dissection and with radiotherapy % (95% CI)	HPV-positive HNSCCUP treated without neck dissection and with radiotherapy % (95% CI)	HPV-negative HNSCCUP treated with neck dissection and without radiotherapy % (95% CI)	HPV-negative HNSCCUP treated with neck dissection and with radiotherapy % (95% CI)	HPV-negative HNSCCUP treated without neck dissection and with radiotherapy % (95% CI)
At 2 years									
OS	81.0 (77.4, 84.7)	90.6 (87.1, 94.3)	69.3 (61.9, 77.5)	96.8 (90.8, 100)	100 (100, 100)	92.6 (87.1, 98.5)	93.8 (82.6, 100)	77.2 (65.1, 91.6)	74.2 (59.4, 92.7)
DFS	69.9 (65.8, 74.3)	81.3 (76.7, 86.2)	54.8 (47.1, 63.8)	69.0 (54.0, 88.1)	97.3 (93.8, 100)	83.7 (76.4, 91.7)	75.0 (56.5, 99.5)	68.2 (55.3, 84.2)	62.9 (46.9, 84.3)
DSS	84.9 (81.6, 88.3)	92.8 (89.7, 96.1)	74.4 (67.3, 82.3)	100 (100, 100)	100 (100, 100)	94.8 (90.0, 99.9)	93.8 (82.6, 100)	86.4 (75.8, 98.4)	76.9 (62.3, 95.0)
LC	95.9 (93.9, 98.0)	96.8 (94.6, 99.2)	95.0 (91.0, 99.1)	81.5 (68.0, 97.6)	98.6 (95.9, 100)	98.8 (96.5, 100)	87.1 (71.8, 100)	96.6 (90.1, 100)	100 (100, 100)
At 5 years									
OS	66.4 (60.2, 73.4)	85.0 (78.4, 92.3)	43.5 (32.9, 57.5)	96.8 (90.8, 100)	96.9 (92.8, 100)	89.5 (82.8, 96.8)	66.8 (43.9, 100)	46.3 (29.6, 72.7)	57.9 (40.2, 83.2)
DFS	54.2 (47.6, 61.7)	70.5 (62.0, 80.2)	33.7 (24.2, 46.9)	24.9 (8.5, 73.1)	94.3 (89.0, 99.9)	82.3 (74.7, 90.6)	-	44.4 (28.3, 69.9)	40.4 (23.7, 68.9)
DSS	78.5 (73.4, 83.9)	91.7 (88.2, 95.3)	55.8 (43.6, 71.3)	100 (100, 100)	100 (100, 100)	93.1 (87.3, 99.2)	93.8 (82.6, 100)	71.1 (54.1, 93.5)	64.6 (46.7, 89.4)
LC	90.2 (85.4, 95.2)	90.4 (84.2, 97.2)	89.7 (82.9, 97.1)	41.8 (21.5, 81.4)	98.6 (95.9, 100)	98.8 (96.5, 100)	-	96.6 (90.1, 100)	93.3 (81.5, 100)

Table 2-11: Results from multivariable Cox regression analysis for HNSCCUP with unilateral nodal disease treated with curative intent in the HNSCCUP National Audit.
HNSCCUP is head and neck squamous cell carcinoma from an unknown primary, HPV is human papillomavirus, HR is hazard ratio, CI is confidence interval, OS is overall survival, DFS is disease-free survival, DSS is disease-specific survival, LC is local control.

			OS		DFS		DSS		LC	
Prognostic factor	**Reference**	**Comparator**	**HR (95% CIs)**	**p**	**HR (95% CIs)**	**p**	**HR (95% CIs)**	**p**	**HR (95% CIs)**	**p**
HPV status	Negative	Positive	0.132 (0.066, 0.265)	<0.001	0.308 (0.190, 0.498)	<0.001	0.104 (0.039, 0.283)	<0.001	-	-
Contralateral TBM	No	Yes	-	-	2.149 (1.199, 3.853)	0.010	-	-	-	-
Chemotherapy	No	Yes	-	-	0.607 (0.373, 0.988)	0.045	-	-	-	-
Ipsilateral neck radiotherapy	No	Yes	-	-	-	-	-	-	0.049 (0.016, 0.151)	<0.001

Table 2-12: Results from univariable Cox regression analysis for HNSCCUP with unilateral nodal disease treated with curative intent in the HNSCCUP National Audit.
HNSCCUP is head and neck squamous cell carcinoma from an unknown primary, HPV is human papillomavirus, HR is hazard ratio, CI is confidence interval, OS is overall survival, DFS is disease-free survival, DSS is disease-specific survival, LC is local control, ECOG is Eastern Cooperative Oncology Group, FDT is first definitive treatment.

			OS			DFS			DSS			LC		
				Univariable Cox			Univariable Cox			Univariable Cox			Univariable Cox	
Prognostic factor	Reference	Comparator	Schoenfeld residuals test	HR (95% CIs)	p	Schoenfeld residuals test	HR (95% CIs)	p	Schoenfeld residuals test	HR (95% CIs)	p	Schoenfeld residuals test	HR (95% CIs)	p
HPV status	Negative	Positive	0.516	0.132 (0.066, 0.265)	<0.001	0.325	0.287 (0.181, 0.455)	<0.001	0.346	0.104 (0.039, 0.283)	<0.001	0.819	0.627 (0.234, 1.68)	0.353
Age (median 59 years)	< median	≥ median	0.186	1.05 (1.02, 1.08)	0.001	0.061	1.49 (0.938, 2.35)	0.092	0.300	1.48 (0.641, 3.43)	0.357	0.510	0.975 (0.385, 2.47)	0.958
Sex	Female	Male	0.830	1.63 (0.728, 3.63)	0.236	0.424	1.04 (0.587, 1.84)	0.891	0.737	1.83 (0.541, 6.19)	0.331	0.420	0.891 (0.291, 2.73)	0.839
Smoking	Non/ Ex-smoker	Current smoker	0.737	1.94 (0.991, 3.81)	0.053	0.094	1.87 (1.08, 3.22)	0.025	0.074	1.24 (0.504, 3.03)	0.643	0.884	4.7 (1.07, 20.6)	0.040
Alcohol	Nil/ Light alcohol	Heavy alcohol	0.189	0.503 (0.275, 0.919)	0.026	0.106	0.538 (0.324, 0.893)	0.017	0.874	0.367 (0.159, 0.85)	0.019	0.326	0.277 (0.097, 0.791)	0.017
ECOG performance status	0	1/ 2/ 3	0.398	0.25 (0.14, 0.444)	<0.001	0.929	0.551 (0.337, 0.9)	0.017	0.395	0.34 (0.144, 0.8)	0.014	0.168	0.664 (0.231, 1.91)	0.448
Principal nodal level	2	1/ 3/ 4/ 5	0.341	1.88 (1.04, 3.39)	0.036	0.935	1.49 (0.896, 2.48)	0.124	0.224	2.46 (1.05, 5.78)	0.038	0.950	0.795 (0.229, 2.75)	0.717
Clinical nodal stage	cN1	cN2a/ cN2b	0.890	1.34 (0.697, 2.56)	0.383	0.508	0.885 (0.543, 1.44)	0.623	0.899	0.952 (0.388, 2.34)	0.915	0.995	0.68 (0.263, 1.75)	0.425
Prior tonsillectomy	No	Yes	0.971	0.537 (0.24, 1.2)	0.130	0.913	0.616 (0.33, 1.15)	0.128	0.547	0.683 (0.23, 2.03)	0.492	0.801	0.901 (0.294, 2.77)	0.856
Ipsilateral tonsillectomy	No	Yes	0.482	1.32 (0.737, 2.35)	0.353	0.928	1.32 (0.823, 2.13)	0.248	0.515	1.67 (0.679, 4.08)	0.265	0.606	1.22 (0.474, 3.15)	0.679
Contralateral tonsillectomy	No	Yes	0.828	1.48 (0.842, 2.61)	0.173	0.509	1.31 (0.829, 2.08)	0.247	0.728	1.66 (0.71, 3.89)	0.242	0.044	0 (0, 6.635)	0.083
Ipsilateral TBM	No	Yes	0.418	1.16 (0.563, 2.4)	0.684	0.091	1.6 (0.942, 2.7)	0.082	0.236	1.71 (0.669, 4.39)	0.261	0.066	3.66 (1.38, 9.72)	0.009
Contralateral TBM	No	Yes	0.639	1.69 (0.792, 3.62)	0.174	0.304	2.02 (1.14, 3.58)	0.016	0.338	2.3 (0.846, 6.25)	0.103	0.238	2.74 (0.886, 8.48)	0.080

Ipsilateral neck dissection	No	Yes	0.242	0.794 (0.452, 1.4)	0.424	0.054	0.989 (0.62, 1.58)	0.964	0.901	0.481 (0.206, 1.13)	0.092	0.747	5.52 (1.27, 24)	0.023
Contralateral neck dissection	No	Yes	0.363	1.59 (0.385, 6.54)	0.523	0.956	1.1 (0.153, 7.91)	0.926	0.193	3.58 (0.482, 26.7)	0.213	1.000	0 (0, Inf)	0.998
Ipsilateral neck radiotherapy	No	Yes	0.767	1.15 (0.516, 2.57)	0.730	0.039	0.990 (0.174, 5.631)	0.991	0.099	3.95 (0.531, 29.4)	0.180	0.541	0.049 (0.016, 0.151)	<0.001
Contralateral neck radiotherapy	No	Yes	0.333	1.27 (0.693, 2.33)	0.438	0.104	0.753 (0.439, 1.29)	0.302	0.772	1.66 (0.701, 3.95)	0.248	0.822	0.145 (0.019, 1.1)	0.062
Chemotherapy	No	Yes	0.333	0.458 (0.255, 0.825)	0.009	0.079	0.468 (0.291, 0.753)	0.002	0.929	0.79 (0.335, 1.86)	0.589	0.599	0.145 (0.042, 0.505)	0.002
Time to FDT (median 94 days)	< median	≥ median	0.907	1.4 (0.778, 2.52)	0.262	0.381	1.09 (0.681, 1.74)	0.722	0.511	1.59 (0.657, 3.83)	0.306	0.886	0.576 (0.222, 1.49)	0.256

2.3 The HNSCCUP Consensus Exercise

2.3.1 Full title

Development of National Multidisciplinary Recommendations for the Management of Head and Neck Squamous Cell Carcinoma of Unknown Primary (HNSCCUP) using a Multi-Stage Meta-Consensus Initiative.

2.3.2 Contributions

Alongside the primary supervisor, Vinidh Paleri, the author co-led all stages of this initiative, from conceptualisation to delivery. Further, the author led on writing, reviewing and editing the text contained herein, which has been published in BMC Medical Research Methodology.[5]

The author is grateful to the following individuals for their contributions towards the delivery of this study and its write-up (full delineation of roles and affiliations available in **Appendix 24**):

- Tom Roques and Kevin Harrington, for their invaluable input from early in the process to ensure the oncologists perspective was adequately incorporated.
- Frank Stafford, for his help in organising the Consensus Day and in particular arranging the SAGE venue in Gateshead.
- Sanjai Sood, as president of the ENT UK Head & Neck Society, and the other members of the Council, for their support and endorsement of the initiative.
- Oracle Cancer Trust, who supported the National Consensus Day with a Grant of £5k.
- The 39 health care professionals who contributed content to the National Consensus Day.
- The 58 ENT Consultants who acted as representatives for their local HN MDTs and responded to the Delphi exercise.

2.3.3 Abstract *[350 words]*

Background

Methods for developing national recommendations vary widely. The successful adoption of new guidance into routine practice is dependent on buy-in from the clinicians delivering day-to-day patient care and must be considerate of existing resource constraints, as well as being aspirational in its scope. This initiative aimed to produce guidelines for the management of head and neck squamous cell carcinoma of unknown primary (HNSCCUP) using a novel methodology to maximise the likelihood of national adoption.

Methods

A voluntary steering committee oversaw three phases of development: 1) clarification of topic areas, data collection and assimilation, including systematic reviews and a National Audit of Practice; 2) a National Consensus Day, presenting data from the above to generate candidate consensus statements for indicative voting by attendees; and 3) a National Delphi Exercise seeking agreement on the candidate consensus statements, including representatives from all 58 UK Head and Neck Multidisciplinary Teams (MDT). Methodology was published online in advance of the Consensus Day and Delphi exercise.

Results

Four topic areas were identified to frame guideline development. The National Consensus Day was attended by 227 participants (54 in-person and 173 virtual). Results from seven new systematic reviews were presented, alongside seven expert stakeholder presentations and interim data from the National Audit and from relevant ongoing Clinical Trials. This resulted in the generation of 35 statements for indicative voting by attendees which, following steering committee ratification, led to 30 statements entering the National Delphi exercise.

After three rounds (with a further statement added after round one), 27 statements had reached 'strong agreement' (n=25, 2, 0 for each round, respectively), a single statement achieved 'agreement' only (round three), and 'no agreement' could be reached for three statements (response rate 98% for each round). Subsequently, 28 statements were adopted into the National MDT Guidelines for HNSCCUP.

Conclusions

The described methodology demonstrated an effective multi-phase strategy for the development of national practice recommendations. It may serve as a cost-effective model for future guideline development for controversial or rare conditions where there is a paucity of available evidence or where there is significant variability in management practices across a healthcare service.

2.3.4 Aim

This initiative aimed to produce National Guidelines for the management of HNSCCUP using a novel multi-phase meta-consensus methodology.

2.3.5 Methods

The ENT UK Head and Neck Society Council and the author formed the Steering Committee to oversee the initiative (first-line authors in the subsequent publication).[5] The author and primary supervisor (who was also a Steering Committee Member as part of the Head and Neck Society Council) adopted central leadership roles to maintain project momentum. The development of recommendations was divided into three phases: 1) clarification of topics and data assimilation; 2) a National Consensus Day; and 3) a National Delphi Exercise. An outline of the methodology was published online and shared with participants in advance of phase two, at https://bit.ly/HNSCCUPconsensusprocess.

2.3.5.1 Phase 1: Clarification of topics and data assimilation

2.3.5.1.1 Identification of topics to be investigated through systematic reviews

Topics felt to be amenable to systematic review of the published literature were selected and the specific research question agreed by the steering committee (**Appendix 21**). Consultants who were identified as national experts in their specialty, with appropriate experience of critical appraisal, were approached to supervise senior trainees and clinical fellows delivering these reviews. The agreed minimum output was a presentation of the results during the National Consensus Day, though write-up for publication was also encouraged, and submitted manuscripts will undergo peer review for consideration of inclusion in a dedicated HNSCCUP in Clinical Otolaryngology.

2.3.5.1.2 Identification of topics to be presented by expert stakeholders

For topics not felt amenable to systematic review, expert stakeholders were approached to assimilate the literature with an agreed output of a presentation for the National Consensus Day.

2.3.5.1.3 Identification of data to be collated from National Audit of Practice

To learn from the contemporary management of HNSCCUP patients in the UK, a National Audit was conducted in collaboration with INTEGRATE (The UK ENT Trainee Research Network). The full methodology is outlined in **The HNSCCUP National Audit 2021**. In brief, all UK centres managing HNSCCUP patients were invited to participate via mailouts from ENT UK, the Association of Otolaryngologists in Training (AOT) and the INTEGRATE network. Patients undergoing PET-CT for the identification of a primary site cancer, having presented with cervical metastases without a clinically evident primary site between 2015 and 2020, were eligible for inclusion. Pathway data were collected to understand the patient's diagnostic journey and outcome data were collated with a median follow up of 30 months for survivors. Methodology was agreed by the HNSCCUP Consensus Steering Committee.

2.3.5.1.4 Interim reports from ongoing clinical trials

The Chief Investigators of ongoing clinical trials relevant to the management of HNSCCUP were approached to outline the research design and outputs, and to see if they were able to present any interim results relevant to the recommendations being considered.

2.3.5.2 Phase 2: National Multidisciplinary Consensus event to generate draft statements

2.3.5.2.1 Draft statements generated by section chairs in advance of event

In advance of the Consensus Day, all presentations of evidence outlined in phase one were shared with chairs for each of four sessions, focused around key steps in the management pathway: 1) investigations for clinically suspected HNSCCUP; 2) diagnostic surgery to try and identify the primary site; 3) surgical treatments; and 4) non-surgical treatments. Chairs reviewed the evidence and generated draft consensus statements using NICE guidance for recommendations language.[111] The evidence and draft statements were subsequently shared with delegated breakout group leads who would be leading discussions on the consensus day, to incorporate any feedback prior to further dissemination/development.

2.3.5.2.2 Presentations of evidence to event attendees

The consensus day was a hybrid event, accepting both virtual and in-person attendees, structured around four sessions which reflected the patients' diagnostic and treatment pathways (Consensus Day Programme in **Appendix 21**). All presentations were pre-recorded to facilitate the generation of draft consensus statements, as above.

2.3.5.2.3 Breakout group discussions to amend statements

At the end of each of the four sessions, both virtual and in-person attendees were split into equal-sized breakout groups. Each breakout group was chaired by a pre-identified attendee who had advanced access to the evidence used to generate the draft statements ahead of the day. Individual breakout groups were allocated unique pre-drafted statements to discuss and revise as appropriate, including generating new statements or removing statements entirely. If time allowed, groups were able to discuss statements allocated to other groups too.

Statements were edited by the breakout group lead live on an online Google Document. Once the breakout groups were brought back together, the session chair invited the group leads to summarise their discussions and any revisions made to the statements. This was then opened up to all attendees for input. Edits were again made live on the Google Document while discussions proceeded.

2.3.5.2.4 Indicative voting on draft statements

At the end of each session, the draft consensus statements were transferred to an online voting system (sli.do) which was accessible via a weblink and/or QR code. Attendees were invited to indicate their support (agree/disagree) for each statement. Voting remained open for a minimum of 90 minutes. The raw results of the indicative vote were disseminated to attendees alongside feedback requests the day after the meeting.

2.3.5.3 Phase 3: Delphi exercise leading to national adoption of recommendations

2.3.5.3.1 Ratification of draft statements for clarity and consistency of wording by steering committee

The steering committee reviewed all draft statements from the consensus day to ensure consistency of style, and phrasing. Finalised statements for the Delphi process were piloted amongst the steering committee for readability and suitability to upload to the Google Forms platform.

2.3.5.3.2 Three rounds of online Delphi voting with consensus view from all national MDTs

Following ratification by the Steering Committee, representatives from each UK HN MDT were invited to participate in an online modified Delphi process, hosted on Google Forms, recording their support for each statement with a binary agree/disagree response.

Schedule

The following schedule was employed:

- 10 days for MDT responses, to ensure time for discussion at a weekly MDT meeting.
- Four days for chasing final responses, analysis and preparation of statements for the next round.

Thresholds

Up to three rounds of the Delphi process were planned, with thresholds as follows:

- ≥80% strong agreement (≤20% strong disagreement)
- ≥67% agreement (≤33% disagreement) (applied only after the third round)

Achieving consensus

The following strategies to achieve consensus were set out *a priori*:

Statements reaching the 'strong agreement' threshold at any stage will be removed from further rounds.

- After round one, statements using the term 'offer' which do not achieve 'strong agreement' will be duplicated with the term 'consider' in place of 'offer' for subsequent rounds. Both the 'offer' and 'consider' statements will be presented in parallel for subsequent rounds.
- After round three, if both the 'offer' and 'consider' statements achieve the same level of agreement, then the 'offer' statement will be adopted in preference.
- After round three, if the 'consider' statement achieves 'strong agreement' and the 'offer' statement achieves 'agreement', then the 'consider' statement will be adopted.
- Action terms like 'Perform/refer/include' will be considered to have the same impact as 'offer' terms/statements as above

Comments were invited at each round. The Steering Committee considered any feedback given by participants for incorporation into subsequent rounds. The Steering Committee was the final arbitrator of amendments between rounds and the ultimate production of the consensus statements.

2.3.5.3.3 Final ratification of adopted statements by stakeholder organisations

The finalised consensus statements were distributed to the representatives of all UK HN MDTs for endorsement. Accepted statements were incorporated into the 6th edition of the 'United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer'. This document was endorsed by all UK HN MDT stakeholder organisations and is due publication imminently at time of submission of this thesis.

2.3.5.4 Deviations from a priori methodology

Pre-recorded presentations were late to arrive from some speakers which limited the time that some session chairs and delegated breakout group leads had to generate the draft consensus statements ahead of the consensus event. As such, the intention to share draft statements with consensus day attendees was necessarily abandoned.

During the first session discussions on the Consensus Day, virtual participants were limited to having their comments/questions fielded through the written chat portal due to technical difficulties with the audio link.

Where 'offer' and 'consider' statements were presented in parallel, if the respondent indicated support for 'offer' but not 'consider' they were reminded that the statements would be analysed separately.

2.3.6 Results

At the outset of the exercise, the Steering Committee used its national networks to compile a comprehensive list of 58 HN MDTs throughout the UK. Additionally, an ENT UK contact was identified who sat on each of these MDTs and who agreed to act as the MDT representative for the forthcoming Consensus Process. This work will be built on by a subsequent BAHNO initiative to map HN MDT services across the UK.

2.3.6.1 Consensus Day

The National Consensus Day was attended by 227 participants (54 in-person and 173 virtual). Within the four sessions, there were 20 pre-recorded presentations delivered by 39 health professionals: seven novel systematic reviews; seven expert stakeholder viewpoints, three focused summaries of interim data from the National Audit; and three presentations from ongoing Clinical Trials (MOSES NCT04151134 and FIND NCT03281499). After each of the four sessions, attendees were divided into five breakout groups (two in-person, three virtual) to scrutinise the statements that had been pre-drafted, having been presented with the best available evidence.

Following subsequent discussions amongst all attendees (virtual and in-person) led by the session chairs, 29 statements were agreed upon for indicative voting. The response rate for each statement varied between 61 and 115 indicative votes (median n=91), with agreement ranging between 62.3% and 98.1% (median 90.2%)(**Figure 2-11**, **Table 2-14**,**Table 2-15** and **Table 2-16**).

The Consensus Day received income from ticket sales (both virtual and in-person) and from exhibitor fees. Costs were related to venue hire, catering, information technology resources (the Zoom online platform and sli.do voting subscription) and event coordinator time. There was a net profit from the day which was distributed to ENT UK and the Head and Neck Society.

Delphi Exercise

Following the Consensus Day, ratification by the steering committee led to clarifications of the wording for 12 statements, the addition of a single statement (to accommodate HPV-positive as well as HPV-negative disease) and the removal of six statements due to duplicated content.

2.3.6.1.1 Responses

Results from the three rounds of Delphi are presented in **Figure 2-11**. The overall response rate was 98% (n=57/58) for each of the three rounds. A response to every statement was required in order to submit the Delphi form. However, for nine instances (0.4% of 2,280 total responses), requests were made to abstain from the vote for that statement as a consensus from within that MDT could not be reached.

2.3.6.1.2 Changes between rounds and adoption

A single statement was added after round one for round two, incorporating 'consider' phrasing as per the *a priori* methodology. No further statements were added for round three. Strong agreement was reached for 27 statements (n=25 in round one, two in round two and none in round three, and a single statement only reached agreement at the end of round three. No agreement could be reached for 3 statements and none reached thresholds for any level of disagreement. Consequently, following the 3-round Delphi process, 28 statements

were re-distributed to the representatives of UK HN MDTs for endorsement and were subsequently incorporated into the 6th edition of the 'United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer' (**Figure 2-11 Table 2-14, Table 2-15** and **Table 2-16** and the **Final HNSCCUP MDT Consensus Guidelines**).

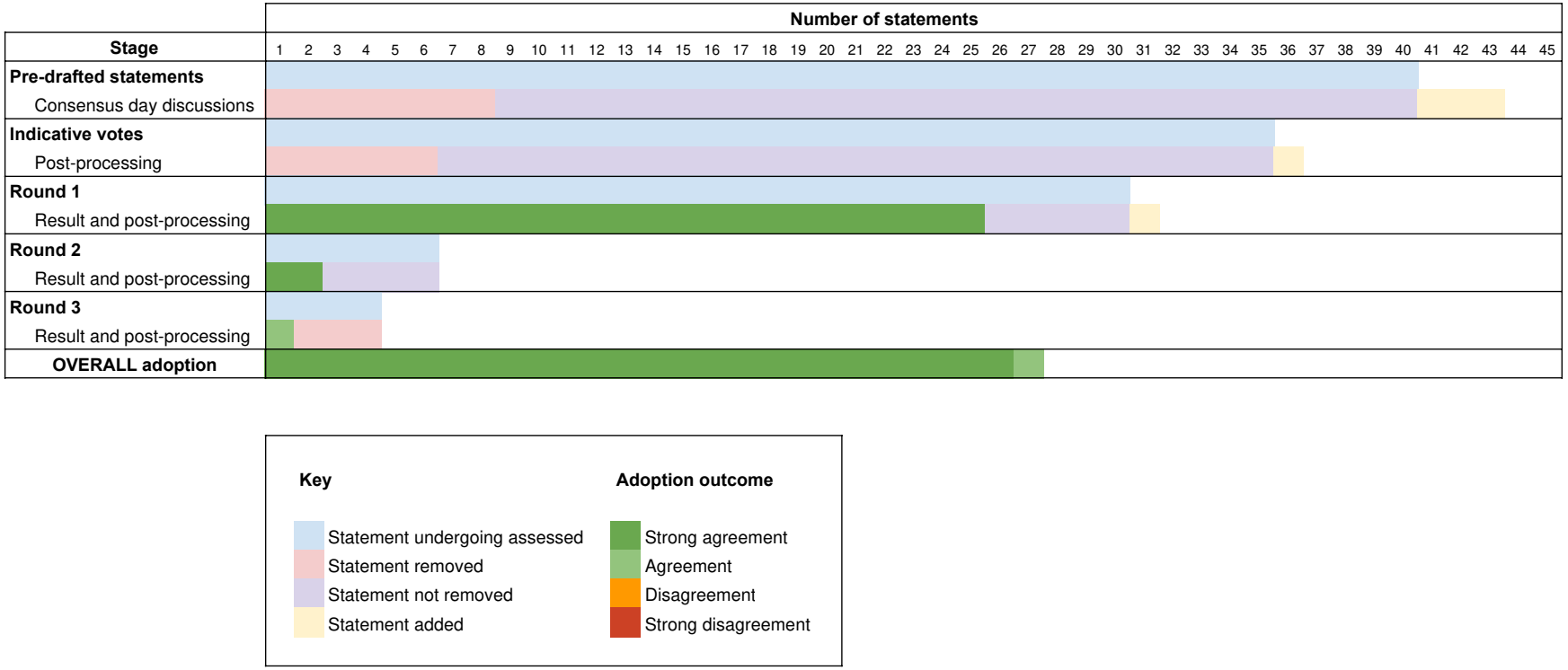


Figure 2-11: Graphical summary of outcomes from the multi-stage meta-consensus exercise for HNSCCUP recommendation development.

Table 2-13: Section 1: Investigations before diagnostic surgery for clinically suspected HNSCCUP.

No.	Statement	Indicative vote	Round 1	Round 2	Round 3	Outcome
1a	Offer all patients with clinically suspected HNSCCUP ultrasound guided sampling as a first-line investigation to diagnose cervical metastasis of SCC, which must include p16 and/or HPV subtyping and ancillary tests	[98.1%][a]	[96.5%]	-	-	Strong agreement
1b	Do not offer open biopsy to patients with a neck lump as a first line investigation to diagnose cervical metastasis	[98.1%][b]	[98.2%]	-	-	Strong agreement
1c	Offer all patients with clinical suspicion of HNSCCUP a concurrent MRI and PET-CT as first-line cross-sectional imaging investigations	[77.1%][b]	[82.5%]	-	-	Strong agreement
1d	Consider image enhancement technology (including narrow band imaging) as an adjunct to white light endoscopy in the examination of all patients with clinically suspected HNSCCUP	[96.2%][a]	[89.5%]	-	-	Strong agreement
1e	Refer all patients with clinically suspected pathologically confirmed HNSCCUP to a core member of head and neck MDT for further investigations	[93.4%][a]	[98.2%]	-	-	Strong agreement

[a] *n=106,* [b] *n=105*

Table 2-14: Section 2: Diagnostic surgery for clinically suspected pathologically confirmed HNSCCUP.

No.	Statement	Indicative vote	Round 1	Round 2	Round 3	Outcome
2a	Perform all radiological investigations aiming to identify the primary site prior to discussion at head and neck MDT and diagnostic surgery	[93.0%][a]	[94.7%]	-	-	Strong agreement
2b	Offer nasopharyngeal biopsies when the cervical node sampling reveals Epstein-Barr virus positive metastasis	[93.0%][b]	[98.2%]	-	-	Strong agreement
2c	Do not offer biopsies of clinically and radiologically normal upper aerodigestive tract mucosa. This excludes tonsillectomy or tongue base mucosectomy	[93.0%][b]	[91.2%]	-	-	Strong agreement
2d	Offer ipsilateral tonsillectomy (rather than incisional biopsy) to all patients	[80.0%][a]	[89.5%]	-	-	Strong agreement
2e	Consider contralateral tonsillectomy (rather than incisional biopsy) in all patients	[94.7%][b]	[100%]	-	-	Strong agreement
2fi	Offer ipsilateral tongue base mucosectomy to all patients	[73.5%][c]	[71.9%]	[59.6%]	[61.4%]	No agreement
2fii	Consider ipsilateral tongue base mucosectomy in all patients	-	-	[89.5%]	-	Strong agreement
2g	Consider contralateral tongue base mucosectomy for all patients	[87.6%][c]	[78.9%]	[80.7%]	-	Strong agreement
2h	The term 'Ipsilateral oropharyngeal MALTectomy' is appropriate to represent the removal of the palatine tonsil and the lingual tonsil on the affected side	[68.8%][d]	[59.6%]	[47.4%]	[49.1%]	No agreement
2i	Perform tongue base mucosectomy using one of the following transoral techniques, when indicated: endoscopic, microscopic or robot-assisted	[97.4%][b]	[96.5%]	-	-	Strong agreement

[a] n=115, [b] n=114, [c] n=113, [d] n=109

Table 2-15: Section 3: Surgical management of patients diagnosed as HNSCCUP.

Unless otherwise specified, the HNSCCUP patients referred to in this session are assumed to have undergone an adequate diagnostic work-up, as per their MDT, and are due to commence treatment as a true HNSCCUP.

No.	Statement	Indicative vote	Round 1	Round 2	Round 3	Outcome
3ai	Consider ipsilateral tonsillectomy and tongue base mucosectomy (ipsilateral oropharyngeal MALTectomy) and ipsilateral neck dissection in HPV positive HNSCCUP with a single node less than 3cm and with no radiological evidence of extranodal extension	[84.1%][d]	[87.7%]	-	-	Strong agreement
3aii	Consider ipsilateral tonsillectomy and tongue base mucosectomy (ipsilateral oropharyngeal MALTectomy) and ipsilateral neck dissection in HPV negative HNSCCUP with a single node less than 3cm and with no radiological evidence of extranodal extension	-	[68.4%]	[75.4%]	[77.2%]	Agreement
3b	Consider adding regular cross-sectional imaging to regular clinical examination for post-treatment surveillance of patients treated with surgery as a single modality, following bilateral oropharyngeal MALTectomy and pN1 disease with no extranodal extension	[84.8%][a]	[84.2%]	-	-	Strong agreement
3c	Consider neck dissection prior to treatment in HPV negative HNSCCUP undergoing radical radiotherapy with advanced disease unsuitable for concomitant chemotherapy	[84.3%][c]	[93.0%]	-	-	Strong agreement
3d	Consider neck dissection prior to radiotherapy +/- chemotherapy in HPV -ve HNSCCUP patients with N3 neck disease	[87.9%][b]	[89.5%]	-	-	Strong agreement
3e	Consider contralateral staging neck dissection where there is no clinical or radiological evidence of disease to allow omission of contralateral neck radiotherapy	[62.3%][e]	[38.6%]	[35.1%]	[38.6%]	No agreement

[a] *n=92,* [b] *n=91,* [c] *n=89,* [d] *n=88,* [e] *n=61*

Table 2-16: Section 4: Non-surgical management of patients diagnosed as HNSCCUP.

Unless otherwise specified, the HNSCCUP patients referred to in this session are assumed to have undergone an adequate diagnostic work-up, as per their MDT, and are due to commence treatment as a true HNSCCUP.

No.	Statement	Indicative vote	Round 1	Round 2	Round 3	Outcome
4a	Consider omitting adjuvant radiotherapy after an ipsilateral neck dissection where there is a solitary involved node less than or equal to 3cm with no extranodal extension.	[90.2%][b]	[100%]	-	-	Strong agreement
4b	Offer adjuvant radiotherapy +/- chemotherapy to the ipsilateral neck after an ipsilateral neck dissection where there is one node greater than 3cm, or there is more than one node involved, or where there is extranodal extension	[95.1%][b]	[94.7%]	-	-	Strong agreement
4c	Consider adjuvant radiotherapy +/- chemotherapy to bilateral neck after an ipsilateral neck dissection where there is more than one node involved or where there is extranodal extension	[90.2%][b]	[85.7%]c	-	-	Strong agreement
4d	Consider radiotherapy +/- chemotherapy to the bilateral neck if there are multiple involved ipsilateral nodes or there is radiologically obvious extranodal extension	[93.4%][b]	[87.5%]c	-	-	Strong agreement
4e	Consider including the ipsilateral oropharynx in the treated volume when giving radiotherapy to the neck for unilateral HPV positive HNSCCUP	[83.9%][a]	[94.6%]c	-	-	Strong agreement
4f	Consider including possible mucosal primary sites when giving radiotherapy to the neck for unilateral HPV negative HNSCCUP. Decide possible sites based on pattern of nodal involvement and other clinicopathological features (e.g. smoking)	[87.1%][a]	[89.3%]c	-	-	Strong agreement
4g	Offer 50Gy in 2Gy fractions or equivalent* as the radiotherapy dose for possible mucosal primary sites when they are intentionally included in the target volume *e.g. 54Gy in 30 fractions or 56Gy in 35 fractions	[95.1%][b]	[91.1%]c	-	-	Strong agreement
4h	Offer concomitant cisplatin chemotherapy with primary radiotherapy if there are multiple involved nodes or obvious extranodal extension and the patient is suitable to receive cisplatin	[96.7%][b]	[96.4%]c	-	-	Strong agreement
4i	Offer concomitant cisplatin chemotherapy with adjuvant radiotherapy if there is pathological extranodal extension and the patient is suitable to receive cisplatin	[96.7%][b]	[100%]c	-	-	Strong agreement
4j	Include the ipsilateral retropharyngeal and retrostyloid nodes in the elective target volume when giving radiotherapy to the ipsilateral neck where level II is involved	[93.4%][b]	[94.5%]d	-	-	Strong agreement

[a] *n=62,* [b] *n=61,* [c] *n=56,* [d] *n=55*

PART 2 Discussion

Summary of findings

These three linked projects have significantly advanced our understanding and application of the care of HNSCCUP.

The MOSES Study prospectively analysed 58 patients with clinically and radiologically occult primary disease undergoing TBM for investigation of both HPV-positive and HPV-negative HNSCCUP. TBM was performed using a variety of transoral surgical techniques, reflecting contemporary national practice. TBM was most commonly performed following an historic tonsillectomy (36%), as a staged procedure after negative palatine tonsillectomy (26%) and then concurrently with tonsillectomy (24%).

All resected oropharyngeal tissues underwent CH at their local centre followed by SSS, according to **The MOSES Study** protocol, with a median of 320 sections being cut and 64 sections analysed per patient. Only a single additional 5.8 mm ipsilateral tongue base tumour was identified using SSS, in addition to a contralateral tongue base tumour in the same patient. Review by a second pathologist led to the identification of two additional cancers and 'downgrading' of two cancers (one felt to be inflammatory change and one found to be two separate lesions, not a single entity). Multifocal disease was seen in 8.6%, all HPV-related and all in the tongue base. The overall TBM identification rate in **The MOSES Study** was 48.3% though this varied, as expected, related to the timing of removal of the palatine tonsils.

In **The HNSCCUP National Audit 2021**, evidence is presented from a nationwide multi-centre study of clinical practice of a protracted and variable diagnostic pathway for suspected HNSCCUP patients managed in the UK. Only a minority of patients undergoing treatment with curative intent received their first definitive treatment within the FDT 62-day target (15.2%, median of 92 days) (**Figure 2-4**). A significant contributing factor to this appears to be a relative delay until PET-CT, which for most patients takes place over two weeks after cross-sectional imaging of the neck and four weeks after ultrasound evaluation (**Figure 2-5**). TBM is infrequently employed with only around a fifth of patients with 'no clear primary' on PET-CT undergoing at least a unilateral TBM (21.7%) but, despite this, the identification rate was higher than for contralateral tonsillectomy (15.4% vs 0.9%, see also **Figure 2-6**).

The HNSCCUP National Audit 2021 identified a large cohort of 482 patients who received contemporary treatment for HNSCCUP, where knowledge of HPV status and extended work-up, including PET-CT and TBM, are aiding the identification of an increasing number of primary sites. Notable differences in outcomes are reported, with 5-year OS for HPV-positive patients of 85.0% compared to 43.5% for HPV-negative patients (**Figure 2-7**A and **Table 2-10**). Further, single modality surgery for unilateral neck disease was associated with statistically significantly worse outcomes in both HPV-positive and negative patients for local control (**Figure 2-8**D and **Figure 2-9**D).

*TBM identification rates in **The MOSES Study***

There are no published randomised clinical trials investigating the benefits of tongue base mucosectomy and so observational data alone must be relied upon. MOSES hypothesised that conventional histopathological techniques may miss very small oropharyngeal tumours and sought to establish the true incidence of clinico-radiologically occult tumours in this population. Recently, Al-Lami et al. have published their systematic review of histopathological detection of a primary tumour in HNSCCUP, which included over 700 patients.[120] The focus was on comparing the effectiveness of different transoral surgical techniques. Of note, the timing of palatine tonsillectomy was not considered. Whether conducted concurrently, as a staged procedure or not at all, this will have a significant impact on the apparent incidence of primary disease in the lingual tonsil. In **The MOSES Study**, with a prospectively recruited cohort, this can be accounted for and has shown that the TBM identification rates vary, as expected, with the highest rate seen in the absence of any palatine tonsil tissue due to historic tonsillectomy (57.1%).

Farooq et al. conducted a very similar systematic review with searches performed only two years previously.[57] They identified that 17 studies had reported TBM results related to their timing with palatine tonsillectomy, though unfortunately they did not use this to stratify their pooled analysis. Inclusion criteria differed slightly between these two systematic reviews and the present study, but overall tongue base primary pick-up rates were shown to be fairly similar at 45%, 53% and 48%, respectively.

Incomplete diagnostic oropharyngeal surgery MOSES

A number of patients underwent some level of TBM to be included in **The MOSES Study** but did not have full clearance of the putative oropharyngeal lymphoepithelial tissue (bilateral tonsillectomy and bilateral TBM). Interpreting incidence rates within the oropharynx should take account of the extent of surgery, not least due to the presence of multifocal disease. Farooq et al. reported only 0.9% (n=4/432) of cases with multifocal disease (one bilateral tongue base, three bilateral palatine tonsils). **The MOSES Study** cohort saw a markedly higher rate of 8.6%, all as synchronous tumours within the tongue base, more in keeping with other studies around 5 to 10%.[74,93]

Contralateral disease was also more common in **The MOSES Study** cohort than previously reported, though this was entirely confined to the tongue base and was only seen with multifocal disease (i.e., a rate of 8.6%). Notably, no contralateral palatine tonsil tumours were identified either as single entities or as part of multifocal disease. Farooq et al. identified a contralateral tonsil primary rate of only 0.9% (n=4/432, three in patients with bilateral tonsil primaries). Further (as explored later), **The HNSCCUP National Audit 2021** corroborated these findings with higher rates of contralateral tongue base primaries than contralateral tonsil, despite significantly more palatine tonsillectomy surgery being performed.[121]

Regardless of low pick-up rates, full clearance of the oropharyngeal lymphoepithelial tissue would inevitably increase primary site identification rates. However, this must be weighed against the inherent morbidity associated with the procedure: most notably, pain and bleeding risk in the short-term and pharyngeal stenosis in the longer-term.[91,122,123] The psychological impact of persistent unknown primary disease is also not to be overlooked. Patients have reported frustration from not knowing the original site of disease, anxiety from not

being able to have focused treatment and even denial of the cancer diagnosis when unable to relate to its origin[124]

The rates of pharyngeal stenosis are not well established, though the extension of **The MOSES Study** will be able to report on this from a prospectively recruited cohort in due course. What has not been satisfactorily demonstrated is a longer-term functional or oncological benefit from either identifying or not identifying these clinically and radiologically occult primary sites. Subsequent treatment has been shown to vary considerably for HNSCCUP patients (see **The HNSCCUP National Audit 2021**) with no randomised trials to reference. Many of these patients will receive radiation therapy to at least some part of the upper aerodigestive tract mucosa and so diagnostic surgery, which may well leave residual disease (54.5% had a margin of <1 mm in this study) could be seen as superfluous. The 8th edition of the AJCC Cancer Staging Manual considers p16 positive and negative cervical metastases without an identified primary tumour separately, as Tx and T0 disease, respectively.[125] However, the required diagnostic workup to reach this categorisation is not stipulated and can vary considerably between patients and centres.[93] Due to its high prevalence in oropharyngeal disease, HPV-associated HNSCCUP is presumed to have originated in either the palatine or lingual tonsil.[61,93,104] With the high rates of clinico-radiologically occult tongue base primaries seen, should TBM take precedence as a minimum requirement for diagnostic work-up over and above a contralateral tonsillectomy? Data presented here would suggest so.

Of the 50.1% of patients with 'no clear primary' on PET-CT identified in **The HNSCCUP National Audit 2021**, only 74.5% underwent an ipsilateral tonsillectomy and 62.9% a contralateral tonsillectomy as part of their diagnostic work-up (when taking into account prior tonsillectomy unrelated to investigation of the unknown primary). TBM rates in the study were much lower, with 21.7% undergoing at least unilateral clearance and only 15.1% in **The HNSCCUP National Audit 2021** underwent full clearance of putative oropharyngeal mucosa-related lymphoid tissue. When considering which oropharyngeal tissue to sample, **The HNSCCUP National Audit 2021** strongly suggests the yield from TBM exceeds that from contralateral tonsillectomy, with 7.0% of primaries identified in the tongue base compared with 0.4% in the contralateral tonsil, despite the relative imbalance in the rates of surgery performed. A large recently published cohort study of known ipsilateral tonsillar HPV related SCC noted a low occult synchronous primary incidence of only 2.7% in the contralateral tonsil.[126] It is likely that the currently widespread practice of incomplete oropharyngeal sampling (most commonly omission of TBM) may be contributing to an underestimation of the true synchronous primary rate. Furthermore, where a single tumour is identified but reported as 'completely excised' on histopathological processing, it may provide false reassurance that the putative mucosal sites have been adequately managed, even if tongue base or palatine tonsil tissue remains.

Staging of TBM separately from tonsillectomy remains problematic. Whilst current guidelines recommend a combination of ipsilateral +/- contralateral palatine tonsillectomy and TBM, the optimal sequence of these procedures has not been determined.[88,103,109] As the majority of occult tumours were found in the ipsilateral oropharynx in both **The MOSES Study** and **The HNSCCUP National Audit 2021**, a single stage negative EUA that confirms no macroscopic evidence of disease, immediately followed by an ipsilateral tonsillectomy and TBM may be justified, particularly when a second general anaesthetic is undesirable, including those unlikely to undergo primary surgical treatment. The potential for missed synchronous tumours should also not be ignored and considered along with diagnostic surgery-related morbidity, and the potential benefit of identifying

a primary site, allowing for more focussed treatment.[126,127] Patients and clinicians should discuss the benefits and risks of each of these diagnostic procedures as well as the relative merits of staged versus concurrent diagnostic approaches.

The role of diagnostic surgery is to identify an occult primary site, which has been suggested to potentially reduce the size of the irradiated volume, any morbidity associated with this, and improve survival.[91,128] It is logical to extrapolate that interventions at the putative primary sites will likely have a marked impact on LC. This includes removal of the oropharyngeal lymphoepithelial tissue through diagnostic tonsillectomy and TBM. However, multivariable analysis did not show these surgeries to be significantly associated with LC (**Table 2-11**) with only ipsilateral neck radiotherapy (of the variables investigated) remaining statistically significant. Sites of primary emergence in **The HNSCCUP National Audit 2021** included the cervical oesophagus, larynx and hypopharynx, with mucosal disease manifesting almost exclusively in patients who did not undergo any radiation therapy and were treated with surgery alone. (It is acknowledged that these sites may represent unrelated second primary tumours. Unfortunately, given the study design, we do not have the individual pathology available to confidently attribute these subsequent cancers to the primary focus of the original disease.) Clearly, focused surgery to remove the palatine and lingual tonsils will have had an impact on LC at these sites, but the idea of managing the risk of primary site emergence with these diagnostic surgeries alone must be questioned. To date, research on diagnostic oropharyngeal surgery has focused on the primary site identification rate. The longer-term impacts of these surgeries on oncological and functional outcomes from a prospectively identified or randomised cohort have not yet been reported but are needed to fully appreciate any overall benefit they may confer. **The MOSES Study** extension will go some way to address these concerns, outside of the scope of this thesis.

Expediting the radiological investigative pathway

In **The HNSCCUP National Audit 2021**, **Figure 2-5** suggests a pattern of three temporally distinct investigation cycles: (ultrasound-guided) biopsy, cross-sectional imaging (i.e., MRI and/or CT), and PET-CT. By rationalising this to two investigation cycles, with PET-CT and concurrent cross-sectional imaging being performed concurrently after confirmation of clinical-HNSCCUP on US-guided nodal biopsy, the observed median of 92 days to FDT could be reduced by approximately 17 days. Historically, justification for obtaining PET-CT prior to cross-sectional imaging has been questioned from a purely diagnostic perspective. However, with evidence demonstrating that PET-CT alters treatment decisions in up to 20% of patients, a previously scarce resource is now an integral part of the patient journey.[129,130] In **The HNSCCUP National Audit 2021**, 26.9% of patients undergoing PET-CT had a 'clear primary site' identified, with 89.2% subsequently having a primary tumour site confirmed. A further 23.2% reported equivocal PET-CT findings with 56.8% then having primary sites identified. It is clear then that a significant number of patients have benefitted from the relatively high diagnostic yield observed, supporting the early use of PET-CT in these patients.

Data from **The HNSCCUP National Audit 2021** suggests that patients undergoing concurrent MRI and PET-CT were statistically more likely to have a primary site diagnosed following biopsies compared to those undergoing concurrent CT and PET-CT alone. Contemporary literature suggests the sensitivity of MRI as a sole modality may now reach around 90% in these patients.[131,132] If MRI were performed concurrently with

PET-CT, three distinct complementary imaging modalities would be available, allowing synchronous interpretation and maximising the opportunity for primary site identification prior to diagnostic surgeries. However, it is acknowledged that local expertise and resource constraints may be barriers to the implementation of a concurrent complementary imaging strategy.

The role of HPV in HNSCCUP

The incidence of HNC has increased in recent years, as has the recognition of the role that HPV infection plays in the disease process.[61,89] Patients with HPV-related disease tend to have different demographic and clinicopathological characteristics with improved survival.[133] This has prompted numerous studies to look at de-escalating treatment regimens for HPV-related disease.[133–136] The disease profile for HNSCCUP has seen similar changes over time,[93] meaning historic studies (and so also single institution studies accruing patients over many years) will include fewer patients with HPV related disease and may not stratify patients by HPV status. As a result, they may not be reflective of contemporary management and outcomes.

In **The HNSCCUP National Audit 2021** all patients completed their treatment within the last seven years and 89% of patients had a known HPV status. HPV-positive disease was seen in the majority (66%) of cases, confirming findings from other contemporary studies.[87,93,137] An HPV-positive status was shown to be statistically significantly associated with OS, DFS and DSS. Diagnostic practices, management strategies and patient characteristics were shown to be different between the respective HPV groups also, with HPV-negative patients more likely to be heavy smokers and alcohol consumers with poorer performance status (**Table 2-4**).

The role of radiotherapy in HNSCCUP

To allow for meaningful comparisons, patients in **The HNSCCUP National Audit 2021** with unilateral neck disease undergoing treatment with curative intent were stratified according to their HPV status and by the definitive management delivered to their ipsilateral neck. Omission of ipsilateral neck irradiation was seen to be associated with worse outcomes: HPV-negative patients had significantly worse LC (**Figure 2-9**D); HPV-positive patients also experienced significantly more primary site failures which was reflected in LC and DFS (**Figure 2-8**B and **Figure 2-8**D).

Intentionally in **The HNSCCUP National Audit 2021**, data were not collected on the reported radiation dose delivered to the oropharyngeal mucosal tissue as it was felt accurate reporting would require the review of radiotherapy planning data, which this multi-institution study was not resourced for. Differences were seen between treatment groups for a number of diagnostic and management strategies, but ipsilateral neck radiation therapy was the only factor to remain significant on multivariable analysis (HR = 0.0491, 95% CI 0.016 to 0.151, p <.001). This is the first study to demonstrate a clear disbenefit to single modality surgery alone in HNSCCUP. It is reasonable to assume that the surgery alone group had earlier stage, low volume disease. Given the significant differences in outcome for this treatment group, it seems prudent that surgery alone be offered only to patients who are able and willing to comply with a rigorous follow up schedule, supplemented by regular imaging. As a result, it is hypothesised that UADT irradiation, whether included intentionally in the target volume or not, impacts on primary emergence, and MDTs should take especial consideration when omitting radiation therapy for treatment of unilateral HNSCCUP. The rapid implementation of prospective studies to

explore this issue further is also recommended. INTEGRATE will be working with NOTCH, the UK Clinical Oncology trainee research network, to set up such a study in 2023 which has been approved by the NOTCH executive committee.

Moving towards consensus

Interim analysis from both **The MOSES Study** and **The HNSCCUP National Audit 2021** contributed to **The HNSCCUP Consensus Exercise**. This was a novel initiative which pioneered a multi-stage meta-consensus methodology, building on presentations of the best available evidence, and culminated in the generation of multidisciplinary recommendations for the management of a controversial disease. The Consensus Day itself involved 61 health professionals who facilitated the delivery of the evidence-based presentations and breakout discussions, with 227 attendees helping to generate 35 draft statements, prior to a Delphi exercise directly involving 58 MDT contacts, with many other members of head and neck MDTs also consulted. **The HNSCCUP Consensus Exercise** was delivered by a voluntary steering committee and, though not intended, generated a net profit for the parent organisations.

Following the Consensus Day, 83% of statements achieved 'strong agreement' after the first round of the modified Delphi process. Ultimately, only three out of the 31 statements considered did not reach consensus according to our prespecified thresholds. It is likely the inclusive methodology employed by the Consensus Day, encouraging input from myriad UK health professionals, ensured that, by the time of the subsequent Delphi consultation exercise, there was already widespread support for the statements generated during the opening round. Support may have been further garnered by the widespread participation in **The HNSCCUP National Audit 2021**, which saw data submitted from 57 centres representing 38 of 58 UK HN MDTs.

Table 2-17: Summary of commonly used guidelines in the management of HNSCCUP and their methodology.

Publishing/ endorsing organisation(s)	Organisation(s) abbreviation/ acronym	Year published/ updated	Publishing country	Journal	Title	Publication dedicated solely to HNSCCUP	Number of recommendations/ statements dedicated to HNSCCUP	Methodology	Patient/ public inclusion
United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer**	UK MDT	Anticipated 2022	UK	Journal of Laryngology and Otology	Management of head and neck squamous cell carcinoma of unknown primary (HNSCCUP): United Kingdom National Multidisciplinary Guidelines	Yes	28	A National Consensus Day including 227 multidisciplinary attendees generated draft statements based on systematic reviews and expert presentations. A priori methodology published. Consultation included a National Delphi Exercise to gauge consensus for inclusion of recommendation. Peer reviewed.	Patient experience presentation delivered at National Consensus Day prior to generation of draft consensus statements.
British Association of Head and Neck Oncologists standards	BAHNO	2021	UK	Journal of Oral Pathology and Medicine	British Association of Head and Neck Oncologists (BAHNO) standards 2020	No	5	20 multidisciplinary authors took reference from national published guidance to inform the recommendations. No a priori methodology published. No wider consultation following development was declared. Peer reviewed.	Nil
National Comprehensive Cancer Network	NCCN	2021	USA	-	Head and Neck Cancer Guidelines (Version 1.2022)	No	4 flowchart and roughly 9 statements	Developed by a multidisciplinary panel of 36 experts and 2 support staff. A priori methodology published. No wider consultation following development was declared. No Peer review prior to publication.	Inclusion of a patient advocate on the panel is encouraged but their involvement is not explicitly declared.
American Society of Clinical Oncology	ASCO	2020	USA	Journal of Clinical Oncology	Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck: ASCO Guideline	Yes	33	15 multidisciplinary authors formed an Expert Panel who assessed 100 relevant articles from systematic reviews. A priori methodology published. Consultation included an open public comment period of two weeks. Peer reviewed.	Draft recommendations were open to public comment on signing a confidentiality agreement.

European Head and Neck Society, European Society for Medical Oncology, and European SocieTy for Radiotherapy and Oncology	EHNS/ ESMO/ ESTRO	2020	Europe	Annals of Oncology	Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up	No	Roughly 250 words of prose	20 multidisciplinary authors assessed evidence and wrote guidelines. A priori methodology published. No wider consultation following development declared. Peer reviewed.	Nil
National Institute for Health and Care Excellence	NICE	2018	UK	-	Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over	No	8	A multidisciplinary advisory group forms a writing committee to generate draft statements based on 'evidence reviews'. A priori methodology published. Consultation included release of draft guidelines for input from registered stakeholders. Peer reviewed 'may occasionally be considered' but not explicitly declared.	Included in the guideline generating committee.
United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer*	UK MDT	2016	UK	Journal of Laryngology and Otology	Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines	Yes	10	Five multidisciplinary experts HNC. No a priori methodology published. No wider consultation following development was declared. Peer reviewed.	Nil

*guidelines endorsed: by the British Association of Otorhinolaryngology-Head & Neck Surgery (ENT UK); the British Association of Oral and Maxillofacial Surgeons (BAOMS); the British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS); British Association of Head and Neck Oncologists (BAHNO); The Royal College of Pathologists (RCPath); The Royal College of Radiologists (RCR); and the British Association of Endocrine and Thyroid Surgeons (BAETS).

**endorsing organisations to be confirmed prior to publication.

Alternative guidelines of management of HNSCCUP

There are a number of alternative guidelines available for management of HNSCCUP which are summarised in **Table 2-17**.[88,98,102,103,109,113] However, the bespoke methodology employed herein was developed and implemented as it was felt more appropriate due to a relative paucity of available evidence and to maximise the potential for adherence to the resultant output. It is accepted that adherence to the newly generated guidelines will be hard to measure and is beyond the scope of this thesis.

The previous iteration of the United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer (published in 2016) were drafted by five multidisciplinary experts in HNC, with backgrounds in speech and language therapy, oncology and ENT surgery. They were then reviewed and adopted by representatives from a variety of multidisciplinary stakeholder organisations.[109,138] These guidelines considered the contemporary evidence but did not declare any systematic methodology for identification or appraisal. Further, with a limited number of professionals involved in their generation, without further consultation, the guidelines risk being unacceptable to many centres across the UK where practice may be constrained by available resources and services.

National Institute for Health and Care Excellence (NICE) Guidance 36, for Cancer of the upper aerodigestive tract (2018), underwent NICE's standard rigorous process for guidance development.[98,111] It goes further to specify how the evidence was appraised: identifying a topic, agreeing its scope amongst stakeholder organisation and then agreeing review questions. The literature was then searched to produce 'evidence reviews' which were then 'considered by a committee made-up of practitioners, professionals, care providers, commissioners, service users and family members or carers'. Draft guidelines were produced by the committee and sent to stakeholders for comment before being revised and sent to the senior 'Guidance Executive' before publication. Whilst this also goes further in attempting to engage more widespread opinions, response rates from the consultation process tend to be low. Additionally, the 'consider' phraseology adopted by NICE (and replicated in **The HNSCCUP Consensus Exercise**) has drawn criticism for being too broad in scope, covering recommendations that may lack sufficient evidence to reach an 'offer' threshold, but also those where the intervention may be thought of as optional or as only occasionally appropriate.

Guidelines from the European Head and Neck Society (EHNS), European Society for Medical Oncology (ESMO), and European SocieTy for Radiotherapy and Oncology (ESTRO)[113] and from the National Comprehensive Cancer Network (NCCN) have similar development methodology to the NICE recommendations in that they cover all of head and neck cancer (not just HNSCCUP specifically) and rely on a limited multidisciplinary panel of experts in their initial stages.[88,139]

The American Society of Clinical Oncology (ASCO) published 33 recommendations in 2020.[103] Guidelines were generated by an expert multidisciplinary panel who had reviewed systematic reviews, including 100 articles, and then rated the certainty of the evidence and the strength of the recommendation using GRADE (Grading of Recommendations Assessment Development and Evaluation) methodology.[110] Importantly, they go further in seeking widespread consensus by releasing the draft recommendations for open comment from the public. This process allows any individual to give input, but responses are not required or expected and any feedback

must be approved by a Clinical Practice Guideline Committee before adoption. Their effort to be inclusive of lay members, including patients, are to be commended, though it is acknowledged that vocal minorities may be over-represented without a comprehensive countrywide framework for seeking and processing feedback in place.

An area for potential improvement in all the methodologies explored here, is the engagement of a greater number of stakeholders giving more representation. Particularly, seeking more input from the multidisciplinary team (MDT) members who are actually delivering the care day-to-day in the majority of UK centres, not just a selection of 'experts' who may not have an informed picture of the limitations of delivering care outside of tertiary referral centres. The methodology employed in **The HNSCCUP Consensus Exercise** aimed to address these potential deficiencies through the Consensus Day and Delphi Process. Without this comprehensive engagement, recommendations for this challenging and controversial condition risk being admirably aspirational, but adoption may be limited if they do not garner sufficient buy-in from individual units, and they may be unachievable, depending on local service arrangements. Buy-in is essential if guidelines are to be adopted and, ultimately, to achieve their aim of influencing clinical practice.

*Influence of **The MOSES Study** and **The HNSCCUP National Audit 2021** on the **Final HNSCCUP MDT Consensus Guidelines***

The MOSES Study contributed directly to the drafting of statements 2c, 2d, 2e, 2f, 2g and 2i regarding the extent and timing of oropharyngeal diagnostic surgery (**Table 2-14**).

The HNSCCUP National Audit 2021 heavily influenced statement 1c, regarding concurrent PET-CT and MRI to expedite the diagnostic pathway (**Figure 2-11**). It also influenced statement 2i where the diagnostic yield from direct vision diathermy TBM was found to possibly be lower than for other methods (**Figure 2-10**, **Table 2-14**). The concern regarding the risk of omitting radiotherapy and offering only single modality surgery led to more cautious statements being generated than found in the 2016 guidelines. For example, Statements 4a suggests only 'considering' omitting adjuvant therapy and statement 4e suggests including ipsilateral oropharyngeal primary sites in the irradiated volume in HPV-positive disease, even when a primary site is not identified (**Table 2-16**). Further, statement 3b suggests the inclusion of regular cross-sectional imaging for surveillance if single modality surgery is offered (**Table 2-15**).

Limitations of work contributing to the **National Consensus for HNSCCUP Care**

The MOSES Study reports the largest prospectively identified cohort of HNSCCUP undergoing TBM but is not without its limitations. Firstly, stratification of patients by timing of palatine tonsillectomy delivered relatively small subgroups for analysis. However, SSS was the focus of this initial phase of **The MOSES Study** and it is felt this question was answered adequately. Secondly, a variety of surgical techniques were used to obtain the tissue (TORS/TLM/TOEC) and surgery did not mandate a standard operating procedure across all centres. Whilst homogenisation for quality assurance may seem desirable, the study intentionally set out to report on the contemporary clinical practice in a pragmatic national setting, to ensure results were as generalisable as possible to day-to-day care.

In **The HNSCCUP National Audit 2021**, the method of identifying HNSCCUP patients (those undergoing PET-CT midway through their diagnostic journey) limits the ability to comment on the early pathway as many clinical-HNSCCUP patients will have had their primary sites identified before this investigation took place. However, PET-CT was chosen as a pragmatic screening tool to provide a manageable number of records for review to determine if the patient's initial presentation included a negative clinical examination. It also allowed for appropriate analysis of diagnostic surgeries which most commonly take place after PET-CT has been performed. Additionally, having a PET-CT was an essential inclusion criterion, excluding those who did not have this investigation and potentially biassing results to include only patients from better resourced units.

Given the retrospective nature of **The HNSCCUP National Audit 2021**, where patient care was split between more than one hospital or department, clinical data could not always be sourced. However, multiple rounds of data cleaning and clarifications were conducted, resulting in the high levels of data completeness reported, reducing the potential for misreporting and minimising the chance of including duplicate records. Additionally, in the analysis, treatments were not stratified by chemotherapy as this would have reduced the number in each group available for analysis even further.

For **The HNSCCUP Consensus Exercise**, firstly, attendance at the Consensus Day was self-selected, giving the potential for disproportionate representation from one or more stakeholder groups. Secondly, during the Delphi exercise, the contact was asked to record the consensus view of their MDT. However, the level of true consultation cannot be gauged or recorded using this methodology, and so responses may have been biased towards the specialty viewpoint of the contact (ENT in this instance). Thirdly, organisation of the hybrid consensus event was relatively labour intensive, particularly corralling the contributors to deliver their contributions on time. This work fell largely to the author and the primary supervisor and was essential to ensure successful delivery. Finally, the degree of patient consultation was limited. However, patient views were considered at multiple points: a 'patient experience' interview was delivered as the opening presentation at the Consensus Day to provide qualitative data; and data presented from **The HNSCCUP National Audit 2021** were presented to better consider the timeline for interventions in the patients' diagnostic pathway from all across the UK.

Conclusions for the **National Consensus for HNSCCUP Care**

A great deal has been learnt through these three linked projects that has furthered our understanding of the management of HNSCCUP and will influence care for these challenging patients over the coming years.

The HNSCCUP National Audit 2021 evaluated the diagnostic pathways of patients with suspected HNSCCUP and showed the condition to be a challenging clinical entity with variable management. The majority of suspected HNSCCUP patients experienced a protracted diagnostic pathway and waited over 3 months to start definitive treatment. This has led to the proposal that standard practice to arrange earlier PET-CT with concurrent MRI may improve primary site detection rates and expedite diagnosis.

For the clinico-radiologically occult HNSCCUP, **The HNSCCUP National Audit 2021** showed TBM was not widely adopted. When TBM was employed, it provided a higher diagnostic yield compared with contralateral tonsillectomy, concurring with **The MOSES Study**. The audit suggested concurrent ipsilateral tonsillectomy and TBM could improve primary site detection rates and reduce the number of diagnostic theatre episodes. Once oropharyngeal specimens have been obtained, **The MOSES Study** showed that, in a prospectively identified multi-centre cohort of patients undergoing TBM, step serial sectioning added a considerable histopathological workload with minimal additional diagnostic benefit when processing lingual and palatine tonsillar tissue. It is suggested that a second opinion using conventional histological techniques for HNSCCUP diagnostic specimens may be more beneficial than SSS. Overall, for optimal care, patients should be engaged early in the decision-making process regarding the extent and timing of diagnostic surgery to balance the benefits of finding a primary site in the shortest time with the morbidity associated with the procedures.

The HNSCCUP National Audit 2021 also showed that contemporary management of HNSCCUP shows notable differences in the management and outcomes related to HPV status. Unilateral neck disease was shown to be treated variably and, when managed with surgery alone, was associated with poorer local control and disease-free survival, possibly due to the omission of radiation to putative primary sites. The impact and extent of diagnostic oropharyngeal surgery on primary site emergence remains unestablished and is particularly of interest considering the prevalence of multifocal oropharyngeal disease found in **The MOSES Study**.

The HNSCCUP Consensus Exercise described the methodology to implement an effective and inclusive multi-phase strategy for the development of national practice recommendations for the management of HNSCCUP. The initiative achieved widespread engagement, including a well-attended Multidisciplinary National Consensus Day and a Delphi process including representation from all 58 UK Head and Neck MDTs. The exercise may serve as a model for future guideline development for controversial or rare conditions where there is a paucity of available evidence or where there is significant variability in management practices across a health service, and where widespread buy-in for the resultant output is desirable. The **Final HNSCCUP MDT Consensus Guidelines** generated have been adopted into the 6th edition of the 'United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer' and will be published imminently at time of thesis submission.

2.3.7 Final HNSCCUP MDT Consensus Guidelines

Presented below are the final guidelines, as submitted for peer-review and endorsement in the 6th edition of the 'United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer', Chapter 27: Management of head and neck squamous cell carcinoma of unknown primary (HNSCCUP).

2.3.7.1 Introduction

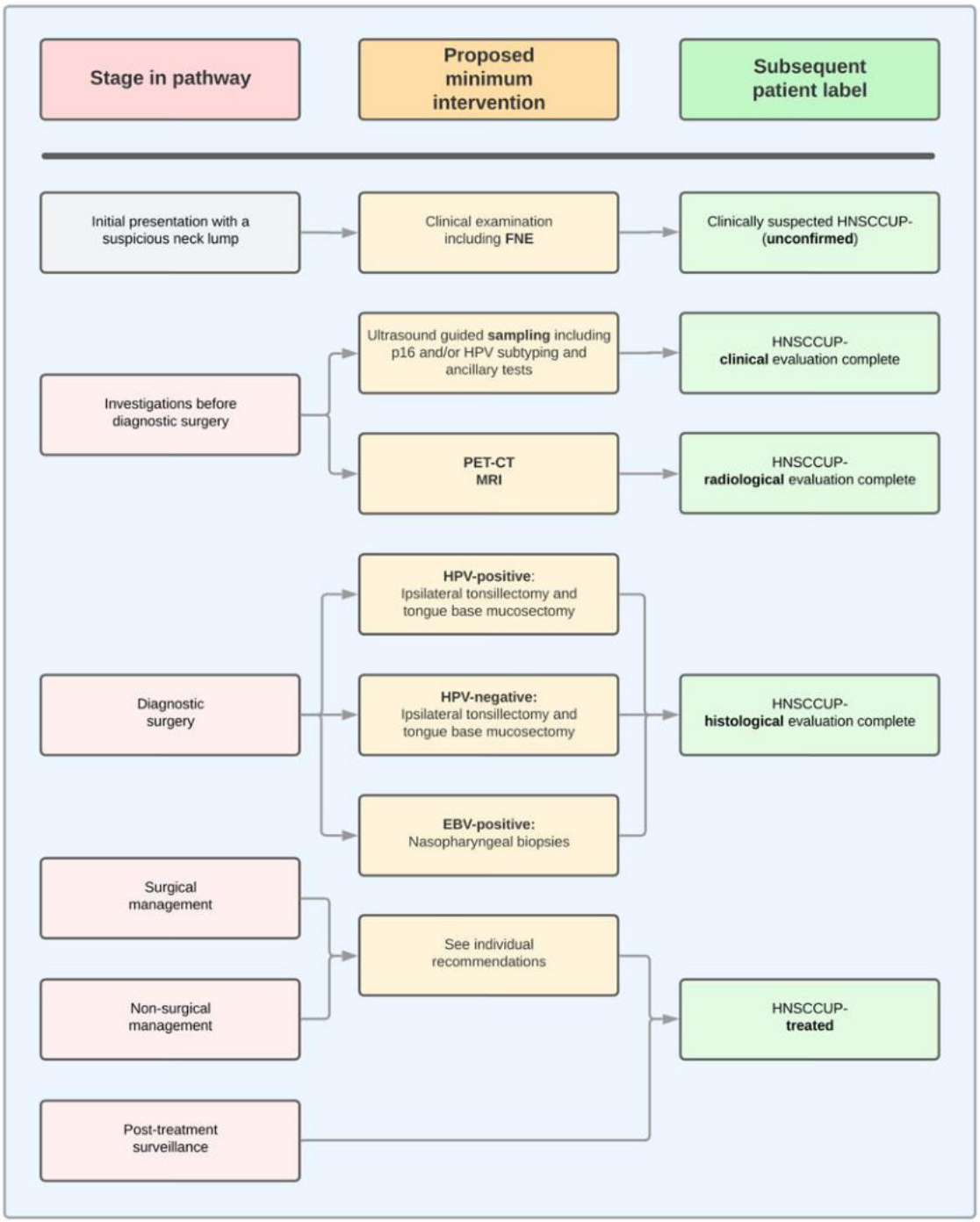
Producing and interpreting guidelines for the management of head and neck squamous cell carcinoma of unknown primary (HNSCCUP) is inherently challenging. Firstly, there is a paucity of robust contemporary evidence on the topic. Many historic studies predate our understanding of the role of human papillomavirus (HPV) in head and neck cancer (HNC)[59] and, with the incidence of HPV-related disease rising,[140] management recommendations must necessarily be updated to be most effective at improving patient care. Secondly, the understanding and definition of what is considered an 'unknown primary' evolves during the diagnostic pathway. During this process, clinical examination, imaging investigations and surgical biopsies all may identify a primary disease. As a result, direct inter-study comparisons or meta-analysis are complicated by incongruent cohort definitions and eligibility criteria. Thirdly, true unknown primary disease is not common, and so establishing both a substantial evidence base and reasonable clinical experience regarding its management can be challenging, particularly in single-centre settings.

Despite these limitations, many organisations have produced guidelines covering the management of HNSCCUP, using a variety of methodologies.[98,102,103,109,141] The present guidelines were produced following a multi-stage meta-consensus initiative that was developed specifically for this work. This incorporated a National Audit of Practice, a National Consensus Day and a National Delphi Exercise. Through this process, novel data were generated, the most up to date published and unpublished studies were considered, draft statements were generated before being scrutinised by representatives from all UK head and neck Multi-Disciplinary Teams (MDT's) to produce these final recommendations. The full outline of this methodology has been published separately.[5]

These guidelines follow the patient journey from presentation to post-treatment surveillance with unknown primary disease. Recommendations are included as statements at the beginning of each section, followed by further guidance and commentary to add context. NICE phraseology has been used when generating the statements to reflect the strength of evidence and level of certainty in the benefit of the intervention for each recommendation presented.[111] The terms 'offer', 'perform', 'refer' and 'include' reflect confidence in a strong patient benefit. Where the evidence offers less certainty in a clear benefit, the term 'consider' is used.

These guidelines do not describe the management of non-SCC disease of unknown primary origin.

Figure 2-12: Illustration of the patient pathway for HNSCCUP guidelines, related to proposed minimum required interventions and patient labels for these groups



2.3.7.2 Investigations before diagnostic surgery

2.3.7.2.1 Recommendations

- Offer all patients with clinically suspected HNSCCUP ultrasound guided sampling as a first-line investigation to diagnose cervical metastasis of SCC, which must include p16 and/or HPV subtyping and ancillary tests
- Do not offer open biopsy to patients with a neck lump as a first-line investigation to diagnose cervical metastasis
- Offer all patients with clinical suspicion of HNSCCUP a concurrent MRI and PET-CT as first-line cross-sectional imaging investigations
- Consider image enhancement technology (including narrow-band imaging) as an adjunct to white-light endoscopy in the examination of all patients with clinically suspected HNSCCUP
- Refer all patients with clinically suspected pathologically confirmed HNSCCUP to a core member of the head and neck MDT for further investigations

All patients presenting with a neck mass will need a comprehensive history and clinical examination, including flexible nasendoscopy (FNE). Alongside FNE, there is good evidence that virtual chromoendoscopy (e.g. narrow band imaging (NBI)) can aid recognition of otherwise occult mucosal lesions, though it is acknowledged that not all UK centres have access to this technology.[76]

All patients will require cytological or cytopathological confirmation of cancer. HPV subtyping is important for the effective management of all clinically suspected HNSCCUP patients and so, if this is not available on fine needle aspiration cytology (FNAC) then core biopsy should be performed. This is particularly important in patients in whom no primary site is identified by the end of the diagnostic pathway and who do not undergo neck dissection, as they will have no other tissue on which to perform HPV and EBV analysis. Ultrasound guidance increases the diagnostic accuracy of the biopsy.[142] Open biopsy is not felt to be an appropriate alternative to US guided core biopsy.

Patients presenting with clinically suspected HNSCCUP often experience long diagnostic pathways before starting definitive treatment with a significant amount of time on the pathway awaiting imaging investigations, and PET-CT in particular.[121] Current NICE guidance is to consider a PET-CT for patients with confirmed metastatic disease in whom no primary is evident on clinical examination.[98] Immediately following cyto or cytopathological confirmation of metastatic disease, requesting concurrent MRI and PET-CT as first-line cross-sectional imaging would allow synchronous interpretation, cover staging of the chest and expedite progression to diagnostic surgery in search of a primary site.

Timely referral to a head and neck MDT was deemed essential to ensure appropriate oversight of the diagnostic pathway, as well as subsequent treatment.[143]

2.3.7.3 Diagnostic surgery

2.3.7.3.1 Recommendations

- Perform all radiological investigations aiming to identify the primary site prior to discussion at head and neck MDT and diagnostic surgery
- Offer nasopharyngeal biopsies when the cervical node sampling reveals Epstein-Barr virus positive metastasis
- Do not offer biopsies of clinically and radiologically normal upper aerodigestive tract mucosa. This excludes tonsillectomy or tongue base mucosectomy
- Offer ipsilateral tonsillectomy (rather than incisional biopsy) in all patients
- Consider contralateral tonsillectomy (rather than incisional biopsy) in all patients
- Consider ipsilateral tongue base mucosectomy in all patients
- Consider contralateral tongue base mucosectomy in all patients
- Perform tongue base mucosectomy using one of the following transoral techniques, when indicated: endoscopic, microscopic or robot-assisted

Strategies for obtaining oropharyngeal biopsies remain contentious. In 2016 NICE guidance included offering surgery to identify the unknown primary. However, as with all surgery, these procedures are associated with their own morbidities and complications and so, if offered to the patient, each element should be clinically justifiable and the patient fully informed of the risks and benefits.[92,144]

Ipsilateral tonsillectomy is widely accepted as being diagnostically beneficial. However, the pick-up rate of primary disease from a contralateral tonsillectomy is lower.[82,121] Consequently, the marginal benefit from removing the contralateral tonsil for diagnostic purposes, as well as the advantage of a symmetrical oropharynx being easier to monitor for future disease, must be weighed against the additional morbidity from the procedure.[145]

Removal of the lingual tonsillar tissue (also known as tongue base mucosectomy (TBM)) as a diagnostic procedure in search of a primary tumour has become more prevalent. This is, in part, due to the advent of robotic technology, albeit that other transoral techniques are available and have proved efficacious. TBM has been reported to increase the identification of the primary tumour.[57] There remains debate about the extent of TBM (whether it should be unilateral or bilateral) as well as the timing of the procedure (whether it should be performed at the same time as palatine tonsillectomy or only following negative histology from palatine tonsillectomy), both of which will affect its apparent pick-up rate. Practice regarding the extent of oropharyngeal clearance is influenced by concerns of pharyngeal stenosis, though a rate of symptomatic narrowing has not been established in any large-scale cohorts.

2.3.7.4 Surgical management

Unless otherwise specified, patients with HNSCCUP referred to in this section are assumed to have undergone an adequate diagnostic work-up, as per their MDT, and are due to commence treatment as HNSCCUP.

2.3.7.4.1 Recommendations

- Consider ipsilateral tonsillectomy and tongue base mucosectomy and ipsilateral neck dissection in both HPV-**negative** and HPV-**positive** HNSCCUP with a single involved node 3 cm or less with no radiological extranodal extension
- Consider neck dissection prior to treatment in HPV-**negative** HNSCCUP undergoing radical radiotherapy with advanced disease unsuitable for concomitant chemotherapy
- Consider neck dissection prior to radiotherapy +/- chemotherapy in HPV-**negative** HNSCCUP patients with N3 neck disease

Single modality surgery for patients undergoing ipsilateral surgery to the oropharynx and the neck with a single involved node 3 cm or less with no radiological extranodal extension may be considered to be appropriate treatment. Clearance of the contralateral tonsil and/or tongue base may also help reassure the MDT that the putative primary sites have been adequately addressed to manage the risk of primary emergence.

Concomitant chemotherapy has been shown to have a significant benefit HPV-negative disease, which is more commonly associated with an aggressive course.[146] If concomitant chemotherapy is not felt to be suitable then upfront surgery should be considered in these patients to ensure dual modality therapy is delivered.

In HPV-negative HNSCCUP patients with N3 disease, upfront neck dissection should be considered before radiation therapy regardless of their suitability for chemotherapy, owing to their poorer survival outcomes.[146]

Some MDTs currently advocate a limited 'staging' neck dissection of the clinically negative contralateral neck, with the intention being to show the contralateral neck is histologically disease-free and so to spare this volume from subsequent radiotherapy. However, there is currently a lack of evidence in the literature to support this strategy and so it is not recommended (or opposed) by these guidelines.

2.3.7.5 Non-surgical management

Unless otherwise specified, patients referred with HNSCCUP to in this section are assumed to have undergone an adequate diagnostic work-up, as per their MDT, and are due to commence treatment as HNSCCUP.

2.3.7.5.1 Recommendations

- Consider omitting adjuvant radiotherapy after an ipsilateral neck dissection where there is a single involved node 3 cm or less with no extranodal extension
- Offer adjuvant radiotherapy +/- chemotherapy to the ipsilateral neck after an ipsilateral neck dissection where there is a single involved node greater than 3 cm, or there are multiple involved nodes, or there is extranodal extension
- Consider adjuvant radiotherapy +/- chemotherapy to bilateral neck after an ipsilateral neck dissection where there are multiple involved nodes or there is pathological extranodal extension
- Consider radiotherapy +/- chemotherapy to the bilateral neck if there are multiple involved ipsilateral nodes or there is radiological extranodal extension
- Consider including the ipsilateral oropharynx in the treated volume when giving radiotherapy to the neck for unilateral HPV-positive HNSCCUP
- Consider including possible mucosal primary sites when giving radiotherapy to the neck for unilateral HPV-negative HNSCCUP. Decide possible sites based on pattern of nodal involvement and other clinicopathological features (e.g. smoking)
- Offer 50 Gy in 2 Gy fractions or equivalent* as the radiotherapy dose for possible mucosal primary sites when they are intentionally included in the target volume.
  **e.g. 54 Gy in 30 fractions or 56 Gy in 35 fractions*
- Offer concomitant cisplatin chemotherapy with adjuvant radiotherapy if there is pathological extranodal extension and the patient is suitable to receive cisplatin
- Offer concomitant cisplatin chemotherapy with primary radiotherapy if there are multiple involved nodes or radiological extranodal extension and the patient is deemed fit to receive cisplatin
- Include the ipsilateral retropharyngeal and retrostyloid nodes in the elective target volume when giving radiotherapy to the ipsilateral neck where level II is involved

Adjuvant radiation therapy to the ipsilateral neck in more advanced HNSCCUP disease is essential.[147] Contralateral radiation should be considered in the case of ENE or where multiple nodes are involved. For the majority of HSNCCUP who present with level II involvement, retropharyngeal and retrostyloid nodes should be included in the elective target volume.

There is insufficient evidence to support or oppose ipsilateral radiation to the oropharynx in all unilateral HPV-positive HNSCCUPs, or indeed to any putative mucosal sites in HPV-negative disease. Where radiation therapy is given for HPV-negative HNSCCUP disease, the mucosal sites should be chosen based on the pattern of nodal involvement and any other relevant clinicopathological features. In all cases where radiation therapy is given to mucosal target volumes, these guidelines advocate the use of a prophylactic dose, not as high as used in adjuvant or radical dosing regimens, though it is accepted this is based on consensus opinion rather than any

high level evidence. Omission of radiation to putative mucosal sites may be considered under MDT supervision but assumes an adequate diagnostic work-up and appropriate clinico-radiological surveillance.

2.3.7.6 Post-treatment surveillance

2.3.7.6.1 Recommendations

- Consider adding regular cross-sectional imaging to regular clinical examination for post-treatment surveillance of patients treated with surgery as a single modality, following bilateral tonsillectomy and tongue base mucosectomy and pN1 disease with no extranodal extension.
- Follow up is discussed in a separate chapter but, due to the nature of unknown primary disease, cross-sectional imaging is recommended, in particular, for those who have received single modality surgical treatment.

National Audit data has suggested that loco-regional control rates may be lower in patients treated by surgery alone.[148] As such, this group has been highlighted for regular imaging surveillance, for primary emergence, in addition to regular clinical review. It is possible that the addition of radiation directed at the neck may give enough dose to putative mucosal sites to treat any occult primary disease that is not clinically, radiologically or histologically evident by the time some patients commence definitive treatment for their HNSCCUP.

2.3.7.7 Limitations of these HNSCCUP MDT consensus guidelines

A complete outline of the methodology used to develop these guidelines is published elsewhere which outlines the initiative used to generate these consensus recommendations [note to the reader, please see **The HNSCCUP Consensus Exercise**].[5] The following limitations are highlighted here as particularly relevant to the process. Firstly, attendance at the Consensus Day was self-selecting, giving the potential for disproportionate representation individual stakeholder groups during the generation of the draft consensus statements. Secondly, during the Delphi exercise, the MDT contact was asked to record the consensus view of their team. However, the true level of consultation with each MDT was not recorded and may have varied. Responses may, therefore, have been biased towards those who engaged in the process locally, and specifically towards ENT team members who were the contact specialty for this exercise. Finally, our Delphi exercise used a binary response to register support either for or against each statement under consideration. As such, there may have been an under-representation of clinical oncology input. This methodology is unable to present the strength of opinion from individual units and could be seen to misrepresent the views of a minority of respondents who may have had strong opposition to the statement as presented, compared to a majority who felt only weakly in favour.

PART 3 TORS FOR RECURRENT HNC

Precis of studies contributing to **PART 3**

- **The RECUT Review** assessed the current literature for TORS in the management of the recurrence HNC.
- **The RECUT Study** assessed the use of TORS in the management of the recurrence HNC in a retrospective observational cohort study across 16 international centres.

Introduction to **PART 3**

Recurrent head and neck cancer

Head and neck cancer (HNC) is the sixth most common type of cancer in the world and is increasing in incidence.[149,150] Squamous cell carcinomas (SCC) account for the majority of these tumours, with an increasing number associated with the human papillomavirus (HPV) and a more favourable oncological outcome.[59,151,152] These HPV-related cancers tend to affect younger patients with fewer comorbidities.[153] As such, there is an increasingly large group of cancer survivors living for many years after their primary treatment.

Despite optimal management, a significant number of patients treated for HNC will experience further disease.[154,155] HNC patients are over 11 times more likely to experience a second head and neck primary cancer than the general population over 20 years of follow-up (standardized incidence ratio 11.2, 95% CI [10.6–11.8]).[156] In addition to second primaries, patients may suffer from residual disease after treatment for their initial primary, identified within a 12 month period, or recurrent disease identified at the same site within five years.[157]

Commonly, in such cases, radiotherapy will have formed part of the treatment regimen at either the primary site, and/or to the neck, in either a radical or adjuvant capacity. Radiotherapy is known to cause detrimental changes in irradiated tissues, reducing healing potential and complicating potential surgery with trismus and altered tissue planes.[158] For such patients with new or recurrent tumours arising within a previously irradiated volume, curative-intent treatment may be offered, commonly involving either re-irradiation or surgical excision. Both approaches are associated with morbidity for the patient. When surgical excision is considered, the standard-of-care is open resection, traditionally involving either transmandibular or transcervical routes, necessary to access the tumour site.[158–162] The surgery may require free-flap reconstruction, though not necessarily to repair the deficit left from resection of the tumour itself as, in some instances, it may be necessary to repair the irradiated tissues that have been disrupted for access alone.[141,163,164]

Minimally invasive surgical techniques, such as transoral laser microsurgery (TLM) and transoral robotic surgery (TORS), have emerged in recent decades, seeking to lessen the disruption caused to normal anatomy during

tumour resection, seeking to optimise functional outcomes without compromising oncological results.[165] TORS confers significant advantages to the surgeon and to the patient.[166–168] For the surgeon, the endoscopic view is three-dimensional and binocular, giving a close objective lens and excellent depth perception. Further, the instruments have wrists which sit within the body cavity, allowing manipulation of the tissues beyond the direct line of sight through the mouth. For the patient, the reduced volume of disrupted tissue and avoidance of mandibulotomy has the potential to reduce functional impairment in the early stages, speed recovery and facilitate better long-term functional outcomes, in addition to reducing complications from delayed healing, including fistula formation, wound dehiscence and osteoradionecrosis.

Concurrent with the emergence of these minimally invasive techniques like TORS, the required minimum surgical margin has come under increased scrutiny, with a similar ethos of maximising the preservation of normal tissues. In salvage cases, the fibrosis related to prior irradiation can collapse the anatomy, bringing tumours into closer proximity to vital structures, thereby limiting the potential resection margin that can be achieved, regardless of the surgical modality used.[169]

The interest in moving away from the traditional 5mm target minimum margin is reflected in the lower values used in contemporary trials employing minimally invasive techniques.[134,170] Such trials are not investigating the oncological impact of the reported minimum resection margins following TORS, but rather, they adopt lower margin values as a randomisation criterion for adjuvant treatment regimes. It is important to emphasise that all such studies are in the primary disease setting. The optimal minimum margin for tumours arising in previously irradiated fields, either as recurrences or de novo disease, has not yet been addressed.

And so to **PART 3**...

TORS for recurrent HNC is an emerging technique. As such, individual centres only have a limited experience of operating on such patients. This is reflected in the published literature as well as, fundamentally, the experience of individual centres. **PART 3** therefore conducts a comprehensive systematic review and meta-analysis of the literature to understand the current body of knowledge (**3.1**). It goes on to conduct a multi-centre cohort study analysing the individual patient data contributed by 16 high volume international units (**3.2**).

3.1 The RECUT Review

3.1.1 Full title

transoral Robotic surgery for rECurrent tumours of the Upper aerodigestive Tract (RECUT): Systematic review and meta-analysis

3.1.2 Contributions

Under supervision, the author led this review from conceptualisation, through protocol development, data collection, assimilation, analysis, visualisation and interpretation. Further, the author led on writing, reviewing and editing the text contained herein, which has been published in the journal **Head & Neck**.[7]

The author is grateful to the following individuals for their contributions towards the delivery of this study and its write-up (full delineation of roles and affiliations available in **Appendix 25**):

- Zi Wei Liu, who acted as second reviewer for identification of relevant studies and extraction of data, and who also reviewed and edited the manuscript, which benefitted from her insight as a senior head and neck surgical trainee.
- Yi Wen Hon, Knowledge Resources Manager at the David Adams Library, Royal Marsden NHS Foundation Trust, who assisted in the construct and conduct of the literature searches.
- Grainne Brady and Justin Roe, who reviewed and edited the manuscript, which benefitted from their insights as senior Speech and Language Therapists.
- Cyrus Kerawala, Francesco Riva, Peter Clarke and Dae Kim, who reviewed and edited the manuscript, which benefitted from their insights as senior head and neck surgeons.
- Shreerang Bhide and Christopher Nutting, who reviewed and edited the manuscript, which benefitted from their insights as senior head and neck oncologists.
- Vinidh Paleri and Kevin Harrington, who supervised the work from conceptualisation to production and approval of the final report.

3.1.3 Abstract *[150 words]*

Background

Transoral robotic surgery (TORS) for recurrent head and neck cancer (HNC) is an emerging but relatively infrequent procedure.

Methods

Systematic review and meta-analysis of studies reporting survival data and functional outcomes for patients undergoing TORS for previously treated HNCs.

Results

878 records were identified, of which eight were eligible for inclusion, covering 161 cases (range 1-64). The pooled rates were as follows: 2-year overall survival 73.8% (4 studies, range 70.6 to 75.0, 95% confidence intervals (CI) 65.4 to 81.5, [I2 0.0%, p=1.0]); 2-year disease-free survival 74.8% (4 studies, range 56.2 to 92.0, 95% CI 63.3 to 84.8, [I2 36.9%, p=0.2]); post-operative haemorrhage 9.3% (4 studies, range 3.3 to 13.3, 95% CI 4.7 to 15.1, [I2 0.0%, p=0.5]).

Conclusions

Functional and oncological outcomes are favourable, although the follow-up is limited in the literature. Larger cohorts with longer follow up are needed for definitive conclusions to be drawn.

3.1.4 Aim

The RECUT Review aims to collate and assess the contemporary evidence from international centres performing TORS for head and neck tumours occurring in irradiated volumes.

3.1.5 Methods

3.1.5.1 Protocol and registration

This systematic review was conducted in accordance with PRISMA statement.[171] The protocol for this review was preregistered with PROSPERO (CRD42019127609). The following clarifications and deviations were made from the registered protocol: Studies reporting solely on nasopharyngeal carcinoma were excluded; survival data must have been specific for the recurrent cohort, not combined with primary surgery patients; a minimum requirement of one year follow-up for survival data was mandated; with cumulative reports, only the most recent publication was included; for the pooled analysis, only publications with cohorts of greater than 10 patients were included; and, finally, a second reviewer was used, as outlined below.

3.1.5.2 Eligibility criteria

Study characteristics

Types of study to be included

- All types of observational and experimental study designs will be eligible for inclusion.

Setting

- All countries and health systems will be considered.

Time frame

- TORS is a fairly recently developed procedure and so no limitations on date of surgery will be placed.

Report characteristics

- Any report date.
- All years of publication or presentation will be considered.
- English language.
- Any publication status, including grey literature.

Participants

Inclusion criteria

- Patients with previously treated head and neck cancer.
- Aged over 18.
- Both sexes.

Undergoing TORS as part of their management for recurrent disease with a therapeutic or palliative intention, ie not diagnostic surgery.

Exclusion criteria

- Studies reporting purely on thyroid and nasopharyngeal cancers.

Intervention

- TORS.

Comparator

- No comparator was chosen.

Outcome measures

Primary outcome

- Overall survival (OS) at two years.

Secondary outcomes

- Disease-free survival (DFS) and disease-specific survival (DSS) at two years.
- Rates of positive and close surgical resection margins, as reported.
- Complications of surgery: fistula and haemorrhage rate.
- Functional outcomes, including perioperative and longer-term tracheostomy and gastrostomy usage.

3.1.5.3 Information sources

Sources to be searched: Databases MEDLINE, PubMed, Cochrane Controlled Register of Trials (CENTRAL). References of articles from any previous reviews of chosen papers and backward citation check.

3.1.5.4 Search strategy

Searches were limited to English language entries and were last conducted on 19 September 2019. Search terms for the MEDLINE database are included in **Table 3-1**. Briefly, terms related to robotics, head and neck anatomic subsites and recurrence.

3.1.5.5 Data extraction

Selection of studies

The titles and abstracts of all studies were screened independently by two authors (the author and Zi Wei Liu). Where necessary, the full texts of articles were obtained. Where there was disagreement for inclusion, these discrepancies were resolved by the senior author (the primary supervisor, Vinidh Paleri). Where abstracts and titles were identified in English language, but the main report was in a foreign language, the main report was translated, and eligibility criteria applied.

Data Extraction and Management

Two reviewers (the author and Zi Wei Liu) independently used a pre-piloted data extraction proforma to extract data from the included studies. Raw numbers and percentages were recorded where relevant. Data were entered onto a Microsoft Excel spreadsheet and final approval was ratified by consensus of the first two authors, with discrepancies resolved by the senior author (Vinidh Paleri).[172] Data were reported as presented in the articles. The corresponding authors were contacted on three occasions,[166,173,174] to clarify ambiguous or incomplete survival data, receiving a reply from two.[166,174]

Data items

The data items were chosen to reflect the primary and secondary outcome measures and are detailed in the results tables below.

3.1.5.6 Data Synthesis

Summary of findings tables are used to present results from the studies. For meta-analyses, only studies with over 10 patients were included. Owing to low numbers and anticipated heterogeneity in the data, sub-group analysis was not felt to be appropriate. A random-effects meta-analysis of the pooled proportions was performed using *metaprop*.[175] Forest plots were generated using the Freeman-Tukey Double Arcsine Transformation to stabilize the variances, the Wilson method was used for 95% confidence intervals.[176,177] Heterogeneity was assessed using the I^2 statistic with p values <0.05 considered statistically significant. Statistical analyses were conducted using Stata Release 13, StataCorp LLC, College Station, Texas USA.

3.1.5.7 Risk of bias

Individual studies

A study-level risk of bias assessment was performed for all included studies. The Cochrane Risk of Bias tool and/or the MINORS tool was used for randomised controlled trials and observational studies, as appropriate.[178] If any other study types had been encountered, then the appropriate bias assessment tool would have been used. Risk of bias of the cumulative evidence also is also commented on.

3.1.6 Results

3.1.6.1 Study selection

A total of 878 potentially relevant records were identified, reducing to 588 once duplicates had been removed. **Figure 3-1** displays the results of the review process in a PRISMA flowchart. On detailed review of full text articles, many records were ineligible as: they were review articles; they did not report any TORS salvage cases, the salvage cases were indistinguishable from the primary cases/combined cohort, there were insufficient survival data, the reports were limited conference abstracts, the studies related to nasopharyngeal carcinoma only; or the reports were superseded by more contemporary publications from the relevant institutions. A total of eight studies met the eligibility criteria and have been presented in the results.[166,173,174,179–183]

3.1.6.2 Study characteristics

Table 3-3 summarises the characteristics of the studies included in this systematic review. The studies were published between 2013 and 2018 and originate from centres in the USA,[179,181] Europe,[166,174,180,183] India[173] and Australia.[182] Two of the studies were multi-institutional.[174,181] All of the studies identified their patients based on the intervention and reported on the subsequent outcomes and, as such, were considered observational cohort studies. A single study compared outcomes to matched open surgery patients[181] and another study compared 'salvage' patients to primary surgery patients.[174] The remaining studies made no comparisons. The eight reports were published in seven different journals from publishing houses across the world.

The eight studies included 161 cases in total, ranging from a single eligible case to a cohort of 64 patients. In three studies, the final number of cases eligible for inclusion in this review was small (one[182], two[180] and four[179] cases). All these studies satisfied the predetermined eligibility criteria, presenting valid outcome data which were discernible for the included cases. In one study, the author provided updated data for the oropharyngeal SCC cohort covering 17 of the 21 TORS patients that were included in the original publication.[166]

In six of the eight studies, the previous treatment was clearly reported, with the majority of patients having previously undergone radiotherapy or chemoradiotherapy to the head and neck (**Table 3-3**) (six of eight studies; radiotherapy 98.3%, n=117/119; chemoradiotherapy 63.9%, n=76/119). No studies reported the use of bioradiotherapy. The most common subsite for the TORS intervention was the oropharynx, with surgeries also covering the hypopharynx, supraglottis, glottis and nasopharynx. There was a male preponderance and the mean ages were around 60 years. Nearly all cases were SCC, but HPV rates were inconsistently reported. Most cases were early stage disease, rT0-T2 and rN0-N2b (**Table 3-3**).

The timing of treatment for the cancers in the included studies was not consistently reported. Studies often contained cases presenting at a variety of timepoints, including residual disease (within 12 months of prior treatment)[166,174], recurrent disease (within five years of prior treatment)[166,174] and some including cases of new primaries either at a new subsite (any time after initial treatment)[166,174,180,183] or at a new subsite (within five years of initial treatment)[166,174,183].

Five of the eight studies included more than 10 subjects and so were eligible for inclusion in the meta-analysis.

3.1.6.3 Risk of bias within studies

MINORS scores are presented alongside study characteristics in **Table 3-3**, with full scores displayed in **Table 3-2**. The mean MINORS score was 12 (range 8-14) out of a maximum score of 16. In general, studies were good at prospectively identifying their aims and the data to be collected, at specifying and assessing the study end points, and following up consecutively identified patients. However, no prior consideration was given to the cohort size and minimum follow-up was inconsistently reported, or not adequate, impacting on the reliability of the survival data presented.

3.1.6.4 Risk of bias across studies

Publication bias may be suggested in the studies identified by this review by the higher survival rates seen in studies reporting on fewer patients. The survival data reported therein did not include any statistical analysis and so publication of only statistically relevant studies could not be assessed. In the majority of cases, it was not possible to identify any selective reporting within the studies, and the majority of studies implied that consecutive cases were included (seven of eight studies; see MINORS scores, **Table 3-2**).

3.1.6.5 Survival

Survival data at two-years were available in seven of the eight studies (**Table 3-4**), having contacted two authors to obtain further data.[166] Survival estimations were presented in Kaplan Meier charts in two studies.[174,183]

The pooled survival rates were as follows: 2-year overall survival 73.8% (four studies, range 70.6 to 75.0, 95% CI 65.4 to 81.5, [I^2 0.0%, p=1.0]) (**Figure 3-2**); 2-year disease-free survival 74.8% (four studies, range 56.2 to 92.0, 95% CI 63.3 to 84.8, [I^2 36.9%, p=0.2]) (**Figure 3-3**); 2-year disease-specific survival 83.7% (four studies, range 74.0 to 92.0, 95% CI 71.3 to 93.4, [I^2 54.2%, p=0.1]) (**Figure 3-4**).

3.1.6.6 Margins

All but one study reported on rates of positive resection margins, with five studies also reporting rates of close resection margins (**Table 3-4**). In a single study, the margin data could not be distinguished between primary and secondary cancers, and so they were not included.[183]

The pooled positive margin rate was 18.2% (four studies, range 6.7 to 33.3, 95% CI 8.4 to 30.4, [I^2 60.1%, p=0.1]) (**Figure 3-6**). The pooled close margin rate (not including positive margins) was 25.7% (three studies, range 6.7 to 52.9, 95% CI 4.9 to 54.2, [I^2 84.3%, p=<0.01]) (**Figure 3-7**).

The criteria used for a 'close' margin cut off was reported by four studies, ranging between two and five millimetres. A single study reported criteria for considering a margin as 'positive' (**Table 3-4**).

3.1.6.7 Functional outcomes

Functional outcomes are summarised in **Table 3-5**. The pooled peri-operative gastrostomy rate was 25.0% (three studies, range 16.7 to 35.9, 95% CI 13.7 to 38.2, [I^2 56.9%, p=0.1]) (**Figure 3-8**). The pooled peri-operative tracheostomy rate was 22.3% (three studies, range 21.9 to 23.5, 95% CI 14.7 to 30.8, [I^2 0.0%, p=1.0]) (**Figure 3-9**).

Definitions of what constituted 'long-term' outcomes are reported in **Table 3-5**. Only a single study declared the time point at which this assessment was made in the published report,[181] with another study providing clarification via communication.[166] The pooled long-term gastrostomy rate was 5.0% (four studies, range 0.0 to 20.0, 95% CI 0.1 to 13.9, [I^2 63.7%, p=0.04]) (**Figure 3-10**). The pooled long-term tracheostomy rate was 1.9% (three studies, range 0.0 to 10.0, 95% CI 0.0 to 10.6, [I^2 54.3%, p=0.1]) (**Figure 3-11**).

3.1.6.8 Complications

Data on complications are reported in **Table 3-5**. The pooled post-operative haemorrhage rate was 9.3% (four studies, range 3.3 to 13.3, 95% CI 4.7 to 15.1, [I^2 0.0%, p=0.5]) (**Figure 3-5**).

Not all studies reported rates of concurrent neck dissection, but rates are reported in **Table 3-5** as they are relevant to pharyngocutaneous fistula formation. Similarly, free flap reconstruction may be utilised prophylactically to address potential fistula formation and so these data are reported in **Table 3-5**.

The pooled post-operative fistula rate was 0.6% (four studies, range 0.0 to 3.3, 95% CI 0.0 to 3.3, [I^2 3.1%, p=0.4]) (**Figure 3-12**). The pooled free flap rate was 1.6% (four studies, range 0.0 to 23.5, 95% CI 0.0 to 10.4, [I^2 75.8%, p=0.01]) (**Figure 3-13**).

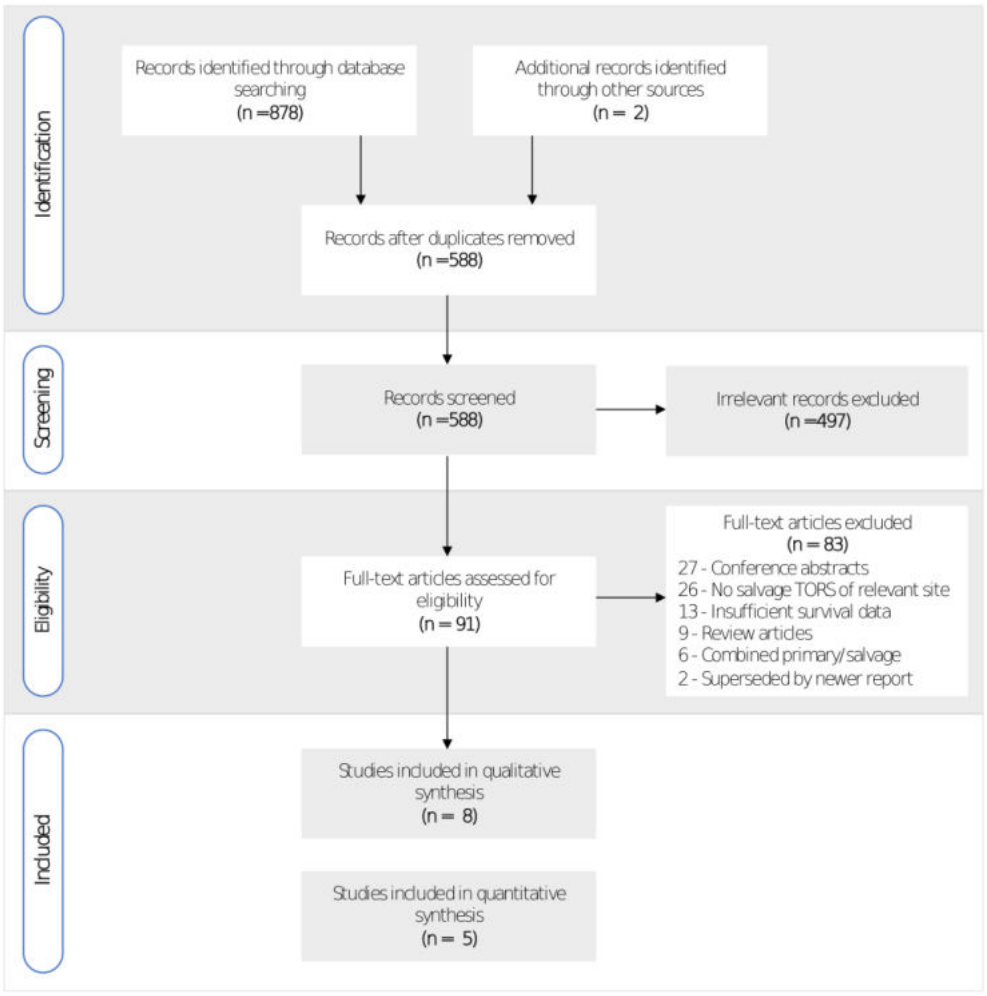


Figure 3-1: PRISMA flowchart for The RECUT Review, with results of the searches, screening and application of eligibility criteria.
PRISMA is Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

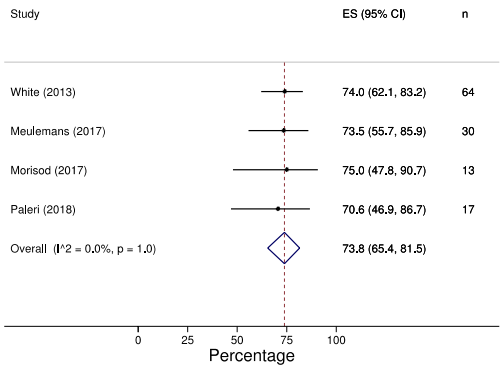


Figure 3-2: Pooled 2-year overall survival rate in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

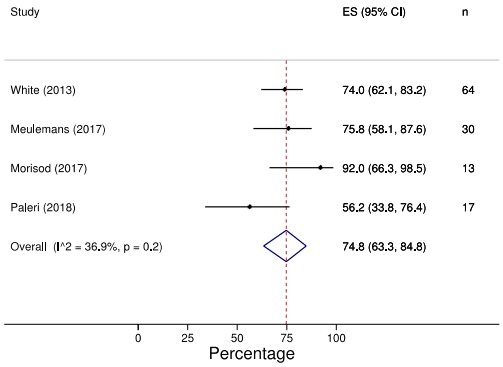


Figure 3-3: Pooled 2-year disease-free survival in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

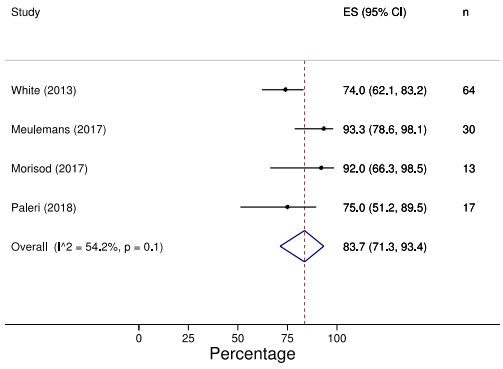


Figure 3-4: Pooled 2-year disease-specific survival in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

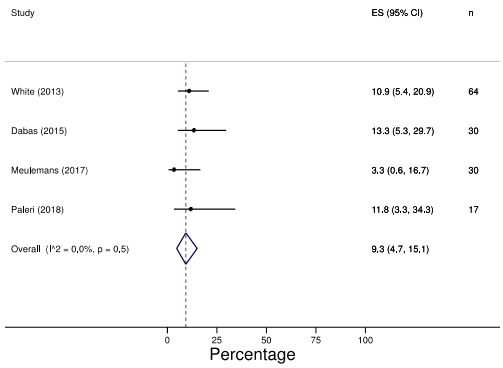


Figure 3-5: Pooled post-operative haemorrhage rate in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

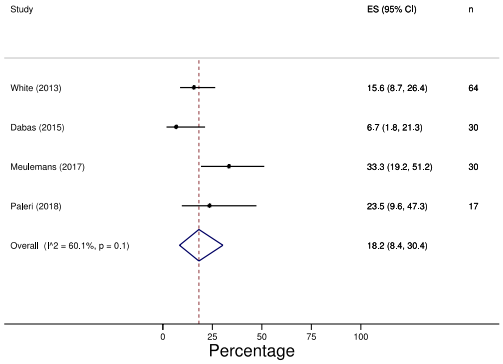


Figure 3-6: Pooled positive margin rate in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

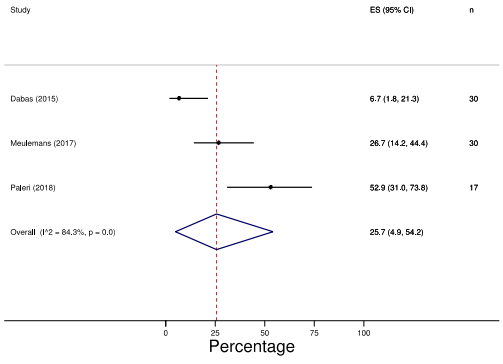


Figure 3-7: Pooled close margin rate in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size

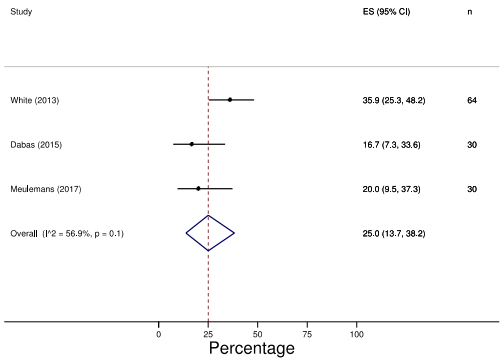


Figure 3-8: Pooled peri-operative gastrostomy rate in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

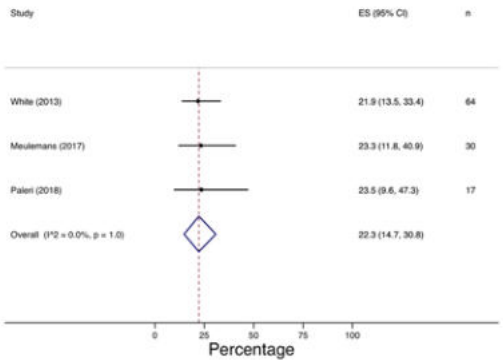


Figure 3-9: Pooled peri-operative tracheostomy rate in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

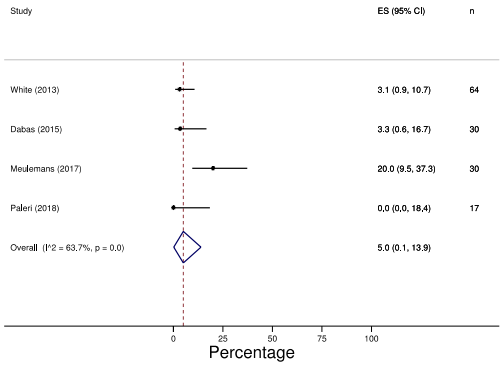


Figure 3-10: Pooled long-term gastrostomy rate in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

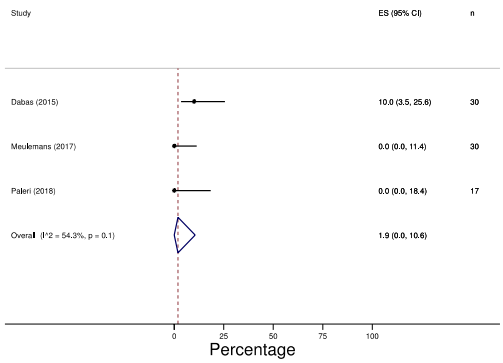


Figure 3-11: Pooled long-term tracheostomy rate in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

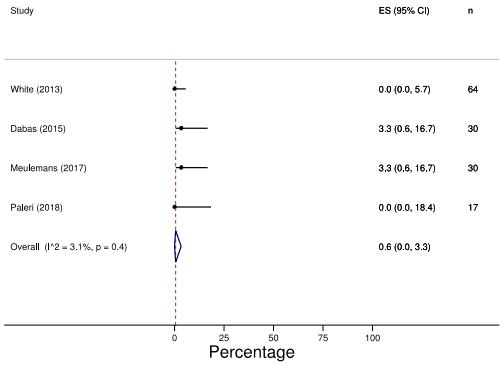


Figure 3-12: Pooled fistula rate in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

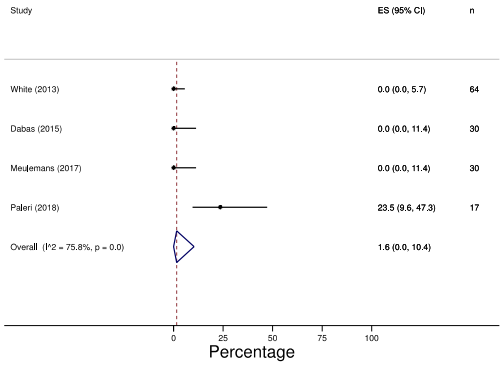


Figure 3-13: Pooled free flap rate in The RECUT Review (for studies reporting this outcome and with more than 10 subjects). ES = effect size.

Table 3-1: Example search strategy for The RECUT Review from Ovid MEDLINE®. Including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® <1946 to September 19, 2019>

Search	Entry
1	Robotic Surgical Procedures/ (5244)
2	(TORS or robot*).ab,ti. (36657)
3	(transoral or "trans oral" or pharyn* or oropharyn* or hypopharyn* or nasopharyn* or glott* or subglott* or supraglott* or larynx* or laryng* or "upper aerodigestive tract" or "H&N" or head or "head and neck" or "head & neck").ab,ti. (458794)
4	exp "Head and Neck Neoplasms"/ (293542)
5	1 or 2 (37067)
6	3 or 4 (663940)
7	(recurren* or salvage).ab,ti. (532127)
8	5 and 6 and 7 (322)

Table 3-2: MINORS scores for studies included in The RECUT Review. Items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score for non-comparative studies is 16.

Study	Clearly Stated Aim	Inclusion of Consecutive Patients	Prospective Data Collection	Appropriate Endpoints	Unbiased Assessment of Endpoint	Follow-up Appropriate Length	Loss to Follow-Up less than 5%	Prospective Calculation of Study Size	(Total max 16)
Blanco 2013	2	2	0	2	2	0	0	0	8
Hans 2013	2	0	2	1	2	2	2	0	11
White 2013	2	2	2	2	2	0	0	0	10
Dabas 2015	2	2	2	2	2	1	2	0	13
Krishnan 2017	2	2	2	2	2	2	2	0	14
Meulemans 2017	2	2	2	2	2	1	2	0	13
Morisod 2017	2	2	2	2	2	1	2	0	13
Paleri 2018	2	2	2	2	2	1	2	0	13

Table 3-3: Characteristic for Studies included in The RECUT Review.
[a] no separate data for second primary cohort
[b] author contacted for clarification
[c] no separate data for salvage cohort
[d] authors report "biopsy proven residual/recurrent disease had no evidence of malignancy on final histopathology report"
[e] author provided updated data for the 17 of the 26 patients who underwent TORS for confirmed SCC of the oropharynx

Study	Country	Centre(s)	Summary	n	Previous radiotherapy?	Mean age /yrs [range]	Sex proportion [M:F]	Interval between initial treatment and surgery	Sub-sites	T classification after surgery	N classification after surgery	Histology	HPV +ve rate	MINORS score
Blanco 2013	USA	Johns Hopkins, Baltimore, Maryland	Early experience of TORS	4	Not reported	Not reported	Not reported	Not reported	Oropharynx and/or larynx	Not reported	Not reported	SCC	Not reported	8
Hans 2013	France	Hôpital Européen Georges-Pompidou, Paris	TORS with free flap for recurrent hypopharyngeal SCC	2	100% (1 RT 1 CRT)	66.6 [59-74]	1:1	5 and 13 years	Hypopharynx (n=2)	T3 (n=2)	N0 (n=2)	SCC	Not reported	11
White 2013	USA	University of Alabama, Birmingham; M.D. Anderson Cancer Center, Houston, Texas; Mayo Clinic, Rochester, Minnesota; Henry Ford Hospital, Detroit, Michigan	TORS for recurrent oropharyngeal SCC, comparing to open surgery	64	100% (25 RT 37 CRT)	61 [not reported]	48:16	Not reported	Oropharynx (n=64)	T1 (n=25) T2 (n=34) T3 (n=2) T4 (n=3)	N0 (n=37) N1 (n=7) N2b (n=17) N2c (n=2) N3 (n=1)	SCC	Not reported	10
Dabas 2015	India	Rajiv Gandhi Cancer Institute & Research Centre, Delhi	TORS for recurrent or residual H&N SCC	30	100% (8 RT 22 CRT)	56.8 [31-86]	29:1	Not reported	Oropharynx (n=26) Larynx (n=3) Hypopharynx (n=1)	T0 (n=2)d T1 (n=10) T2 (n=14) T4 (n=4)	NX (n=20) N0 (n=3) N1 (n=1) N2b (n=5) N2c (n=1)	SCC	Not reported	13
Krishnan 2017	Australia	Royal Adelaide Hospital, Adelaide	TORS total laryngectomies, 5 cases with single incidence of recurrent cancer	1	100% (1 RT)	80	1:0	Not reported	Glottis (n=1)	T2 (n=1)	N0 (n=1)	SCC	Not reported	14
Meulemans 2017	Belgium	University Hospitals of Leuven; General Hospital AZ Sint-Lucas, Ghent; General Hospital AZ Sint-Jan, Bruges	TORS for primary and salvage oropharyngeal, supraglottic and hypopharyngeal cancers	30	Not reported	[c]	[c]	Not specified "10 local recurrence 20 second primaries"	Oropharynx (n=17) Hypopharynx (n=6) Supraglottis (n=6) Glottis (n=1)	T1 (n=18) T2 (n=12)	N0 (n=25) N1 (n=3) N2 (n=2)	SCC (n=29) mucinous cystadeno-carcinoma (n=1) [b]	0.0% (0/9)	13
Morisod 2017	Switzer-land	Lausanne University Hospital	TORS for oropharyngeal SCC, looking to minimise adjuvant therapy. 13/29 were 'second primaries'	13	46.2% (6 RT)	[a]	[a]	Not specified "13 second primaries"	[a]	[a]	[a]	SCC	[a]	13

Paleri 2018	UK	Freeman Hospital, Newcastle upon Tyne	TORS for recurrent oropharyngeal SCC	17 [e]	100% (2 RT 15 CRT)	59.7 [51-85]	16:1	Median 24.5 months [3-96]	Oropharynx (n=17)	T1 (n=3) T2 (n=13) T3 (n=1)	N0 (n=13) N1 (n=2) N2b (n=2)	SCC	60.0% (11/17)	13

Table 3-4: Survival data and surgical margins for studies included in The RECUT Review. [a] derived from Kaplan Meier, [b] as reported, [c] author provided updated data for the 17 of the 26 patients who underwent TORS for confirmed SCC of the oropharynx, [d] 4 returned to theatre for re-resection and subsequently achieved negative margins, [e] no separate data for second primary cohort. OS overall survival, DFS disease-free survival, DSS disease-specific survival.

Study	n	Follow-up [Mean and range] /months	2-yr survival data	Other reported survival data	Positive margins % (n)	Close margins % (n)	Margin cut-offs -Close -Positive
Blanco 2013	4	Not reported	OS 100% DFS 25% DSS 100%	-	Not reported	Not reported	- -
Hans 2013	2	27 [24-30]	OS 100% DFS 100% DSS 100%	-	0% (0/2)	0% (0/2)	- -
White 2013	64	Not reported	OS 74% DFS 74% DSS 74%	-	15.6% (10/64) d	Not reported	- -
Dabas 2015	30	Median 19 [range 7 -122]b	Not reported	OS 86% DFS 56.7% (at median of 19 [7-122] months)	6.7% (2/30)	6.7% (2/30)	2mm -
Krishnan 2017	1	54 [-]	OS 100% DFS 100% DSS 100%	DFS 100% at 54 months	0% (0/1)	Not reported	- -
Meulemans 2017	30	16.9 [0-38]a	OS 73.5% DFS 75.8% DSS 93.3%	-	33% (10/30)	26.7% (8/30)	5mm -
Morisod 2017	13	20.8 [8-35]a	OS 75% DFS 92% DSS 92%	-	e	e	3mm 1mm
Paleri 2018	17c	28 [3-68]	OS 70.6% DFS 56.3% DSS 75.0% c	-	23.5% (4/17)	52.9% (9/17)	3mm -

Table 3-5: Functional outcomes and complications for studies included in The RECUT Review. [a] minimum of neck surgery for vessel ligation in all cases, [b] all inserted for the procedure, [c] laryngectomy, [d] no separate data for second primary cohort, [e] unclear if any returned to theatre, [f] no time point given for assessment, [g] no usage beyond peri-operative period, [h] assessed at 1 year, [i] author provided updated data for the 17 of the 26 patients who underwent TORS for confirmed SCC of the oropharynx

Study	n	Concurrent neck surgery	Peri-operative gastrostomies % (n)	Peri-operative tracheostomies % (n)	Long-term gastrostomies % (n)	Long-term tracheostomies % (n)	Free flap rate	Fistula rate	Return to theatre with haemorrhage rate	Additional long-term functional results
Blanco 2013	4	-	Not reported	Not reported	25.0% (1/4) [f]	0.0% (0/4) [g]	0.0% (0/4)	0.0% (0/4)	0.0% (0/4)	-
Hans 2013	2	100% (2/2)	50% (1/2)	50% (1/2)	0.0% (0/2) [g]	0.0% (0/2) [g]	100% (2/2)	0.0% (0/2)	0.0% (0/2)	-
White 2013	64	-	35.9% (23/64)	21.9% (14/64)	3.1% (2/64) [h]	Not reported	0.0% (0/64)	0.0% (0/64)	10.9% (7/64)[e]	-
Dabas 2015	30	33.3% (10/30)	16.7% (5/30)[b]	Not reported	3.3% (1/30) [f]	10.0% (3/30) [f]	0.0% (0/30)	3.3% (1/30)	13.3% (4/30)	-
Krishnan 2017	1	100% (1/1)	100.0% (1/1)	NA[c]	100.0% (1/1) [f]	NA[c]	0.0% (0/1)	100% (1/1)	0.0% (0/1)	'Soft diet with enteral supplementation'; 'Failed electrolarynx, poor voice outcomes following secondary TEP'
Meulemans 2017	30	-	20.0% (6/30)	23.3% (7/30)	20.0% (6/30) [f]	0.0% (0/30) [g]	0.0% (0/30)	3.3% (1/30)	3.3% (1/30)	-
Morisod 2017	13	100% (13/13)	Not reported	Not reported	Not reported	Not reported	[d]	[d]	[d]	[d]
Paleri 2018	17	100% (17/17)[a]	Not reported	58.8% (10/17) [i]	0.0% (0/17) [i]	0.0% (0/17) [g i]	23.5% (4/17) [i]	0.0% (0/17) [i]	11.8% (2/17) [i]	Normalcy of diet scores recorded pre-op and at 3 and 6 months.

3.2 The RECUT Study

3.2.1 Full title

transoral Robotic surgery for rECurrent tumours of the Upper aerodigestive Tract (RECUT): an international multi-centre cohort study

3.2.2 Contributions

Under supervision, the author led this study from conceptualisation, through protocol development, data collection, assimilation, analysis, visualisation and interpretation. Further, the author led on writing, reviewing and editing the text contained herein, which has been published in the Journal of the National Cancer Institute.[7]

The author is grateful to the following individuals for their contributions towards the delivery of this study and its write-up (full delineation of roles and affiliations available in **Appendix 26**):

- Arun Balaji, Helen Starmer, Sarah Stephens, Grainne Brady and Justin Roe, who reviewed and edited the manuscript, which benefitted from their insights as senior Speech and Language Therapists.
- Chris Holsinger, Surender K. Dabas, John R. de Almeida, Umamaheswar Duvvuri, Tamer A. Ghanem, Philippe Gorphe, Neil D. Gross, David Hamilton, Scott Magnuson, Brett A. Miles, Eric J. Moore, Gouri Pantvaidya, Niclas Rubek, Christian Simon, Vincent Vander Poorten, who, in their roles as Principal Investigators at their institutions, facilitated local registration of the study and the contribution of anonymised patient data, as per the study protocol. Further, these individuals reviewed and edited the manuscript, which benefitted from their insights as senior head and neck surgeons.
- Avinash Beharry, Alec T. Bonifer, Gregoire D'Andréa, Peter Floros, Chareeni Kurukulasuriya, Mikkel Hjordt Holm Larsen, Daniel J. Lin, Jeroen Meulemans, Scott Roof, Anand Subash, Michael C. Topf, Kathryn M. Van Abel, Evan S. Walgama, who, in their roles as Co-Investigators, facilitated local registration of the study and the contribution of anonymised patient data, as per the study protocol. Further, these individuals reviewed and edited the manuscript, which benefitted from their experiences in head and neck surgery.
- Emily Greenlay and Laura Potts, who supervised the statistical analysis in their roles as senior statisticians at The Royal Marsden Clinical Trials Unit.
- Vinidh Paleri and Kevin Harrington, who supervised the work from conceptualisation to production and approval of the final report.

3.2.3 Abstract *[250 words]*

Background

Transoral robotic surgery (TORS) is an emerging minimally-invasive surgical treatment for residual, recurrent and new primary head and neck cancers (HNC) in previously irradiated fields, with limited evidence for its oncological effectiveness.

Methods

A retrospective observational cohort study of consecutive cases performed in 16 high-volume international centres before August 2018 was conducted. Overall (OS), disease-free (DFS), disease-specific survivals (DSS) and local control (LC) were calculated using Kaplan-Meier estimates, with subgroups compared using log-rank tests and Cox proportional hazards modelling for multivariable analysis. Maximally-selected rank statistics determined the cut-point for closest surgical resection margin based on LC.

Results

Data for 278 eligible cases were analysed, with median follow-up of 38.5 months. Two-year and five-year outcomes were 69.0% and 62.2% for LC, 71.8% and 49.8% for OS, 47.2% and 35.7% for DFS, and 78.7% and 59.1% for DSS. The most discriminating margin cut-point was 1.0 mm; the 2-year LC was 80.9% above and 54.2% below or equal to 1.0 mm. Increasing age, current smoking, primary tumour classification and narrow surgical margins (≤1.0 mm) were significantly associated with lower OS. Haemorrhage with return to theatre was seen in 8.1% (n=22/272) and 30-day mortality was 1.8% (n=5/272). At one-year, 10.8% (n=21/195) used tracheostomies, 33.8% (n=66/195) used gastrostomies and 66.3% (n=53/80) had maintained or improved normalcy of diet scores.

Conclusions

Data from international centres show TORS to treat HNCs in previously irradiated fields yields favourable outcomes for LC and survival. Where feasible, TORS should be considered the preferred surgical treatment in the salvage setting.

3.2.4 Aim

The RECUT Study aims to report the oncological and functional outcomes in patients undergoing TORS for the treatment of residual, recurrent and new primary HNC in previously irradiated fields. It also aims to explore the importance of surgical resection margins in this cohort.

3.2.5 Methods

3.2.5.1 Ethical considerations and regulatory approvals

The protocol was reviewed and approved by the study sponsor (The Royal Marsden NHS Foundation Trust), East of England - Cambridge Central Research Ethics Committee (19/EE/0307) and the Health Research Authority (IRAS268830). Additional approvals were obtained locally as required. The Study was registered at clinicaltrials.gov (NCT04673929). This study report has been prepared with reference to the STROBE checklist for cohort studies (STrengthening the Reporting of OBservational studies in Epidemiology).

3.2.5.2 Study design and setting

A retrospective observational cohort study was undertaken in 16 international tertiary referral units across North America, Europe and Asia. Centres with a high volume practice and known to use TORS in the management of HNC were invited to participate.

3.2.5.3 Participants

Eligible patients were aged over 18, with a history of previous HNC treated with (chemo)radiotherapy, who subsequently experienced a residual, recurrent or new primary HNC which was treated using TORS.

Patients were not eligible if the TORS was performed only for diagnostic purposes, or to treat nasopharyngeal or thyroid cancers.

Practices for identifying patients varied by contributing centre but it was stipulated that consecutive eligible patients must be submitted to limit selection bias. All subjects had their TORS performed prior to 1 August 2018, with data submission only accepted after 1 August 2020, to allow an appropriate period for the primary outcome event.

3.2.5.4 Data collection

Data were collected by participating sites onto a standardised electronic case report form, created using Excel software (Microsoft Corporation, Washington, USA). Restricted data fields and data validation were used to improve data completeness and homogeneity. Missing or ambiguous data were queried and the data point excluded from the relevant analysis if unresolved. ACE-27 scores were calculated for comorbidities and Performance Status Scale for Head & Neck Cancer Patients - Normalcy of Diet (PSS-HN NoD)[184] scores reported swallow function.

3.2.5.5 Data analysis

The primary outcome was local control (LC) at 2 years. No a priori sample size calculation was performed. Categorical variables were compared using the Fisher's exact test and continuous variables using the Wilcoxon test. Time-to-event outcomes [overall (OS), disease-free (DFS), disease-specific survivals (DSS) and local control (LC)] were estimated using the Kaplan-Meier (KM) method, with subgroups compared using log-rank

tests. Endpoints were as follows: death from any cause for OS; diagnosis of residual/recurrent local, regional or distant disease or death from any cause for DFS; death from residual/recurrent disease for DSS; and diagnosis of local residual/recurrent disease for LC. Analyses used the 'survival' and 'survminer' packages in R. A competing events sensitivity analysis was completed for sub-groups showing a significant difference in the primary endpoint (LC). Regional recurrence, distant recurrence and death from any cause were classed as competing events and analysed with Gray's test using the 'cmprsk' package in R.

Prognostic factors for time-to-event outcomes were assessed using Cox proportional hazards regression analysis. The proportional hazards assumption was assessed using Schoenfeld residuals and visual assessment of the KM curves. Time varying coefficients were further assessed using a Log(time) interaction, which was adopted if returning a significant, or close to significant, result. The multivariable model was constructed using a backward stepwise elimination process. The initial model was built with variables found to be significant on univariable analysis. At each stage, the least significant variable above the threshold was eliminated until only significant variables remained using a P value threshold of <0.05 throughout to denote significance.

3.2.5.6 Surgical margin analysis

Centres were asked for the nearest mucosal and deep surgical resection margins from the main TORS specimen, as recorded on the histopathology report. Positive margins were considered to be equal to 0 mm. For patients who had both mucosal and deep margins reported, the lowest millimetre value was recorded. Where further oncological resection margins were taken, they were orientated and combined with the main specimen resection margin wherever possible. Patient-side biopsies, taken primarily to provide additional information to the MDT/tumour board that the tumour bed was free from disease (commonly referred to 'margins' but not intended as oncological resections), were not considered as it was felt the size and position of the sampled tissue could not be reliably combined with data from the main resection. Data regarding intraoperative frozen sections were not specifically collected, rather the resultant reports and resection specimens were interpreted according to the methodology above.

Two methods were then used to investigate the optimal cut-point of this closest margin, to dichotomise our cohort with the greatest differentiation in LC : maximally selected rank statistics using the full survival data ('maxstat' package in R); and receiver operator characteristic (ROC) analysis at two years using Youden's index ('ROCit' package in R).

3.2.5.7 The impact of free flap reconstruction on surgical margins

To investigate the relationship between free flap reconstruction and the closest surgical margins at TORS, a 1:1 propensity score matching (PSM) was conducted using the optimal method and the 'MatchIt' package in R. The following variables were chosen to match groups based on potential influence on pre-operative decision making: clinical tumour classification; incidence of concurrent neck surgery; and comorbidity score (ACE-27). The mean closest surgical resection margins for each subgroup were then compared using a Student's t-test.

All analyses were performed using RStudio statistical software (RStudio, PBC, Boston, MA, USA).

3.2.5.8 Deviations from the protocol

The following deviations and clarifications from the published protocol were made: death from any cause was added as an endpoint for DFS; local control is reported as the primary outcome and to calculate the margin cut-off, in place of disease-free survival. This decision was made prior to any analysis as it was felt it would better reflect the effectiveness of TORS as a treatment for local disease. Confidence intervals were used in place of prediction intervals for the Kaplan-Meier estimates.

3.2.6 Results

3.2.6.1 Characteristics of the Study Population

3.2.6.1.1 Centres and participants

Data from 306 cases from the 16 participating centres (**Figure 3-14**) were submitted and reviewed for eligibility. Following strict application of the eligibility criteria, 278 cases were eligible for analysis (median 13 cases per centre; range 3-49; interquartile range [IQR] 7.25-23.75). One centre maintained reliable records for oropharyngeal cancers only, and so only these cases were contributed to ensure data integrity. The following cases were screened out on central eligibility check: no previous head and neck radiotherapy (24); no confirmed malignancy on either pre- or post-TORS histology (three) and a case of nasopharyngeal cancer (one). The year of the first included patient from each participating centre ranged from 2007 to 2017 (median 2013).

The median age for all subjects was 61 (range 38 to 93; IQR 9.5 to 46.0) and 20.1% were female (n=56/279). The median follow-up for survivors was 38.5 months (range 0.1 to 107.5; IQR 23.5 to 60.0) and for all subjects was 28.5 months (range 0.1 to 107.5; IQR 13.7 to 48.7).

Clinico-pathological characteristics and peri-surgical management are shown in **Table 3-6** (and by subgroups in **Table 3-7**). Histopathological and functional outcomes following TORS, presented for all subjects and by subgroups, are shown in **Table 3-8**. **Table 3-9** gives details of the previous HNCs for the cohort. The majority had had a single previous HNC (86%, n=240) with 11.5% having had two previous cancers (n=32) and 2.5% having had three (n=7).

3.2.6.1.2 Patterns of disease

The majority of cancers in this cohort were oropharyngeal, representing 93.8% (n=259/276), with tongue base cancers constituting over half of all subjects (52.9%, n=146/276). Neck disease was identified pre-operatively in 21.5% of cases (n=58/270) with 60.4% (n=168/278) undergoing some form of neck surgery alongside TORS.

The median time since completion of treatment for the previous HNC was 761.5 days, with 29.3% (n=79/270) of surgeries performed within 1 year and 13.0% (n=35/270) being more than 10 years after initial treatment; 8.5% (n=23/272) were recorded as new primary disease within 5 years of the previous cancer but at a separate site.

3.2.6.2 Survival outcomes

Time-to-event analyses are presented for all subjects (**Figure 3-16**), by margin status (**Figure 3-17**), by HPV status in oropharyngeal disease (**Figure 3-19**), and by timing of TORS relative to previous HNC (**Figure 3-20**). For all subjects, the 2-year LC was 69.0% (95% CI [63.2, 75.3]) and 5-year LC was 62.2% (95% CI [55.6, 69.5]). Further 2- and 5-year outcomes are summarised in **Table 3-12**. Over the study period, there were 83 deaths from disease, 32 deaths from other causes, 82 local recurrences, 24 regional recurrences and 26 patients with distant metastases.

On log-rank test, there was no significant difference in LC by HPV status in oropharyngeal disease (p=0.43) or by timing of TORS relative to previous HNC (p=0.51). However, there was a significant difference in LC by margin status (p<0.001). Sensitivity analysis corroborated this significance for LC (Cox hazard ratio (HR) 2.87; 95% CI [1.66, 4.96]; p<0.001) and showed no significant difference in competing events (Gray's HR 0.97; 95% CI [0.57, 1.66]; p=0.90).

Following TORS, 6.1% of patients had further disease recurrence that was subsequently successfully treated to leave them disease-free (n=17/278): 10 were treated for local disease, three for regional metastases and four for distant metastases.

3.2.6.2.1 Prognosticators of time-to-event outcomes

Results from univariable analysis are shown in **Table 3-10** and multivariable analysis in **Table 3-11**. The closest surgical resection margin was the only factor to remain significant for all four time-to-event scenarios, including LC (HR 2.87 (95% CI [1.66, 4.96]; p<0.001) and OS (HR 2.51 (95% CI [1.56, 4.03]; p<0.001).

3.2.6.3 Complications

Data on peri-operative complications for TORS were available for 97.8% (n=272). The post-TORS haemorrhage rate, requiring return to theatre, was 8.1% (n=22/272) with a single case of haemorrhage resulting in death. The overall mortality related to the TORS procedures was 1.8% (n=5/272) with the remaining four patients dying from chest sepsis (n=3) and a stroke (n=1) within 30 days of surgery.

The median time to post-operative haemorrhage was 6 days (range 1 to 42; IQR 2 to 8; data available for 19 of 22 bleeds).

Fistulae were reported in 0.7% (n=2/272) of all patients. Flap failure was seen in 5.4% (n=3/56) of those undergoing free-flap reconstruction. Overall, no notable complications were reported in 89.0% (n=243/272) of patients.

3.2.6.4 Surgical resection margin analysis

Closest surgical resection margin data were available for 194 cases (69.8% of 278 cohort). The closest surgical resection margin was reported as mucosal in 24.7% (n=48), deep in 49.0% (n=95) and equal mucosal/deep in 26.3% (n=51). The positive margin rate was 25.3% (n=49).

Most margins were reported to whole millimetre values, except 13 cases which were reported to one decimal place (**Figure 3-21**). The most discriminating cut-point for surgical resection margin was found to be ≤1.0 mm by both methods [maxstat 3.919 and AUC 0.679 (95% CI [0.589, 0.769]); sensitivity 69.8% (95% CI [55.7, 81.7]), specificity 62.8% (95% CI [52.2, 72.5])]. The 2-year LC around this cut-point was 80.9% for >1.0 mm and 54.2% for ≤1.0 mm.

By way of sensitivity analysis, and to explore the implications of selecting different margin cut-points, KM analyses were produced for all whole millimetre values from 0 to 5 mm (**Figure 3-22** to **Figure 3-26**).

When the closest surgical resection margin was reported as positive (equal to 0 mm) 2-year LC was 48.2% (95% CI [34.9, 66.5]) versus 74.6% (95% CI [67.2, 82.8]) for all higher values. The greatest separation of 2-year LC was around a cut point of 1.0 mm, with survival of 80.9% (95% CI [72.8, 89.8]) more than 1.0 mm and 54.2% (95% CI [44.1, 66.1]) no more than 1.0 mm (**Figure 3-17**). Increasing the cut-point incrementally at millimetre intervals had the effect of reducing the separation of the 2-year LC outcomes. The highest 2-year LC was seen above a cut-point of 3mm, though it should be recognised that the number of patients contributing data at these greater closest surgical resection margin cut-points is limited, and is reflected in the widening confidence intervals with notable overlaps at these higher cut-point values.

3.2.6.5 The impact of free flap reconstruction on surgical margins

After PSM for the chosen variables, 32 cases undergoing free flap reconstruction were matched with 32 cases undergoing no reconstruction. PSM reduced the standardised mean difference distance score by 66.9% from 1.520 to 0.503 (**Figure 3-27**). The mean closest surgical resection margin for those undergoing free flap reconstruction was 2.0 mm (SD 1.92) compared with 2.2 mm (SD 1.98) for no reconstruction, which was not significantly different (p=0.6816).

3.2.6.6 Functional outcomes

3.2.6.6.1 Peri-operative

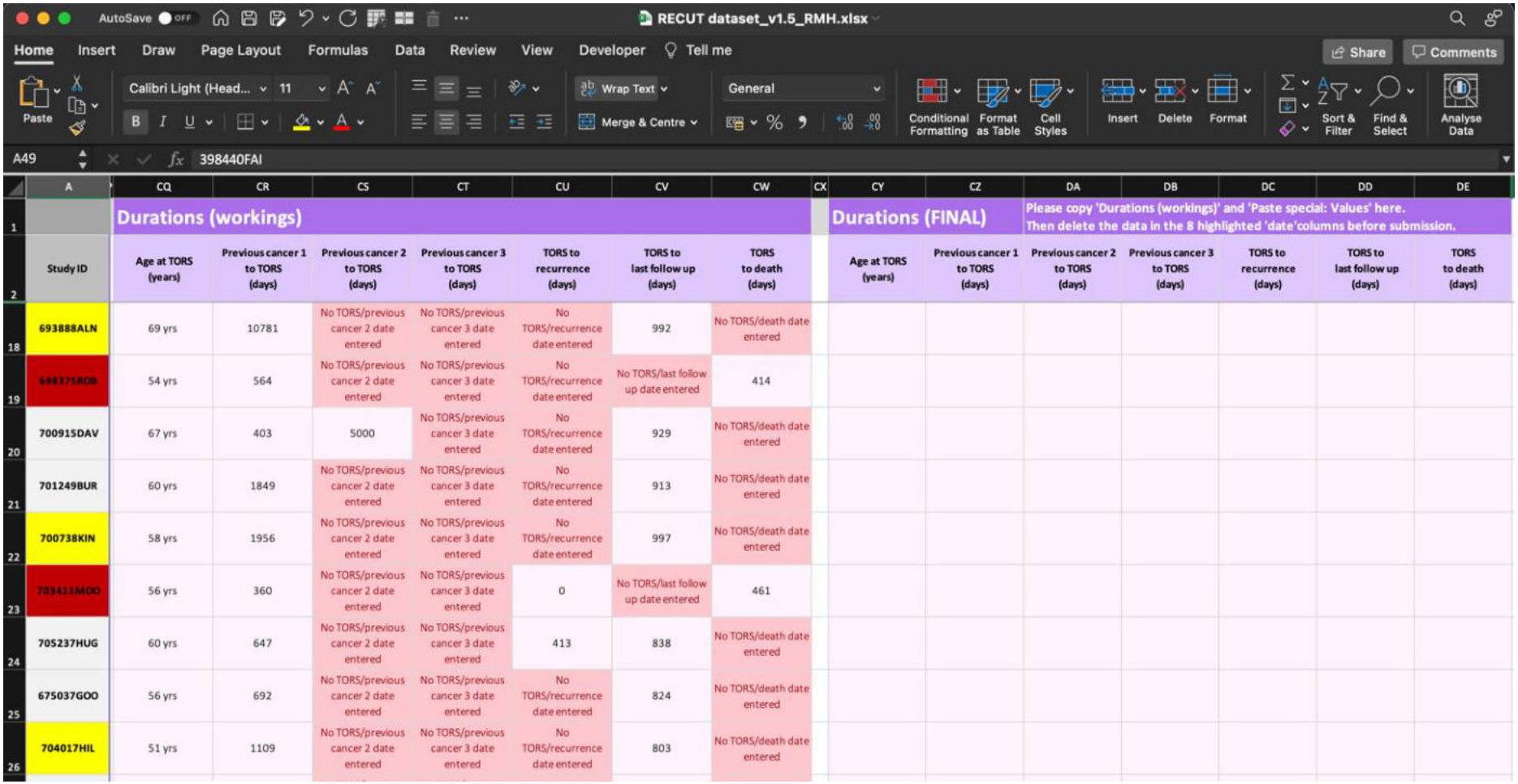
Peri-operative tracheostomy and gastrostomy rates are shown in **Table 3-8**. Tracheostomies were used at the time of TORS in 37.9% of patients (n=105/277) and gastrostomies in 39.2% (n=109/278). Overall rates at 1 year for all subjects were 10.8% (n=21/195) for tracheostomy usage and 33.8% (n=66/195) for gastrostomy usage.

At the time of last follow-up, 74.7% were tolerating soft chewable foods or better (PSS-HN NoD score ≥50, n=68/91) and 4.4% were taking no oral diet (PSS-HN NoD score =0, n=4/91) (median follow-up 43.0 months; range 0.1 to 107.5; IQR 26.5 to 62.3).

3.2.6.6.2 Outcomes in patients disease-free at one year

There were 188 patients with no evidence of local recurrence who were followed up for over 1 year. For these patients, the change in tracheostomy rates, gastrostomy rates and PSS-HN NoD scores at baseline and at 1 year were available for 90.4% (n=170/188) and 42.6% (n=80/188), respectively. The change in status for these variables are visualised in Sankey plots in **Figure 3-18**. The majority (92.9%) of patients were tracheostomy-free at 1 year, 67.6% were gastrostomy-free and 73.8% were tolerating a soft diet or better on PSS-HN NoD score following TORS (score ≥50).

Figure 3-14: International centres contributing to The RECUT Study.



	A	CQ	CR	CS	CT	CU	CV	CW	CX	CY	CZ	DA	DB	DC	DD	DE
1		Durations (workings)								Durations (FINAL)		Please copy 'Durations (workings)' and 'Paste special: Values' here. Then delete the data in the 8 highlighted 'date'columns before submission.				
2	Study ID	Age at TORS (years)	Previous cancer 1 to TORS (days)	Previous cancer 2 to TORS (days)	Previous cancer 3 to TORS (days)	TORS to recurrence (days)	TORS to last follow up (days)	TORS to death (days)		Age at TORS (years)	Previous cancer 1 to TORS (days)	Previous cancer 2 to TORS (days)	Previous cancer 3 to TORS (days)	TORS to recurrence (days)	TORS to last follow up (days)	TORS to death (days)
18	693888ALN	69 yrs	10781	No TORS/previous cancer 2 date entered	No TORS/previous cancer 3 date entered	No TORS/recurrence date entered	992	No TORS/death date entered								
19	698375ROB	54 yrs	564	No TORS/previous cancer 2 date entered	No TORS/previous cancer 3 date entered	No TORS/recurrence date entered	No TORS/last follow up date entered	414								
20	700915DAV	67 yrs	403	5000	No TORS/previous cancer 3 date entered	No TORS/recurrence date entered	929	No TORS/death date entered								
21	701249BUR	60 yrs	1849	No TORS/previous cancer 2 date entered	No TORS/previous cancer 3 date entered	No TORS/recurrence date entered	913	No TORS/death date entered								
22	700738KIN	58 yrs	1956	No TORS/previous cancer 2 date entered	No TORS/previous cancer 3 date entered	No TORS/recurrence date entered	997	No TORS/death date entered								
23	703411MOO	56 yrs	360	No TORS/previous cancer 2 date entered	No TORS/previous cancer 3 date entered	0	No TORS/last follow up date entered	461								
24	705237HUG	60 yrs	647	No TORS/previous cancer 2 date entered	No TORS/previous cancer 3 date entered	413	838	No TORS/death date entered								
25	675037GOO	56 yrs	692	No TORS/previous cancer 2 date entered	No TORS/previous cancer 3 date entered	No TORS/recurrence date entered	824	No TORS/death date entered								
26	704017HIL	51 yrs	1109	No TORS/previous cancer 2 date entered	No TORS/previous cancer 3 date entered	No TORS/recurrence date entered	803	No TORS/death date entered								

Figure 3-15: Screenshot of the Excel Data Tool used in The RECUT Study. Columns shown display the calculations made from the entered dates. This information is then transferred to the area on the right and then the dates removed to preserve the durations but remove identifiable data.

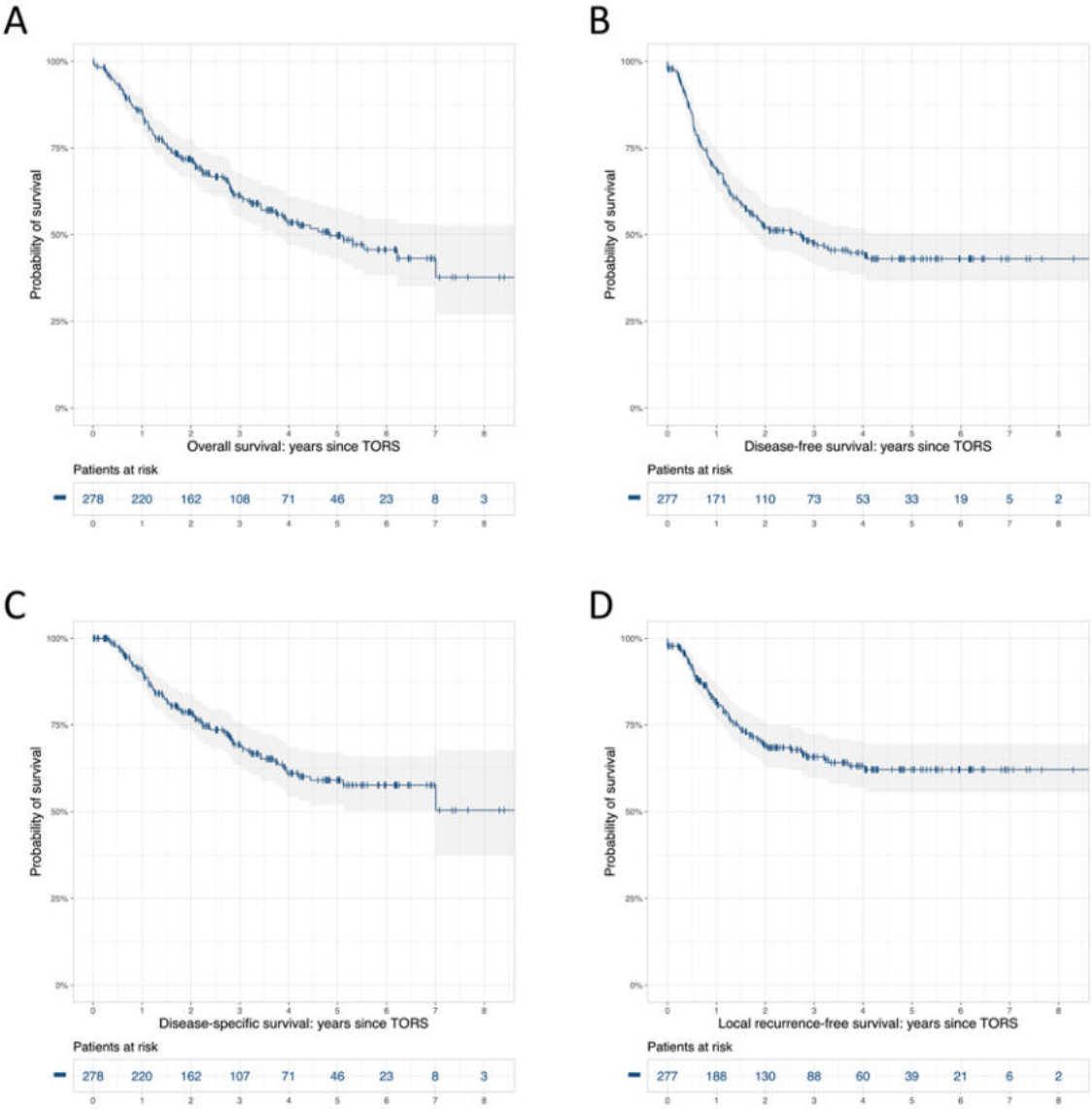


Figure 3-16: Kaplan-Meier survival estimates for all subjects in the RECUT Study. (A, overall survival; B, disease-free survival; C, disease-specific survival; D, local recurrence-free survival).

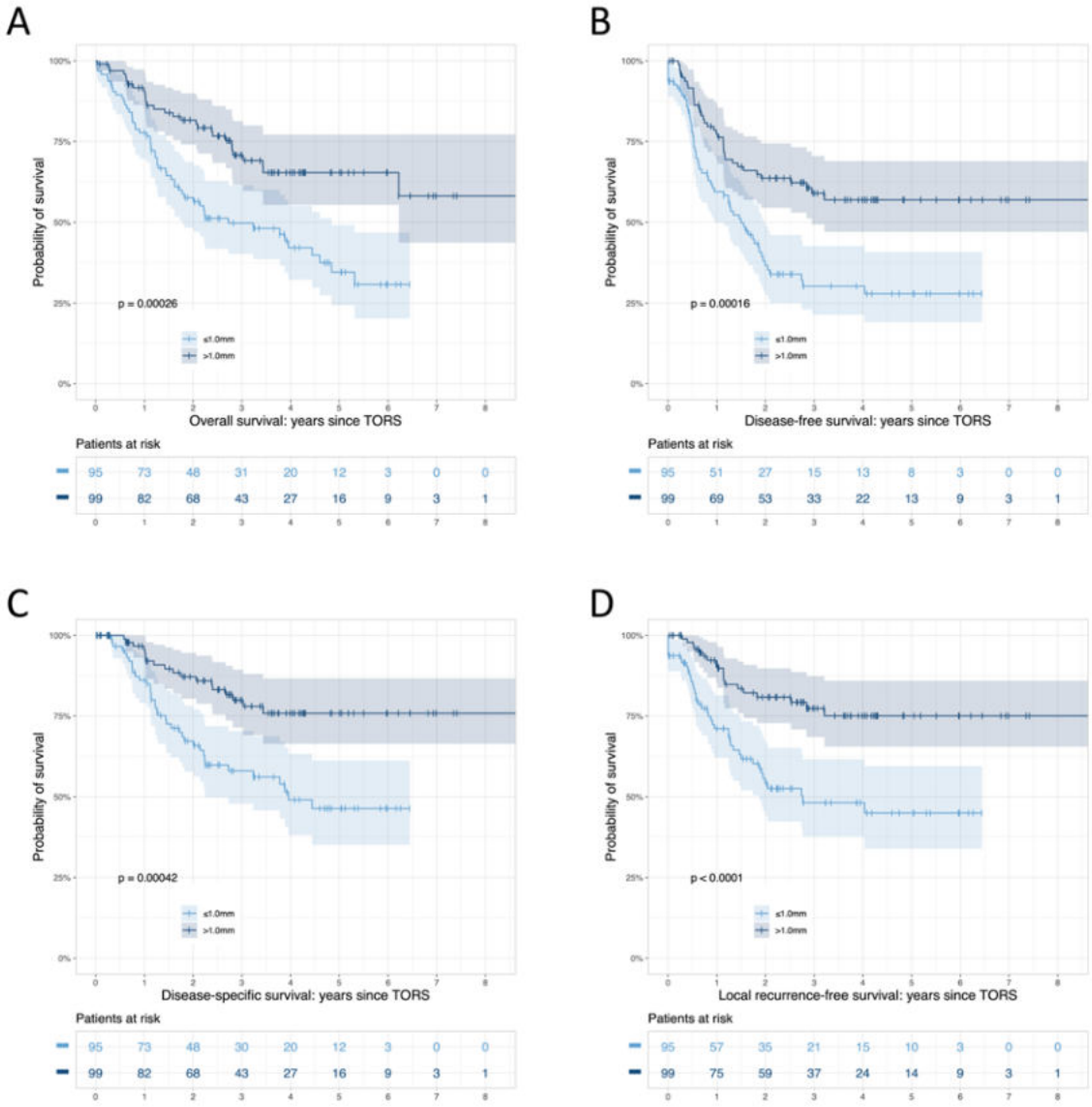


Figure 3-17: Kaplan-Meier survival estimates around a 1.0 mm margin cut-point in The RECUT Study (p value given for log rank test).
(A, overall survival; B, disease-free survival; C, disease-specific survival; D, local recurrence-free survival).

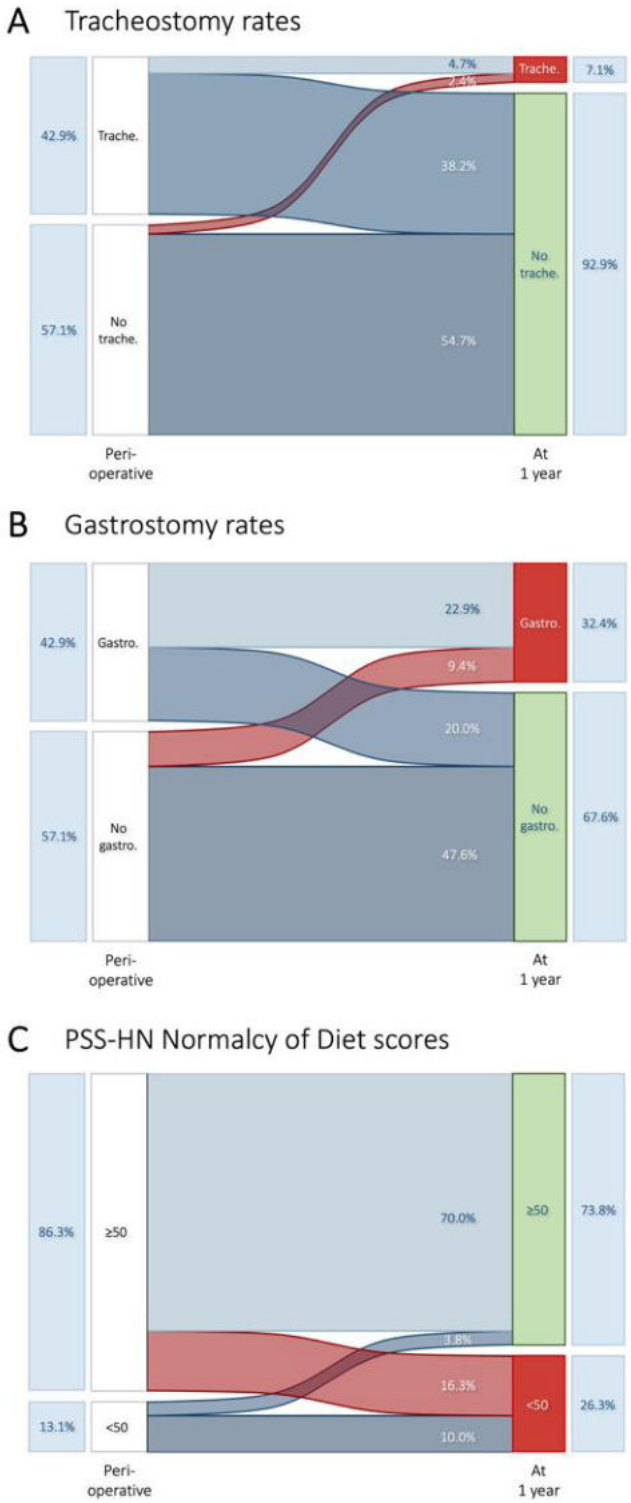


Figure 3-18: Sankey plots showing functional outcomes for patients free from local disease recurrence at baseline and at one year follow-up in The RECUT Study. (A) tracheostomy rates, (B) gastrostomy rates, and (C) PSS-HN NoD scores. Red highlighting indicates patients who had tracheostomies or gastrostomies placed at a time following the TORS procedure, or who had worsening of PSS-HN NoD scores. (Trache is tracheostomy; gastro is gastrostomy)

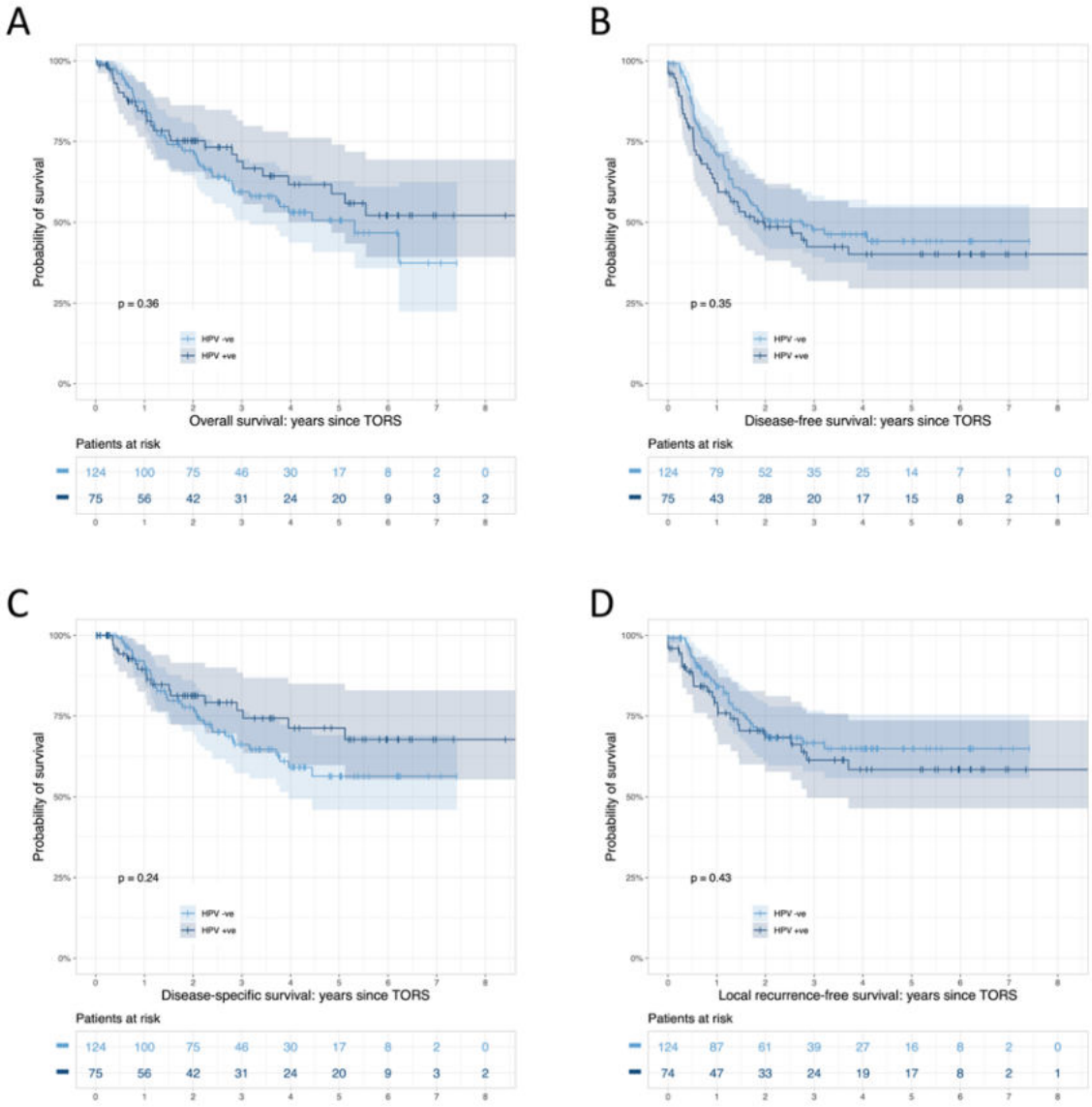


Figure 3-19: Kaplan-Meier survival estimates by HPV status for oropharyngeal SCCs in The RECUT Study (p value given for log rank test).
(A, overall survival; B, disease-free survival; C, disease-specific survival; D, local recurrence-free survival).

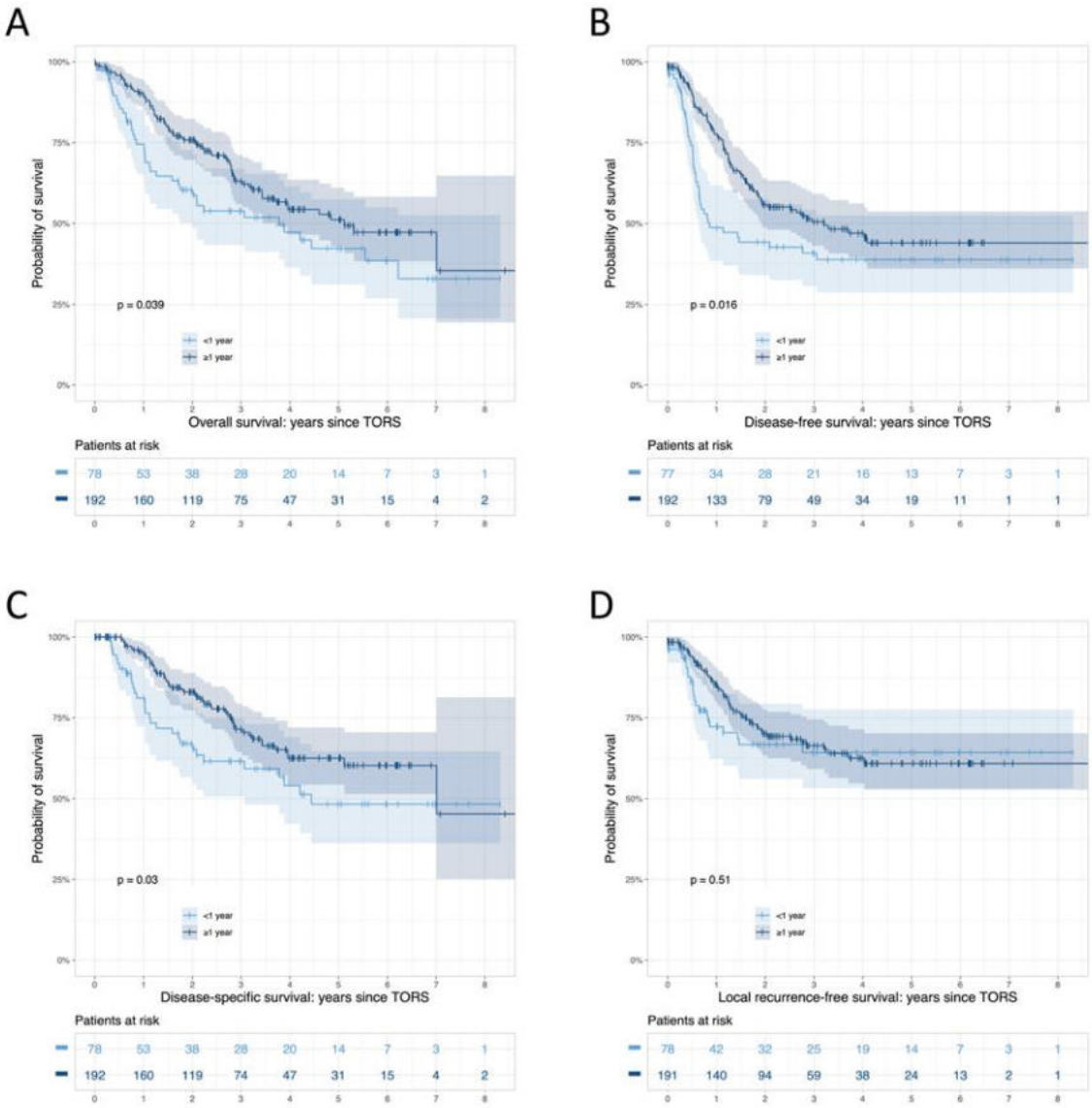


Figure 3-20: Kaplan-Meier survival estimates by timing of TORS since previous HNC in The RECUT Study (p value given for log rank test).
(A, overall survival; B, disease-free survival; C, disease-specific survival; D, local recurrence-free survival).

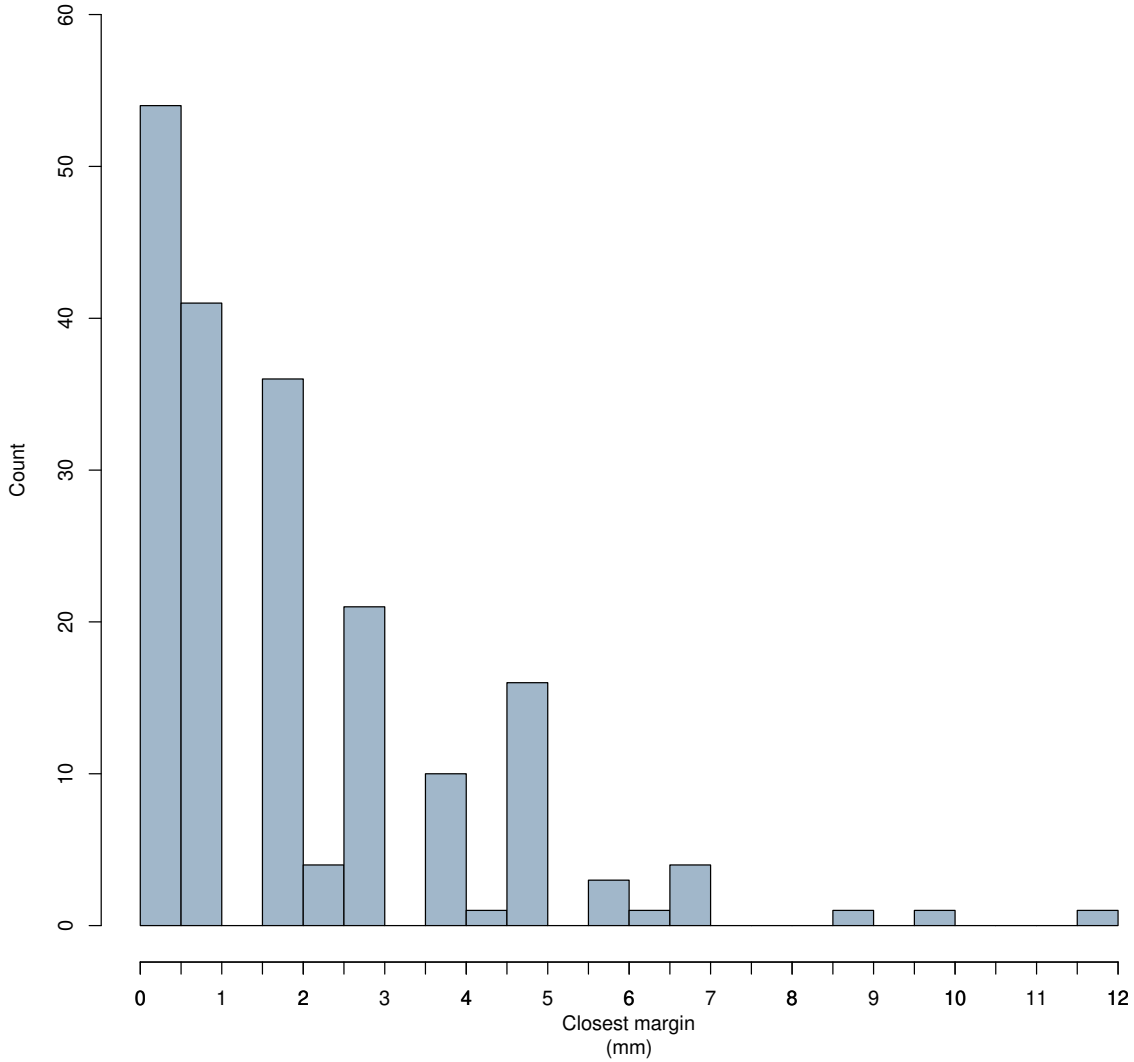


Figure 3-21: Histogram of closest surgical resection margin values for all subjects in The RECUT Study.

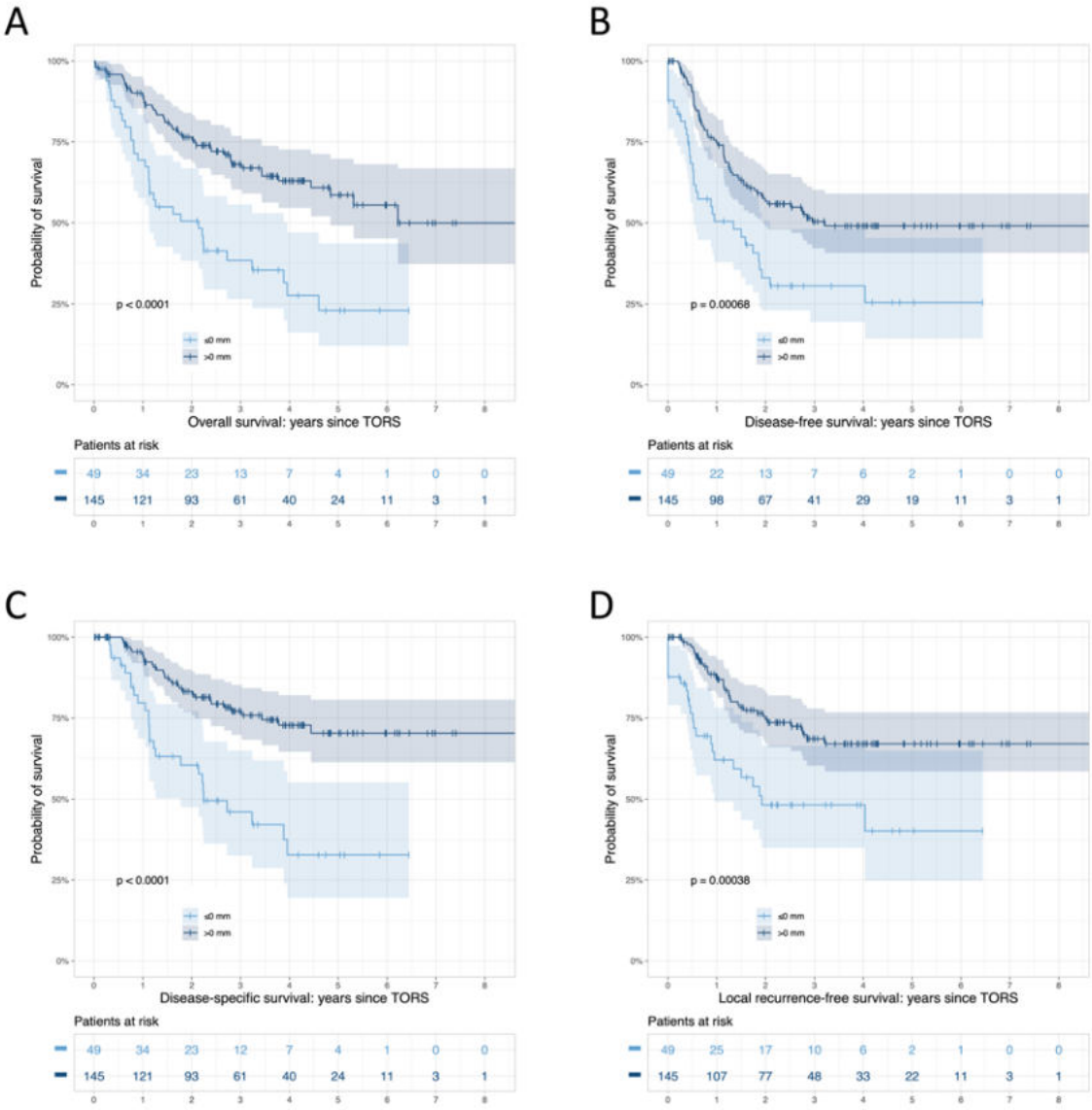


Figure 3-22: Kaplan-Meier survival estimates around a 0 mm margin cut-point in The RECUT Study (p value given for log rank test).
(A, overall survival; B, disease-free survival; C, disease-specific survival; D, local recurrence-free survival).

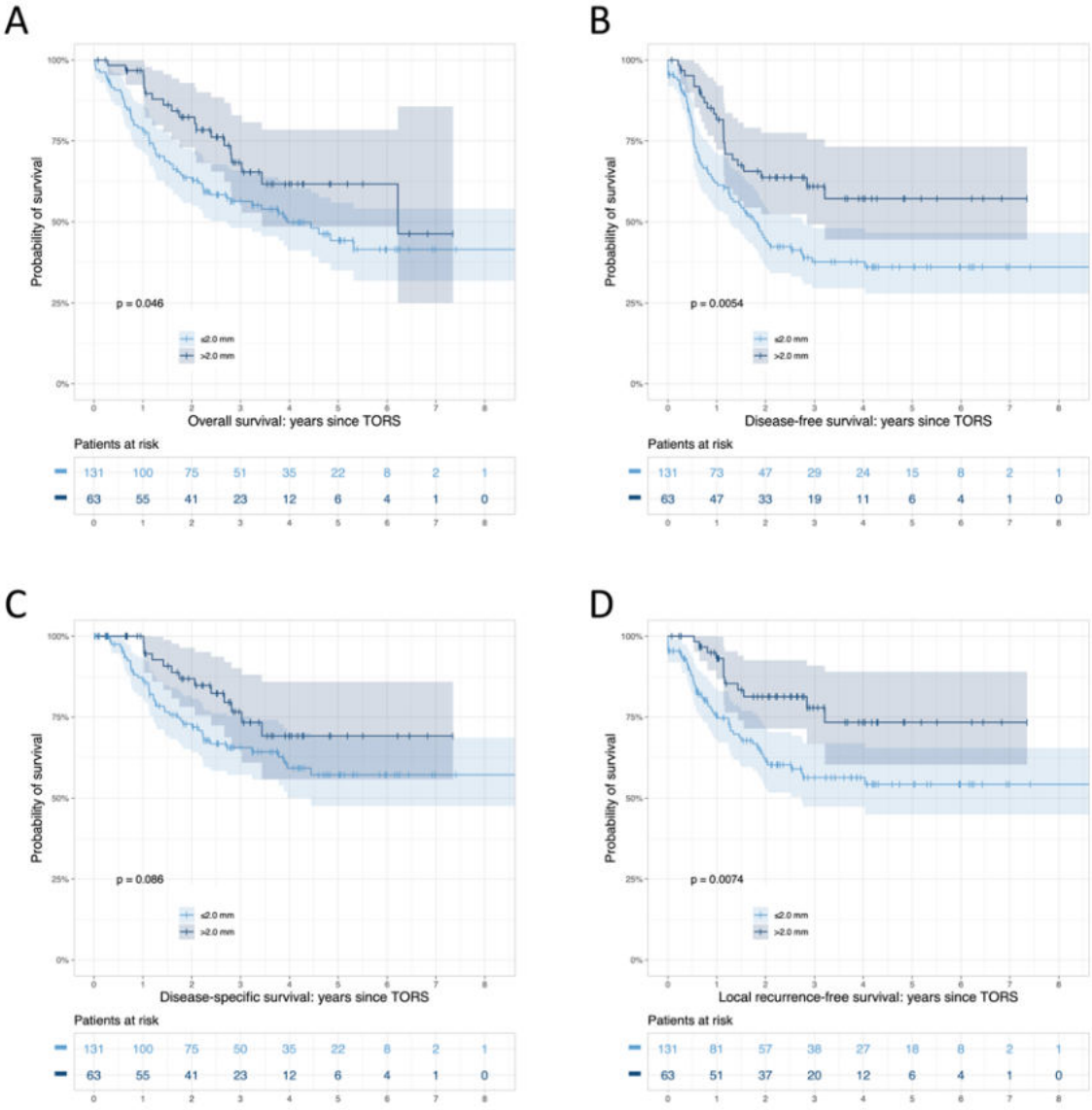


Figure 3-23: Kaplan-Meier survival estimates around a 2 mm margin cut-point in The RECUT Study (p value given for log rank test).
(A, overall survival; B, disease-free survival; C, disease-specific survival; D, local recurrence-free survival).

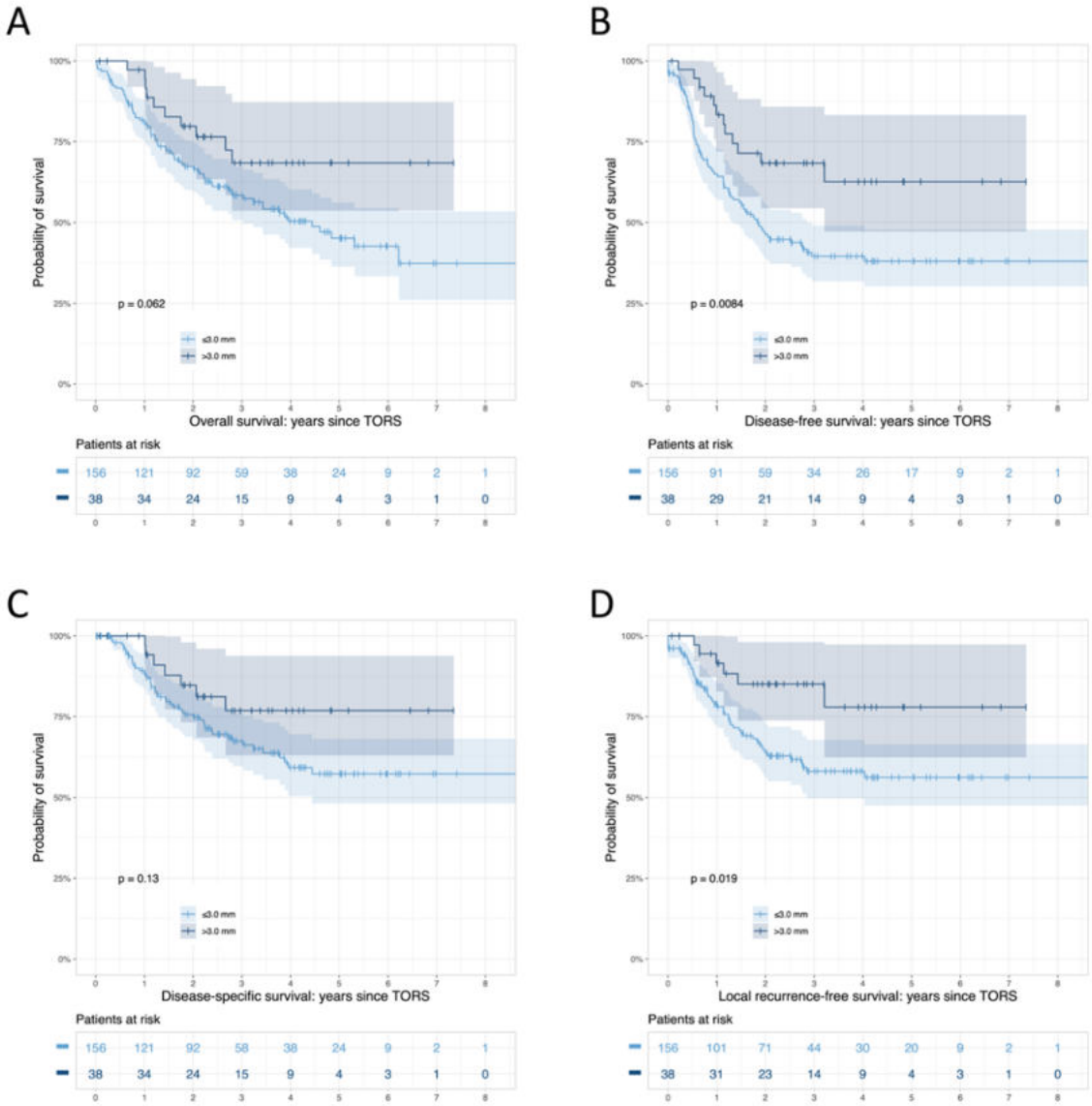


Figure 3-24: Kaplan-Meier survival estimates around a 3 mm margin cut-point in The RECUT Study (p value given for log rank test).
(A, overall survival; B, disease-free survival; C, disease-specific survival; D, local recurrence-free survival).

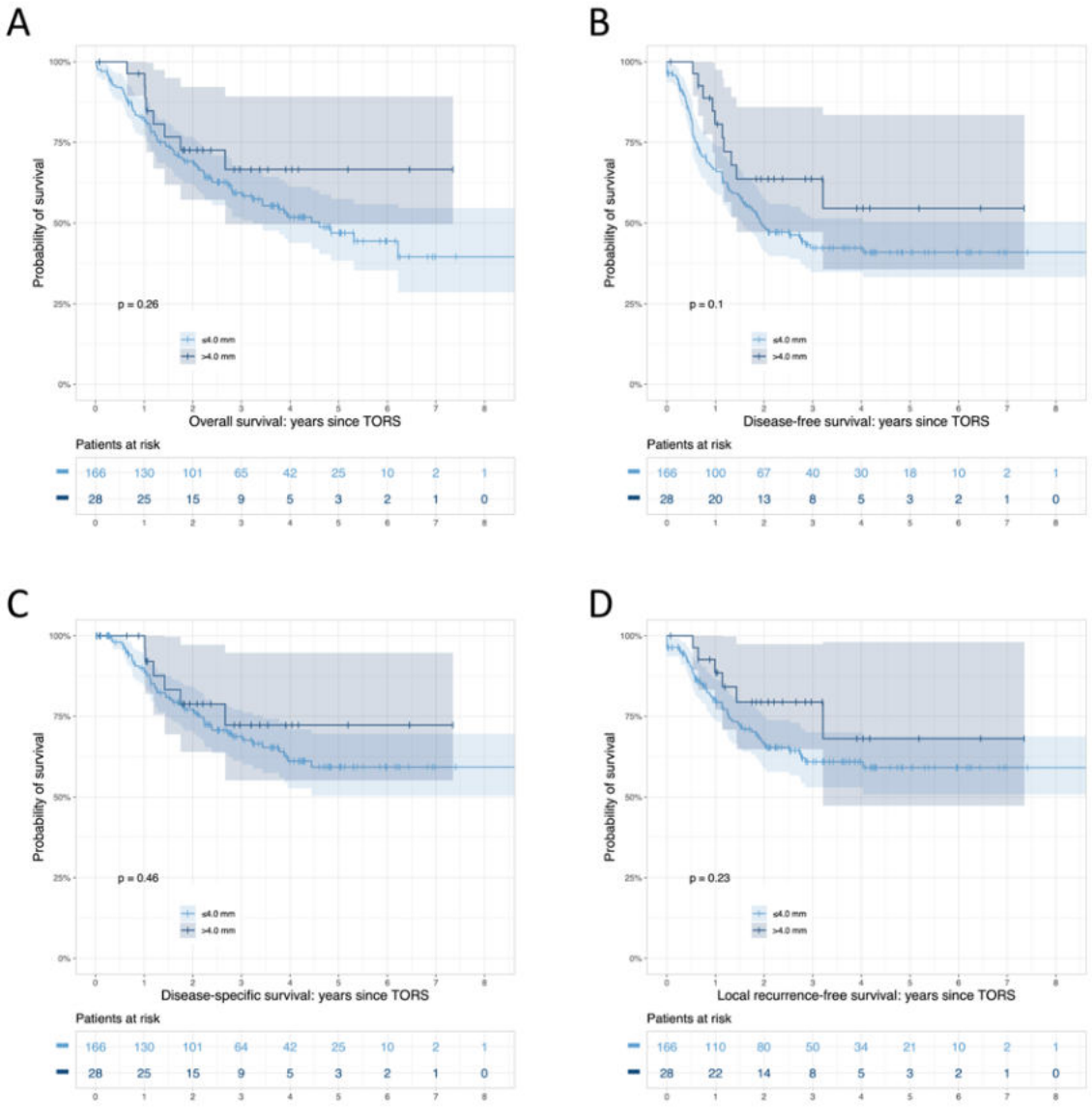


Figure 3-25: Kaplan-Meier survival estimates around a 4 mm margin cut-point in The RECUT Study (p value given for log rank test).
(A, overall survival; B, disease-free survival; C, disease-specific survival; D, local recurrence-free survival).

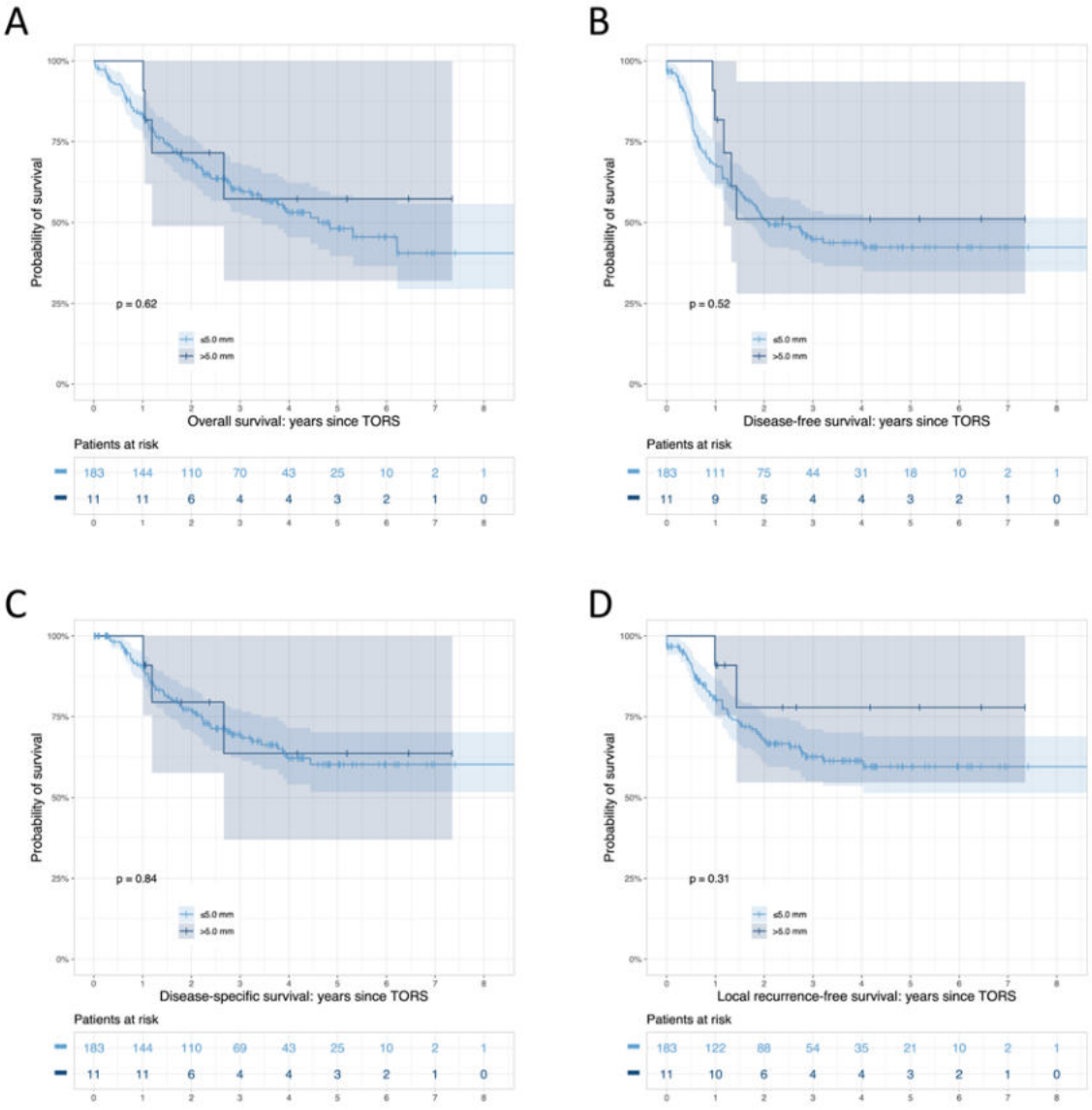


Figure 3-26: Kaplan-Meier survival estimates around a 5 mm margin cut-point in The RECUT Study (p value given for log rank test).
(A, overall survival; B, disease-free survival; C, disease-specific survival; D, local recurrence-free survival).

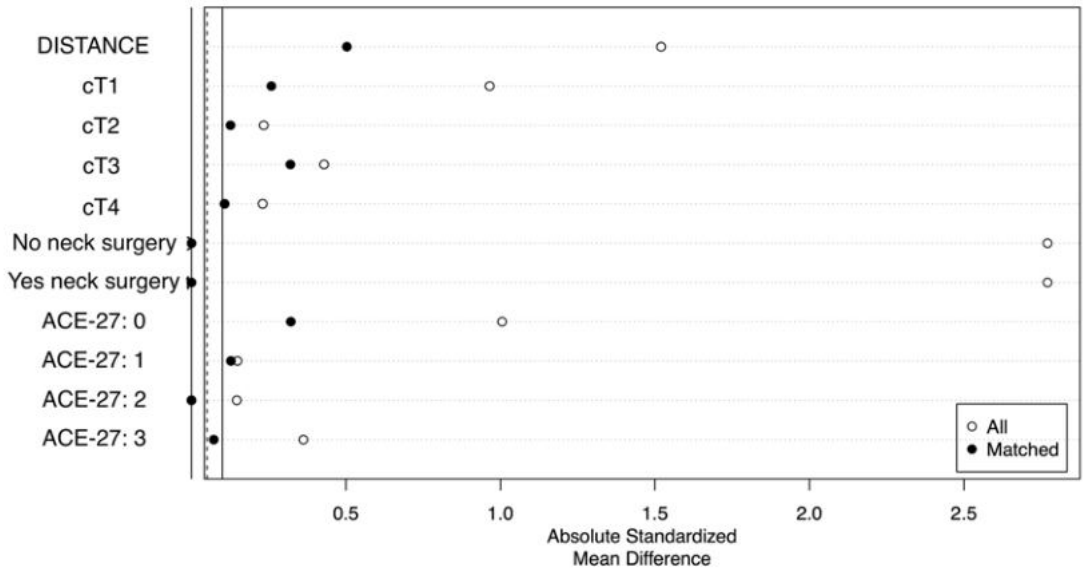


Figure 3-27: Propensity Score Matching showing reduction of standardised mean difference distance score for all free flap subjects in The RECUT Study (white dots) and matched patients not undergoing free flap (black dots).

Table 3-6: Details of clinico-pathological characteristics, peri-operative management and non-surgical oncological therapies, presented for all subjects in the RECUT Study.
**compared as continuous data*

Category	Variable	Classification	n	%
General	**Age***	Data available	278	100
		31 to 40	3	1.1
		41 to 50	23	8.3
		51 to 60	99	35.6
		61 to 70	94	33.8
		71 to 80	46	16.5
		81 to 90	12	4.3
		91 to 100	1	0.4
	Sex	Data available	278	100
		Female	56	20.1
		Male	222	79.9
	Smoking	Data available	231	83.1
		Never smoker	61	26.4
		Ex-smoker	105	45.5
		Current smoker	65	28.1
	Alcohol	Data available	243	87.4
		No alcohol	107	44.0
		Light alcohol	87	35.8
		Heavy alcohol	49	20.2
	Comorbidities (ACE-27)	Data available	220	79.1
		0	76	34.5
		1	79	35.9
		2	40	18.2
		3	25	11.4
Previous HNCs	**Number of previous HNC**	Data available	278	100
		1	239	86.0
		2	32	11.5
		3	7	2.5
	RT to primary site	Data available	271	97.5
		Yes	270	99.6
		No	1	0.4
	RT to neck	Data available	249	89.6
		Yes	242	97.2
		No	7	2.8
TORS	**Timing by diagnosis**	Data available	272	97.8
		Residual (<12 months)	83	30.5
		Recurrence (12 months to 5 years)	101	37.1
		New primary (>5 years)	65	23.9
		New primary (<5 years, separate site)	23	8.5
	Timing by time to surgery*	Data available	270	97.1
		0 to 1yr	79	29.3
		1 to 2yrs	53	19.6
		2 to 3yrs	37	13.7
		3 to 4yrs	16	5.9
		4 to 5yrs	16	5.9
		5 to 6yrs	13	4.8
		6 to 7yrs	4	1.5
		7 to 8yrs	7	2.6
		8 to 9yrs	6	2.2
		9 to 10yrs	4	1.5
		> 10yrs	35	13.0
		Median (days)	761.5	
	Primary site	Data available	276	99.3
		Nasopharynx	0	0
		Tonsil	88	31.9
		Tongue base	146	52.9
		Soft palate	11	4.0
		Posterior oropharyngeal wall	14	5.1
		Piriform fossa	7	2.5
		Post cricoid	1	0.4

		Posterior hypopharyngeal wall	0	0
		Supraglottis	9	3.3
		Glottis	0	0
		Subglottis	0	0
Clinical staging	**cT**	Data available	268	96.4
		Tx	0	0
		T0	0	0
		Tis	0	0
		T1	127	47.4
		T2	120	44.8
		T3	12	4.5
		T4	4	1.5
		T4a	5	1.9
		T4b	0	0
	cN	Data available	270	97.1
		Nx	5	1.9
		N0	207	76.7
		N1	31	11.5
		N2	5	1.9
		N2a	2	0.7
		N2b	12	4.4
		N2c	6	2.2
		N3	1	0.4
		N3a	0	0
		N3b	1	0.4
	cM	Data available	267	96.0
		Mx	4	1.5
		M0	261	97.8
		M1	2	0.7
Peri-operative management	**Concurrent neck surgery**	Data available	278	100
		None	110	39.6
		ND for access/ vessel ligation only	34	12.2
		Prophylactic ND	82	29.5
		Therapeutic ND	52	18.7
	Reconstruction	Data available	278	100
		None [secondary intention]	202	72.7
		Pedicle flap	20	7.2
		Free flap	56	20.1
	Tracheostomy	Data available	277	99.6
		Yes	105	37.9
		No	172	62.1
	Gastrostomy	Data available	278	100
		Yes	109	39.2
		No	169	60.8
Non-surgical oncological therapy	**Post-op radiotherapy**	Data available	262	94.2
		None	232	88.5
		Yes	30	11.5
	Chemotherapy	Data available	258	92.8
		None	232	89.9
		Neoadjuvant	10	3.9
		Adjuvant	16	6.2
	Immunotherapy	Data available	275	98.9
		None	259	94.2
		Neoadjuvant	7	2.5
		Adjuvant	9	3.3

Table 3-7: Details of clinico-pathological characteristics, peri-operative management and non-surgical oncological therapies, presented by subgroups in the RECUT Study.
**compared as continuous data*
OPSCC is oropharyngeal squamous cell carcinoma, ND is neck dissection, TORS is transoral robotic surgery, HNC is head and neck cancer, RT is radiotherapy, HPV human papillomavirus.

			OPSCC HPV +ve		OPSCC HPV -ve			Closest margin ≤1.0 mm		Closest margin >1.0 mm			<1 year from previous cancer to TORS		≥1 year from previous cancer to TORS		
Category	**Variable**	**Classification**	**n**	**%**	**n**	**%**	**p**	**n**	**%**	**n**	**%**	**p**	**n**	**%**	**n**	**%**	**p**
General	**Age***	**Data available**	75	100	124	100	<0.0001	95	100	99	100	<0.0001	78	100	192	100	<0.0001
		31 to 40	1	1.3	1	0.8		0	0	0	0		2	2.6	0	0	
		41 to 50	4	5.3	15	12.1		4	4.2	12	12.1		7	9.0	16	8.3	
		51 to 60	30	40.0	40	32.3		36	37.9	36	36.4		30	38.5	64	33.3	
		61 to 70	26	34.7	41	33.1		36	37.9	34	34.3		24	30.8	69	35.9	
		71 to 80	12	16.0	22	17.7		16	16.8	14	14.1		11	14.1	34	17.7	
		81 to 90	2	2.7	5	4.0		2	2.1	3	3.0		3	3.8	9	4.7	
		91 to 100	0	0	0	0		1	1.1	0	0		1	1.3	0	0	
	Sex	**Data available**	75	100	124	100	0.1263	95	100	99	100	1.0000	78	100	192	100	1.0000
		Female	9	12.0	26	21.0		19	20.0	19	19.2		15	19.2	39	20.3	
		Male	66	88.0	98	79.0		76	80.0	80	80.8		63	80.8	153	79.7	
	Smoking	**Data available**	65	86.7	95	76.6	0.1015	81	85.3	82	82.8	0.3178	65	83.3	163	84.9	0.8159
		Never smoker	23	35.4	24	25.3		24	29.6	18	22.0		15	23.1	44	27.0	
		Ex-smoker	28	43.1	36	37.9		33	40.7	43	52.4		30	46.2	74	45.4	
		Current smoker	14	21.5	35	36.8		24	29.6	21	25.6		20	30.8	45	27.6	
	Alcohol	**Data available**	69	92.0	106	85.5	0.1782	83	87.4	88	88.9	0.1362	70	89.7	169	88.0	0.4186
		No alcohol	24	34.8	51	48.1		30	36.1	45	51.1		35	50.0	69	40.8	
		Light alcohol	33	47.8	37	34.9		34	41.0	26	29.5		23	32.9	63	37.3	
		Heavy alcohol	12	17.4	18	17.0		19	22.9	17	19.3		12	17.1	37	21.9	
	Comorbidities (ACE-27)	**Data available**	54	72.0	104	83.9	0.0033	90	94.7	96	97.0	0.9895	71	91.0	142	74.0	0.5833
		0	12	22.2	40	38.5		30	33.3	32	33.3		28	39.4	44	31.0	
		1	31	57.4	28	26.9		31	34.4	32	33.3		23	32.4	54	38.0	
		2	7	13.0	21	20.2		17	18.9	20	20.8		11	15.5	28	19.7	
		3	4	7.4	15	14.4		12	13.3	12	12.5		9	12.7	16	11.3	
Previous HNCs	**Number of previous HNC**	**Data available**	75	100	124	100	0.0941	95	100	99	100	0.0033	78	100	192	100	0.2289
		1	71	94.7	105	84.7		71	74.7	91	91.9		64	82.1	167	87.0	
		2	3	4.0	15	12.1		20	21.1	7	7.1		10	12.8	22	11.5	
		3	1	1.3	4	3.2		4	4.2	1	1.0		4	5.1	3	1.6	
	RT to primary site	**Data available**	74	98.7	118	95.2	0.2581	92	96.8	96	97.0	1.0000	75	96.2	190	99.0	0.2862

		Yes	74	100	118	100			92	100	96	100			75	100	189	99.5	
		No	0	0	0	0			0	0	0	0			0	0	1	0.5	
	RT to neck	**Data available**	69	92.0	113	91.1	1.0000		78	82.1	92	92.9	0.0517		71	91.0	172	89.6	0.9435
		Yes	69	100	112	99.1			75	96.2	90	97.8			69	97.2	167	97.1	
		No	0	0	1	0.9			3	3.8	2	2.2			2	2.8	5	2.9	
TORS	**Timing by diagnosis**	**Data available**	75	100	121	97.6	0.1071		91	95.8	97	98.0	0.1997		76	97.4	192	100	<0.0001
		Residual (<12 months)	24	32.0	32	26.4			23	25.3	29	29.9			68	89.5	13	6.8	
		Recurrence (12 months to 5 years)	33	44.0	42	34.7			35	38.5	32	33.0			2	2.6	98	51.0	
		New primary (>5 years)	11	14.7	36	29.8			28	30.8	23	23.7			1	1.3	63	32.8	
		New primary (<5 years, separate site)	7	9.3	11	9.1			5	5.5	13	13.4			5	6.6	18	9.4	
	Timing by time to surgery*	**Data available**	72	96.0	120	96.8	<0.0001		92	96.8	95	96.0	<0.0001		78	100	192	100	NA
		0 to 1 year	23	31.9	29	24.2			25	27.2	28	29.5			78	100	1	0.5	
		1 to 2 years	18	25.0	20	16.7			14	15.2	18	18.9			0	0	53	27.6	
		2 to 3 years	11	15.3	15	12.5			15	16.3	11	11.6			0	0	37	19.3	
		3 to 4 years	3	4.2	8	6.7			7	7.6	4	4.2			0	0	16	8.3	
		4 to 5 years	4	5.6	10	8.3			4	4.3	7	7.4			0	0	16	8.3	
		5 to 6 years	3	4.2	7	5.8			5	5.4	5	5.3			0	0	13	6.8	
		6 to 7 years	1	1.4	1	0.8			2	2.2	2	2.1			0	0	4	2.1	
		7 to 8 years	1	1.4	5	4.2			4	4.3	2	2.1			0	0	7	3.6	
		8 to 9 years	1	1.4	4	3.3			3	3.3	3	3.2			0	0	6	3.1	
		9 to 10 years	0	0	2	1.7			3	3.3	0	0			0	0	4	2.1	
		> 10 years	7	9.7	19	15.8			10	10.9	15	15.8			0	0	35	18.2	
		Median (days)	602		816.5				759		767				192		1113.5		
	Primary site	**Data available**	75	100	124	100	0.1843		93	97.9	99	100	0.1065		76	97.4	192	100	0.5192
		Nasopharynx	0	0	0	0			0	0	0	0			0	0	0	0	
		Tonsil	31	41.3	39	31.5			26	28.0	37	37.4			29	38.2	55	28.6	
		Tongue base	41	54.7	70	56.5			48	51.6	45	45.5			37	48.7	107	55.7	
		Soft palate	1	1.3	8	6.5			7	7.5	2	2.0			3	3.9	7	3.6	
		Posterior oropharyngeal wall	2	2.7	7	5.6			8	8.6	5	5.1			2	2.6	11	5.7	
		Piriform fossa	0	0	0	0			1	1.1	5	5.1			1	1.3	6	3.1	
		Post cricoid	0	0	0	0			1	1.1	0	0			0	0	1	0.5	
		Posterior hypopharyngeal wall	0	0	0	0			0	0	0	0			0	0	0	0	
		Supraglottis	0	0	0	0			2	2.2	5	5.1			4	5.3	5	2.6	
		Glottis	0	0	0	0			0	0	0	0			0	0	0	0	
		Subglottis	0	0	0	0			0	0	0	0			0	0	0	0	
Clinical staging	**cT**	**Data available**	73	97.3	120	96.8	0.8707		92	96.8	99	100	0.0121		73	93.6	187	97.4	0.0619
		Tx	0	0	0	0			0	0	0	0			0	0	0	0	
		T0	0	0	0	0			0	0	0	0			0	0	0	0	

		Tis	0	0	0	0		0	0	0	0		0	0	0	0	
		T1	35	47.9	57	47.5		27	29.3	52	52.5		27	37.0	97	51.9	
		T2	34	46.6	54	45.0		55	59.8	39	39.4		37	50.7	78	41.7	
		T3	2	2.7	5	4.2		6	6.5	4	4.0		4	5.5	8	4.3	
		T4	2	2.7	2	1.7		1	1.1	2	2.0		3	4.1	1	0.5	
		T4a	0	0	2	1.7		3	3.3	2	2.0		2	2.7	3	1.6	
		T4b	0	0	0	0		0	0	0	0		0	0	0	0	
	cN	Data available	74	98.7	120	96.8	0.0545	92	96.8	99	100	0.4516	75	96.2	187	97.4	<0.0001
		Nx	3	4.1	2	1.7		2	2.2	2	2.0		1	1.3	4	2.1	
		N0	50	67.6	99	82.5		72	78.3	75	75.8		45	60.0	157	84.0	
		N1	10	13.5	10	8.3		7	7.6	13	13.1		10	13.3	19	10.2	
		N2	2	2.7	2	1.7		0	0	2	2.0		2	2.7	2	1.1	
		N2a	1	1.4	0	0		0	0	0	0		2	2.7	0	0	
		N2b	4	5.4	5	4.2		8	8.7	4	4.0		8	10.7	4	2.1	
		N2c	4	5.4	0	0		2	2.2	2	2.0		5	6.7	1	0.5	
		N3	0	0	1	0.8		1	1.1	0	0		1	1.3	0	0	
		N3a	0	0	0	0		0	0	0	0		0	0	0	0	
		N3b	0	0	1	0.8		0	0	1	1.0		1	1.3	0	0	
	cM	Data available	73	97.3	119	96.0	0.5660	93	97.9	97	98.0	0.0555	73	93.6	186	96.9	0.4786
		Mx	1	1.4	3	2.5		2	2.2	0	0		2	2.7	2	1.1	
		M0	71	97.3	116	97.5		89	95.7	97	100		71	97.3	182	97.8	
		M1	1	1.4	0	0		2	2.2	0	0		0	0	2	1.1	
Peri-operative management	Concurrent neck surgery	Data available	75	100	124	100	0.0085	95	100	99	100	0.3684	78	100	192	100	0.1463
		None	29	38.7	45	36.3		43	45.3	38	38.4		27	34.6	80	41.7	
		ND for access/ vessel ligation only	9	12.0	16	12.9		9	9.5	10	10.1		7	9.0	25	13.0	
		Prophylactic ND	17	22.7	50	40.3		24	25.3	36	36.4		23	29.5	58	30.2	
		Therapeutic ND	20	26.7	13	10.5		19	20.0	15	15.2		21	26.9	29	15.1	
	Reconstruction	Data available	75	100	124	100	0.6770	95	100	99	100	0.9695	78	100	192	100	0.0687
		None [secondary intention]	55	73.3	83	66.9		69	72.6	74	74.7		62	79.5	134	69.8	
		Pedicle flap	5	6.7	11	8.9		8	8.4	8	8.1		7	9.0	13	6.8	
		Free flap	15	20.0	30	24.2		18	18.9	17	17.2		9	11.5	45	23.4	
	Tracheostomy	Data available	75	100	123	99.2	0.0697	94	98.9	99	100	1.0000	78	100	191	99.5	0.0275
		Yes	22	29.3	53	43.1		35	37.2	37	37.4		22	28.2	82	42.9	
		No	53	70.7	70	56.9		59	62.8	62	62.6		56	71.8	109	57.1	
	Gastrostomy	Data available	75	100	124	100	0.4628	95	100	99	100	0.0708	78	100	192	100	0.0284
		Yes	31	41.3	59	47.6		39	41.1	28	28.3		23	29.5	85	44.3	
		No	44	58.7	65	52.4		56	58.9	71	71.7		55	70.5	107	55.7	
Non-surgical oncological therapy	Post-op radiotherapy	Data available	73	97.3	115	92.7	0.8204	93	97.9	95	96.0	0.3524	73	93.6	182	94.8	0.8327
		None	64	87.7	102	88.7		81	87.1	87	91.6		64	87.7	161	88.5	
		Yes	9	12.3	13	11.3		12	12.9	8	8.4		9	12.3	21	11.5	

	Chemotherapy	**Data available**	71	94.7	115	92.7	0.5660		91	95.8	93	93.9	0.5126		69	88.5	182	94.8	0.0715
		None	63	88.7	103	89.6			83	91.2	86	92.5			60	87.0	165	90.7	
		Neoadjuvant	4	5.6	3	2.6			2	2.2	0	0			1	1.4	9	4.9	
		Adjuvant	4	5.6	9	7.8			6	6.6	7	7.5			8	11.6	8	4.4	
	Immunotherapy	**Data available**	75	100	123	99.2	0.5803		94	98.9	98	99.0	0.0028		77	98.7	190	99.0	0.2500
		None	69	92.0	117	95.1			86	91.5	98	100			74	96.1	177	93.2	
		Neoadjuvant	3	4.0	2	1.6			2	2.1	0	0			0	0	7	3.7	
		Adjuvant	3	4.0	4	3.3			6	6.4	0	0			3	3.9	6	3.2	

Table 3-8: Histopathological and functional outcomes following TORS, presented for all subjects and by subgroups in the RECUT Study.
**compared as continuous data*
OPSCC is oropharyngeal squamous cell carcinoma, HPV is human papillomavirus, SCC is squamous cell carcinoma.

			All subjects		OPSCC HPV +ve		OPSCC HPV -ve			Closest margin ≤1.0 mm		Closest margin >1.0 mm			<1 year from previous cancer to TORS		≥1 year from previous cancer to TORS		
Category	**Variable**	**Classification**	**n**	**%**	**n**	**%**	**n**	**%**	**p**	**n**	**%**	**n**	**%**	**p**	**n**	**%**	**n**	**%**	**p**
Histopathology	**Histology**	**Data available**	278	100	75	100	124	100	NA	95	100	99	100	0.3610	78	100	192	100	1.0000
		SCC	271	97.5	75	100	124	100		92	96.8	98	99.0		76	97.4	188	97.9	
		Other	7	2.5	0	0	0	0		3	3.2	1	1.0		2	2.6	4	2.1	
	HPV status	**Data available**	210	75.5	75	100	124	100	NA	67	70.5	86	86.9	0.4911	56	71.8	147	76.6	0.2521
		Positive	76	36.2	75	100	0	0		24	35.8	26	30.2		24	42.9	49	33.3	
		Negative	134	63.8	0	0	124	100		43	64.2	60	69.8		32	57.1	98	66.7	
Margins	**Nearest margin**	**Data available**	194	69.8	49	65.3	94	75.8	0.8248	95	100	99	100	0.1152	52	66.7	135	70.3	1.0000
		Mucosal	48	24.7	12	24.5	25	26.6		21	22.1	27	27.3		10	19.2	35	25.9	
		Deep	95	49.0	20	40.8	49	52.1		55	57.9	40	40.4		22	42.3	69	51.1	
		Equal	51	26.3	17	34.7	20	21.3		19	20.0	32	32.3		20	38.5	31	23.0	
	Nearest mucosal margin*	**Data available**	211	75.9	52	69.3	100	80.6	<0.0001	93	97.9	99	100	<0.0001	60	76.9	143	74.5	<0.0001
		=0 mm	26	12.3	9	17.3	7	7.0		26	28.0	0	0		9	15.0	17	11.9	
		0.1 to 1.0 mm	22	10.4	4	7.7	12	12.0		20	21.5	0	0		9	15.0	12	8.4	
		1.1 to 2.0 mm	36	17.1	14	26.9	16	16.0		14	15.1	18	18.2		8	13.3	26	18.2	
		2.1 to 3.0 mm	31	14.7	9	17.3	12	12.0		9	9.7	19	19.2		9	15.0	21	14.7	
		3.1 to 4.0 mm	18	8.5	3	5.8	9	9.0		3	3.2	11	11.1		4	6.7	14	9.8	
		4.1 to 5.0 mm	42	19.9	8	15.4	23	23.0		15	16.1	24	24.2		12	20.0	30	21.0	
		≥ 5.0 mm	36	17.1	5	9.6	21	21.0		6	6.5	27	27.3		9	15.0	23	16.1	
	Nearest deep margin*	**Data available**	193	69.4	50	66.7	92	74.2	<0.0001	92	96.8	99	100	<0.0001	51	65.4	135	70.3	<0.0001
		=0 mm	38	19.7	10	20.0	13	14.1		38	41.3	0	0		11	21.6	26	19.3	
		0.1 to 1.0 mm	38	19.7	7	14.0	21	22.8		37	40.2	0	0		9	17.6	28	20.7	
		1.1 to 2.0 mm	38	19.7	16	32.0	16	17.4		8	8.7	29	29.3		10	19.6	27	20.0	
		2.1 to 3.0 mm	23	11.9	5	10.0	11	12.0		3	3.3	20	20.2		8	15.7	14	10.4	
		3.1 to 4.0 mm	17	8.8	4	8.0	8	8.7		1	1.1	16	16.2		4	7.8	12	8.9	
		4.1 to 5.0 mm	18	9.3	5	10.0	8	8.7		3	3.3	15	15.2		3	5.9	15	11.1	
		≥ 5.0 mm	21	10.9	3	6.0	15	16.3		2	2.2	19	19.2		6	11.8	13	9.6	
	Closest margin*	**Data available**	194	69.8	49	65.3	94	75.8	0.1466	95	100	99	100	NA	52	66.7	135	70.3	0.0215

		=0 mm	49	25.4		14	28.6	17	18.1			49	51.6	0	0			13	25.0	35	25.9	
		0.1 to 1.0 mm	46	23.8		10	20.4	25	26.6			46	48.4	0	0			11	21.2	33	24.4	
		1.1 to 2.0 mm	36	18.7		13	26.5	16	17.0			0	0	36	36.4			10	19.2	25	18.5	
		2.1 to 3.0 mm	25	13.0		5	10.2	12	12.8			0	0	25	25.3			8	15.4	17	12.6	
		3.1 to 4.0 mm	10	5.2		2	4.1	7	7.4			0	0	10	10.1			3	5.8	6	4.4	
		4.1 to 5.0 mm	17	8.8		2	4.1	11	11.7			0	0	17	17.2			5	9.6	12	8.9	
		≥ 5.0 mm	11	5.7		3	6.1	6	6.4			0	0	11	11.1			2	3.8	7	5.2	
Functional status	**Tracheostomy use at 1 year**	**Data available**	195	88.6		53	94.6	86	86.0	0.1317		60	82.2	74	90.2	0.0365		47	88.7	143	89.4	0.2994
		Yes	18	9.2		1	1.9	8	9.3			8	13.3	4	5.4			6	12.8	12	8.4	
		No	177	90.8		52	98.1	78	90.7			52	86.7	70	94.6			41	87.2	131	91.6	
		NA (last follow-up <1yr)	58			19		24				22		17				25		32		
	Gastrostomy use at 1 year	**Data available**	195	88.6		52	92.9	86	86.0	0.5082		61	83.6	74	90.2	0.3853		46	86.8	144	90.0	0.6373
		Yes	66	33.8		15	28.8	33	38.4			18	29.5	21	28.4			16	34.8	49	34.0	
		No	129	66.2		37	71.2	53	61.6			43	70.5	53	71.6			30	65.2	95	66.0	
		NA (last follow-up <1yr)	58			19		24				22		17				25		32		

Table 3-9: Details of previous head and neck cancers and their treatments for all subjects in the RECUT Study.
HNC is head and neck cancer, SCC is squamous cell carcinoma, ND is neck dissection, RT is radiotherapy.

		Previous HNC 1		Previous HNC 2		Previous HNC 3	
Variable	**Classification**	**n**	**%**	**n**	**%**	**n**	**%**
Primary site	**Data available**	249	89.6	26	66.7	6	85.7
	Nasopharynx	3	1.1	0	0	0	0
	Tonsil	81	29.1	4	10.3	3	42.9
	Tongue base	96	34.5	10	25.6	2	28.6
	Soft palate	11	4.0	2	5.1	0	0
	Posterior oropharyngeal wall	5	1.8	0	0	0	0
	Piriform fossa	13	4.7	2	5.1	1	14.3
	Post cricoid	0	0	0	0	0	0
	Posterior hypopharyngeal wall	0	0	1	2.6	0	0
	Supraglottis	19	6.8	2	5.1	0	0
	Glottis	14	5.0	2	5.1	0	0
	Subglottis	0	0	0	0	0	0
	Cancer of unknown primary	0	0	0	0	0	0
	Other	7	2.5	3	7.7	0	0
T classification	**Data available**	225	80.9	33	84.6	6	85.7
	Tx	5	2.2	2	6.1	0	0
	T0	13	5.8	2	6.1	0	0
	Tis	1	0.4	0	0	0	0
	T1	37	16.4	8	24.2	3	50.0
	T2	101	44.9	14	42.4	2	33.3
	T3	46	20.4	3	9.1	1	16.7
	T4	11	4.9	4	12.1	0	0
	T4a	10	4.4	0	0	0	0
	T4b	1	0.4	0	0	0	0
N classification	**Data available**	224	80.6	32	82.1	6	85.7
	Nx	2	0.9	1	3.1	0	0
	N0	88	39.3	18	56.3	3	50.0
	N1	41	18.3	4	12.5	0	0
	N2	14	6.3	3	9.4	2	33.3
	N2a	7	3.1	0	0	0	0
	N2b	44	19.6	3	9.4	1	16.7
	N2c	19	8.5	2	6.3	0	0
	N3	6	2.7	1	3.1	0	0
	N3a	0	0	0	0	0	0
	N3b	3	1.3	0	0	0	0
M classification	**Data available**	248	89.2	32	82.1	6	85.7
	Mx	2	0.8	2	6.3	0	0
	M0	246	99.2	30	93.8	6	100
	M1	0	0	0	0	0	0
Histology	**Data available**	255	91.7	35	89.7	7	100
	SCC	248	97.3	35	100	7	100
	Adenoid cystic carcinoma	2	0.8	0	0	0	0
	Adenocarcinoma	2	0.8	0	0	0	0
	Carotid body tumour	1	0.4	0	0	0	0
	Clear cell carcinoma	1	0.4	0	0	0	0
	Undifferentiated nasopharyngeal carcinoma	1	0.4	0	0	0	0
HPV status	**Data available**	123	44.2	7	17.9	3	42.9
	Positive	56	45.5	4	57.1	1	33.3
	Negative	67	54.5	3	42.9	2	66.7
Primary site surgery	**Data available**	267	96.0	37	94.9	7	100
	None	201	75.3	20	54.1	3	42.9
	Open resection	40	15.0	13	35.1	4	57.1
	Transoral laser resection	13	4.9	1	2.7	0	0
	Transoral robotic resection	10	3.7	1	2.7	0	0
	Other	3	1.1	2	5.4	0	0
Primary site radiotherapy	**Data available**	271	97.5	39	100	7	100
	None	22	8.1	12	30.8	1	14.3
	Radical	202	74.5	20	51.3	3	42.9
	Adjuvant	44	16.2	6	15.4	3	42.9
	Prophylactic	3	1.1	1	2.6	0	0
Neck surgery	**Data available**	263	94.6	39	100	7	100
	None	195	74.1	29	74.4	4	57.1

	Unilateral ND	54	20.5	7	17.9	3	42.9
	Bilateral ND	14	5.3	3	7.7	0	0
Neck radiotherapy	**Data available**	246	88.5	34	87.2	4	57.1
	None	28	11.4	13	38.2	2	50.0
	Unilateral RT	36	14.6	4	11.8	1	25.0
	Bilateral RT	182	74.0	17	50.0	1	25.0
Chemotherapy	**Data available**	237	85.3	38	97.4	6	85.7
	None	94	39.7	26	68.4	5	83.3
	Neoadjuvant	11	4.6	2	5.3	0	0
	Neoadjuvant and concomitant	8	3.4	3	7.9	0	0
	Concomitant	114	48.1	6	15.8	0	0
	Adjuvant	10	4.2	1	2.6	1	16.7
Immunotherapy	**Data available**	277	99.6	37	94.9	7	100
	None	259	93.5	34	91.9	7	100
	Neoadjuvant	3	1.1	0	0	0	0
	Neoadjuvant and concomitant	0	0	0	0	0	0
	Concomitant	12	4.3	3	8.1	0	0
	Adjuvant	3	1.1	0	0	0	0

Table 3-10: Results from univariable Cox regression analysis, for all subjects in the RECUT Study. Where Schoenfeld residuals testing of the proportional-hazards assumption gave a significant result (indicating a possible time dependent relationship) the hazard ratios and p values for the variable incorporating a log(time) interaction are presented.
TORS is transoral robotic surgery, SCC is squamous cell carcinoma, HPV is human papillomavirus.
OS is overall survival, DFS is disease-free survival, DSS is disease-specific survival, LC is local control.

			OS			DFS			DSS			LC		
			Schoenfeld residuals test	Univariable Cox		Schoenfeld residuals test	Univariable Cox		Schoenfeld residuals test	Univariable Cox		Schoenfeld residuals test	Univariable Cox	
Prognostic factor	**Reference**	**Comparator**		**HR (95% CIs)**	**p**		**HR (95% CIs)**	**p**		**HR (95% CIs)**	**p**		**HR (95% CIs)**	**p**
Age	**Continuous**		0.8000	1.04 (1.02, 1.06)	0.0004	0.5480	1.01 (0.989, 1.03)	0.4290	0.9950	1.02 (0.999, 1.05)	0.0602	0.1900	1 (0.981, 1.03)	0.7170
Sex	**Female**	**Male**	0.4330	0.795 (0.519, 1.22)	0.2930	0.8660	0.846 (0.566, 1.26)	0.4140	0.8380	0.626 (0.389, 1.01)	0.0541	0.6860	0.891 (0.533, 1.49)	0.6580
Smoking	**Non/ Ex-smoker**	**Current smoker**	0.1750	1.67 (1.12, 2.47)	0.0109	0.2220	0.991 (0.656, 1.5)	0.9670	0.9010	1.38 (0.861, 2.23)	0.1790	0.3790	0.652 (0.37, 1.15)	0.1390
Alcohol	**None/ light alcohol**	**Heavy alcohol**	0.0289	0.113 (0.00553, 2.29)	0.1552	0.2860	1.24 (0.796, 1.93)	0.3440	0.2860	1.67 (1, 2.79)	0.0490	0.5760	1.25 (0.718, 2.17)	0.4330
ACE-27	**None/ mild**	**Moderate/ severe**	0.4740	1.74 (1.14, 2.65)	0.0099	0.9540	0.756 (0.486, 1.17)	0.2120	0.1430	1.21 (0.708, 2.07)	0.4830	0.3750	0.608 (0.324, 1.14)	0.1230
Reconstruction	**No free flap**	**Free flap**	0.6780	1.01 (0.639, 1.6)	0.9610	0.5870	0.843 (0.542, 1.31)	0.4490	0.5270	0.672 (0.364, 1.24)	0.2030	0.7110	0.94 (0.544, 1.62)	0.8250
Closest surgical resection margin distance	**>1.0 mm**	**≤1.0 mm**	0.8240	2.28 (1.45, 3.6)	0.0004	0.7470	2.18 (1.44, 3.29)	0.0002	0.8310	2.64 (1.51, 4.64)	0.0007	0.4520	2.87 (1.66, 4.96)	0.0002
Closest surgical resection margin site	**Mucosal**	**Deep**	0.2950	1.1 (0.635, 1.9)	0.7390	0.2560	0.768 (0.479, 1.23)	0.2720	0.2420	0.855 (0.456, 1.6)	0.6250	0.3370	0.692 (0.388, 1.23)	0.2120
Histology HPV	**HPV -ve**	**HPV +ve**	0.4030	0.899 (0.564, 1.44)	0.6570	0.0932	1.27 (0.86, 1.89)	0.2280	0.2920	0.826 (0.472, 1.45)	0.5040	0.3660	1.31 (0.792, 2.18)	0.2900
Site	**Other subsites**	**Oropharyngeal**	0.8710	0.953 (0.482, 1.88)	0.8890	0.3640	1.04 (0.529, 2.05)	0.9080	0.2670	1.05 (0.459, 2.42)	0.9010	0.4510	0.939 (0.409, 2.16)	0.8810
Histology SCC	**Other histology**	**SCC**	1.0000	25700000 (0, Inf)	0.9950	0.1200	2.4 (0.595, 9.71)	0.2190	1.0000	25700000 (0, Inf)	0.9950	0.2350	2.84 (0.395, 20.4)	0.3000

Any adjuvant therapy	**None**	**Any**	0.3600	1.12 (0.703, 1.78)	0.6340	0.3490	1.06 (0.688, 1.64)	0.7820	0.7190	0.881 (0.487, 1.59)	0.6750	0.1340	0.923 (0.519, 1.64)	0.7850
Post-op radiotherapy	**None**	**Yes**	0.2790	1.54 (0.92, 2.58)	0.1000	0.9600	1.37 (0.811, 2.31)	0.2390	0.5010	0.953 (0.459, 1.98)	0.8970	0.5830	0.957 (0.461, 1.99)	0.9060
Peri-operative chemotherapy	**None**	**Neoadjuvant/ adjuvant**	0.4960	1.27 (0.698, 2.32)	0.4320	0.0781	1.41 (0.822, 2.42)	0.2120	0.6590	1.18 (0.567, 2.45)	0.6610	0.2210	1.12 (0.541, 2.33)	0.7550
Peri-operative immunotherapy	**None**	**Neoadjuvant/ adjuvant**	0.5920	0.59 (0.217, 1.6)	0.3010	0.9540	1.02 (0.501, 2.09)	0.9480	0.7230	0.809 (0.296, 2.21)	0.6790	0.1060	0.747 (0.273, 2.04)	0.5690
Post TORS haemorrhage	**None**	**Bleed**	0.7500	1.54 (0.805, 2.96)	0.1910	0.5020	1.33 (0.735, 2.42)	0.3440	0.8830	1.08 (0.435, 2.67)	0.8720	0.3900	0.915 (0.37, 2.27)	0.8490
Cancer clinical timing	**≥1yr**	**<1yr**	0.0261	11.5 (1.29, 103)	0.0289	0.0001	10.0 (1.95, 51.5)	0.0058	0.0111	849 (10.7, 67300)	0.0025	0.0026	4.83 (1.00, 23.3)	0.0499
Pre-op cT classification	**T1/T2**	**T3/4**	0.8670	2.55 (1.5, 4.33)	0.0006	0.1460	1.6 (0.881, 2.9)	0.1230	0.1780	2.25 (1.16, 4.38)	0.0168	0.1540	1.13 (0.494, 2.61)	0.7660
Pre-op cN classification	**N0**	**N+**	0.158	1.54 (1.01, 2.36)	0.0466	0.0915	1.37 (0.91, 2.07)	0.13	0.0278	1.44 (0.853, 2.42)	0.173	0.413	1.15 (0.671, 1.96)	0.615

Table 3-11: Results from multivariable Cox regression analysis, for all subjects in the RECUT Study. TORS is transoral robotic surgery, SCC is squamous cell carcinoma, HPV is human papillomavirus. OS is overall survival, DFS is disease-free survival, DSS is disease-specific survival, LC is local control.

			OS		DFS		DSS		LC	
Prognostic factor	**Reference**	**Comparator**	**HR (95% CIs)**	**p**	**HR (95% CIs)**	**p**	**HR (95% CIs)**	**p**	**HR (95% CIs)**	**p**
Age	**Continuous**		1.06 (1.03, 1.09)	0.0001	-	-	-	-	-	-
Smoking	**Non/ Ex-smoker**	**Current smoker**	2.05 (1.28, 3.29)	0.0027	-	-	-	-	-	-
Closest margin distance	**>1.0 mm**	**≤1.0 mm**	2.51 (1.56, 4.03)	0.0002	2.52 (1.63, 3.89)	<0.0001	2.64 (1.51, 4.64)	0.0007	2.87 (1.66, 4.96)	0.0002
Cancer clinical timing	**≥1 year**	**<1 year**	-	-	2.98 (1.54, 5.76)	0.0012	-	-	-	-
Pre-op cT classification	**T1/T2**	**T3/4**	2.21 (1.21, 4.06)	0.0102	-	-	-	-	-	-

Table 3-12: Oncological outcomes following TORS, presented for all subjects and by subgroups in the RECUT Study. OS is overall survival, DFS is disease-free survival, DSS is disease-specific survival, LRFS is local control. OPSCC is oropharyngeal squamous cell carcinoma, HPV is human papillomavirus.

Oncological status	All subjects	OPSCC HPV +ve	OPSCC HPV -ve	Closest margin ≤1.0 mm	Closest margin >1.0 mm	<1 year from previous cancer to TORS	≥1 year from previous cancer to TORS
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
at 2 years							
OS	71.8 (66.5, 77.5)	75.2 (65.6, 86.2)	72.2 (64.5, 80.9)	57.6 (48.3, 68.7)	81.6 (74.1, 89.9)	60.4 (50.1, 72.8)	75.8 (69.7, 82.4)
DFS	52.2 (46.3, 58.8)	48.5 (38.0, 62.0)	51.3 (42.8, 61.5)	36.7 (27.6, 48.8)	63.7 (54.5, 74.4)	44.3 (34.1, 57.5)	55.8 (48.8, 64.0)
DSS	78.7 (73.7, 84.1)	81.3 (72.3, 91.5)	77.8 (70.3, 86.1)	67.3 (57.8, 78.3)	87.2 (80.4, 94.6)	67.0 (56.6, 79.4)	83.0 (77.4, 88.9)
LC	69.0 (63.2, 75.3)	68.5 (57.8, 81.2)	69.4 (61.0, 79.0)	54.2 (44.1, 66.6)	80.9 (72.8, 89.8)	66.7 (56.1, 79.4)	70.1 (63.3, 77.5)
at 5 years							
OS	49.8 (43.0, 57.7)	58.8 (46.7, 74.1)	50.6 (40.8, 62.8)	34.6 (24.3, 49.1)	65.4 (55.4, 77.2)	42.3 (31.1, 57.4)	51.2 (42.9, 61.1)
DFS	43.0 (36.7, 50.4)	40.1 (29.5, 54.6)	44.2 (35.2, 55.5)	27.9 (19.1, 40.7)	56.9 (47.0, 69.0)	38.8 (28.7, 52.4)	44.0 (36.1, 53.8)
DSS	59.1 (52.1, 67.0)	71.3 (59.8, 85.0)	56.3 (45.9, 69.1)	46.4 (35.1, 61.2)	75.9 (66.4, 86.7)	48.3 (36.1, 64.6)	62.5 (54.3, 72.0)
LC	62.2 (55.6, 69.5)	58.5 (46.4, 73.7)	64.9 (55.8, 75.4)	45.0 (34.0, 59.5)	75.0 (65.5, 85.9)	64.2 (53.2, 77.6)	60.9 (52.7, 70.2)

PART 3 discussion

Despite the broad search strategy, **The RECUT Review** identified a relatively limited number of studies which reported on TORS for head and neck tumours in previously treated patients. TORS in this context remains a relatively infrequent procedure conducted in a limited number of centres across the world. There are no randomised trials to inform us of comparative outcome data with open surgery and there is significant heterogeneity within the cohorts identified in **The RECUT Review**. As such, the data presented here must be interpreted with great caution.

The RECUT Study goes further providing evidence from individual patient data contributed by multiple international tertiary referral centres, to support the use of TORS to treat HNCs in previously irradiated fields. The survival and functional outcome data presented corroborate the findings of previous smaller studies and those in **The RECUT Review**.[7,181,185] Overall survival in **The RECUT Study** cohort was 71.8% at 2 years and 49.8% at 5 years, which compares very favourably to alternative treatments that may be considered for these patients, including re-irradiation and open surgery. It is accepted that direct comparisons between studies and treatment modalities are difficult in the absence of randomised studies and that, generally, patients undergoing surgery are more likely to have smaller volume, lower-stage disease, with a performance status which may tolerate the physiological strains of a general anaesthetic.[186]

Survival

The principal objective of **The RECUT Review** was to report on survival amongst patients undergoing TORS who had had a previously treated HNC, with 2-year survival being the longest standardised follow-up reported in the identified studies. TORS is a relatively recently developed technique and so longer-term outcome data have not yet permeated the literature.[187]

The RECUT Review identified overall survival and disease-free survival rates of 73.8% and 74.8%, respectively. The similarity between these two rates suggest a low incidence of death from other causes during the follow-up period, implying appropriate case selection. This may be anticipated where tumour boards may have a higher threshold for listing new cases for an emerging surgical technique. Unfortunately, rates of adjuvant therapy for the previous cancers were inconsistently reported in the identified studies. This information is essential for interpreting the impact of TORS for recurrence in patients who may not be able to undergo re-irradiation. Future reports on TORS for recurrence should clearly report the rates of adjuvant therapies to better understand the complex management of this patient group.

The disease-free survival reported in **The RECUT Review** improves significantly on the historical rate reported by Goodwin et al. in 2000 (74.8% vs 51%) in a similar patient group but undergoing open surgery.[188] However, this improved rate may not be directly comparable for two notable reasons. Firstly, the case mix included considerably fewer cases of pharyngeal cancer (11.4%, n=57/499) and these were not differentiated further by sub-site, and so may have further underrepresented the oropharyngeal tumours. Secondly, the prevalence of HPV-positive disease has significantly increased since Goodwin's publication.[189] This has

conferred improved survival to this patient group regardless of treatment modality and may account for much of the higher survival rate seen herein.

The 2-year survival rates seen in **The RECUT Review** were reassuring when compared to equivalent rates for open surgery.[163] White et al. compared their TORS salvage results to matched open surgery cases, reporting disease-free survival of 74% vs 43%, respectively (p=0.01).[181] It is acknowledged that significantly fewer patients in the open surgery group had had their primary tumours treated with radiation and chemotherapy, and so the recurrent tumour biology may have differed. The positive margin rate was also seen to be higher in the matched open surgery group (29% vs 9%) which is likely to account for some of this difference. Criticism of TORS, when compared to open surgery, has included a lack of tactile feedback, theoretically making resection more problematic if the tumour cannot be handled to aid the surgeon's decision-making in attempting to achieve appropriate clearance. Reassuringly, this does not appear to be the case for the White et al. cohort but more data will be needed on margins to give confidence to this assessment.

Various studies reporting re-irradiation with IMRT record 2-year OS around 40 to 50%, albeit at the expense of severe acute toxicity in around a quarter of patients,[161,190,191] though the majority of these patients may have been considered unsuitable for attempted surgery with curative intent. Ward et al. considered patients undergoing salvage surgery in addition to re-irradiation with IMRT and reported 2-year OS of 61.9%, although this cohort would have included patients undergoing open procedures too based on the tumour subsites presented.[162]

Comparisons of TORS with open salvage surgery alone are also very favourable for residual/recurrent HNC. For example, Patel et al. reported 5-year DFS of only 19% compared with 43.0% in **The RECUT Study**.[159] Additionally, Hamoir et al. reported markedly lower OS for their oropharyngeal patients treated with salvage surgery, with a 2-year rate of 51.9% (95% CI [38.1, 70.7]) compared to 71.8% (95% CI [66.5, 77.5]), and a 5-year rate of 29.3% (95% CI [17.1, 50.1]), compared to 49.8% (95% CI [43.0, 57.7]) presented in **The RECUT Study**.[160] Again, it is important to recognise that these open surgery patients may have had more advanced disease, in different head and neck subsites, than those undergoing transoral surgery.

HPV status, largely based on immunohistochemistry for p16 as a surrogate, was available for 75.5% of eligible SCCs in **The RECUT Study**, with 62.3% of oropharyngeal SCCs being reported as HPV-negative (n=124/199). There was no significant distinction between the survival curves by HPV status for any of the four time-to-event analyses presented (**Figure 3-19**). In the primary setting, HPV status has a significant impact on overall survival, with HPV-negative oropharyngeal SCCs faring worse overall.[59] In residual and recurrent cases, the influence of HPV status is less clear.[192] Fakhry presents a comparison of outcomes in patients who have experienced disease progression in OPSCC initially treated under RTOG 0129 and 0522. Outcomes in their analyses were better for their HPV-positive cases, though overall their cohort had higher incidence of both residual disease and regional/distant metastases, limiting comparability.[193] The lack of differentiation in survival based on HPV status in **The RECUT Study** may be explained by a change in the biological behaviours of these cancers having been subjected to radiation.[194,195]

Alternatively, it could be postulated that although most HPV-driven tumours are associated with a significant survival advantage, 15% have a poor 5-year survival, and run a similar clinical course to those patients with

HPV-negative disease.[196] By definition, HPV-positive patients enrolled into the RECUT study were not afforded the survival advantage often associate with HPV disease, as they had failed their primary treatment. This group of HPV-positive patients were likely to have had a low number of infiltrating T cells in their tumour, behaving in a similar biological way to HPV negative tumours.[196] Therefore, it would be expected that both the HPV-positive and HPV-negative tumours within our RECUT cohort to behave in a biologically similar way, as demonstrated (**Figure 3-19**).

Margins

From the published literature considered by **The RECUT Review**, across the four applicable identified studies, the positive margin rate for included patients was 18.2% (**Table 3-4**). A further 25.7% of cases were reported to have close margins. Whilst these rates may seem high, the role of close margins in recurrent HNCs has not been definitively established, and certainly not in the heterogeneous group included in **The RECUT Review**. This is where **The RECUT Study** has significantly increased our understanding.

In **The RECUT Review, t**here was notable variation between the studies in what was considered a 'close' margin with four studies reporting three different distances, ranging between two and five millimetres. Additionally, the locations of these margins were not consistently reported; specifically, whether the margin was mucosal or deep, which are perhaps better and more traditionally considered differently. For example, for tonsillar tumours, a deep margin of more than 2-3 mm may be unachievable, as this is the depth of the superior constrictor muscle in this location.[197] It is proposed that this anatomical barrier should be taken into consideration when interpreting the histopathology results of these resections. If it is not breached, then it could be argued that there is limited justification for further resections, or adjuvant therapy, if available. Morisod et al. 2017[183] undertook further resections of the deep margin in two cases, including of the parapharyngeal fat. In two additional cases, further resections were indicated, according to their management protocol, but surgery did not take place, as in one case the patient refused and in the other case surgery was precluded due to co-morbidities. Unfortunately, we do not have specific outcome data for this subgroup, but we do know that the two patients who did undergo further surgery had their major vessels exposed and so required free flap reconstructions. As such, further resections in these patients are not without morbidity, with the inevitable donor site trauma and the impact the free flap may have on functional outcomes once inset. To be able to adequately address this question of margins in the patients, a larger cohort is needed with more information about previous treatments and adjuvant therapy.

And that is where **The RECUT Study** steps in. Details of surgical resection margins were available for 69.8% of our cohort. Using a data-driven approach, it was shown by two methods that the most discriminating cut-point for the closest surgical resection margin (with local disease control as the outcome) was achieved with groups ≤1.0 mm and >1.0 mm. Dichotomising the cohort around this cut-point moved the combined cohort's 2-year LC from 69.0% (95% CI [63.2, 75.3]) to 54.2% (95% CI [44.1, 66.6]) for those ≤1.0 mm and 80.9% (95% CI [72.8, 89.8]) for those >1.0 mm. The margin status around this cut-point was the only factor to remain significant on multivariable analysis for all four time-to-event scenarios investigated (**Table 3-11**). Understandably, it may be asked whether a greater margin would improve outcomes further and this is explored in **Figure 3-22** to **Figure 3-26**. It is noted that minimum resection margins at millimetre values >1.0 mm do appear to yield additional protection from local recurrence. However, the impact is incremental and these

estimates should be interpreted with caution as the data around these cut-points become more scarce and statistical confidence reduces as the millimetre cut-point increases.

The data analysed in **The RECUT Study** for closest surgical resection margin are derived from the histopathological reports of the resected specimens, as is the standard practice for both observational and interventional studies.[134,170,198–201] What this margin value does not reflect is the surgeons' intraoperative intentions, where greater resection margins are often strived for should a) the anatomy allow it, and b) in consideration of the potential added morbidity of unnecessarily resecting additional healthy tissue. It is common practice to mark out a mucosal resection margin of around five millimetres, in an attempt to ensure a reasonable buffer of unaffected tissue around the primary tumour. The planned deep margin is harder to delineate at the outset of surgery and, where tumours abut vital structures such as the internal carotid artery and cranial nerves, further resection margin cannot be added without risking considerable morbidity/mortality. Additionally, the better outcomes observed in patients with wider minimum margins may be a surrogate for smaller more superficial tumours, which lend themselves to be more resectable and/or less likely to involve critical structures.

In **The RECUT Study**, even where minimum margins were very narrow and/or positive, the cancer control outcomes were relatively favourable, with a 2-year local recurrence-free survival around 50% for those between 0 and 1 mm inclusive. The interpretation of minimum margins in this bracket may be that the surgery was a 'failed' intervention, but the attempt at curative resection appears to have conveyed a survival benefit over and above even the most current systemic anti-cancer therapies (SACT).[202] There are a number of reasons why local disease control following TORS procedures with close or positive margins may be better than expected. Firstly, piecemeal resections may be reported as incompletely excised if not orientated appropriately, falsely exaggerating the perceived narrowness of excision. Secondly, the diathermy effect at the resection margin may have an ablative effect on any residual cancer cells left *in situ*. Thirdly, the ex vivo handling and fixation of the specimen are known to disrupt the architecture of the tissue, reducing the measurable margin by at least a fifth.[203] And conversely, the emergence of second primary tumours within the surgical field during the surveillance period may unjustly be reported as local failures.[204] For these reasons, the intraoperative impression of the completeness of the resection may be a more reliable predictor of local control, over and above the minimum margin value appearing on the histopathologist's report.

Regardless of such considerations, histopathological margin status has been used to generate our evidence-base and so must be given appropriate consideration. It is important to stress that **The RECUT Study** authors are not recommending that surgeons should aim for a 1.0 mm minimum resection margins as routine practice for recurrent cancer TORS; surgeons should continue to strive for higher minimum margins where safely feasible and appropriate. However, the results presented here indicate that favourable outcomes can be achieved even when minimum margins are reported as being >1.0 mm. With a paucity of effective, alternative, curative-intent treatments for these patients, the prospect of a narrow resection margin at TORS, where otherwise complete resection is felt feasible, should not deter clinical teams from offering such an intervention to this patient group.

Complications

Post-operative haemorrhage

Post-operative haemorrhage remains a concern in TORS in general, particularly when wounds are left to heal by secondary intention, potentially leaving vulnerable vessels exposed to the effects of saliva.[205] The 9.3% pooled rate seen in **The RECUT Review** is in keeping with rates seen for primary oropharyngeal resections and may have been reduced by the small number of patients also undergoing concurrent free flap reconstruction. The low rate is perhaps surprising, however, considering the majority of patients identified had previously undergone radiotherapy or chemoradiotherapy to the region, theoretically worsening the healing potential of the exposed tissues (**Table 3-3**). Delayed healing contributed to a late fatality in Meuleman's cohort, where necrosis at the resection site reportedly led to a carotid blowout. However, most bleeds identified here were not life-limiting and were managed with or without a return to theatre for local haemorrhage control.

The post-operative haemorrhage rate requiring return to theatre observed in **The RECUT Study** was similar at 8.1% with a median time to bleed of six days. A single case was recorded as late as day 42 that was attributed to the procedure and another single case resulted in death. Post-operative haemorrhage in this cohort is a significant concern and appears higher than for patients with primary disease.[206] It is a significant factor influencing placement of peri-operative tracheostomy tubes, though it is unclear how long such prophylactic tubes should then remain in situ when very delayed bleeds may be experienced.

To reduce the chances of catastrophic post-operative haemorrhage, ligation of one or more feeding vessels branching off the external carotid artery (ECA) is commonly performed. There is good retrospective evidence that this reduces the incidence and severity of bleeds following TORS.[207] However, in previously irradiated fields, ligation is not always straight forward due to the fibrotic changes observed in the exposed tissues. Additionally, neck dissection is not indicated in these patients in a residual/recurrent setting with no clinico-radiological evidence of disease. Consequently, alternatives to ligation are justified, such as endovascular embolisation. The author and primary supervisor are pursuing a non-randomised interventional feasibility study to look at the safety and efficacy of embolisation in this recurrent group, run out of The Royal Marsden Hospital, called The HELPR Study (IRAS 279065) (Haemorrhage risk reduction using endovascular Embolisation in place of vessel Ligation for Patients undergoing transoral Robotic surgery).

Fistulae and free-flaps

TORS offers notable advantages to this group of patients. Open surgery to this area may necessitate mandibulotomy for adequate exposure of the tumour, inviting a range of complications not seen in TORS alone, namely osteoradionecrosis, oro/pharyngocutaneous fistulae, bone exposure, malunion and the potential need for hardware removal.[208] The fistula rate was only 0.6% in **The RECUT Review**. This may be attributed to the reduced tissue disruption seen in TORS when compared to open surgery.[166] It may also be due to low rates of concurrent neck surgery for vessel identification if free flap reconstruction can be avoided. It seems, therefore, that the side effect profile of TORS, in this context, is acceptable, and even preferable to open surgical options.

The fistula rate was almost identical in **The RECUT Study** at 0.7% compared to 0.6% in **The RECUT Review**, giving validity to the latter. However, the rate of free-flap reconstruction was considerably higher with 20.1% (n=56/278) participants undergoing the procedure compared to only 4.1% (n=6/148) in **The RECUT Review**. Of note, the free-flap failure rate observed in **The RECUT Study** was comparable to that seen in

primary cases in the HNC literature at 5.4% (n=3/56), compared to Crawley et al.'s 4.8%.[209] This is reassuring in the context of previous radiation therapy which, will have impacted on the viability of the recipient vessels in the neck, and is evidence of appropriate case selection.

Functional outcomes

In primary HNC patients, the long-term swallowing results may be worse in radiotherapy patients than those undergoing surgical resection.[210,211] Additionally, swallowing outcomes following radiation frequently continue to worsen over time.[212,213] Newer techniques like intensity-modulated radiation therapy (IMRT) attempt to spare sensitive structures important for swallowing, such as the superior constrictors, to mitigate the impact of irradiation.[214]

The majority of cases identified in **The RECUT Review** had their TORS for tumours present in previously irradiated volumes (**Table 3-3**), and so, their swallowing potential may have been inherently limited. Despite this, perioperative and long-term gastrostomy rates were relatively low at 25.0% and 5.0%, respectively. Tracheostomy rates were also low (22.3% perioperatively, 1.9% long-term).

The peri-operative use of gastrostomies and tracheostomies may be particularly influenced by local departmental policies and practices. The principal indication for peri-operative tracheostomy usage in these patients is for airway control in the event of haemorrhage. At around one in 10 patients having a bleed, it is unlikely that this tracheostomy rate will change considerably in the future. Conversely, rates of prophylactic peri-operative gastrostomies may fall as better understanding is gained of the predictors of post-operative swallowing function in this cohort.

The presence of a gastrostomy tube has often been used as a surrogate measure of swallowing in the literature.[215] This may underestimate the extent of oropharyngeal dysphagia in the head and neck cancer population as many will continue eating and drinking in the absence of a feeding tube, despite patient-reported and instrumentally-defined swallowing safety and efficiency issues. However, more granular and validated measures of swallowing function are utilised widely, both in clinical practice and in the literature. For example: Morisod et al. used the Functional Outcome Swallowing Scale (FOSS) to report outcomes but did not differentiate results for the second primary tumour cohort[183,216] and Paleri et al. used the Performance Status Scale for Head and Neck Cancer Patients (PSS-HN), reporting 11 patients with valid data at six months with variable outcomes.[166,184] The MD Anderson Dysphagia Inventory has also been widely utilised to record the impact of dysphagia on HNC patients.[217] Consistent reporting of any change in swallow function would be welcomed in future reports of TORS in previously treated HNC patients, as would the adoption of a consistent timeframe for what is considered 'long-term' for these functional outcomes. Increasing numbers of HNC clinical trials are adopting a more uniform and targeted approach to multidimensional swallowing evaluation.[134,218] Careful consideration should be given to which swallowing measures are selected. A recent study evaluated commonly used dysphagia outcome measures and mapped them to the International Classification of Functioning, Disability and Health (ICF).[219] Measures primarily addressed body functions with few concepts linking to activity, participation and environmental factors. This impacts on a more holistic and representative understanding of the impact of dysphagia following HNC treatment.

Voice outcomes have not been well reported in the studies in **The RECUT Review**. A significant proportion of the patients identified had had oropharyngeal resections, which would have inevitably affected the soft palate, and so the naso-oropharyngeal junction, integral to normal voice production and avoidance of hypernasality. Velopharyngeal insufficiency is further impaired by low rates of free flap reconstruction in these TORS oropharyngeal resections, giving less tissue bulk at the junction, and reduced tissue pliability, as a result of previous irradiation.[212,213] Two of the included studies made comment on voice outcomes: Dabas et al..[173] reported altered resonance in 10% of patients in the immediate post-operative period that persisted into the long-term and Krishnan and Krishnan[182] reported 'poor voice outcomes' following secondary tracheoesophageal puncture in their single case of TORS total laryngectomy performed for recurrent glottic SCC. Full functional outcome data, including any impact on speech production, should be presented to patients considering TORS for recurrence, to enable informed decision-making.

Mandatory prospective, systematic data collection of both survival and functional outcomes should be considered to ensure high quality reliable data are available to facilitate decision making by patients and clinicians alike. The authors propose the use of PSS-HN pre-operatively and at 12 months as a minimum dataset for future reports.

The functional outcomes presented in **The RECUT Study** compare favourably to open surgery alternatives, with only 37.9% and 39.2% peri-surgical tracheostomy and gastrostomy rates, respectively, compared to 79% and 75% reported previously by White et al..[181] Further comparisons between studies is challenging due to the lack of consistent reporting of standardised measures of swallowing. However, even in isolation, the high rate (73.8%) of disease-free patients tolerating a soft diet or better on PSS-HN NoD score at one year post-surgery, is in support of TORS in this population.

The RECUT Study collected data on peri-operative tracheostomy and gastrostomy usage but, as can be seen from the one year data in **Table 3-8** and **Figure 3-18**, the vast majority of tracheostomy placement (89%), and around half of gastrostomy placement (47%), appears to be prophylactic as usage did not persist into the longer-term. Tracheostomy is performed before TORS to facilitate surgical access to the tumour in a pharynx crowded with instruments during the procedure by removing the need for an endotracheal tube. It is also commonly placed to cover for bleeding in the post-operative period for one to three weeks. Additionally, a prophylactic gastrostomy is commonly performed to avoid the logistics of feeding via a narrow nasogastric tube for several weeks. Thus, these procedures are not necessarily undertaken for organ dysfunction in the preoperative setting, rather they may be sited for their anticipated short-term benefits.

Ward et al. conducted a similar retrospective multi-centre review from seven institutions and including 412 participants, with 39.1% having pre-existing organ dysfunction (defined as feeding tube or tracheostomy tube dependence).[162] It is noted that they specifically excluded routine prophylactic placement of feeding tubes from their definition of organ dysfunction. Organ dysfunction is used to partition those less than or equal to two years from first course of radiation into the poorest prognostic group (Class III) if present. However, it is not clear what proportion of the 39.1% with organ dysfunction were at this time from treatment and how many were more than two years (for whom organ dysfunction was not used as a classifier). Further, it is not clear how many were tracheostomy dependent versus gastrostomy dependent, or both. Nor is it clear how the classification of organ dysfunction related to the further tumour site undergoing re-irradiation, which may also

have differed considerably from that seen in our cohort as only 27.2% of their cohort was oropharyngeal, compared to 93.2% in **The RECUT Study.**

3.2.7 Limitations to our understanding about TORS for recurrent HNC

Due to the relative scarcity of these surgeries, the search strategy for **The RECUT Review** was intentionally broad and the inclusion/exclusion criteria were not too stringent. As a result, the case mix is fairly heterogeneous. The cases identified covered surgery for residual disease, for recurrence and for new primaries, both at the same subsite and elsewhere in the head and neck. The tumour biology of the tumours seen in these various scenarios may be very different and ideally these groups would be considered separately. Similarly, a variety of head and neck subsites are reported on and considered together where they may be observed to have differing outcomes if the volume of cases were sufficient to allow sub-group analysis (although the majority are acknowledged to be early stage oropharyngeal SCCs).

Publication bias must be considered when interpreting the results of **The RECUT Review**. It is possible that only favourable outcomes will have been submitted by centres performing this type of surgery and also that smaller series which did not produce statistically significant outcomes may not have been considered by journals. Information regarding adjuvant treatment following TORS was not reliably reported and was not considered separately in **The RECUT Review**. Adjuvant therapy, including re-irradiation and systemic therapies such as chemotherapy and immunotherapy, may significantly affect both the disease free and overall survival.

The RECUT Study was able to address many of the drawbacks of meta-analysis of already published data by collecting data at an individual patient level. Regardless, there are some areas where limitations are insurmountable. The study was observational, without random assignment of subjects. As such, there will inevitably be an inherent selection bias in the participants included. However, the comprehensive reporting of clinicopathological characteristics from this multi-centre consecutive cohort should allow the meaningful translation of outcomes to similar patients across multiple settings. Additionally, there was no centralised pathological review for the included cases with the local assessment instead being relied upon to determine histopathological classification and margin status. Finally, margin status was not available for all cases (69.8%).

Conclusions about TORS in recurrent HNC

TORS in patients with previously treated head and neck cancers is an emerging but relatively infrequent procedure. Analysis of the contemporary literature in **The RECUT Review** and of individual patient data from multiple international institutions in **The RECUT Study**, has shown favourable survival and functional outcomes from TORS used for the management of residual, recurrent and new primary HNC in previously irradiated fields. In selected patients, who predominantly have early-stage recurrent oropharyngeal SCCs, serious complications from TORS were not common and functional results were appreciable, but acceptable. The required surgical resection margin in these patients may be narrower than previously thought and concerns about potential narrow margins should not, in themselves, be a contraindication to consideration for TORS. Where feasible, and where resources and expertise allow, TORS should be considered as the preferred surgical treatment in the salvage setting for HNC. In practice, this may mean not all centres can or should be offering TORS for residual or recurrent disease but should ensure patients should have access to this treatment through onward referral, as appropriate.

THESIS CONCLUSIONS

The three parts of this thesis consider three different aspects of head and neck cancer care over seven chapters. All three parts have used direct engagement of surgeons around the UK to exploit a multi-centre collaborative network to conduct the research therein. In addition to the immediate clinical knowledge gained from these works (which have been discussed and concluded in their relevant parts), the novel techniques employed by the author and the research team have demonstrated the efficacy of the surgeon-led multi-centre collaborative model. A summary of the benefits of these is presented below.

Independence

Traditional research models rely on Research and Development (R&D) departments to oversee and help conduct multi-centre research studies. Moving away from this framework gives autonomy to the surgeon researcher. The project management team can still insist on local registration with appropriate supervising bodies but, for most, this will be a more accessible clinical governance department, sitting separate to the commonly more onerous R&D structure that fully sponsored studies mandate.

This had the added benefit that, during the COVID-19 pandemic, when research efforts and resources were being directed to a minority of supported studies, the present research team could still pursue their work without reliance on the R&D framework.

Additionally, even set-up and close-down of the most basic study will attract costs from trial manager time at participating units. This is often a barrier to participation and avoiding these costs helps increase the number of contributing centres, being more likely to include centres who may not have established research departments and so spare resources to lend to studies without funding or reimbursement. Without the wide engagement of multiple centres, our opportunity to learn from recent advances in knowledge or management (e.g., the impact of HPV status or the adoption of TORS or PET-CT) could be delayed.

Rapid deployment and conduct

Core development by a project management team and overall support from national bodies, such as ENT UK and BAHNO, allowed for suitable projects to be developed and disseminated rapidly. Handling of only anonymised data and the commitment to perform no centre level analysis also ensured data submission could be processed in a timely manner, commonly limited only by time availability from the clinicians collecting it, and without having to rely on undue scrutiny from the local Caldicott Guardian.

Simplicity to promote engagement

The project management team produced study protocols, user guides and standardised data collection tools to make participation straightforward for clinicians. For projects using the traditional R&D framework, these efforts were still relevant and appreciated as clinicians were ultimately the driving force behind bringing the studies into their centres and overseeing the collection of accurate clinical data as the Principal Investigators.

Data completeness and integrity

The use of standardised electronic data collection tools, with drop-down menus and data validation, ensured homogeneity of data from the submitting units. They also facilitated simple amalgamation of data by the project management team as the submitted digital records were all in a harmonised format that could be combined into a single master database. As data were received and added to the amalgamated master database it could be continually monitored, using prewritten code, to check for data completeness and unique variables. Standardised automated emails were produced to highlight missing or ambiguous data, allowing any remaining queries to be challenged in an efficient and clear way.

Reward

Clinicians satisfying criteria pre-specified in the study protocol could be included in the final authorship, including collaborative authorship, where appropriate. Other contributions could be recognised with standardised certificates emailed out, benefiting from the use of automated processes due to numbers involved (e.g., **Appendix 2**). Both these outputs provided evidence for participation in the projects which is essential for recognition at appraisals or revalidations. During the conduct of this doctorate, in response to the take-up of collaborative projects such as those contained within this thesis (and instigated in ENT by the trainee-led collaborative model championed by INTEGRATE), the higher surgical training appointment process for ENT registrar began attributing credit for involvement in multi-centre collaborative research projects (**Appendix 27**).

Rapid feedback to clinical practice

Rapid assimilation of data in a standardised format allowed analysis to progress apace, even before all data had been received and cleaned. This facilitated the timely production of interim reports, national presentations and final manuscripts for peer-reviewed publication for prompt dissemination of knowledge to the HNC community.

Final conclusions

Collectively, the studies within this thesis have moved the field of HNC forward and their outputs have helped demonstrate the benefits of surgeon-led multi-centre collaborative research.

Evidence has been provided in support of remote triage for suspected HNC referrals, as well cautioning against its adoption in post-treatment HNC surveillance. This helped lay the groundwork for the largest randomised trial in ENT which will continue to research this topic in the coming years.

Our knowledge base for unknown primary head and neck squamous cell carcinoma has grown. Step-serial sectioning was shown to be superfluous in the processing of diagnostic oropharyngeal specimens obtained from tonsillectomy and TBM and single modality surgery has been questioned as an appropriate treatment for those with unilateral neck disease starting treatment without a primary site identified. All HNC MDTs in the

UK have inputted into the next iteration of the UK MDT guidelines which followed these works and the largest consensus event ENT UK have ever conducted.

TORS for residual and recurrence HNC has been shown to be effective even in the presence of what might be regarded as close surgical margins. Data from international centres has shown, where feasible, TORS should be considered the preferred surgical treatment in the salvage setting.

Surgeon-led multi-centre collaborative research places the onus for developing and disseminating, then conducting and concluding, research projects onto the clinician. The projects within this thesis have engaged hundreds of surgeons across the UK rapidly to report real-world data both within and aside from the traditional R&D framework. The resultant knowledge has already been widely disseminated to the HNC community, incorporated into national guidelines, and has catalysed the largest randomised trial in HNC care. Therefore, the overarching hypothesis can be accepted, surgeon-led multi-centre collaborative has been shown to be an effective model.

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APPENDICES

Appendix 1: The HNCTT Study user guide

ENTUK
Head and Neck Society

A user guide to the ENT UK 2WW telephone triage service evaluation

Thank you for your interest in the ENT UK 2WW telephone triage service evaluation.

Please find the latest version of all relevant documents here: https://entintegrate.co.uk/entuk2wwtt

Email 2wwtt@entintegrate.co.uk for support.

You can start using the tool immediately but will not be able to submit any data to the project management team until local approvals are in place.

Key steps to get started

- Download and save a personal copy of the Excel spreadsheet, in line with local data governance (links above).
- **Each clinician should take responsibility for their own spreadsheet.**
- Multiple Excel spreadsheets can be amalgamated at the end of the Telephone Triage period, before submission of any data.
- **This Triage Tool is a decision aid. You should use your clinical judgement at all times.**

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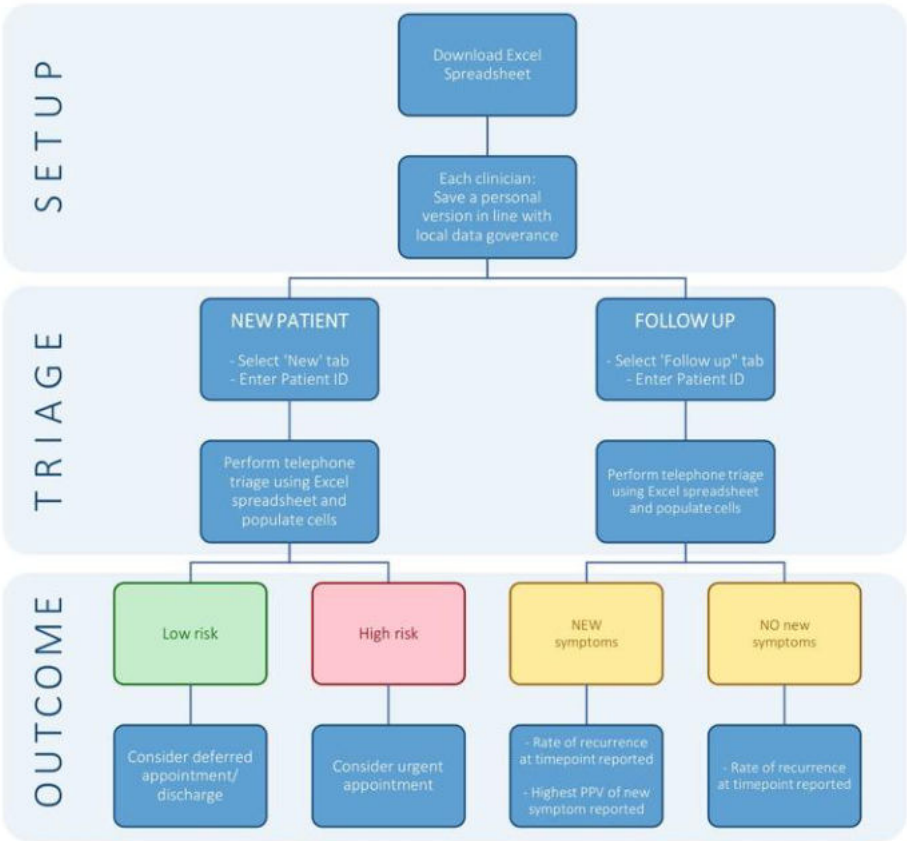
Flowchart



Notes:

- Clinician should use clinical judgement, alongside the result from the triage tools, when advising the patient of the recommended outcome.
- Patient preference should be recorded. Some may decide not to attend for face to face consultation even if recommended. Others may be very anxious and warrant face to face review for reassurance.
- Record both clinician and patient views, alongside the outcome from the discussion.

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New patients: Suggested script

Introduction:

You have been referred to us by your doctor with a suspected head and neck cancer. Owing to the coronavirus pandemic, we are trying to reduce unnecessary hospital visits for outpatient appointments to prevent the spread of the infection. We have therefore converted your appointment into a telephone consultation. I will be asking you a series of questions about you and your symptoms, after which I will estimate the probability of head and neck cancer in your case. This will be done using a risk calculator that we have created from over 10,000 UK patients. We will then decide together whether we should see you in a face to face clinic appointment.

[Perform consultation using calculator]

Outcome:

Low risk (If the outcome box is GREEN):

The risk calculator suggests that people with your type of symptoms have a very low probability of a cancer in the head and neck region. By not being seen in clinic, the chance of missing a cancer in people such as yourself is less than 2%.

Either :

We would therefore recommend bringing you in for a consultation once the pandemic issues have settled.

Or:

We would therefore recommend discharging you.

Or:

I still have clinical concern and would recommend we arrange an urgent appointment to see you in clinic.

High risk (If the outcome box is RED):

The risk calculator suggests that people with your type of symptoms might have a higher risk of a cancer in the head and neck region.

Either :

We would therefore recommend we arrange an urgent appointment to see you in clinic.

Or:

However, I don't have much clinical concern and would therefore recommend bringing you in for a consultation once the pandemic issues have settled.

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Follow up patients: Suggested script

Introduction to decision tool

You are under follow up for your previous cancer in the head and neck region.

Owing to the coronavirus pandemic, we are trying to reduce unnecessary hospital visits for outpatient appointments to prevent the spread of the infection. We have therefore converted your appointment into a telephone consultation.

I will be asking you a series of questions about you and your symptoms to help us decide if we need to see you in clinic.

Information from over 5,000 consultations have been used to help inform this decision.

[Perform consultation using decision aid]

Outcome:

Clinical Judgement

Taking everything into account:

Either :
We would recommend bringing you in for a consultation once the pandemic issues have settled.
Or:
I think you would benefit from being reviewed face to face, so I would recommend we arrange an urgent appointment to see you in clinic.

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Process for obtaining local approvals

- Identify a Consultant at your trust who will take responsibility for the project at your hospital. This person will be known as the '**lead consultant**'.
- Identify one member of clinical staff who will be responsible for collating the data and submitting the anonymised data to the project management team. This person will be known as the '**site lead**'. This may be the same person as the lead consultant.
- Register your interest in participating here: https://forms.gle/hLtLSY6zHuMhktDq9
- Identify clinical staff who will be performing telephone triage and inform them of the project and procedures.
- Register the project with your local Clinical Governance Department responsible for the conduct of local service evaluations. This may be done by the lead consultant and/or the site lead.
- Data collection can begin in anticipation of local approvals, but data cannot be submitted to the project management team until local approvals are in place.
- You may have rotated away from your trust when the follow up data is due to be collected. Please ensure you hand over appropriately to ensure the service evaluation is completed.

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Troubleshooting

The 'Results' section is empty

Please some data to activate the row.

The 'Results' section isn't giving me an answer

Not all of the triage questions have been answered. Results will only be given when all relevant fields are completed.

I can't copy and paste data in the sheet

The 'Results' column(s) is protected so can't be overridden. You can copy and paste all the other data but will have to do it in two 'halves', either side of the 'Outcomes' box.

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Final steps

Follow up data collection

6 months after the triage period has concluded, we'll ask you to contact the patients' GPs to see if the patients have developed H&N or oesophageal cancer since the triage was performed. This outcome is entered onto the eCRF data collection tool in the final column.

Amalgamating multiple Excel files

If you have used more than one file, you can copy and paste the data into a single document for submission. However, you can't override the 'Outcomes' box as it is protected. So the data must be copied in two 'halves': everything to the left of the outcomes box and everything to the right of the outcomes box.

Any problems, please email 2wwtt@entintegrate.co.uk for support.

Submission

Once follow up data has been recorded, and local approvals are in place, please remove the patient ID and submit the Excel file to the email address provided.

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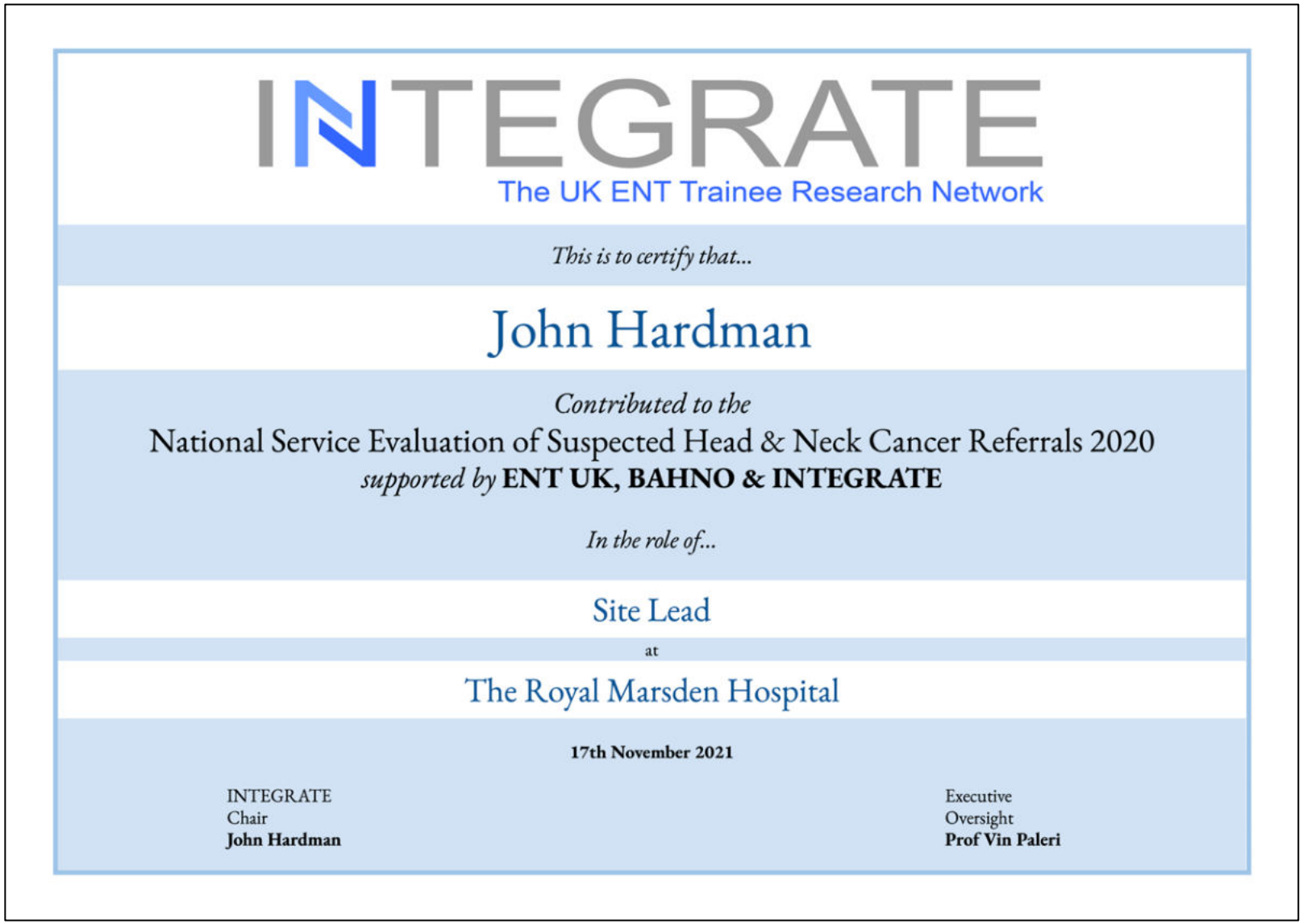
Appendix 2: Certificate of participation for the HNCTT Study for suspected HNC



INTEGRATE

The UK ENT Trainee Research Network

This is to certify that...

John Hardman

Contributed to the

National Service Evaluation of Suspected Head & Neck Cancer Referrals 2020

supported by **ENT UK, BAHNO & INTEGRATE**

In the role of...

Site Lead

at

The Royal Marsden Hospital

17th November 2021

INTEGRATE
Chair
John Hardman

Executive
Oversight
Prof Vin Paleri

Appendix 3: The HNCTT Study contributors and affiliations

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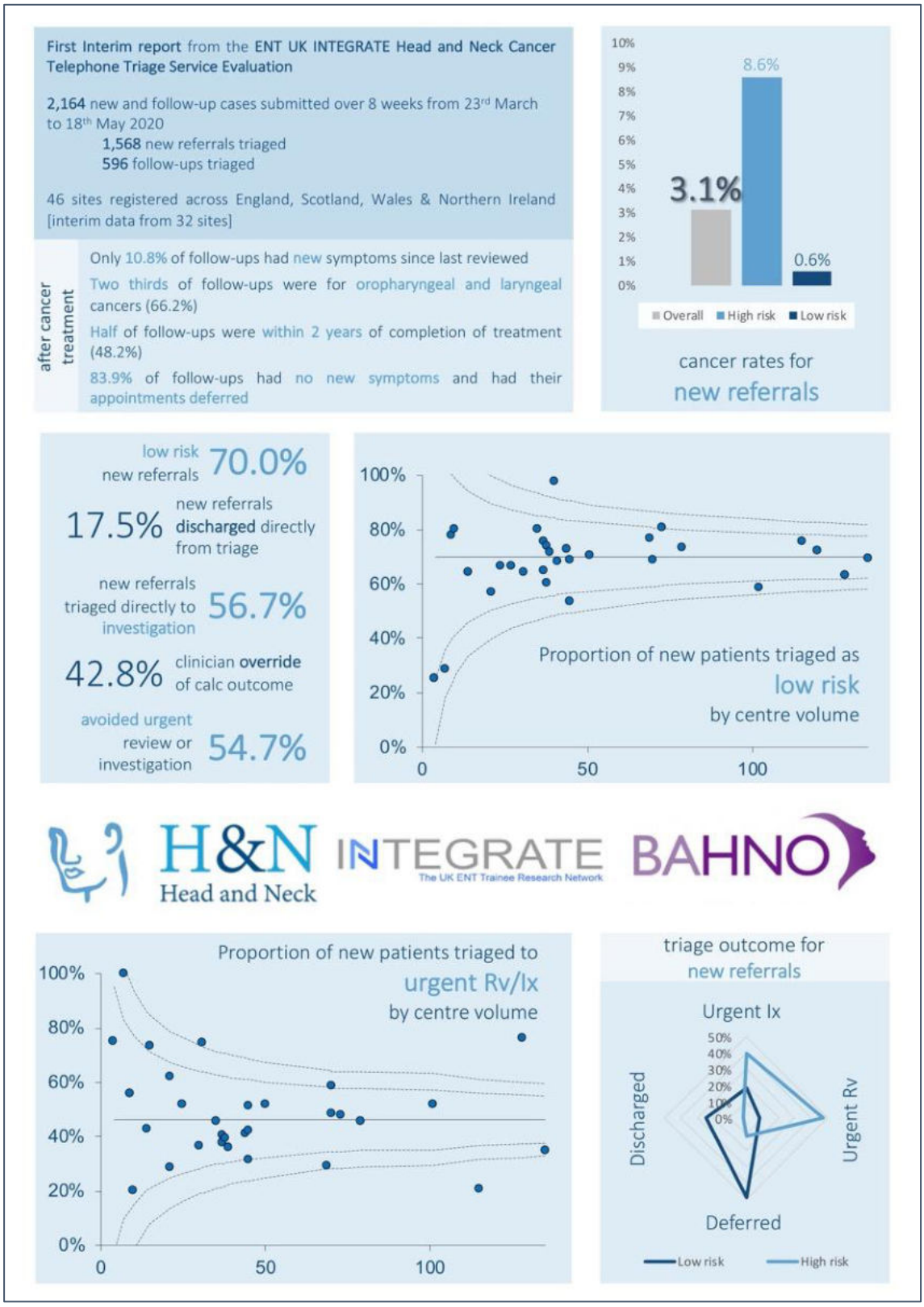
Appendix 4: The HNCTT Study Interim Report


First Interim report from the ENT UK INTEGRATE Head and Neck Cancer Telephone Triage Service Evaluation
2,164 new and follow-up cases submitted over 8 weeks from 23rd March to 18th May 2020
1,568 new referrals triaged
596 follow-ups triaged
46 sites registered across England, Scotland, Wales & Northern Ireland [interim data from 32 sites]
after cancer treatment
Only 10.8% of follow-ups had new symptoms since last reviewed
Two thirds of follow-ups were for oropharyngeal and laryngeal cancers (66.2%)
Half of follow-ups were within 2 years of completion of treatment (48.2%)
83.9% of follow-ups had no new symptoms and had their appointments deferred
10%
9%
8%
7%
6%
5%
4%
3%
2%
1%
0%
8.6%
3.1%
0.6%
Overall
High risk
Low risk
cancer rates for
new referrals
low risk new referrals 70.0%
17.5% new referrals discharged directly from triage
new referrals triaged directly to investigation 56.7%
42.8% clinician override of calc outcome
avoided urgent review or investigation 54.7%
100%
80%
60%
40%
20%
0%
0
50
100
Proportion of new patients triaged as
low risk
by centre volume
H&N
Head and Neck
INTEGRATE
The UK ENT Trainee Research Network
BAHNO
Proportion of new patients triaged to
urgent Rv/Ix
by centre volume
triage outcome for
new referrals
Urgent Ix
50%
40%
30%
20%
10%
0%
Discharged
Urgent Rv
Deferred
Low risk
High risk

ENT UK
INTEGRATE
HN Cancer Telephone Triage
Service Evaluation

Registered site list available here

Thank you to everyone who is taking part

1ST June 2020

Introduction

This report provides a snapshot of early experience with rapid implementation of a remote triaging system for assessment of suspected head and neck cancer (HNC) referrals, based on the head and neck cancer risk calculator (HaNC-RC) [1, 2]. Remote triaging has never been used in such a large scale for new head and neck cancer (HNC) referrals or follow-up patients, and thus no prior data exists. This interim report aims to achieve the following:

- Allow comparison of **local performance** against the **national average**
- Provide information on the proportion of **low and high risk referrals**, and their **triage outcomes**
- Provide early insight into the **oncological outcomes** of the remote triage implementation

Two systematic reviews have identified pooled detection rate of cancer in patients referred for assessment of suspected HNC from primary care as 8.8% [3] and 11.1% [4] respectively, with the range being from 2.2% to 14.6%.

Results

Interim data were submitted by 32 of the 46 NHS centres signed up to this national service evaluation. This submission covered an 8 week period, from announcement of the study on the 23rd March, to the 18th May. Data were available for 1,568 cases of suspected HNC, with diagnosis of confirmed cancer being recorded in 3.1% of all cases at the time of this interim submission. The cancer rate is currently 0.6% for low risk referrals and 8.6% for high risk referrals (see bar chart).

The majority of referrals were low risk (70.0% , n=1,069/1,528) with larger volume centres showing less spread (see funnel plot). Only one of 30 centres was outside three standard errors of the mean, likely related to incomplete data submitted by the unit.

Following telephone triage, 17.5% of referrals (1.6% of high risk and 24.4% of low risk) were **discharged** on the basis of the telephone consultation alone. Less than half of all referrals (45.3% , n=768/1,404) were planned for urgent clinic review and/or investigation (urgent Rv/Ix; see radar chart); thus, 54.7% of suspected HNC patients **avoided an urgent hospital visit** during the peak of the pandemic. All centres except two were within three standard errors of this mean figure; the centre with the lowest rate of urgent Rv/Ix (20.9%) was declared the epicentre of COVID-19 in the early days of the pandemic outbreak in the UK.

An **investigation** was performed as the first urgent contact in 56.7% (n=250/441) with 75.2% (n=188/250) of these either being subsequently discharged or offered delayed follow up only; thus avoiding an urgent face to face review during the worst of the pandemic. Among patients who were recommended urgent Rv/Ix, 6.6% (n=42/636) have been diagnosed with cancer by the time of this interim submission.

[Please note, only 45.3% (n=288/636) of those urgently investigated/reviewed had a confirmed outcome for cancer. As this data has been collected for an interim submission, this rate reflects patients still on the diagnostic pathway as well as those for whom cancer outcome data is missing. Patients who underwent urgent Rv/Ix, and were subsequently discharged, were assumed to be cancer free for this interim analysis.]

Impact of the findings

The pressure on resources placed by the suspected cancer referrals system prior to the pandemic is well known and described in the literature. Cancer Research UK estimates that 2,300 cancer cases per week are likely to go undiagnosed every week across the UK during the pandemic [5].

Across all cancers, it has been estimated that a delay of three months across all 94,912 patients who would have had surgery to remove their cancer over the course of a year would lead to an additional 4,755 deaths in England [6]. Thus, the pressure on resources for provision of cancer care, both diagnosis and treatment, is likely to be even greater in the coming months. Even when clinical services resume, more clinic time and PPE resources are needed to evaluate patients as the assessment of the majority within this patient group involve aerosol generating procedures. Any appropriate reduction in hospital visits, face to face assessment and investigations will thus be beneficial. The proportion of patients discharged following remote triage alone (17.5%), is an immediate resource gain.

Next steps

In 2018/19, 207,501 suspected HNC referrals were seen within NHS England. While HNC specialty associations have generated guidelines for the management of confirmed cancers [7], none exist for these suspected cancer referrals. Unlike other cancers (lung, breast, prostate) no screening tests exist for HNCs; however, symptom inventories seem to be an efficient way to separate the high risk individuals referred in from primary care. In our parallel survey, 92.3% of respondents indicated that the remote triaging system was likely to carry on at their centre for at least the next **3 months**.

This is an opportunity to radically **reform** the system, arisen due to a unique need to rationalise healthcare. A key priority of a service implementation such as this should be to ensure a safe system that does not miss out cancers following remote triage. Generated from over 10,000 patients, HaNC-RC has a high negative predictive value, with only a 1.4% chance of missing cancers in patients categorised as low risk. A large proportion of low risk patients were still urgently investigated or reviewed from our data and so it is hoped this chance is even lower for these patients triaged during the pandemic. However, this is a new implementation of the calculator in a new population and so it's **safety** needs to be robustly evaluated.

An important measure to assure patients and clinicians will be to assess the HNC status in those patients who have been discharged, or have their appointments deferred on the basis of the triage, at a defined period in the future. Based on the natural history of HNCs, it is reasonable to confirm cancer status at 6 months from the date of the initial referral, and use this as the gold standard. We would therefore urge all centres to make a special effort to submit complete data for further reports as patients migrate through the diagnostic pathway.

This also is an opportunity to **evolve** the HaNC-RC based on the data emerging from the real world implementation. As experience with the system increases, it has become evident that the remote triaging process can be cumbersome. Work is progressing apace to allow patients to complete their symptomatology electronically (subsequently risk stratified by the HaNC-RC) and to submit these data alongside audio recordings, photos and videos as applicable, to allow asynchronous remote triaging based on the most relevant and informative data.

Registered centres: Colchester General Hospital (Arcot Maheshwar, Emma Nunn); Royal Albert Edward Infirmary, Wigan (Vijaya Pothula, John Rocke); Royal Blackburn Hospital (Anurag Daudia); Sunderland Royal Hospital (Nashreen Oozeer, Chris Rusius); Aberdeen Royal Infirmary (Kim Ah-See, Anas Gomati); Princess Alexandra Hospital, Harlow (Elina Kiverniti); Northwick Park Hospital, London (Taran Tatla, Phui Yee Wong); Raigmore Hospital, Inverness (Angus Cain, Fergus Cooper); Royal Berkshire Hospital, Reading (Dilip Nair, Jenny Walton); Countess of Chester Hospital (Fernando Galli, Rohan Pinto, Robert Temple, Shehzad Ghaffar); Guy's Hospital (Jean-Pierre Jeannon, Misha Verkerk, Ali Al-Lami, Aina Brunet); Craigavon Area Hospital (Ramesh Gurunathan, Brendan Wright); Ninewells Hospital, Dundee (Jaiganesh Manickavasagam, Richard Steven); Walsall Manor Hospital (Mark Simmons, Ahmad K. Abou-Foul, Emmanuel Diakos); Hinchingbrooke Hospital, Huntingdon (Xenofon Kochilas); York Hospital (Richard Taylor); Queen Elizabeth Hospital Birmingham (Neil Sharma, Nikoleta Skalidi); Paul Montgomery Private Practice (Paul Montgomery); Stepping Hill Hospital, Greater Manchester (Vivek Kaushik, Shameena Shinaz, Namit Agarwal, Laxmi Ramamurthy, Milan Rudic, Mamoona Khalid Raja); West Suffolk Hospital, Bury St Edmunds (Martinez Del Pero, Laura leach); Antrim Area Hospital (Andrew Kelly, David McCrory); John Radcliffe Hospital (Stuart Winter); Cumberland Infirmary, Carlisle (Paul Counter, Harry Tustin, Graham Putnam, Andrew Robson); The Royal Liverpool University Hospital (Katherine Davies , Anne markey); East Surrey Hospital, Redhill (Karan Kapoor, Sean Fang); Watford General Hospital (Chee Toh, Rohit Pratap); The Royal Marsden Hospital (Vinidh Paleri, Bhav Patel); Blackpool Victoria Hospital (Paul Hans , Catriona Shenton); Royal Preston Hospital (Arun Cardozo, Babatunde Oremule); Kent & Canterbury Hospital (Vikram Dhar, Katherine Steele); Northampton General Hospital (Mrinal Supriya , Elizabeth Mathew); Milton Keynes University Hospital (Adam Shakir, Prathibha Nanoo); Aintree University Hospital (Christopher Loh, Mila Roode); Glangwili General Hospital, Carmarthen (Vinod Prabhu); Chase Farm Hospital, London (Yogesh Bhatt, Guled Jama); University Hospital Crosshouse, Kilmarnock (Richard Townsley, Robin Crosbie, Lorna Langstaff); St John's Hospital, Livingston (Iain Nixon, Shiying Hey); University Hospital Monklands, Airdrie (Ian Smillie, Theofano Tikka); Manchester Royal Infirmary (MRI) (Jarrod Homer, Melanie Dowling); Pinderfields Hospital, Wakefield (Sinnappa Gunasekaran, George Brown); Wythenshawe Hospital, Greater Manchester (Rohit Kumar, Rupali Sawant); Royal Victoria Hospital, Belfast (Barry Devlin, Gillian Gray); Broomfield Hospital, Chelmsford (Mark Puvanendran, Maria Kiakou); Basingstoke and North Hampshire Hospital (Paul Spraggs, Daniel O'Sullivan); Warrington Hospital (Sri Bathala , Rosie Wright); Princess Royal University Hospital, Orpington (Roland Terry, Rohan Vithlani)

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British Association of Head and Neck Oncology: President Cyrus Kerawala

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7. Mehanna H, et al. Recommendations for Head and Neck Surgical Oncology Practice in a setting of acute severe resource constraint. A Consensus Statement. Lancet Oncology 2020 (in press)

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Prathibha Nanoo	Trainee Site Lead	Milton Keynes University Hospital
Rajeev Advani	Local Collaborator	Manchester Royal Infirmary (MRI)
Robert Temple	Local Collaborator	Countess of Chester Hospital
Rohan Pinto	Trainee Site Lead	Countess of Chester Hospital
Rohit Kumar	Consultant Lead	Wythenshawe Hospital, Greater Manchester
Rupali Sawant	Trainee Site Lead	Wythenshawe Hospital, Greater Manchester
Sabarinath Vijayakumar	Trainee Site Lead	Birmingham City Hospital
Shameena Shinaz	Trainee Site Lead	Stepping Hill Hospital, Greater Manchester
Shehzad Ghaffar	Local Collaborator	Countess of Chester Hospital
Shiying Hey	Trainee Site Lead	St John's Hospital, Livingston
Sian Dobbs	Trainee Site Lead	Royal Preston Hospital
Stuart C Winter	Consultant Lead	John Radcliffe Hospital
Sumrit Bola	Trainee Site Lead	John Radcliffe Hospital
Thushanth Sooriyamoorthy	Local Collaborator	Chase Farm Hospital, London
Vanushia Thirumal	Local Collaborator	Aberdeen Royal Infirmary
Vinod Prabhu	Consultant Lead	Glangwili General Hospital, Carmarthen
Vivek Kaushik	Consultant Lead	Stepping Hill Hospital, Greater Manchester
Yogesh M Bhatt	Consultant Lead	Chase Farm Hospital, London

Appendix 6: EVEREST-HN contributors and affiliations

Name	Position	Role	Affiliation
Vinidh Paleri	Co-Lead Applicant/ Chief Investigator	Consultant ENT surgeon and Professor of Head and Neck Surgery	The Royal Marsden NHS Foundation Trust
Joanne Patterson	Co-Lead Applicant/ Chief Investigator	Professor of Speech and Language Therapy	University of Liverpool
John Hardman	Deputy Chief Investigator	Clinical Research Fellow and ENT Specialty Registrar John, as deputy CI, will provide overall programme leadership, will co-lead on WP4 and coordinate national recruitment with INTEGRATE for successful delivery of EVEREST-HN.	The Royal Marsden NHS Foundation Trust
Nikki Rousseau	Co-applicant	Dr Rousseau is a University Academic Fellow in Healthcare Technology Evaluation; expert in qualitative and mixed methods in health care technology development and evaluation; she will lead on process evaluations and phase 1 of SYNC platform development. Dr Rousseau will also be involved in phase 2 and phase 3 of the platform development, especially in the co-design stages	University of Leeds
Kimberley Kavanagh	Co-applicant	Senior Lecturer in Public Health Statistics; will lead on algorithm exploration and development in WP4	University of Strathclyde
Rebecca Randell	Co-applicant	Professor in Digital Innovations in Healthcare; expert in digital innovation; will lead on intervention co-design and human-computer interaction in WP2.	University of Bradford
Richard Hooper	Co-applicant	Professor of Medical Statistics at the world leading Pragmatic Clinical Trials Unit; experts in cluster RCTs; will lead on cluster RCT design and analyses (WP5)	Queen Mary University of London
Borislava Mihaylova	Co-applicant	Professor of Health Economics at the world leading Pragmatic Clinical Trials Unit; experts in cluster RCTs; will lead WP6, the health economic analyses.	Queen Mary University of London
Chris Elkington	Co-applicant (PPI representative)	Chris will be an active member of the overall PMG and Trial Management Group, contributing to running of the project; being involved in decision-making, collaboratively pre-empting barriers, highlighting any delays against the timeline and jointly generating solutions, providing his unique perspective. Chris is integral to the dissemination plan, advising on outputs to non-specialist audiences, ensuring clear, accessible messages and language. Chris has already commented on several aspects of research plan, detailed in the PPI section.	Member of the public
Paula Bradley	Co-applicant	General Practitioner with a special interest in Head and Neck diseases, PhD on HNC referrals, former head and neck surgical trainee: will lead on scoping review for symptom inventory in WP1 and primary care engagement and dissemination.	Northumbria Healthcare NHS Foundation Trust
Lisa Emery	Co-applicant	Lisa Emery is a certified Healthcare Chief Information Officer, member of Digital Health Advisory Panel; will lead on the technical liaison with Microsoft, and integration of SYNC system in hospital workflows. Lisa will lead on WP2.4 and on the roll out of the SYNC system to centres when the clinical WPs commence. At the end of the study, Lisa will liaise with NHS Digital on the implementation of intervention nationwide	The Royal Marsden NHS Foundation Trust
Karan Kapoor	Co-applicant	Consultant Head & Neck and Thyroid Surgeon; industry liaison lead (Microsoft) and will lead on engagement with all multidisciplinary professional organisations.	East Surrey Hospital
Theofano Tikka	Co-applicant	ENT surgical trainee, PhD student (Public Health); will be clinical champion for Scotland, Wales and Northern Ireland and coordinate trainee engagement through the INTEGRATE network.	NHS Greater Glasgow & Clyde
Jan van der Meulen	Co-applicant	Professor Jan van der Meulen will work closely with Dr Kate Walker (Associate Professor of Medical Statistics, and Prof. David Cromwell, Professor of Health Services Research at the LSHTM. Both will bring advanced skills in analysing large complex data sets for the purpose of healthcare performance monitoring. They have extensive experience in developing risk modules, linkage of multiple datasets, handling missing and inaccurate data. Both will co-lead WP2 for the entire duration of the project.	London School of Hygiene and Tropical Medicine
Ian Kellar	Co-applicant	Dr Ian Kellar is a health/social psychologist with extensive experience of developing and evaluating interventions that use behaviour change techniques for implementation both in the UK and in LMICs. Ian has been an investigator on research grants totalling £18.7 million of funding. He will lead on co-design of behaviour change intervention materials for the EVEREST-HN pathway for the intervention for EVEREST-HN.	University of Leeds
Cyrus Kerawala	Co-applicant	Professor Kerawala is Consultant Maxillofacial and Head and Neck Surgeon. He is also Vice President of the British Association of Oral and Maxillofacial Surgeons. CK was Clinical Lead for the NICE guidelines on HNC management (2016) and has experience as chair in other NICE cancer guidelines. Cyrus will lead on engaging the maxillofacial/oral medicine community, patient groups, NICE for implementation strategy and also offer strategic leadership in outputting the results into the wider NHS.	The Royal Marsden NHS Foundation Trust

Correct at time of grant application submission

Appendix 7: EVEREST-HN Letter of support from RMH

The ROYAL MARSDEN
NHS Foundation Trust

30 March 2021

The Royal Marsden
Fulham Road
London SW3 6JJ
Tel 020 7352 8171
www.royalmarsden.nhs.uk

NIHR PGfAR Funding Committee
NIHR Central Commissioning Facility
Grange House
15 Church Street
Twickenham TW1 3NL

Dear NIHR funding committee,

RE: NIHR202862: Evolution of a patient-reported symptom-based risk stratification system to redesign the suspected Head and Neck cancer referral pathway (EVEREST-HN)

We jointly write to you in our capacities as the Chief Executive and Clinical Director of Research and Development of The Royal Marsden NHS Foundation Trust. We strongly support the highly collaborative and ambitious programme of work developed by Professor Paleri and Mr Hardman, alongside Professor Cyrus Kerawala. Together, they have assembled an impressive team, across a broad range of clinical and methodological fields and we look forward to supporting the delivery of this work.

The Royal Marsden is a research active and comprehensive cancer centre rated 'Outstanding' by the Care Quality Commission. It has an internationally recognised track record in research, and together with its academic partner, the Institute of Cancer Research (ICR), the joint institution is ranked in the top 5 cancer centres in the world for research impact. The team will have access to significant research infrastructure, including an extensive programme of patient and public involvement (PPI) work. The Royal Marsden benefits from a dedicated lead expert in PPI, a large cohort of patient and carer representatives, many patient and public involvement fora, and a bespoke digital platform for engagement with patient and public representatives. Finally, through RM Partners Cancer Alliance, the Royal Marsden plays an important leadership role in delivering NHS England's National Cancer Strategy. The research team will be able to draw on this experience of leading the rapid transformation of cancer care systems to improve cancer outcomes, improve survival and quality of life.

The proposed programme will be driven by a strong clinical research leadership. Professor Paleri is a member of the ICR faculty and a pioneering surgeon at The Royal Marsden, with a focus on and outstanding research track-record on the processes of care, decision making and functional outcomes for head and neck oncology patients. He is a well-respected thought leader, currently serving as Chair of Research for the British Association of Head and Neck Oncologists (BAHNO) and recently appointed as their President Elect. He regularly contributes to national discussions in his field through the National Cancer Research Institute, NIHR and NICE Guideline committees. Professor Paleri also has an excellent track record in developing clinical research capacity and we endorse his efforts to support Mr Hardman on his path toward research leadership. Mr Hardman is a surgeon and clinical researcher who works alongside Professor Paleri at The Royal Marsden and will shortly complete his PhD at the ICR. He helped establish, and now Chairs, the UK Ear Nose and Throat Trainee Research Network and has delivered a number of national and international

multicentre collaborative studies. Most recently he led the work that underpins this funding application; analysing symptom data and cancer status from almost 5,000 patients undergoing risk stratified remote triage in 41 UK centres. Professor Kerawala is a maxillofacial surgeon based at The Royal Marsden and is Clinical Lead of the Head and Neck Unit. He specialises in surgical treatment of mucosal and cutaneous malignancy of the head and neck and, in particular, reconstruction of the post-ablative defect. He is current President of BAHNO and is President Designate of the British Association of Oral and Maxillofacial Surgeons (BOAMS). He has chaired and contributed to NICE guidelines on Upper aerodigestive tract and Oesophago-gastric cancers and was former Chair of the Intercollegiate Board in Oral and Maxillofacial Surgery.

We understand that the key product of the programme will be a digital triage platform that could revolutionise the cancer care pathway for those with suspected head and cancer, and in turn have a transformative impact for cancer waiting times, patient experience, time to treatment and clinical outcomes. The Trust is particularly well positioned to innovate in the digital space, with strong supplier partnerships (including through its local Microsoft agreement) which are already delivering novel technology solutions. Our c-suite includes a Chief Information Officer (CIO), who is a co-applicant on EVEREST-HN team, is a member of national professional advisory groups, and chairs the London CIO Council. We believe her strong networks and influence at a local and national level with NHS digital bodies will be an important enabler to the spread and adoption of the main research product.

On behalf of The Royal Marsden, we provide our strong commitment and support for Professor Paleri, Mr Hardman, Professor Kerawala and their team's application. We are confident that they will successfully deliver this programme that aims to improve the diagnostic pathway for suspected head and neck cancer patients. Most importantly, the results of this programme could greatly improve the experiences of cancer patients, both at The Royal Marsden and across the UK.

With best wishes.

Yours sincerely,

Cally Palmer

Dame Cally Palmer DBE
Chief Executive
The Royal Marsden NHS Foundation Trust

Professor David Cunningham OBE MD FRCP FMedSci
Head of the Gastrointestinal & Lymphoma Unit
Director of Clinical Research
Director of The Royal Marsden/Institute of Cancer Research NIHR Biomedical Research Centre

Appendix 8: EVEREST-HN NIHR PGfAR award letter (£3.0m)

NIHR | National Institute for Health Research

Professor Vinidh Paleri
Professor Jo Patterson
By Email

CENTRAL COMMISSIONING FACILITY
Grange House
15 Church Street
Twickenham
TW1 3NL

Tel: 020 8843 8000
Fax: 020 8843 8001
Email: ccf@nihr.ac.uk
www.nihr.ac.uk/ccf

16 August 2021

Dear Professor Paleri and Professor Patterson,

NIHR Programme Grants for Applied Research reference number: NIHR202862
Programme Title: EVolution of a patiEnt-REported symptom-based risk stratification sySTem to redesign the suspected Head and Neck cancer referral pathway (EVEREST-HN)

I am pleased to inform you that the committee has recommended your application submitted for consideration in Competition 34 for funding and the Department of Health and Social Care, in their capacity as the National Institute for Health Research (NIHR), has confirmed their intention to award funding upon acceptance of the terms and conditions set out in the Standard Research Contract and pending agreement to the suggested *key* amendments recommended by the committee, as detailed in the accompanying document.

The Standard Research Contract, between Contractors and the Secretary of State for Health and Social Care for all initiatives can be found on the NIHR research contract - NHS Trust example webpage.

The attached outcomes table contains the anonymised scores from the Stage 2 Committee meeting where your application was assessed. It is intended to aid you in contextualising your feedback from the Committee.

Your anonymised code is: C34-0621-2004

Next Steps

The NIHR is committed to the rapid initiation of research following the decision to fund to benefit patients as soon as possible. Therefore, we expect funded researchers to be working towards gaining the necessary contractual agreements and governance approvals required to start the project by a date mutually agreed by both parties on acceptance of the award.

The NIHR acknowledges the risk to organisations around committing resource to research before a contract is in place; however, it is rare to not reach contractual terms unless the circumstance of the research team changes. The NIHR, therefore, encourages organisations to commit staff to setting up projects at as early an opportunity as possible in order to expedite the formal commencement of research.

It is acknowledged that there can be unforeseen delays in starting up a research project, but in order to help reduce these it is your responsibility to work closely with your organisation's R&D department or equivalent as well as other colleagues / departments involved in the administration and management of the research, and to start these discussions at the earliest opportunity.

To ensure that the project starts within the agreed timeframe with all the required agreements and approvals in place, appropriate staff (such as project and/or study managers) need to be in post as early as possible after receiving this letter of intent. These staff costs will ultimately be covered through the research funding award, but you are encouraged to meet them from Research Capability Funding (RCF) prior to the research contract being agreed.

To support the often-iterative process towards agreement of the contract, we have set out the guiding timeframes for the submission of responses or information for each step towards the agreement of the Standard Research Contract as well as the anticipated start date.

- Confirmation of acceptance of funding – no later than 23 August 2021
- Responses to Committee feedback and queries – no later than 31 August 2021
- Response intellectual property queries – 10 September 2021
- Submission of draft collaboration agreements and/or subcontracts (where applicable) – At a mutually agreed date
- Contract signature – 6 months from the date of letter
- Contracted commencement start – A mutually agreed date

On receipt of information as set out above, the NIHR through the Central Commissioning Facility is committed to responding to your submission of information within two weeks or we will update you on progress.

Finance Queries

Alongside the scientific and intellectual property negotiations, you may be also required to provide some further information regarding the application's budget, which will be used to prepare the contract for this award. Please note that you will be contacted about this separately by the CCF Finance Department (finance&contracts@nihr-ccf.org.uk).

Please take the time to carefully read the enclosures to this letter which details the feedback on your application, the processes to be undertaken during the next steps, as well as additional information relating to your award.

Yours sincerely,

RS Flora

Rajinder Flora *Assistant Director, Programme Grants for Applied Research*

The Central Commissioning Facility is based at and managed by LGC Twickenham

Appendix 9: The MOSES Study Grant Award Letter (£118k)

ORACLE
cancer trust

Leading Research into Head and Neck Cancer

13th December 2018

GAL_RMH131218

Oracle Cancer Trust

RESEARCH GRANT AWARD

Oracle Cancer Trust (the "**Trust**") hereby confirms the award of a Research Grant for 24 months with a start date of 3rd October 2018:

Name of Project Research Leader:	Professor Vinidh Paleri
Name of Funded Researcher (if known):	Dr John Hardman
Title of Research Project:	"Evaluation of the role of tongue base MucOsectomy and Step sErial Sectioning in the diagnostic paradigm for unknown squamous cancers (MOSES)"
Name of Research Institution and address:	The Royal Marsden Hospital NHS Trust, Fulham Road, London SW3 6JJ

This award is granted and has been approved by the Research Committee, Finance and Investments Committee and Board of the Trust because the research project "Evaluation of the role of tongue base MucOsectomy and Step sErial Sectioning in the diagnostic paradigm for unknown squamous cancers (MOSES)" complies with the strategic objectives of the Trust as a pioneering piece of research that has shown potential to identify new treatments and discoveries to benefit head and neck cancer.

The amount granted is a fixed sum of £117,991.39 over 24 months. The breakdown of costs is as follows:

- Year 1: £58,995.70
- Year 2: £58,995.70
- Year 3: n/a
- Year 4: n/a

Any additional fees or expenses related to this project will not be covered by the Trust.

This grant is conditional on fulfilling the following:

- grant funding from the Trust will be paid in arrears either quarterly, six monthly, or annually as agreed with the Trust in writing, prior to the commencement of the research project. On signing this agreement by all parties, **The Royal Marsden NHS Trust** agrees to comply with this. Failure to provide a payment schedule prior to the commence date of 1st October 2018 will result in the forfeiture of the grant funding;

- the Trust must be notified, in writing, giving at least one month's notice of the start date of the research project with the full name of the researcher who will be undertaking the funded project;

Registered Charity 1142037
4819-8495-5475\1

Company Registered number 7125497

- should the funded researcher be unable to complete their obligations due to sickness or other reasons, the Trust must be notified immediately; should the project not be completed for any reason, residual funds will revert to the Trust and must be refunded within one month from the termination of the project;
- the recipient must require the researcher **Dr John Hardman** and/or the research leader **Professor Vinidh Paleri** to present, on an annual basis, both a written and verbal update to the Research Committee at a time and date to be confirmed by the Head of Operations at the Trust at a Central London venue. Failure to comply with providing an update will result in forfeiture of funding from the Trust;
- the final grant payment will be settled when a final report on the outcome(s) of the funded project have been received and approved by the Research Committee and Board Members of the Trust;
- during the lifetime of the research project and any subsequent further research work based on the intellectual property of the research project, any publications, written articles, awards, recognitions, blogs, verbal or written presentations or marketing must include a reference to the Trust in the form of a logo, where appropriate, and acknowledgement of funding;
- the Trust reserves the right to withdraw its support if it considers the progress of the research, or the manner in which it is being conducted to be unsuitable; and
- copies of any articles published as a result of the research should be sent to the Trust at least 30 days before submission for consideration before publication. It is expected that the support of the Trust will be acknowledged.

It should be noted that the grant is subject to and forms part of the current overarching grant terms and intellectual property agreement entered into by the Trust and The Royal Marsden Hospital NHS Trust on (this is currently under approval).

For and on behalf of Oracle Cancer Trust:

Peter Rhys Evans
Chairman

Date: 13/12/2018

Jamie Newall
Chief Executive

Date: 07/01/2019

Registered Charity 1142037

Company Registered number 7125497

ORACLE
cancer trust

Leading Research into Head and Neck Cancer

For and on behalf of The Royal Marsden Hospital NHS Trust:

Name: Professor Vinidh Paleri
Position: MOSES Project Research Lead

Date: 13th December 2018

Registered Charity 1142037
4819-8495-5475\1

Company Registered number 7125497

Appendix 10: The MOSES Study BRC Grant application (£20k)

Pilot project title

Part of the MOSES study: Evaluation of the role of tongue base mucosectomy and Step serial Sectioning in the management of the unknown primary squamous cell cancer in the head and neck.

Project lead

Chief Investigator: Professor Vinidh Paleri. Consultant Head & Neck and Thyroid Surgeon, The Royal Marsden Hospital, London. Professor of Head & Neck Surgery, The Institute of Cancer Research, London.

Clinical Research Fellow: Mr John Hardman. The Institute of Cancer Research, London. Specialty Registrar in Otorhinolaryngology, The Royal Marsden Hospital, London.

Total funding amount requested (please note this can be lower than the maximum available per project) and details of the costs

Total funding secured for this project to date:	£ 182,991.39

- Sources included a grant from the Oracle Cancer Trust, and from contributions from ENTUK (British Association of Otolaryngologists) and The Royal College of Surgeons of England.
- This principally covers the histological processing and the Clinical Research Fellow (John Hardman).

Funding requested from the TPT Theme Pump Priming 2019/2020:	**£ 20,000.00**

- Further funding is sought to facilitate transfer of the tissue specimens from participating national centres, via RMH, to the laboratories in Newcastle for processing. We have received the following quote for this work:

  Logistical processing costs are based on biobank accepting, tracking, data management, and dispatching out to Newcastle for 60 patients over a 12 month period. The following is based on 1,800 blocks in total (prediction of 30 blocks per patient – 60 patients in total):

Summary	
Logistical processing costs	*£6,981.23*
Storage costs	*£180.00*
Maintenance and Calibration Costs	*£0.00*
Consumables costs	*£68.75*
Postal Service costs	*£550.00*
Total	***£7,779.98***
Total inc. £5000 set-up fee	***£12,779.98***

- Further funding is also sought for:
  - Transfer of specimens *to* the RMH (60 patients).
  - Repatriation of the slides and any remaining blocks to RMH for storage.
  - Facilitation of Qualitative interviews: Reimbursement of patient travel costs, room hire, basic catering/tea/coffee, interview transcription and a licence for the NVIVO coding analysis software.

Proposed start date (please note that the project should finish by 31 March 2020)

1st May 2019

Unmet clinical need and your proposed solution to meet this need

To improve the identification of the primary site in head and neck (H&N) cancer patients with cancers of unknown primary. Despite improvements in imaging, many patients complete their

diagnostic pathway without successful identification of the primary cancer site. Many of these cancers are thought to have originated from the oropharynx. Recently, a procedure known as a tongue base mucosectomy has allowed removal of the lymphoid tissue from the back of the tongue, known as the lingual tonsil. This is improving detection rates but still a proportion of primary cancers are never identified. A prospective study will compare techniques for tongue base mucosectomy (endoscopic, transoral laser and robotic) and apply a novel histological technique to look at the tissue obtained from this surgery, and from concurrent bilateral tonsillectomy, in greater detail.

Project objectives and plan

The aim of the MOSES study is to establish if step serial sectioning, compared to and conventional histology, improves identification of a primary site in bilateral tonsillectomy and tongue base mucosectomy specimens in cancer of the unknown primary in the H&N.

Patients undergoing tongue base mucosectomy will be recruited prior to surgery. After conventional histology, the remaining tissue blocks will be centralised to the Newcastle laboratories for step serial sectioning.

After step serial sectioning, the tissue will be returned to RMH for storage and for future study of immunolandscaping of these difficult to detect occultomas.

Patients will also be asked to report their pain and functional outcomes prior to surgery and at 3 weeks, 6 weeks, 3 months, 6 months and 12 months.

A smaller cohort of patients will also be interviewed, as part of a qualitative research methodology, to understand their perceptions on management of the unknown primary and on transoral robotic surgery.

Fit with Theme's aims and objectives

Fitting with the BRC TPT Theme global aim, this study (and the subsequent studies that are intended to stem from it on immunolandscaping and the Phase III RCT) will provide evidence for emerging technologies to direct loco-regionally targeted therapies (in this case surgery in the diagnostic setting and subsequent radiotherapy if a further cancer identified). Identification of, and/or complete removal of, the primary site could increase the cure rate from cancer of the unknown primary and/or reduce the size of the radiotherapy field to treat these patients.

There is active patient involvement through questionnaires of pain and functional outcomes, and through qualitative patient interviews.

Potential impact on patients

Increased pick up of cancer of the unknown primary may allow more focused treatment to the primary site while potentially avoiding wide field radiation therapy, which is the current standard of care at some centres. This may also allay anxieties regarding the primary site not being identified.

Planned follow-on funding

The MOSES study will generate and refine a research question for a larger phase III trial in patients with SCC related cancer of the unknown primary, staged N1 to N2b.. Potential topics include precision radiation therapy and assessment of post treatment toxicity and functional outcomes.

Potential funders include CRUK and late phase NIHR and MRC streams.

Appendix 11: The MOSES Study contributors and affiliations

Name	Role	Affiliation
Max Robinson	Lead Pathologist	School of Dental Sciences at Newcastle University
Somiah Siddiq	Principal Investigator	Queen Elizabeth Hospital Birmingham
Vinidh Paleri	Chief Investigator	The Royal Marsden Hospital, London
Emma King	Principal Investigator	Poole Hospital
Sean Mortimore	Principal Investigator	Royal Derby Hospital
Francis Stafford	Principal Investigator	Sunderland Royal Hospital
Naseem Ghazali	Principal Investigator	East Lancashire Hospitals
Jemy Jose	Principal Investigator	Hull Royal Infirmary
Costa Repanos	Principal Investigator	Queen Alexandra Hospital, Portsmouth
Zaid Awad	Principal Investigator	St Mary's Hospital, London
Sandeep Berry	Principal Investigator	University Hospital of Wales
David Hamilton	Principal Investigator	Freeman Hospital, Newcastle upon Tyne
Stuart Winter	Principal Investigator	John Radcliffe Hospital, Oxford
Enyi Ofo	Principal Investigator	St George's Hospital, London
Cameron Davies-Husband	Principal Investigator	Royal Sussex County Hospital, Brighton
Gary Walton	Principal Investigator	University Hospital, Coventry
Asit Arora	Principal Investigator	Guy's and St Thomas' Hospitals
Shane Lester	Principal Investigator	The James Cook University Hospital, Middlesbrough
Ajith George	Principal Investigator	Royal Stoke University Hospital
Naveed Kara	Principal Investigator	Darlington Memorial Hospital
Khalid Ghufoor	Principal Investigator	The Royal London Hospital
David Walker	Principal Investigator	Royal Surrey County Hospital, Guildford
Zi Wei Liu	Principal Investigator	Northwick Park Hospital, London

Appendix 12: The MOSES Study patient information sheet

Patient Information Sheet

THE MOSES STUDY

Evaluation of the role of tongue base MucOsectomy and Step sErial Sectioning in the management of the unknown primary squamous cell cancer in the head and neck

Version:	v1.1
Date:	9th July 2019
Sponsor:	The Royal Marsden NHS foundation Trust Fulham Road London SW3 6JJ
Funders:	Oracle Cancer Trust 32-36 Loman St London SE1 0EH Biomedical Research Centre The Institute of Cancer Research 123 Old Brompton Road London, SW7 3RP
Chief Investigator:	Professor Vinidh Paleri Consultant Head & Neck and Thyroid Surgeon, The Royal Marsden Hospital, London Professor of Robotic & Endoscopic Head & Neck Surgery, The Institute of Cancer Research, London
Clinical Research Fellow:	Mr John Hardman The Institute of Cancer Research, London Specialty Registrar in Otorhinolaryngology, The Royal Marsden Hospital, London
Contact:	info@MOSESstudy.co.uk
URL:	www.MOSESstudy.co.uk

This Patient Information Sheet should be used in conjunction with the Informed Consent Form.

If you have any questions arising from the Patient Information Sheet, or the explanation given to you, please ask the researcher before you to decide whether to join in or not.

You will be given a copy of these documents for you to keep, so that you can refer to them at any time.

Page 1

MOSES (Evaluation of tongue base MucOsectomy & Step sErial Sectioning)

Introduction

We are a team of ENT surgeons and pathologists involved in the care of patients with Head and Neck cancer. We are inviting you to participate in research looking at cancers that are found in the lymph nodes in the neck, but where the original cancer has not yet been found. These pages provide information about for you to read prior to choosing if you would like to take part.

You can talk freely with anyone you feel comfortable talking to about this research. You can take time to reflect on whether you want to participate or not. If there are any words, terms or concepts that are unfamiliar to you, then please ask us to explain them to you. If you have any questions about any aspect of the research then you can ask any members of the research team at any time, including after you have consented.

What is the purpose of this research?

Around 5% of all head and neck cancers present with a lump in the neck but with no obvious site where it has spread from. These patients will undergo examination in clinic and also imaging like MRI, CT or PET CT to try and identify this primary site. One of the common sites where it may have originated is called the 'oropharynx'. This is the area in the back of your mouth and throat that includes the back of your tongue and your tonsils.

In around 1-2% of head and neck cancer patients this primary site is still not identified, and they may be recommended to undergo an operation to try and find it.

- One part of this operation includes looking and feeling around your throat, this is often called a 'panendoscopy'
- One part of this operation includes removal of the tonsils, called a 'tonsillectomy'.
- One part of this operation includes removal of the lining of the back of the tongue, called a 'tongue base mucosectomy (TBM)

This study is looking at patients undergoing tongue base mucosectomy. We want to see if a different way of looking at the tissue that has been removed can increase the number of cancers that are identified. We also want to see how patients recover from the operation by asking about pain and swallowing function.

How are we selecting patients?

We are asking everyone who is undergoing a tongue base mucosectomy operation to take part in this study. You may be having a tonsillectomy at the same time as your tongue base mucosectomy, or you may have had this procedure already. We would like to look at this tissue too, but this will not affect your eligibility to taking part in the study.

What would taking part involve?

Questionnaires

Before you undergo your operation, you will be given a questionnaire to get an idea of your baseline for any pain you may have in your mouth/throat and how good or bad your swallowing function is. The questionnaires take less than 5 minutes to complete.

You will also be given 5 more sets of these questionnaires. We are asking you to complete these at 3 weeks, 6 weeks, 3 months, 6 months and 12 months after your operation. The results of these questionnaires will give us an idea of how you recover over the first year following your operation and any other treatment you might have.

We have provided you with stamped addressed envelopes, so these questionnaires can be posted straight back to the MOSES team. Alternatively, you can give them to your local Doctors or speech and language therapists for them to post back to us instead. The results of these questionnaires will not routinely be fed back to your local team.

Once we receive the questionnaires back from you we will record the information onto a secure computer at the Royal Marsden Hospital in London.

Other research from your participation

Once your operation is complete, and the tissue has been examined by your local team, the results will be discussed at your local Multi-disciplinary Team meeting and will help to influence the management plan recommended to you. Once this decision has been made, the residual tissue from your operation will be sent to the laboratory in Newcastle listed at the beginning of this document. Here, the tissue will be looked at in more detail using a technique called 'step serial sectioning' where more slices are taken more frequently to see if there are any small or additional cancers that had been overlooked using conventional histology techniques. Once the tissue has been looked at in this way, it will be kept in case there is any other analysis that may be informative in future studies. The tissue is anonymised and contains none of your patient identifiable information.

Do I have to take part?

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. If you choose not to participate then your care will continue as normal and nothing will change.

How long will I be involved?

Your involvement in the study will be until the final questionnaire is completed. This will be at 12 months after your operation. You are not being asked to come to the hospital or see your doctor any more than you would normally do so.

You will also be asked if you are happy to be contacted by the MOSES team about answering some more questions about your experience of being diagnosed and investigated for cancer where the original disease has not yet been found. Involvement in this aspect of the study is entirely separate and only if you provide explicit consent and contact details on the consent form.

Will there be any future research coming from this study?

We would also like to keep some of the tissue at the end of this study for further research projects that may become applicable. Please let your researcher know if you would not like this to happen to your tissue.

What are the possible disadvantages and risks from taking part?

We do not anticipate any significant risks to you from taking part in this research.

What are the possible benefits from taking part?

We do not anticipate any direct benefits to you as an individual patient.

We hope that the information we gain from your experience of the operation will help inform care for future patients undergoing tongue base mucosectomy for investigation of cancer of the unknown primary in the head and neck.

We also hope that the information gained from the 'step serial sectioning' will tell us if this method should become the new standard for analysing tissue looking for cancers of the unknown primary in the head and neck.

Reimbursements

There will not be any additional costs to you, the patient, that would require any reimbursement.

Confidentiality

The information that we collect from this research project will be kept confidential. Your case will only be identified by a unique 'study ID' that is listed on this document. Your local team will keep a record that your case relates to this study ID and it will be stored in a secure location at your hospital, as per local data governance rules. The MOSES team will not receive any patient identifiable data. The study ID will be used by the MOSES team to ensure data is tracked appropriately, so we know how the study is recruiting, and so that any missing information is able to be followed up by the local teams.

What will happen with the results of this study?

Results from the study will be submitted for consideration of publication in the medical literature and shared at academic conferences for professionals involved in the care of head and neck cancer patients. Confidential information will not be shared.

What will happen if I don't want to carry on with the study?

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected. Your treatment will not be affected in any way.

Informing my General Practitioner

If you consent to participation in this study then we will inform your GP so that your health record can be kept up to date. If you would not like us to notify your GP, please inform the person asking you to consider taking part in this study.

Who has reviewed this study?

This study has been reviewed by the Committee for Clinical Research (CCR) at the Royal Marsden Hospital, by the London-Riverside Research Ethics Committee (REC) and by the Health Research Authority (HRA).

Who to contact if I have questions?

If you have any questions about this research, you can ask your local team in the first instance. Their contact information is provided below. Alternatively, if you have concerns, you may wish to contact PALS (Patient Advice and Liaison Service) who 'provide advice and support to NHS patients and their relatives and carers'.

Local Principal Investigator: _____

PALS (Patient Advice and Liaison Service): _____

If you would like to speak to the MOSES team directly, then please email the address below:

MOSES team: info@mosesstudy.co.uk

Who is organising the funding of this study?

This study has been supported by a grant from the Oracle Cancer Trust, which is a registered charity in England and Wales (1142037), a company limited by guarantee, a registered company in England and Wales (7125497). Their registered address is 10 Parsons Green House, 27 Parsons Green Lane, London SW6 4HH.

This study has also been funded by a grant from the Biomedical Research Centre, The Institute of Cancer Research, based at the Royal Marsden Hospital and the Institute for Cancer Research. The Institute for Cancer Research is based at 123 Old Brompton Road, London, SW7 3RP. It is a Charity, which is not for Profit, and a company Limited by Guarantee. Registered in England No. 534147. VAT Registration No. GB 849 0581 02.

The Clinical Research Fellow is supported by grants from ENT UK and the Royal College of Surgeons of England.

GDPR transparency statements from RMH

We need to provide you with information about how your data are processed for transparency purposes under the new General Data Protection Regulation, or GDPR as it is more commonly known.

The Royal Marsden NHS Foundation Trust (RM) is the sponsor (or co-sponsor or managing ICR sponsored studies) for this study based in the United Kingdom. We will be using information from your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. RM will not keep any identifiable information about you.

You can find out more about how RM uses your information by contacting the Data Protection Officer at RM. Email: dpo@rmh.nhs.uk.

Data provided directly by you for the purposes of research

Your hospital will collect information from your medical records for this research study in accordance with our instructions.

Your hospital will keep your name, NHS number and contact details confidential and will not pass this information to RM. Your hospital will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from RM and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Your hospital will keep identifiable information about you from this study for at least 1 year after the study has finished, in line with local policies and legal requirements.

Data provided indirectly from your medical records

RM will collect information about you for this research study from your hospital. Your hospital will not provide any identifying information about you to RM. We will use this information as outlined above.

Future research

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care

research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

Appendix 13: The MOSES Study informed consent form

MOSES Study: Informed Consent Form

This Informed Consent Form is for patients invited to participate in the study entitle **'Evaluation of the role of tongue base MucOsectomy and Step sErial Sectioning in the diagnostic paradigm for unknown squamous cancers'**, also known as the MOSES study.

Short title:	Evaluation of tongue base MucOsectomy & Step sErial Sectioning (MOSES)
Version:	1.1
Date:	9th July 2019
Sponsor:	The Royal Marsden NHS foundation Trust Fulham Road London SW3 6JJ
Funder:	Oracle Cancer Trust: GAL_RMH131218 Biomedical Research Centre: W94505-B062
Chief Investigator:	Professor Vinidh Paleri Consultant Head & Neck and Thyroid Surgeon, The Royal Marsden Hospital, London Professor of Robotic & Endoscopic Head & Neck Surgery, The Institute of Cancer Research, London
Clinical Research Fellow:	Mr John Hardman The Institute of Cancer Research, London Specialty Registrar, The Royal Marsden Hospital, London
Pathologist:	Dr Max Robinson Senior Lecturer in Oral Pathology School of Dental Sciences at Newcastle University Honorary Consultant Pathologist Newcastle upon Tyne Hospitals NHS Foundation Trust
Laboratories:	Royal Victoria Infirmary Queen Victoria Rd, Newcastle upon Tyne NE1 4LP

Instructions:

This Informed Consent Form should be used in conjunction with the Patient Information Sheet [version 1.]. Please ensure that there are 3 copies of this form:

- 1 copy for participant
- 1 copy for research study file
- 1 copy for participant's medical notes

Page 1

Evaluation of tongue base MucOsectomy & Step sErial Sectioning (MOSES)

Certificate of Consent

Statement by the patient

Please tick each box:

1. I have been invited to participate in the MOSES study, investigating the role of tongue base mucosectomy in cancer of the unknown primary in head and neck. ☐
2. I have read the relevant Patient Information Sheet [version 1.], or it has been read to me. I have had the opportunity to ask questions about it and, any questions I have been asked, have been answered to my satisfaction. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from this NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I understand my anonymised tissue samples will be shared with the MOSES team ☐
6. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers. ☐
7. I understand that the information held and maintained by this NHS Trust may be used to help contact me or provide information about my health status. ☐
8. I agree to my General Practitioner being informed of my participation in the study. ☐
9. I agree to take part in the above study. ☐

Patient Interviews

I am willing for the MOSES team to contact me using the telephone number below about being interviewed about my experiences to help guide future research. ☐

Signature of Participant: _____ **Date:** _____

Print Name of Participant: _____ **Date I read the Patient Information Sheet:** _____

Contact number: _____

Evaluation of tongue base MucOsectomy & Step sErial Sectioning (MOSES)

Statement by the researcher taking consent

I have accurately covered the information in this document with the potential participant, and to the best of my ability made sure that the participant understands what the research will involve, their rights of refusal and that it will have no impact on their care if they chose not to participate.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily. Copies of this consent form have been filed in accordance with the instructions above.

Print Name of Researcher taking consent: _____

Signature of Researcher taking consent: _____

Date: _____

Appendix 14: The MOSES Study extension IReC grant application (£98k)

The International Centre for Recurrent Head & Neck Cancer
Delivered by The Royal Marsden

Funded by The Royal Marsden Cancer Charity

Research Grant Application Form

This application form for is for research grants to be awarded by The International Centre for Recurrent Head & Neck Cancer (IReC), in partnership with the Royal Marsden Cancer Charity.

IReC is the world's first centre for recurrent head and neck cancers which aims to create a centre of international excellence and to set international standards in the curative treatment of recurrent head and neck cancers.

Application guidance:

- Proposed projects should conduct research for the benefit of patients with recurrent head and neck cancer.
- Funding applications are accepted for single year or multi-year projects.
- There are no formal restrictions on the amount of funding that can be requested.
- Applications will be reviewed initially by IReC management staff for overall alignment with IReC's strategic objectives and completeness of the application form.
- Following initial screening, suitable applications will then be subjected to peer review.
- Applications will not be considered if the project was previously shortlisted by the IReC Scientific Committee and IReC Oversight Committee, but was unsuccessful except those that have been reinvited to apply or deferred for future consideration by the IReC Scientific Committee and IReC Oversight Committee
- Please submit the completed application, and any supporting documents, to **IReC@rmh.nhs.uk**.

Section 1 – Applicant Details

Lead Applicant	
Title	Consultant Head & Neck Surgeon
Full name	Professor Vinidh Paleri
Institution	The Royal Marsden Hospital
Department	Head and Neck Unit
Telephone	07899 997141
Email	**Vinidh.paleri@rmh.nhs.uk**

Please summarise your relevant research experience
(Highlight your track record as a researcher including, but not limited, to examples of past research successes and published results) (max 300 words, bullet points accepted)

- Accrued the largest experience in Transoral Robotic Surgery in the UK.
- Pioneered a new robotic technique to remove radiorecurrent and radioresidual cancers and is the first surgeon in the UK to perform robotic free flap reconstructions
- Primary or co-recipient for 5 million in grant funding
- Published over 190 papers, and edited numerous work
- Currently serves as President of the British Association of Head and Neck Oncologists, and in the following national bodies ENT UK Head Neck Society, British Association of Robotics in Head and Neck Surgery, Laryngology Rhinology Section of the Royal Society of Medicine and Trustee for the Oracle Cancer Trust
- Chief Investigator for both national and international multi-centre clinical research studies including: The RECUT Study, The MOSES Study, The RECUT-Plus Study, EVEREST-HN, The STORM Study

Publications (recent and relevant)

- **Paleri V,** Patterson J, Rousseau N, Moloney E, Craig D, Tzelis D, Wilkinson N, Franks J, Hynes AM, Heaven B, Hamilton D, Guerrero-Urbano T, Donnelly R, Barclay S, Rapley T, Stocken D, (2018). Gastrostomy versus nasogastric tube feeding for chemoradiation patients with head and neck cancer: the TUBE pilot RCT.. Health technology assessment (Winchester, England). 22 (16).
- **Paleri V,** Hardman J, Tikka T, Bradley P, Pracy P, Kerawala C, (2020). Rapid implementation of an evidence-based remote triaging system for assessment of suspected referrals and patients with head and neck cancer on follow-up after treatment during the COVID-19 pandemic: Model for international collaboration.. Head & Neck. 42 (7).
- Tikka T, Kavanagh K, Lowit A, Jiafeng P, Burns H, Nixon IJ, Paleri V, MacKenzie K, (2020). Head and neck cancer risk calculator (HaNC-RC)-V.2. Adjustments and addition of symptoms and social history factors.. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 45 (3). ***Guideline editor***
- Tikka T, Pracy P, **Paleri V**, (2016). Refining the head and neck cancer referral guidelines: a two-centre analysis of 4715 referrals.. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto- Rhino-Laryngology & Cervico-Facial Surgery. 41 (1).

- Mehanna H, Hardman JC, Shenson JA, Abou-Foul AK, Topf MC, AlFalasi M, Chan JYK, Chaturvedi P, Chow VLY, Dietz A, Fagan JJ, Godballe C, Golusinski W, Homma A, Hosal S, Iyer NG, Kerawala C, Koh YW, Konney A, Kowalski LP, Kraus D, Kuriakose MA, Kyrodimos E, Lai SY, Leemans CR, Lennon P, Licitra L, Lou PJ, Lyons B, Mirghani H, Nichols AC, **Paleri V**, Panizza BJ, Parente Arias P, Patel MR, Piazza C, Rischin D, Sanabria A, Takes RP, Thomson DJ, Uppaluri R, Wang Y, Yom SS, Zhu YM, Porceddu SV, de Almeida JR, Simon C, Holsinger FC, (2020). Recommendations for head and neck surgical oncology practice in a setting of acute severe resource constraint during the COVID-19 pandemic: an international consensus.. The Lancet. Oncology. 21 (7).
- Bradley PT, Hall N, Maniatopoulos G, Neal RD, **Paleri V**, Wilkes S, (2021). Factors shaping the implementation and use of Clinical Cancer Decision Tools by GPs in primary care: a qualitative framework synthesis. BMJ Open. 11 (2).

Co-Applicant(s) (duplicate fields for each co-applicant)	
Title	Clinical Lecturer in Oncology
Full name	Dr Ben O'Leary
Institution	The Royal Marsden Hospital
Department	Head and Neck Unit
Telephone	07846 804601
Email	**Ben.OLeary@icr.ac.uk**

Please summarise your relevant research experience
(Highlight your track record as a researcher including, but not limited, to examples of past research successes and published results) (max 300 words, bullet points accepted)

- Clinical Oncology Academic Clinical Lecturer in dual clinical and academic training at The Royal Marsden Hospital and The Institute of Cancer Research.
- Awarded an NIHR Academic Clinical Fellowship at The Royal Marsden Hospital and The Institute of Cancer Research (ICR) in 2012.
- Won a prestigious MRC Clinical Research Training Fellowship to undertake a PhD in Professor Nick Turner's group at in 2015 the ICR. Led a large translational project investigating circulating tumour DNA samples taken in the PALOMA-3 trial, a randomized phase III study in breast cancer examining the benefit of adding palbociclib, a CDK4/6 inhibitor, to fulvestrant, an endocrine therapy. As part of this research developed expertise in droplet digital PCR and next-generation sequencing, using and adapting these techniques to allow genomic interrogation of plasma samples from patients to look for mechanisms of resistance and evolution.
- Awarded the Professor Alan Horwich prize for outstanding achievement in MSc and the ICR Chairman's Prize for outstanding PhD thesis in 2019.
- Work in Professor Turner's group has been at the forefront of the circulating tumour DNA and the CDK4/6 inhibitor fields, making significant contributions to both.
- Published first author articles in high-impact journals including *Cancer Discovery*, *Nature Communications* and the *Journal of Clinical Oncology*, and orally presented findings at both the AACR and ASCO meetings, being awarded a Conquer Cancer/Sherwin Family Endowed ASCO Merit Award and the Royal College of Radiologists Ross Prize in 2019. Invited speaker at AACR, ESMO, SABCS, Unicancer and the UK Interdisciplinary Breast Cancer Symposium.
- In September 2019 awarded an NIHR Academic Clinical Lectureship which allows protected time to further develop independent research career within the supportive environment of Nick Turner's lab, with full access to the key genomics technologies and bioinformatics support.

Co-Applicant(s) (duplicate fields for each co-applicant)	
Title	Clinical Research Fellow in Head and Neck surgery
Full name	Mr John Hardman
Institution	The Royal Marsden Hospital
Department	Head and Neck Unit
Telephone	07929 050304
Email	John.hardman@rmh.nhs.uk

Please summarise your relevant research experience
(Highlight your track record as a researcher including, but not limited, to examples of past research successes and published results) (max 300 words, bullet points accepted)

- Specialty Registrar in ENT in North London, Clinical Research Fellow at The Royal Marsden Hospital, and PhD student at The Institute of Cancer Research. Under the supervision of Professor Vinidh Paleri and Professor Kevin Harrington investigating the use of Transoral Robotic Surgery in the management of recurrent head and neck cancer, including the impact of surgical margins on disease control
- Clinical interest in surgeon led multi centre collaborative projects and helped establish INTEGRATE (The UK ENT Trainee Research Network) in 2015. As part of this, worked on three large prospective studies with national scope. These works have won the Journal of Laryngology & Otology Best Original Paper Prize in 2016, 2017 and 2018. First author on two of these publications (http://doi.org/10/gcs975 & http://doi.org/10/f8558z).
- Presented the National audit of head & neck cancer post-treatment surveillance 2018, winning the Best Podium Presentation at the BAHNO Annual Scientific Meeting 2019.
- Continues to develop multicentre projects, with particular interest in patient experience and quality of life (http://entintegrate.org).
- Clinical Research Fellow for The MOSES Study; The STORM Study; The RECUT Study and The Recut-Plus Study.
- Using this network investigated the use of symptom based remote triage in suspected head and neck cancer referrals, as well as for post treatment surveillance in the detection of recurrence, and will be further investigating this as Deputy CI for EVEREST HN, an NIHR Programme Grant starting in 2022

Publications (most recent):

- Zhu Y, McLaren O, **Hardman J**, Evans J, Williams R. Systematic review and meta-analysis of the diagnostic effectiveness of PET-CT versus MRI in the post-treatment surveillance of head and neck squamous cell carcinoma. J Laryngol Otol. 2022;1–31. doi.org/gpfjnr
- Smith ME, Jones GH, **Hardman JC**, Nichani J, Khwaja S, The INTEGRATE (The UK ENT Trainee Research Network) UK Acute Paediatric Mastoiditis Audit Collaborators, et al. Acute paediatric mastoiditis in the UK before and during the COVID-19 pandemic: A national observational study. Clinical Otolaryngology. 2021. doi.org/g2xr
- **Hardman JC**, Tikka T, Paleri V, on behalf of ENT UK, BAHNO and INTEGRATE. Remote triage incorporating symptom-based risk stratification for suspected head and neck cancer referrals: a prospective population-based study. Cancer. 2021. doi.org/grst.
- Smith ME,^ **Hardman JC,^** Mehta N, Jones GH, Mandavia R, Anderson C, et al. Acute otitis externa: Consensus definition, diagnostic criteria and core outcome set development. PLOS ONE. Public Library

of Science; 2021;16:e0251395. doi.org/gcj5. ^Joint first author.

- INTEGRATE (The UK ENT Trainee Research Network). Admission avoidance in acute epistaxis: a prospective national audit during the initial peak of the COVID-19 pandemic. Clin Otolaryngol. 2021; published online 16 Jan. doi.org/fqzg. ***Corresponding author. Steering committee.***
- INTEGRATE (The UK ENT Trainee Research Network). Admission avoidance in tonsillitis and peritonsillar abscess: a prospective national audit during the initial peak of the COVID-19 pandemic. Clin Otolaryngol. 2020; published online 2 Dec. doi.org/fk93. ***First author. Steering committee.***

Section 2 – Project Summary

Title
Evaluation of the role of tongue base MucOsectomy and Step sErial Sectioning in the management of the unknown primary squamous cell cancer in the head and neck (The MOSES Study).
Lay summary (max. 250 words)
Cancer in the head and neck often spreads to the glands in the neck (lymph nodes). We do not know why or how this happens, but once it does these patients are more likely to experience recurrence. In some patients the original area of the cancer cannot be identified – this is called 'cancer of unknown primary'. If the original cancer cannot be found it cannot be treated, and there is a risk that it will continue to grow and spread. This makes it more likely to be diagnosed after it becomes untreatable, or at a later stage where recurrence is more likely. The support requested from IReC will allow us to study the spread of these cancers to understand why and how it occurs, and how this might relate to recurrence after treatment. This work may also allow us to identify features that might make it easier to find these cancers in the future.

Proposed Start Date	01/03/2022	Proposed End Date	01/12/2027

Scientific Abstract
(max. 250 words)

The MOSES Study (NCT04151134) is a UK-wide multicentre study investigating the adequacy of current histopathological processing in the work-up of Head and Neck Squamous Cell Carcinomas (HNSCC) of unknown primary. The study hypothesis is that microscopic and/or multifocal head and neck squamous cell carcinoma (HNSCC) that present as unknown primaries, often with lymph node metastases, may be missed by conventional histology techniques, with initially occult primaries potentially presenting later as recurrence if untreated. MOSES originally investigated patients undergoing tongue base mucosectomy to try and find small primaries that may be missed by traditional techniques, by using step serial sectioning histopathological processing to look at the tissue in greater detail.

To take advantage of this unique cohort, building on the generosity of the patients who have participated and maximising its potential discovery opportunities, we would like to perform an additional translational phase of the study - using exploratory molecular analysis to better understand the tumour biology for those cancers that are able to evade clinical and radiological detection. As these patients' cancers almost uniformly presented with clinically evident lymph node metastases but occult primaries, this new study phase will also permit biological investigation into why it is that some cancers develop early or rapidly progressive lymph node metastases, but the primary cancer remains small. This in turn may permit insights into the fundamental mechanisms that underpin lymph node metastases more generally – a key unmet need in HNSCC, as patients with cancers that have developed clinically evident lymph node metastases are more likely to experience recurrence, even with the best available therapy.

Study Plan
(Please provide Project Description e.g. background & rationale, hypothesis & aims, methods/work plan and team)
(max. 5000 words)

Background & Rationale

Approximately 5% of head and neck cancer (HNC) present with a neck metastasis with no clinically evident primary site. Patients undergo clinical examination and cross-sectional imaging to attempt to identify this primary site. If the origin of the cancer is still not apparent, then FDG PET combined with CT can be used. A proportion of these patients will still not have their primary cancer identified. In these instances, patients would have traditionally undergone a panendoscopy including bilateral tonsillectomy and random biopsies, including of the tongue base. More recently, a surgical procedure called tongue base mucosectomy (TBM) has been used to remove all the mucosa and lymphoid tissue from the back of the tongue in an attempt to improve on the low diagnostic yield seen in random tongue base biopsies.

Currently, treatment strategies for CUP in H&N are not standardised. Management plans can vary from no radiation therapy addressing potential primary sites, with a watch and wait policy, to Elective Mucosal Irradiation (EMI) which can lead to significant early and late morbidity. Identification of the primary site has a number of potential advantages. The primary site may be completely excised with an adequate margin, in which case it may be suitable for single modality therapy. There may also be a significant negative psychological burden if the primary cancer has not been identified or addressed. Conversely, a positive margin in the resected specimen could indicate escalated therapy, with concomitant chemotherapy, if it felt to be inadequately excised (the procedure is diagnostic not oncological). Further, the identification of multicentric primary sites may also lead to an increased radiation field compared to if this added information were not available. The benefit of TBM is, as such, yet to be fully established.

Human papilloma virus (HPV) is thought to play a significant role in many of these cancers presenting as CUP.[6,7] Smaller or involuted primary foci are known to be more common in HPV related cancers which may be contributing to the apparent incidence of these unknown primaries, or occultomas as they may also be called. A histological technique called step serial sectioning (SSS) allows examination of tissue specimens in greater detail than conventional histology. It has not previously been used to investigate the primary site in head and neck cancer but the oropharyngeal tissues that potentially harbour these small primaries make a sensible target to pioneer its usage. It is hypothesised that utilising SSS on tonsillectomy and TBM specimens may increase the identification rate of the primary site and may subsequently affect recommended management.

Currently, we do not understand why some cancers present with cervical metastases with no evident primary site, and this is an understudied population. There has been an explosion in genomics research in many cancers, but this remains an understudied area in head and neck cancer. There are currently no treatments available to patients with head and neck cancer based on genomic insights. This study aims to begin to address the unmet need of patients who present with these poorly understood cancers and to provide a starting point for more detailed investigations into the relationships between cancer genomics and recurrence in head and neck cancer.

Hypothesis

Lymph node metastases from initially occult primaries have more mutations, copy number aberrations and aneuploidy compared to the primary disease, demonstrating mechanisms of metastasis and escape from immune surveillance.

Research plan

Of 100 recruited patients we anticipate identifying primaries to match with presenting lymph node metastases in 50%, such that the cohort for genomic analyses will comprise n = 50 patients, each with at least a primary cancer and match lymph node metastases.

The main analysis will consist of the exome sequencing of match primary and lymph node cancer. FFPE blocks will be retrieved from participating sites, and an H&E cut for assessment of tumour cellularity.

This will inform subsequent microdissection for extraction using the Qiagen AllPrep DNA/RNA kit. DNA will be quantified using the Invitrogen Qubit assay and with the Agilent TapeStation. Germline DNA will be obtained through buccal swabs provided by study participants.

Exome libraries will be prepared using the Nonacus Exome Tumour kit. Ben O'Leary, the translational lead for the study, has previously through collaboration compared exome sequencing from FFPE DNA to the Agilent SureSelect V6 workflow in cell free DNA (previously published in O'Leary et al 2018, Cancer Discovery), finding comparable quality metrics and feasibility for sub clonal deconvolution. Tumour exomes will be sequenced to a target coverage of 150X with matched germline sequenced to a coverage 50X.

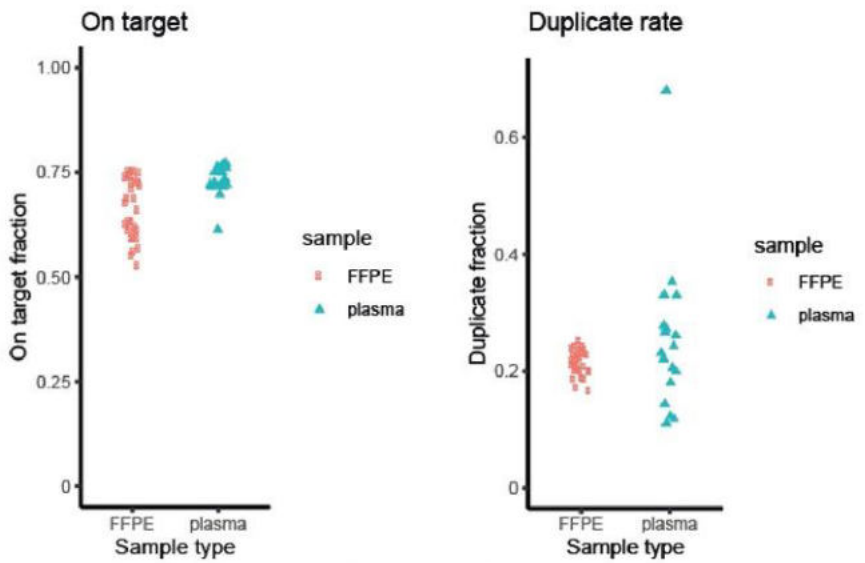

Figure 1. Quality metrics for sequencing from FFPE and plasma DNA.

Genomic variants including mutations, copy number, ploidy and neoantigens will be identified through comparison of tumour and germline DNA, and compared between primary and lymph node disease.

A further exploratory analysis will be performed on a subset of the samples to examine the differences between the primary and lymph node disease in the immune microenvironment at the RNA level, co-extracted with the DNA. A subset of 10 of the pairs will be subjected to assessment with the Nanostring PanCancer Immune Profiling panel. This will allow exploratory comparison between genomic features found in the cancers that might predispose to immune escape, such as loss of heterozygosity of the HLA loci and neoantigen prevalence, and immune signalling as assessed by the NanoString nCounter. This will provide a further discovery element to the project and a potential avenue allowing ongoing work in parallel to the genomics.

Incidence of recurrence will be collected and associated with molecular data in an exploratory, hypothesis-generating analysis, to inform future projects comparing primary and recurrent head and neck cancer.

Particular focus will be placed on any patients who completed their diagnostic pathway without a primary cancer being identified in whom a primary cancer emerges over the extended 5 year follow up period.

Team

The staff who will be supporting the delivery of The MOSES Study are listed below:

- Vinidh Paleri, The Royal Marsden, NHS.
- Ben O'Leary, The Institute of Cancer Research and The Royal Marsden Hospital.
- John Hardman, The International Centre for Recurrent Head and Neck Cancer.
- Amy O'Reilly, The Royal Marsden, Head and Neck Surgical Research Unit.

The costs for the research team are covered by existing resources.

Timeline
(Please detail the timeframe/Gantt chart of your proposal, including any significant milestones)

Please see the attached Gantt chart for this proposal.

Legacy
(If your intention is for the project to continue after the initial funding has finished, please describe what your next steps would be and how the project will be sustained)
(max. 200 words)

The MOSES study has been fully costed with previous funding secured from Oracle, ENT UK and a BRC Pump Priming grant.
The funding requested from IReC will allow us to extend the MOSES Study and conduct the research outlined in this proposal.
Currently we do not have plans to extend the study beyond proposed research plan.

Section 3 – Impact

Please describe the expected impact of the project and measurable outcomes you expect to achieve.
(max. 1000 words)

Impact

Identification and understanding of these cancers could have a number of potential benefits for patients in the future:

- Finding and removing the original cancer may allow optimisation of further treatment to reduce the risk of recurrence. Additionally, these patients may receive additional treatment with radiotherapy and chemotherapy, which have considerable side effects and might be modified or avoided altogether.
- There may also be a significant negative emotional and mental burden regarding the risk of recurrence if the original cancer has not been identified or addressed.
- Discovering new biology could lead to entirely new risk-assessment or even treatments for these cancers to help reduce the risk of recurrence.

Measurable outcomes we expect to achieve include:

- Recruitment of 100 patients to the MOSES Study.
- Completion of exome sequencing of match primary and lymph node cancer.
- Completion of exploratory analysis on a subset of the samples to examine the differences between the primary and lymph node disease in the immune microenvironment at the RNA level, co-extracted with the DNA.
- Exploratory analysis of incidence and patterns of recurrence and molecular features.

How will this proposal benefit recurrent head and neck cancer patients?
Please provide an explanation in lay terms what you hope to happen with the outcome of this grant, explaining the difference this will make to patients.
(max. 800 words)

Cancer in the head and neck often spreads to the glands in the neck (lymph nodes). We do not know why or how this happens, but once it does these patients are more likely to experience disease recurrence. In some patients where the cancer is first picked up in the lymph nodes, the original area of the cancer cannot be identified – this is called 'cancer of unknown primary'. If the original cancer cannot be found it cannot be treated, and there is a risk that it will continue to grow and spread. This makes it more likely to be diagnosed as recurrence after it has become untreatable. The support requested from IReC will allow us to study the spread of these cancers to understand why and how it occurs. This may allow us to identify features that might make it easier to find and treat these cancers in the future, reducing the chance of recurrence. This is discussed in more detail below.

Finding more cancers to reduce recurrences

Around 5% of head and neck cancers (HNC) are first noticed in a lump in the neck, but with no obvious starting place. Patients then undergo clinical examination and imaging scans to attempt to identify this original site where the cancer first started so the site can be treated along with the disease in the neck. If the original cancer is still not found, then specialised and costly imaging scans can be used. Despite this, a number of these patients will still not have their original cancer identified. These patients would have traditionally undergone a detailed examination of the mouth, nose and throat including removing the tonsils on both sides and taking random samples of tissue, including of the back of the tongue. More recently, a surgical procedure called 'tongue base mucosectomy' (TBM) has been used to remove all the tissue from the back of the tongue in an attempt to improve on the low numbers of cancers that are found with the traditional approach of random tissue sampling of the back of the tongue.

One potential way of improving the success rate for finding these cancers could be closely examining the surgical specimen in much more detail using a technique called 'step serial sectioning' (SSS). This involves taking many more slices of the tissue that has been removed and exhaustively examining each slice. SSS has not previously been used in this way in head and neck cancer before, but the tissues that may potentially have these small cancers make a sensible target to pioneer its usage. We think that using SSS in this way could increase the identification rate of the original cancer site and become a new standard of care for these patients.

Understanding why some cancers spread to the neck early

Another way of improving the success rate of finding and treating the original cancers could be by identifying features in the neck disease which give hints as to where the original cancer might be found, or how dangerous or difficult to treat the cancer is. At present we understand very little about how the biology varies between different head and neck cancers, and why some spread very quickly, and others don't.

Research Patient Involvement and Engagement for Head and Neck Patients

Patients can greatly benefit from involvement in research. Through the MOSES Study, we have active patient involvement through questionnaires of pain and functional outcomes, and through qualitative patient interviews. A smaller cohort of people diagnosed with head and neck cancer will be interviewed as we want to find out about patients' experiences of being investigated for the original cancer, including

what their views on the operation are and what their experiences are of any other treatment they have had.

What is the benefit to the NHS and what are the wider impacts of this project?
Please outline any unmet clinical need and your proposed solution to meet this need.
(max. 500 words)

While the NHS is able to support some research costs, the research costs associated with the sample analysis and patient recruitment elements of The MOSES Study are not eligible. We are therefore asking for IReC to consider funding the sample analysis and patient recruitment elements of this research. The MOSES Study is supported by the NIHR Clinical Research Network (CRN) and included on the NIHR CRN Portfolio.

We believe NHS patients and services will benefit significantly from this research in the future. Currently, treatment strategies for cancer of unknown primary (CUP) in Head and Neck (H&N) are not standardised. Management plans can vary from no radiation therapy addressing potential primary sites, with a watch and wait policy, to Elective Mucosal Irradiation (EMI) which can lead to significant early and late morbidity. There are no therapies or treatment approaches that take into account tumour biology.

Please provide evidence explaining why this research is needed now.
How does the existing literature support this proposal?
(max. 300 words)

Our proposed study will help develop a greater understanding of the biology of these cancers. In recent years there has been an explosion in cancer genomics research – the science of looking at cancer DNA. This remains an understudied area in head and neck cancer. There are currently no treatments available to patients with head and neck cancer based on genomic insights. Our research will begin to address the unmet need of patients who present with these poorly understood cancers and to provide a starting point for more detailed investigations into the relationships between cancer genomics and clinical outcomes.

What downstream funding support is available to you following completion of this project?
(max. 200 words)

The costs for the MOSES have been reviewed and approved by RMH CCR. It is not anticipated that further funding will be required. However, if further funding is required to complete this research, the project team will apply for necessary funding to support the costs.

If your application is successful, how will IReC be recognised for its support?
Please state if this project has the potential to attract positive PR
(max. 300 words)

IReC will be recognised on all MOSES Study publications and presentations related to this research.
We would be delighted to speak to the IReC team to discuss the best way to recognise the centre for its support, particularly in regard to publicity and research engagement.

We are keen to support IReC and advocate for improved research into head and neck cancer. Members of the study team would be happy to liaise with IReC in how this might be best achieved, both within the scope of the proposed work and beyond.

Section 4 – Finance

Total Grant Requested (£)	**£97,985**
Term of Grant (years)	**4 year, fixed sum**

Breakdown of costs
Please outline what this grant will be used for, providing a breakdown of costs and include details of any other grant applications in relation to this request. Please do not include staff costs in this section. (max. 500 words)

Category	Details	Justification	Cost (£) inc. VAT
Site payments for recruitment	100 patients will be recruited and followed up on The MOSES Study. In total, the cost for all patient recruitment payments will be £25,000.	Last year only 56.8% of research studies recruited patients to time and target (Data on performance in initiating and delivering clinical research | NIHR). Under-recruitment undermines the scientific integrity and validity of research data. Often this is driven by resource constraint, with units already struggling to deliver core clinical services. Seeking to build on the strong track record of recruitment in the MOSES study to date, we will engage research teams with the MOSES Study and encourage patient recruitment by covering the local costs of patient participation with a payment of £250 per eligible patient recruited.	£25,000
Sample kits and transfer costs	Sample kits and transfer costs are expected to be £30.16 per patient. If all 100 patients participate, the total cost for sample kits and transfer costs is £3,016.	The collection and transfer of buccal swab and blood samples is necessary for securing samples for exploratory molecular analysis.	£3,016
Genomic analyses	The majority of these funds will cover sample analysis costs (£69,969), detailed below in Table A and based on the expectation that 50 matched primaries and lymph nodes would be analysed for genomics, with a 10 pair		£69,969

	exploration cohort for immune signalling analysis at the RNA level.		
Total			**£97,985**

Table A: Genomic Analysis Costs

Category	Description	Justification	Cost (£)
Use of services	Tissue processing	Cutting and staining slides	£450
Consumables	DNA extraction	Extraction, quantification and quality assessment of nucleic acids 25 samples with matched germ line £13.46 per extraction, £3 quantification with digital PCR	£2,019
Consumables	Exome sequencing matched tumour samples	Library preparation and whole exome sequencing to 150X for 100 samples £510/sample based on Illumina NovaSeq	£51,000
Consumables	Exome sequencing germline DNA	Library preparation and whole exome sequencing to 50X for 50 samples £170/sample based on NovaSeq	£8,500
Use of services	Bioinformatic support	Use of high performance cluster	£1,500
Use of services	Data storage	Cost of securely storing bam files on backed-up server	£1,500
Consumables	Nanostring	PanCancer Immune profiling £250/sample, 10 pairs	£5,000
Total			**£69,969**

Staff costs

If this application includes staff costs, please provide details, including name and employer.

Not applicable. All staff costs are covered by existing funding.

Name (if known)			
Role (inc grade)			
	Year 1	**Year 2**	**Year 3**
Basic Salary (£)			
Other costs/allowances (£)			
Subtotals (£)			
Total (£)			

Name (if known)			
Role (inc grade)			
	Year 1	**Year 2**	**Year 3**
Basic Salary (£)			
Other costs/allowances (£)			
Subtotals (£)			
Total (£)			

Name (if known)			
Role (inc grade)			
	Year 1	**Year 2**	**Year 3**
Basic Salary (£)			
Other costs/allowances (£)			
Subtotals (£)			
Total (£)			

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Section 5 – Declaration

I confirm that the information provided is accurate to the best of my knowledge and that delivery of the project in the timeline provided is feasible.

I confirm the staff gradings and salaries quoted in the application are correct and are submitted in accordance with the normal practice of my institution.

Lead Applicant	
Name	
Signature	
Date	

Appendix 15: The HNSCCUP Audit contributors and affiliations

Name	Role	Affiliation
Adam Gaunt	Trainee Site Lead	Royal Hallamshire Hospital, Sheffield
Ahmad K. Abou-Foul	Trainee Site Lead	Royal Stoke University Hospital
Ajith George	Consultant Lead	Royal Stoke University Hospital
Alex Bowen	Consultant Lead	Fairfield General Hospital, Greater Manchester
Alex Charlton	Trainee Site Lead	Queen's Medical Centre, Nottingham (QMC)
Alexander Chadha	Local Collaborator	Leeds General Infirmary
Alison Zander	Local Collaborator	Royal Glamorgan Hospital, South Wales
Amy Round	Local Collaborator	Leeds General Infirmary
Anastasha Herman	Trainee Site Lead	Stepping Hill Hospital, Greater Manchester
Andrea Zuccarelli	Local Collaborator	Royal Victoria Hospital, Belfast
Andreas Hilger	Consultant Lead	Ipswich Hospital
Andrew Carswell	Local Collaborator	Royal United Hospital, Bath
Andrew Harris	Consultant Lead	Royal Gwent Hospital, Newport
Andrew McGaughey	Trainee Site Lead	Poole Hospital
Andrew Mizen	Local Collaborator	West Suffolk Hospital, Bury St Edmunds
Andrew Williamson	Trainee Site Lead	University Hospital Crosshouse, Kilmarnock
Ankit Patel	Local Collaborator	University College London Hospital
Anna Loroch	Local Collaborator	Glasgow Royal Infirmary
Anthony Bashyam	Trainee Site Lead	Basingstoke and North Hampshire Hospital
Antonio Belloso	Consultant Lead	Royal Blackburn Hospital
Anusha Balasubramanian	Trainee Site Lead	East Surrey Hospital, Redhill
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Arcot Maheshwar	Consultant Lead	Colchester General Hospital
Athena Togo	Consultant Lead	Raigmore Hospital, Inverness
Ayla Tabaksert	Trainee Site Lead	Cumberland Infirmary, Carlisle
Basil Al Omari	Consultant Lead	James Paget University Hospital, Great Yarmouth
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Chiugo Ike	Local Collaborator	Ashford Hospital, Surrey
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Christian Johnatty	Trainee Site Lead	Royal Gwent Hospital, Newport
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Chuanyu Gao	Trainee Site Lead	Ashford Hospital, Surrey
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Fatima Seedat	Local Collaborator	Royal Blackburn Hospital
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Gavin Donaldson	Trainee Site Lead	Craigavon Area Hospital
George Garas	Local Collaborator	Heartlands Hospital, Birmingham
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Haleema Siddique	Trainee Site Lead	Wexham Park Hospital, Slough
Hamza Qureshi	Trainee Site Lead	Darlington Memorial Hospital
Hannah Collins	Local Collaborator	Royal Glamorgan Hospital, South Wales
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Haran Devakumar	Trainee Site Lead	Colchester General Hospital
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Iain Nixon	Consultant Lead	St John's Hospital, Livingston
Ian Smillie	Consultant Lead	University Hospital Monklands, Airdrie
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Jacob Thoppil	Trainee Site Lead	Northampton General Hospital
Jaiganesh Manickavasagam	Consultant Lead	Ninewells Hospital, Dundee
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James O'Hara	Consultant Lead	Freeman Hospital, Newcastle
James Rudd	Trainee Site Lead	Churchill Hospital, Oxford

Name	Role	Affiliation
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Sarah Knowles	Local Collaborator	Royal Blackburn Hospital
Saumil Shah	Local Collaborator	Royal Stoke University Hospital

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Stuart Winter	Consultant Lead	Churchill Hospital, Oxford
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Syed Shah	Local Collaborator	Maidstone Hospital
Tanzime Ahmed	Local Collaborator	Broomfield Hospital, Chelmsford
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Trung Ton	Local Collaborator	Cumberland Infirmary, Carlisle
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Victoria Harries	Trainee Site Lead	Royal United Hospital, Bath
Vinidh Paleri	Consultant Lead	The Royal Marsden Hospital
Vinod Prabhu	Consultant Lead	Glangwili General Hospital, Carmarthen
Waqqas Patel	Local Collaborator	Churchill Hospital, Oxford
Zach Shellman	Local Collaborator	Queen's Medical Centre, Nottingham (QMC)

Appendix 16: Example email from the HNSCCUP National Audit as part of multiple rounds of data cleaning

hnsccup@entintegrate.co.uk

Subject: TBM data cleaning for HNSCCUP audit
Date: Thursday, 28 October 2021 at 11:32:05 British Summer Time
From: HARDMAN, John charles (THE ROYAL MARSDEN NHS FOUNDATION TRUST)
To: [redacted]

Dear team,

Please could we ask you to look at the following cases related to their tongue base mucosectomy, to see if we can improve the data for the HNSCCUP audit? We appreciate we may have already asked you about some of these, so apologies if it's not possible to source the data, but any further clarifications you can provide would be greatly appreciated.

The following patients are missing a valid duration for their TBM, following referral:
- Age:59, Sex:F, Referred:Jan 2017, (Pt 01 on our list)
- Age:51, Sex:M, Referred:Jan 2015, (Pt 22 on our list)
_ _ For many patients, this is because they are missing an initial referral date to generate the duration at referral.
_ _ Or, if they have NOT undergone a formal TBM, please let us know so we can remove the entry from the TBM methods column.

Thank you so much for the time you have taken so far to collate these data, and sorry if you've already let us know about unfillable gaps. A real strength of these studies in the past has been the very high rates of data completeness, and so anything you can do to help maintain that high standard will help guarantee the impact of this work.

If you have any queries at any time, please don't hesitate to get in touch.

BW
John
On behalf of the INTEGRATE H&N subspecialty committee
[James Constable, Sian Dobbs, John Hardman, Chris Hogan, Kate Hulse, Shivun Khosla, Kristijonas Milinis, Ben Tudor-Green, Andrew Williamson]

--
John Hardman
Research Fellow | The Royal Marsden NHS Foundation Trust
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Appendix 17: The HNSCCUP Audit standards

HNSCCUP Audit 2021:
National audit of the management of head & neck squamous cell carcinoma of unknown primary

Audit standards

The National Audit Standards relating to management of head and neck squamous cell carcinoma of unknown primary (HNSCCUP) are derived here from the the United Kingdom Multidisciplinary guidelines (2016)[1], the National Institute for health and Care Excellence guideline 36 (2018)[2], American Society of Clinical Oncology guideline (2020)[3], and the British Association of Head and Neck Oncologists standards (2020)[4].

Summary of abbreviations

Abbreviation	Definition
CT	Computed tomography
EBV	Epstein Barr Virus
FNAC	Fine needle aspiration cytology
HPV	Human Papilloma Virus
HNSCCUP	Head and neck squamous cell carcinoma of unknown primary
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
NBI	Narrow band imaging
PET-CT	Positive emissions tomography- computed tomography
SCC	Squamous cell carcinoma
UADT	Upper aerodigestive tract
US	Ultrasound

US guided biopsy

Standard: all patients with suspected unknown primary should undergo an ultrasound guided FNAC or core biopsy to confirm presence of SCC as part of the initial neck lump assessment.

Guideline	Recommendation
UK 5th ed. (2016)	As part of assessment initial assessment in neck lump clinic the lymph node should be sampled by US guided FNAC or core biopsy
NICE 36 (2018)	N/A
ASCO (2020)	FNAC or core biopsy of a clinically suspicious neck mass should be performed
	HPV testing should be done routinely on level II and III HNSCCUP nodes.
	EBV testing should be considered on HPV-negative metastases
BAHNO (2020)	Provide FNA/core biopsy for all neck lumps suspected of being cancer of the UADT. This should be performed by a specialist radiologist, pathologist or clinician.

CT & MRI

Standard: all patients with confirmed cervical lymph node SCC should undergo CT and/ or MRI imaging as part of their initial diagnostic investigations.

Guideline	Recommendation
UK 5th ed. (2016)	All patients should have CT from skull base to diaphragm as part of the assessment of a newly diagnosed SCC of the head and neck.
	If the disease presents in a level II/III lymph node MRI of the oropharynx, in particular the tongue base, tonsil and tonsil lingual angle, should be carried out.
	May be supplanted by PET-CT as first line investigation.
NICE 36 (2018)	Consider an MRI or CT scan before diagnostic surgery to help with radiotherapy treatment planning.
ASCO (2020)	CT neck should be the initial test for workup of metastatic cervical lymphadenopathy
	No recommendations for MRI
BAHNO (2020)	N/A

Whole Body PET-CT

Standard: All patients with confirmed cervical lymph node SCC and no apparent primary site on examination or cross sectional imaging should undergo whole body PET-CT.

Guideline	Recommendation
UK 5th ed. (2016)	All patients with confirmed cervical lymph node and metastatic SCC and no apparent primary site should undergo whole body PET-CT. May be carried out as a first line investigation.
NICE 36 (2018)	Consider a PET-CT as the first investigation to detect the primary site in people with metastatic nodal squamous cell carcinoma of unknown origin that is thought to arise from the upper aerodigestive tract
ASCO (2020)	If a primary is not evident on clinical examination and CT, PET should be the next diagnostic step
BAHNO (2020)	All units treating individuals with HNSCCUP should have access to PET-CT scanning facilities

Panendoscopy & biopsy

Standards:

1. All patients with biopsy confirmed cervical lymph node SCC and no apparent primary site on examination, cross-sectional imaging, or PET CT should undergo a panendoscopy and directed biopsies of suspected primary sites after initial diagnostic imaging.

2. Directed biopsies of suspected primary sites on examination and diagnostic imaging may be performed.

Guideline	Recommendation
UK 5th ed. (2016)	All patients with confirmed cervical lymph node and metastatic SCC and no apparent primary site should undergo panendoscopy + palpation of the oral cavity/ tongue base.
	Should occur after completion of all imaging as instrumentation and biopsy prior to scanning would compromise the accuracy of the subsequent radiological assessments
NICE 36 (2018)	Offer surgical diagnostic assessment if PET does not identify a primary site. This may include guided biopsies, tonsillectomy, and TBM.
	Consider using narrow-band imaging endoscopy to identify a possible primary site when it has not been possible to do so using PET.
ASCO (2020)	Patients should undergo a complete operative upper aerodigestive tract evaluation of mucosal sites at risk including directed biopsy of any suspicious areas.
	Intraoperative advanced visualization techniques (e.g., NBI) may be used to investigate potential primary sites for targeted biopsy
BAHNO (2020)	There should be an agreed protocol for the surgical assessment of the primary site when PET-CT does not identify a possible primary site.

Tonsillectomy

Standard: All patients with biopsy confirmed cervical lymph node SCC and no apparent primary site on examination or cross-sectional imaging should undergo bilateral tonsillectomy.

Guideline	Recommendation
UK 5th ed. (2016)	All patients with confirmed cervical lymph node and metastatic SCC and no apparent primary site should undergo bilateral tonsillectomy
NICE 36 (2018)	See panendoscopy
ASCO (2020)	Unilateral lymphadenopathy: if a primary site is not confirmed, the surgeon should perform ipsilateral tonsillectomy. Bilateral palatine tonsillectomy may be considered according to clinical suspicion.
	Bilateral palatine tonsillectomy after bilateral lingual tonsillectomy should be avoided (see mucosectomy)
BAHNO (2020)	N/A

Mucosectomy

Standard: Where the expertise is available, all patients with biopsy confirmed cervical lymph node SCC and no apparent primary site on examination or cross-sectional imaging should undergo TBM.

Guideline	Recommendation
UK 5th ed. (2016)	All patients with confirmed cervical lymph node and metastatic SCC and no apparent primary site can be offered TBM if facilities and expertise exist
NICE 36 (2018)	See "panendoscopy"
ASCO (2020)	Unilateral lymphadenopathy: if ipsilateral tonsillectomy fails to identify a primary, ipsilateral lingual tonsillectomy may be performed.
	Bilateral lymphadenopathy: if a primary site is not confirmed, the surgeon may perform unilateral lingual tonsillectomy on the side with the greater nodal burden and may perform contralateral lingual tonsillectomy if the ipsilateral procedure fails to identify a primary.
	In patients in whom the primary tumour is identified and definitive surgical management is intended, clinicians should make every effort to resect the identified primary using transoral techniques to a negative surgical margin
	Intraoperative frozen section evaluation of palatine or lingual tonsillectomy specimens should be performed when the primary tumor remains undetected.
BAHNO (2020)	There should be an agreed pathway for a tongue base mucosectomy where indicated.

Excisional biopsy

Standard: patients with suspected or confirmed cervical lymph node SCC and no apparent primary site on examination or cross-sectional imaging should not undergo excisional biopsy without prior MDT discussion

Guideline	Recommendation
UK 5th ed. (2016)	N/A
NICE 36 (2018)	N/A
ASCO (2020)	N/A
BAHNO (2020)	Excisional biopsy of the malignant neck mass must not be undertaken without prior discussion in the H&N MDT.

Surgical intervention

Standards:

1. Patients with early nodal disease (N1) and no ENE can be managed with surgery or radiotherapy alone.
2. Patients with early nodal disease (N1) and obvious ENE can be managed with surgery and post-operative radiotherapy
3. Patients with moderate nodal disease (N2a-c) and those with advanced (N3) disease who are being treated with curative intent can be managed with surgery and post-operative radiotherapy +/- chemotherapy

Guideline	Recommendation
UK 5th ed. (2016)	Small nodal disease with no ENE (T0 N1) can be treated with surgery alone. Patients with ENE should also receive post-operative radiotherapy to the involved nodal level or the entire ipsilateral nodal chain.
	Moderate nodal disease (T0 N2a-N2c) can be treated with selective or modified radical neck dissection, with post-operative radiotherapy to one or both sides of the neck.
	Advanced (N3) disease treated with curative intent can be managed with a radical or Type I modified radical neck dissection with postoperative chemoradiotherapy. There is a potential role for surgery as palliation.
NICE 36 (2018)	Offer patients the choice of: neck dissection and adjuvant radiation +/- chemotherapy OR primary radiation +/- chemotherapy, with surgery for persistent disease
ASCO (2020)	For unilateral, small-volume neck disease, either definitive surgery or radiotherapy may be offered after MDT discussion
	For small-volume bilateral neck disease with no clinical ENE, either definitive surgery (+/- adjuvant therapy) or radiotherapy (+/- concurrent chemotherapy) may be offered after MDT discussion
	When primary surgery is planned, levels IIA, III, and IV should be routinely dissected when an oropharyngeal primary is suspected or confirmed.
BAHNO (2020)	N/A

See appendix I for table of proposed treatment recommendations according to UK 5th ed guidelines

Radiotherapy

Standards:

1. Radiotherapy with or without concomitant chemotherapy can be considered as a primary treatment modality in patients with N2-3 nodal disease and/or evidence of ENE, with planned neck dissection reserved for those who do not achieve a complete metabolic response.
2. Adjuvant radiotherapy with or without chemotherapy should be considered in patients with N2/3 nodal disease and/or pathologic evidence of ENE.

Guideline	Recommendation
UK 5th ed. (2016)	Patients with N1 disease with ENE, N2/ N3 disease can be treated with primary chemoradiation with a planned neck dissection in those without a complete metabolic response on post-treatment PET-CT
	Post-operative patients with N1 disease and evidence of ENE should receive adjuvant ipsilateral neck treatment
	Post-operative patients with N1 disease and evidence of ENE should receive adjuvant ipsilateral or bilateral neck treatment
	TMI remains a controversial issue & there is no conclusive evidence to support its use.
NICE 36 (2018)	See "surgical interventions" recommendations
ASCO (2020)	Large-volume bilateral neck disease and/or gross macroscopic ENE favour definitive chemoradiotherapy
	Patients with unilateral HPV positive and negative nodal disease should receive treatment to the gross node(s) and with consideration of coverage of putative primary sites in the ipsilateral tonsil, ipsilateral soft palate, and the mucosa of the entire base of tongue.
	Patients presenting with bilateral (N2c) nodal disease should receive bilateral treatment of the oropharyngeal mucosa
	Patients with unilateral involvement of multiple nodes and no evidence of ENE should routinely receive bilateral treatment
	Patients with N3 and/or bilateral nodal involvement and/or evidence of ENE require bilateral neck treatment

	Patients receiving radiotherapy or concurrent chemoradiotherapy adjuvant to surgical management should receive treatment to regions of the neck and mucosa at risk of containing microscopic disease.
	Adjuvant radiotherapy should be administered to patients with multiple pathologically involved nodes and/or pathologic evidence of ENE
BAHNO (2020)	All centres should have written protocols for different tumour sites and intents using local or national guidelines. These should be reviewed and updated at least every two years.

Chemotherapy

Standard: Concomitant chemotherapy should be considered alongside radiotherapy in patients with N2-3 nodal disease or evidence of ENE and in select post-operative patients.

Guideline	Recommendation
UK 5th ed. (2016)	Concomitant chemotherapy with radiation should be considered in patients with an unknown primary
	Concomitant chemotherapy with radiation should be considered in suitable patients in the post-operative setting
	Neo-adjuvant chemotherapy can be used in gross 'unresectable' disease
NICE 36 (2018)	See "surgical interventions" recommendations
ASCO (2020)	Concurrent administration of cisplatin with definitive radiotherapy should be offered to patients with a suspected mucosal primary HPV/p16-negative SCC in the presence of unresected N2-N3 nodal disease OR unresected multiple ipsilateral, or bilateral, lymph nodes OR unresected nodes >3cm OR pathologic evidence of ENE OR an EBV encoding region–positive stage II-IVA carcinoma of unknown primary
BAHNO (2020)	N/A

Follow-up

Standard: patients treated for unknown primary SCC of the H&N should be followed up for a minimum of five years, with a PET-CT performed at 3-4 months in those treated with chemoradiation.

Guideline	Recommendation
UK 5th ed. (2016)	Patients should be followed up at least two months in the first two years and three to six months in the subsequent years
	Patients should be followed up to a minimum of five years with a prolonged follow up for selected patients.
	PET-CT at three to four months after treatment is a useful follow-up strategy for patients treated by chemoradiation therapy
NICE 36 (2018)	N/A
ASCO (2020)	N/A
BAHNO (2020)	N/A

References

1. Mackenzie K, Watson M, Jankowska P, Bhide S, Simo R. Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines. The Journal of Laryngology & Otology. 2016 May 12;130(S2).

2. National Institute for health and care excellence. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. NICE guideline [NG36]. 2018.

3. Maghami E, Ismaila N, Alvarez A, Chernock R, Duvvuri U, Geiger J, et al. Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck: ASCO Guideline. Journal of Clinical Oncology. 2020 Aug 1;38(22).

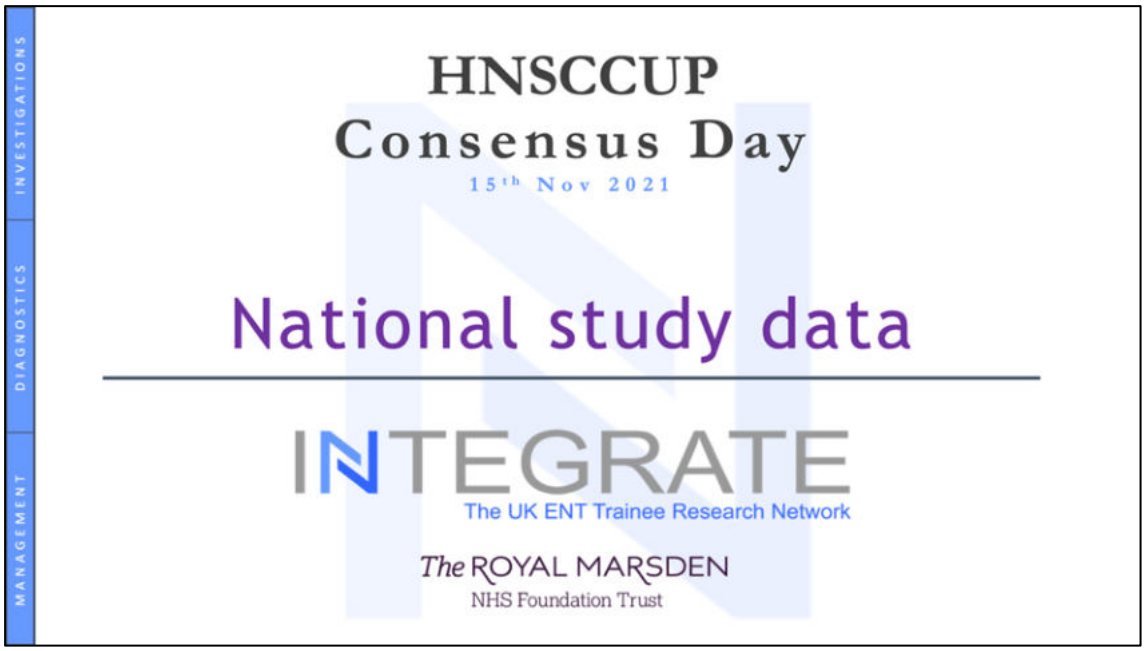
4. Schache A et al. BAHNO standards. British Association of Head and Neck Oncologists. 2020.

Appendix I

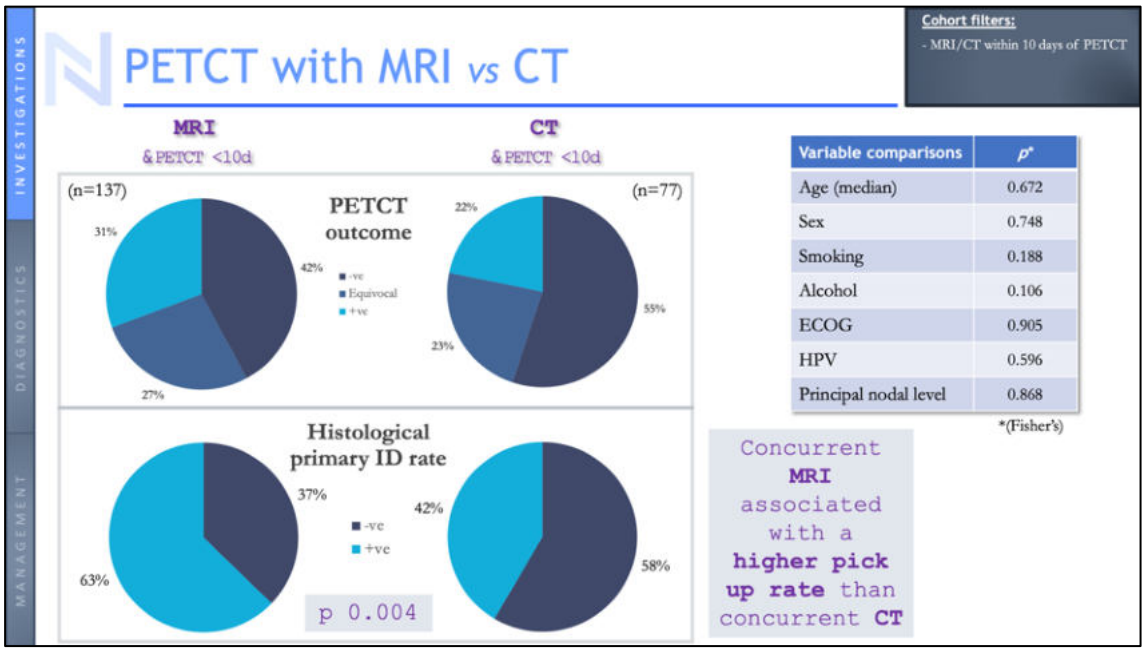
Table of treatment recommendations according to the UK 5th edition guidelines for the Investigation and management of the unknown primary with metastatic neck disease (2016).

Stage	Surgery	Radiotherapy	Chemotherapy
N1 no ECS	Selective or modified radical neck dissection	No, unless for mucosal sites	No
N1 with ECS	Selective or modified radical neck dissection	Yes- either to involved nodes or ipsilateral nodes with boost to involved lymph nodes	Should be considered
N2a-N2c	Selective or modified radical neck dissection +/- contralateral	Yes- ipsilateral but bilateral should be considered	Should be considered
N3	Radical or type 1 neck dissection	Yes- ipsilateral but bilateral should be considered	Should be considered

Appendix 18: Interim HNSCCUP National Audit data presented at the National Consensus Day


MANAGEMENT
DIAGNOSTICS
INVESTIGATIONS
HNSCCUP
Consensus Day
15th Nov 2021
National study data
INTEGRATE
The UK ENT Trainee Research Network
The ROYAL MARSDEN
NHS Foundation Trust

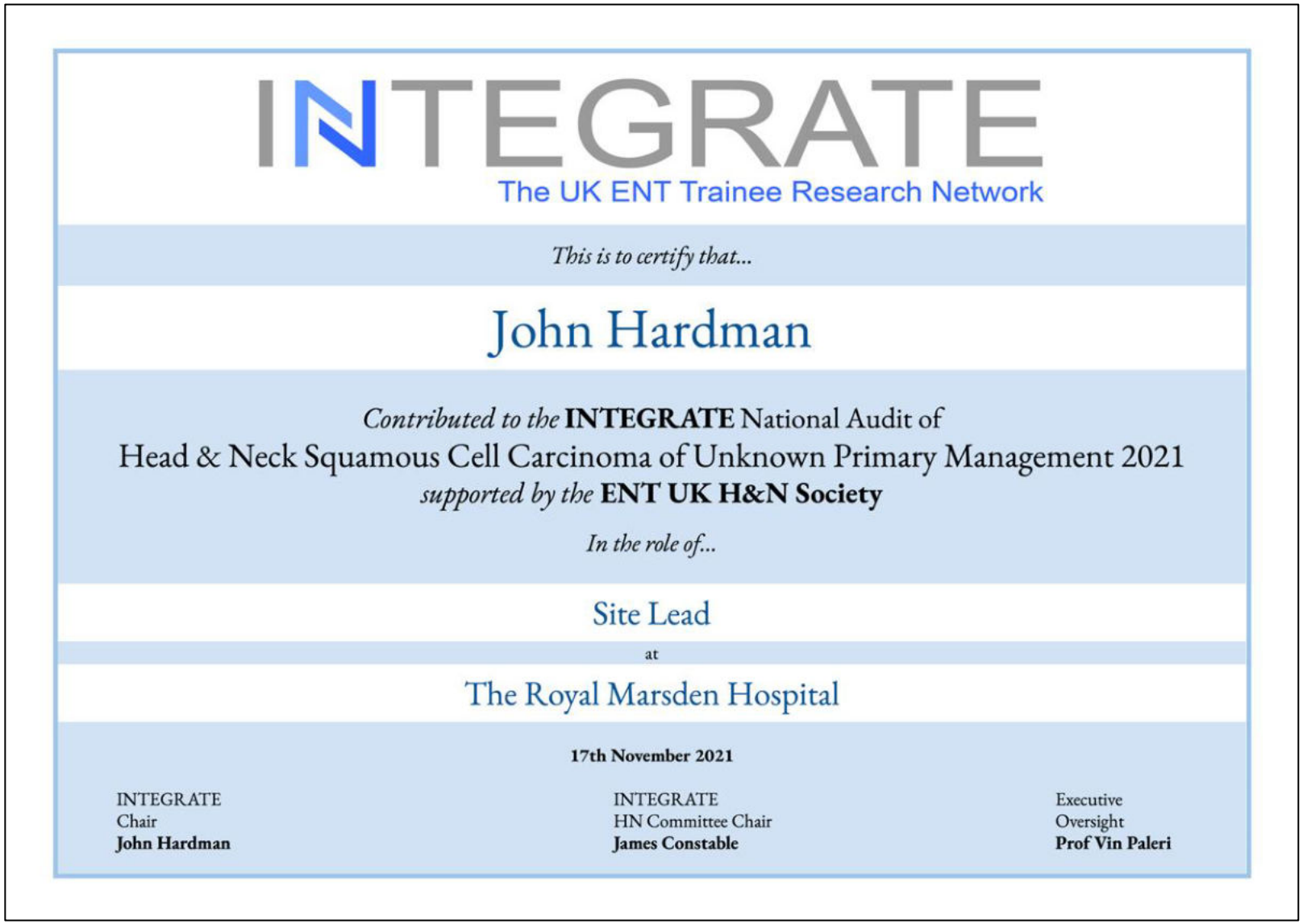

MANAGEMENT
DIAGNOSTICS
INVESTIGATIONS
INTEGRATE HN committee
John Hardman
INTEGRATE Chair
James Constable
HN Committee Chair
Kristijonas Milinis
INTEGRATE secretary
Chris Hogan
HN Committee
Sian Dobbs
HN Committee
Shivun Khosla
HN Committee
Andrew Williamson
HN Committee
Kate Hulse
HN Committee



Variable comparisons	p*
Age (median)	0.672
Sex	0.748
Smoking	0.188
Alcohol	0.106
ECOG	0.905
HPV	0.596
Principal nodal level	0.868

*(Fisher's)

Appendix 19: Certificate of participation for the HNSCCUP National Audit 2021



INTEGRATE

The UK ENT Trainee Research Network

This is to certify that...

John Hardman

Contributed to the **INTEGRATE** National Audit of
Head & Neck Squamous Cell Carcinoma of Unknown Primary Management 2021
supported by the **ENT UK H&N Society**

In the role of...

Site Lead

at

The Royal Marsden Hospital

17th November 2021

INTEGRATE Chair **John Hardman**	INTEGRATE HN Committee Chair **James Constable**	Executive Oversight **Prof Vin Paleri**

Appendix 20: The HNSCCUP Audit ENT UK Foundation Programme Research grant (£1k)

at The Royal College of Surgeons of England
35-43 Lincoln's Inn Fields
London WC2A 3PE

Tel: 020 7404 8373
Email: entuk@entuk.org Web: www.entuk.org

Sent via email: christopher.hogan@doctors.org.uk

Christopher Hogan
INTEGRATE (Head & Neck Sub-Committee)

27 July 2021

Dear Christopher

ENT UK Foundation: Research Grants Programme

"National audit of the management of head and neck squamous cell carcinoma of unknown primary"

We are delighted to be able to inform you that you have been successful in your application to the ENT UK Foundation Research Grants Program.

The panel were very interested in your research on investigating the management of Head and Neck SCC of unknown primary as part of a national cohort study / audit.

The value of this fellowship is £1000. The feedback was that we note that this is not the full amount requested but feel that this is a substantial portion and we are keen for the study to be on NIHR portfolio if applicable.

We hope that you will be able to attend the ENT UK annual meeting on 17 September 2021 where the winners in all categories will be formally announced. We hope that you will be able to present the output from this project at the annual meeting in 2022.

With kind regards on behalf of the ENT UK Foundation

B. Nirmal Kumar

Prof Nirmal Kumar
President ENT UK

Mr Taran Tatla
Honorary Secretary ENT UK

Ms Sadie Khwaja
ENT Consultant

ENT UK trading as
British Academic Conference in Otolaryngology (BACO) and British Association of Otorhinolaryngology – Head & Neck Surgery (BAO-HNS)

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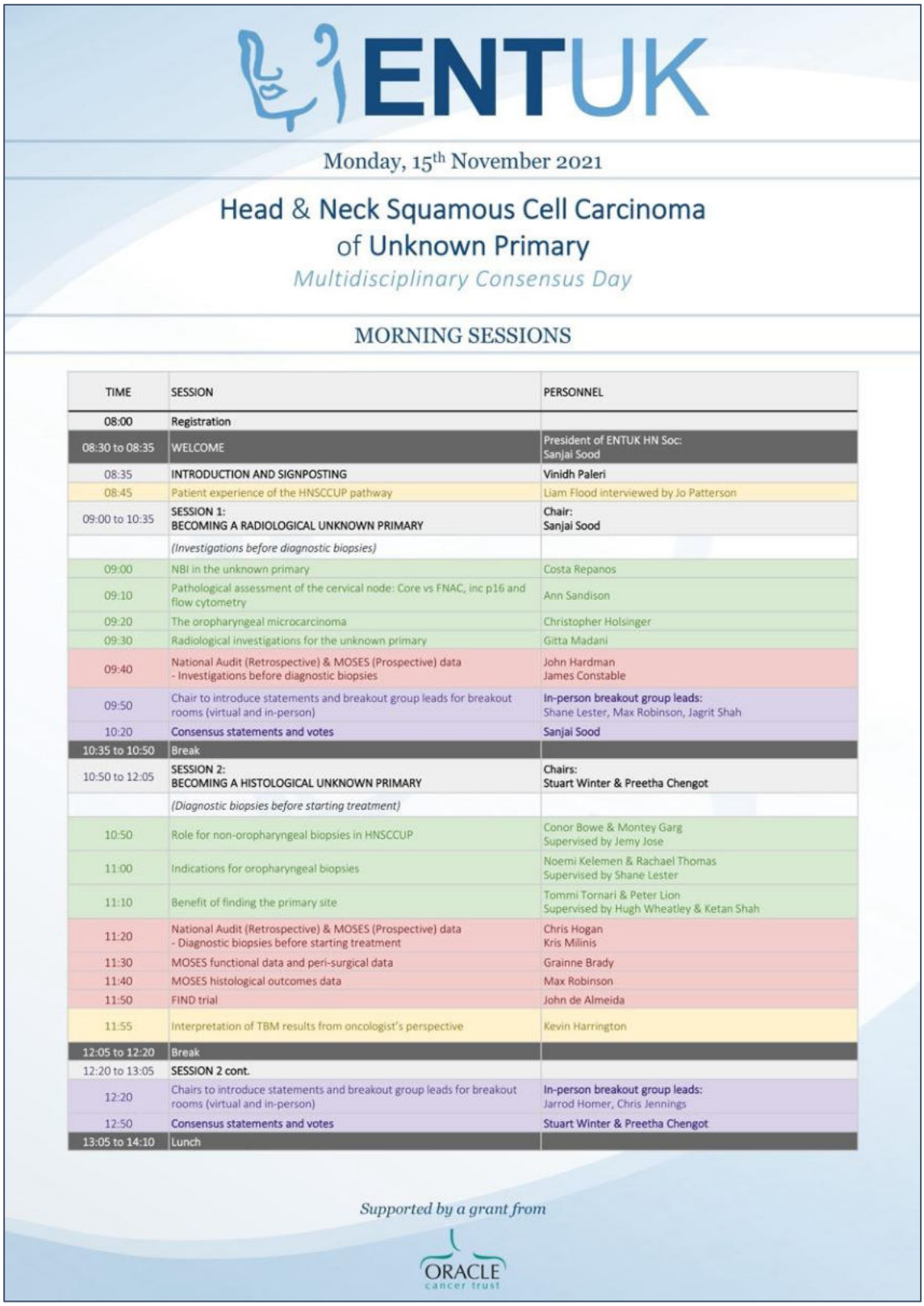
Appendix 21: The HNSCCUP Consensus Day Programme



ENTUK

Monday, 15th November 2021

Head & Neck Squamous Cell Carcinoma of Unknown Primary

Multidisciplinary Consensus Day

MORNING SESSIONS

TIME	SESSION	PERSONNEL
08:00	Registration	
08:30 to 08:35	WELCOME	President of ENTUK HN Soc: Sanjai Sood
08:35	INTRODUCTION AND SIGNPOSTING	Vinidh Paleri
08:45	Patient experience of the HNSCCUP pathway	Liam Flood interviewed by Jo Patterson
09:00 to 10:35	SESSION 1: BECOMING A RADIOLOGICAL UNKNOWN PRIMARY	Chair: Sanjai Sood
	(Investigations before diagnostic biopsies)	
09:00	NBI in the unknown primary	Costa Repanos
09:10	Pathological assessment of the cervical node: Core vs FNAC, inc p16 and flow cytometry	Ann Sandison
09:20	The oropharyngeal microcarcinoma	Christopher Holsinger
09:30	Radiological investigations for the unknown primary	Gitta Madani
09:40	National Audit (Retrospective) & MOSES (Prospective) data - Investigations before diagnostic biopsies	John Hardman James Constable
09:50	Chair to introduce statements and breakout group leads for breakout rooms (virtual and in-person)	In-person breakout group leads: Shane Lester, Max Robinson, Jagrit Shah
10:20	Consensus statements and votes	Sanjai Sood
10:35 to 10:50	Break	
10:50 to 12:05	SESSION 2: BECOMING A HISTOLOGICAL UNKNOWN PRIMARY	Chairs: Stuart Winter & Preetha Chengot
	(Diagnostic biopsies before starting treatment)	
10:50	Role for non-oropharyngeal biopsies in HNSCCUP	Conor Bowe & Montey Garg Supervised by Jemy Jose
11:00	Indications for oropharyngeal biopsies	Noemi Kelemen & Rachael Thomas Supervised by Shane Lester
11:10	Benefit of finding the primary site	Tommi Tornari & Peter Lion Supervised by Hugh Wheatley & Ketan Shah
11:20	National Audit (Retrospective) & MOSES (Prospective) data - Diagnostic biopsies before starting treatment	Chris Hogan Kris Milinis
11:30	MOSES functional data and peri-surgical data	Grainne Brady
11:40	MOSES histological outcomes data	Max Robinson
11:50	FIND trial	John de Almeida
11:55	Interpretation of TBM results from oncologist's perspective	Kevin Harrington
12:05 to 12:20	Break	
12:20 to 13:05	SESSION 2 cont.	
12:20	Chairs to introduce statements and breakout group leads for breakout rooms (virtual and in-person)	In-person breakout group leads: Jarrod Homer, Chris Jennings
12:50	Consensus statements and votes	Stuart Winter & Preetha Chengot
13:05 to 14:10	Lunch	

Supported by a grant from

ORACLE cancer trust

ENTUK

Monday, 15th November 2021

Head & Neck Squamous Cell Carcinoma of Unknown Primary

Multidisciplinary Consensus Day

AFTERNOON SESSIONS

TIME	SESSION	PERSONNEL
14:10 to 15:30	**SESSION 3:** **TREATMENT FOR THE UNKNOWN PRIMARY**	**Chairs:** **Frank Stafford & Jean-Pierre Jeannon**
	(After final MDT diagnosis)	
	3a: Neck dissections	
14:10	Who can be offered surgery as the sole modality?	Arun Takhar and Mark Wilkie Supervised by Emma King & Dev Srinivasan
14:20	National Audit (Retrospective) & MOSES (Prospective) data - Surgical management after MDT diagnosis - Non-surgical management after MDT diagnosis	Kate Hulse Andrew Williamson Sian Dobbs Shivun Khosla
14:35	How does neck dissection pathology influence (C)RT decisions?	Tom Roques
14:45	Chairs to introduce statements and breakout group leads for breakout rooms (virtual and in-person)	**In-person breakout group leads:** Somiah Siddiq, James O'Hara
15:15	**Consensus statements and votes**	**Frank Stafford & Jean-Pierre Jeannon**
15:30 to 15:45	**Break**	
15:45 to 17:00	**3b: (Chemo)radiation**	**Chairs:** **Kevin Harrington & Tom Roques**
15:45	Radiotherapy treatment volumes at primary site in +/-TBM scenarios	Oncology trainee - Dr Zsuzsanna Iyizoba-Ebozue Supervised by Christina Wilson & Mehmet Sen
15:55	Radiotherapy treatment volumes to neck after neck dissection	Oncology trainee - Malcom Jackson Supervised by Shahid Iqbal & Claire Paterson
16:05	Functional outcomes after bilateral neck RT	Joanne Patterson
16:15	Chairs to introduce statements and breakout group leads for breakout rooms (virtual and in-person)	**In-person breakout group leads:** Paul Pracy, Shahid Iqbal
16:45	**Consensus statements and votes**	**Kevin Harrington & Tom Roques**
17:00 to 17:30	**SESSION 4:** **ESTABLISHING DELPHI ITEMS AND FUTURE RESEARCH DIRECTIONS**	**Chair:** **Vinidh Paleri**
17:00	Summary of votes from 4 previous sessions	Respective chairs
17:20	Future research direction	Vinidh Paleri
17:30	CLOSE	

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Appendix 22: The HNSCCUP National Consensus Exercise protocol

Version 2.0 26/Nov/2021

An ENT UK HN Society Initiative

HNSCCUP

Multidisciplinary Consensus Process

Outline of the methodology for generating consensus statements for the management of head and neck squamous cell carcinoma of unknown primary (HNSCCUP)

Introduction

The ENT UK H&N Society is developing consensus statements for the management of HNSCCUP, aiming to reduce variations in practice across the UK. The process is centred around the ENT UK Multidisciplinary Consensus Day held on the 15th November 2021 and is chaired by Professor Vinidh Paleri.

Generating the consensus statements

Prior to the consensus event, multiple work streams were implemented to gather evidence to generate draft consensus statements. These work streams included systematic reviews of the literature, presentations from key stakeholders and data from prospective and retrospective observational cohort studies of UK practice.

On the day, the draft consensus statements will be discussed by Consensus Event attendees and revised as appropriate. Attendees will then take part in an indicative vote to gauge support.

Finalising draft consensus statements for the Delphi process

Prior to the Delphi process, the ENT UK H&N Society Council will review the final draft consensus statements, to remove any duplications and ensure clarity and consistency amongst the statements.

Gaining consensus from UK Head & Neck MDTs

Following ratification by the ENT UK H&N Society Council, representatives from each UK Head & Neck MDT will be invited to participate in an online modified Delphi process. Response rates to the invitation, and participation rates in each round, will be reported. Voting for each statement will be binary agree/disagree and overall results recorded.

Each round will adhere to the following schedule:

- Total of 2 weeks between rounds (with a week break over Christmas)
- 10 days for MDT responses.
- 4 days for chasing final responses, analysis and preparation of statements for the next round.

Up to three rounds of the Delphi process will take place, with thresholds as follows:

- ≥80% strong agreement (≤20% strong disagreement)
- ≥67% agreement (≤33% disagreement) (applied only after 3rd round)

1 of 2

Adoption:

- Statements reaching strong agreement at any stage will be removed from further rounds.
- After round 1, statements using the term 'offer' which have not achieved 'strong agreement' will be duplicated with the term 'consider' used in place of 'offer' for subsequent rounds. Both the 'offer' and 'consider' statements will be presented alongside each other in parallel for subsequent rounds, with the statements numbered to reflect this addition.
- After round 3, if both the 'offer' and 'consider' statements had achieved the same level of agreement, then the 'offer' statement would be adopted in preference.
- After round 3, if the 'consider' statement had achieved 'strong agreement' and the 'offer' statement had achieved 'agreement', then the consider statement would be adopted.
- Action terms like 'Perform/refer/include' were treated the same as 'offer' terms/statements as above.

The ENT UK H&N Society Council will consider any feedback given by participants for incorporation into subsequent rounds. The Council will be the final arbitrators of amendments between rounds and the ultimate production of the consensus statements. These finalised statements will then be distributed to the representatives of UK HN MDTs for endorsement.

Thank you

Thank you to all those taking the time to support this project. If you have any questions at any time, please do not hesitate to get in touch with vinidh.paleri@rmh.nhs.uk or johncharles.hardman@nhs.net.

Appendix 23: The HNSCCUP National Consensus Exercise Delphi comments

An ENT UK H&N Society Initiative

HNSCCUP

Multidisciplinary Consensus Process

Comments from Delphi process

1: Investigations before diagnostic surgery for clinically suspected HNSCCUP

Round 1

- 1c is a game changer for many many units and would certainly improve the pathway - but it lacks evidence really to support the costs of instituting this. Ask our US colleagues. Even Chris Holsinger says on the recent board meetings on line that most US surgeons use CT, based on cost, and struggle with MR and PET CT unless absolutely indicated.
  To me - this is the single biggest gain from the consensus day and I would suggest we look at a prospective cost analysis trial for this question.
- 1c - depends on level of clinical suspicioun. Pure cystic masses this may be overkill
- All patients with a neck mass should be seen in a one stop neck lump clinic with access to same day core biopsy - results should be available within 3 working days. PET-CT should be done as a second line investigation with confirmed pathology. First line PET-CT on the basis of clinical history and examination alone will result in excess radiation, unnecessary investigation of incidental findings, and is a waste of precious resource.
- Question 1a - do ancillary tests cover EBV in HPV/p16-ve samples?
- I would suggest 1d is 'offer' rather than 'consider'?
- Issue of staging chest not explicit.
- Contrast CT comparible to MRI as initial cross sectional imaging modality, is more quickly accessible, and suffers from less movement artefact. NBI is a useful diagnostic tool in dysplastic/ early invasive lesions but I have not seen data validating it's use in this population of patients the majority of whom have a tongue base or tonsil occult primary
- We CT and don't have MRI in our cup pathway. Given CT has pick up rate for primary and avoids pet which is strained service then not sure justify doing 2 together and not sure need for mri above ct and pet
- Should Initial biopsy not be stipulated to be a core biopsy?
- CT neck thorax is adequate rather than MRI I think offer CT neck thorax or MRI neck CT thorax and consider concurrent PET CT
- I would do a CT rather than an MRI as we do not have easy access to timely MRI. Also the patient is this lets us image the thorax for staging. In our area we do not have the resource (radiologist or scannners) to do both on every patient.
- Avoid the Use of NBI as this is only applicable to Olympus (should not favour one company over another). The generic term should be Virtual ChromoEndoscopy (VCE) that also takes into account SPECTRA/SPIES, PIET and NBI
- 1c- concerns about ARSAC permissions in a non confirmed cancer
- PET scans are not available within a few days in our unit (district general hospital) as it is carried out in another larger unit in the region. We usually find a delay of 2 to 3 weeks for our patients to get a PET scan from request. Therefore an MRI scan of the oropharynx and a staging CT neck and chest are obtained as first line by our MDT (both requested as soon as the Ultrasound scan and/ or clinical examination suggests a pathological node without an obvious primary). The CT and MRI scans would usually identify the vast majority of primaries. If no primary is identified on CT and MRI scans, then we would request a PET scan.
- 1c in our opinion should be consider not offer
- Ic consider local radiologists views as has an impact potentially on service
- All members of our MDT advocate upfront core not FNA given requirement/accuracy of P16 analysis. We feel strongly this should be advocated in the consensus. This is clinically the correct thing to do and consensus statement should drive service development if not universally available.
  New national standards advocate same day MRI in a one-stop clinic. We already have this available and this enables us to refer for PET OR CT the day after clinic depending on if a primary is identified on MRI.

- 1c This would depend on the definition of clinical suspicion and the experience of the clinician ordering the investigations
- I think 1e needs to be changed, because it doesn't make much sense to have a suspected cancer if it is pathologically confirmed. It should probably read "pathologically confirmed mets with clinically unknown primary" or simply "pathologically confirmed HNSCCUP"

2: Diagnostic surgery for clinically suspected pathologically confirmed HNSCCUP

Round 1

- I think you need a set of statements that will have an effect. 2c is fairly meaningless. We know that random biopsies yield little - but they don't cause harm. The statement should read to recommend tonsillectomy and base of tongue mucosectomy over random biopsies of these sites. Taking random biopsy of the PNS or PF doesn't cause any harm.
- 2d needs some thought. In experienced hands - most tonsil tumours are visible under GA and should have an incisional biopsy not tonsillectomy especially if transoral surgery is to be considered. We don't want a statement encouraging tonsillectomy over a really considered EUA and biopsy of abnormal looking tissue. These occur a lot and may be MRI / PET CT negative.
- Tongue base mucosectomy can be done without endoscope,microscope or ROBOT
- Mucosectomy is clearly going to be cotroversial here and approach will depend on MDT feelings about accepting P16/HPV as being from oropharynx. I suspect there will be divergent opinions here
- The evidence based that tongue base mucosectomy in p16+ve patients changes treatment or outcomes for the better i.e. safe de escalation, needs to be clearer - I would suggest that it should only be carried out in the contest of a trial.
- 'Oropharyngeal MALTectomy' is unnecessary - it's confusing for patients and clinicians
- 2d: I think bilateral tonsillectomy (if you cannot palpate a lesion to biopsy) is appropriate initially, rather than ipsilateral. 2f: if it not clear if there is an option for palatine tonsils first, then BOT? 2g; is there an option for 2/3 BOT mucosectomy.
- MALTectomy not very popular. New descriptions can be confusing
- Mucosectomy and bilateral tonsillectomy represents a significant oropharynx intervention with associated cicatrisation and will affect function in this swallowing critical zone and may contribute to late radiation associated dysphasia. It has not been demonstrated to improve survival outcomes. The tongue base is a midline structure with bilateral lymphatic drainage and therefore ipsilateral mucosectomy/ tonsillectomy to mitigate has a doubtful rationale.
- Think should have add on about straight forward cases or in cases with no uncertainty. This statement just puts a lot of pressure on referring surgeons not to bring cases to mdt and although that's ok for most there is some cases where earlier discussion might be helpful and statement needs to reflect that and allow some wiggle room
- Malt just reminds me of malt lymphoma
- I'd like clear evidence before recommending increasingly morbid hunts for the primary ahead of radiotherapy, if excellent imaging is negative. The relatively low rates of relapse at primary site implies this is unnecessary.
- It should be more explicit regarding sequencing of removal of tonsils and then TBM if negative?
- Our OMFS colleagues commented on the term 'Lingual Tonsil' . This is indeed MALT tissue in the tongue base but apparently OMFS think this is the tissue laterally on the tongue what is better known as the foliate papillae. Should Lingual Tonsil be define clearly for OMFS?
- 2h) A better term might be 'ipsilateral palatine and lingual tonsillectomy'
- We do bilateral tonsillectomy up front
- I agree that tongue base mucusectomy is often indicated, but I answered 'no' to 2f as not indicated for all patients. Same can apply to tonsils in certain patients (eg surgical v high risk, already have SCC and P16 status on a node core biopsy and oncologists happy to give RT without a definite primary). As bilateral tonsillectomy with tongue base mucusectomy v painful, we will often do bilateral Ts with BOT biopsies and consider mucusectomy if path negative on Ts and BOT Bxs. Often primary is identified without the need for full mucusectomy. we do discuss all options with patients though.
- Everyone in the H&N community is used to the terms 'Bilateral diagnostic tonsillectomy and tongue base mucosectomy' so our MDT sees no advantage in introducing a new term in the H&N vocabulary 'oropharyngeal MALTectomy'
- MALT term is confusing and not clear, better to stick with anatomical description as risk of it otherwise meaning different things to different people. In elderly/ frail patients mucosectomy is a significant undertaking for them so need to consider this and not be too didactic
- Comment was made on 'referral to unpublished MOSES trial'
- It seems bizarre that 73% advocated ipsilateral but 87% advocated contralateral. I'm guessing this is due to offer v consider
- I find it unclear what is advocated if a primary is identified clinically at panendoscopy prior to 'MALTectomy'. I would favour biopsy (+/- frozen section to confirm) as these patients are likely highly suited to PATHOS and extensive oropharyngeal surgery would deny them this opportunity.
- 2d and 2e Offer bilateral tonsillectomy except when an obvious tonsil primary tumour is identified where tonsil biopsy may be appropriate
- 2d- unless there is an obvious tonsil cancer found during EUA

- 2h- MALTectomy likely to cause confusion
- 2a should probably define what is considered 'all radiological investigations', or mention there should be a local agreement as to what that means
- 2c: do not offer us too strong, depends on availability and timeliness of mucosectomy.
- We would have agreed 2f if it were Consider
- 2f should be consider. In the real world a mucosectomy is not readily available and will add to workload to subspecialist surgeons and delay patients unnecessarily

Round 2

- We should at least offer ipsilateral tongue base mucosectomy for unknown primary cancers but not all surgeons perform this or have the service. The vast majority of unknown primary will be identified with TBM and bilateral tonsillectomy. Contra lateral TBM though has a lower yield with more morbidity / pain. MALTectomy is a new term and unsure it fits the current description for TBM.
- no need to add a new terminology in my view
- 2fi & 2fii: I would suggest that this can be discussed with the patient, although not necessarily recommended.
- 2g: I think bilateral tonsillectomy and bilateral mucusectomy at one sitting to much. Possible exception would be a patient who has previously had a tonsillectomy.
- 2h: would add confusion rather than clarification in practice (although may be good in theory!)
- If question 2h remains un-agreed, why not discard it, as it represents a change in terminology rather than a change in clinical practice.
- 2fi may read better if it includes "HPV related SCC confirmed on neck node needle sampling".
- The evidence presented was very strongly in favour of this diagnostic intervention - for HPV related disease, less so for HPV negative disease.
- If we adopted this statement as "offer" it would certainly improve the access to this intervention for patients and would be supported by the presented evidence.
- There was some confusion in the meeting - suggestions that offer ipsilat and consider contralat BoT mucosectomy would result in 2 procedures, or even 4 if we had offer ipsilat tonsillectomy and consider contralat tonsillectomy as well. It would be ideal to somehow get the notion across that the ipsilateral tonsillectomy and BoT mucosectomy have the highest level of pick up - "considering" the contralateral diagnostic interventions (at the same time as the ipsilat) then allows an individual patient decision to be made - eg for an elderly patient, ipsilateral intervention alone may be appropriate.
- I'm not sure what we are hoping to gain from the term MALTectomy - unless we are suggesting that all patients undergo the tonsillectomy with the BoT mucosectomy at the same initial sitting.
- 'Ipsilateral oropharyngeal MALTectomy' is an unnecessarily complex term - will complication communication
- Mucosa associated lymphoid tissue' is used to describe small aggregates of submucosal lymphoid tissue that are not otherwise named, not lymphoid structures like the lingual and pharyngeal tonsil.
- Agree with comments that this extra nomenclature has potential to confuse, and is not necessary
- I Think bilateral tonsillectomy that accompanies tongue base mucosectomy is likely to have significant swallowing implications for some without data demonstrating that it influences prognosis. It's use should therefore be restricted to trials designed to demonstrate an oncological advantage. I am in two minds about an ipsilateral mucosectomy as I regard the posterior third of the tongue (oropharynx tongue) as a midline structure from the standpoint of lymphatic drainage. However, there may be specific circumstances where a lateralised lingual tonsillar primary/ lower pole tonsil seems a distinct likelihood e.g equivocal FDG PET-CT findings or cross sectional imaging asymmetric change.
- MALTectomy is introducing more terminology that is confusing. I think the evidence does not go beyond consider at the moment
- I'd agree, isolateral MALTectomy is likely to be confusing
- Need to carefully consider evidence before suggesting mucosectomy for all unknown primaries, esp HPV negative. For example, recent papers like Kubik etal from Pittsburg and Copenhagen do not show any advantage for mucosectomy in HPV negative patients.
- 2fi and 2fii - our MDT is divided, but the majority consensus is to 'offer ipsilateral' BOT mucosectomy (irrespective of p16 status of neck core biopsy) and 'consider contralateral' BOT mucosectomy as most of the primary has been demonstrated to be identified in the ipsilateral/midline BOT mucosectomy specimen.
- We would do Pan-endoscopy (including nose), EUA+ Biopsy, bilateral tonsillectomy and if all negative bilateral tongue base mucosectomy. I am not sure which option covers this
- TBM has significant morbidity so consider in frail patients otherwise generally if patient is fit then reasonable to offer. We do not feel the term MALTectomy is useful or clear and risks introducing confusion so would be reluctant to use it, better to stick to accurate anatomical descriptions of sites.
- Comment on 2fi - with caveat that would assume should offer total TBM in all patients if no primary in tonsils found/ and oncologists would still wish to irradiate tongue base as only ipsilateral tongue base addressed

Round 3

- 2fi needs to be consider
- Offer ipsilateral tongue base mucosectomy to all patients' is too strong and too vague. Suggest adopt the language of NICE for this recommendation i.e. 'Consider' ipsilateral TBM in all patients.... (NICE also use 'must' and 'should' which equate to 'beyond reasonable doubt' and 'on the balance of probabilities' respectively)
- 'Ipsilateral oropharyngeal MALTectomy': don't see the need for new terminology plus from a purists perspective this would require removal of the the entire oropharyngeal mucosa including sections of the ipsiltateral palate and posterior pharyngeal wall
- We think 2fi should be 'consider' and our oncologist felt that 2h should be kept as simple as possible, and not adding additional terms.
- 2fi I think this statement should be removed as there has already been agreement on "Consider mucosectomy..."
- 2h I don't see where the confusion would come from as it is like any other term we use and it would help not having really long operation titles.
- For 2Fi :we suggest 'consider'. We have seen small contralateral BOT lesions. Knowing all the BOT tissue has been removed offers reassurance to the MDT that this site has been excluded for an unknown primary.
- For 2H : agree on the basis that A MALTECTOMY is different to doing a separate Tonsillectomy and BOT mucosectomy as the MALTECTOMY takes the Glosso Tonsil Sulcus Tissue and this band of tissue can be missed in above procedures.
- The 'offer ipsilateral tongue base mucosectomy' option now becomes slightly out of context without being followed by the 'offer contralateral tongue base mucosectomy option'. We only do bilateral tongue base mucosectomies.
- 2fi: The problem is "offer to all". I would say "consider" because there may be a reason not to offer.
- 2h: I put this to our MDT and they felt it confusing (because of MALToma)
- MALTectomy - There is no need to introduce a new terminology which will not change practice but more likely to confuse others (GPs for eg)
- The term is overly complicated and the feeling is it is not needed. As stated previously we would consider mucosectomy in all patients so that term probably fits better than offer.
- Offering ipsilateral TBM and bilateral tonsillectomy is satisfactory for HPV Unknown primary but TBM may not yield much in HPV negative disease and only adds morbidity.
- Maltectomy is not a universally agreed terminology.
- I have consistently ticked agree for 2f as we believe the evidence is strong enough in favour of BOT mucosectomy - but the statement could be clarified further by specifying for proven HPV related neck disease. The evidence for HPV negative disease was not definitive on the day, in keeping with many surgeons' anecdotal experiences. For HPV neg "consider" may be a more appropriate statement. "In patients with appropriate transoral access" could be a useful addition too, as for some patients with poor access, the procedure is difficult to perform and remove all lymphoid tissue - in these situations a poorly performed mucosectomy may lead to more harm (both pain and lack of definitively negative specimen) than good.
- I have considered MALTectomy and refer to my previous comment - I am not sure what we are trying to achieve with it. The greatest gain in the UK would be to promote appropriate BOT mucosectomy use. Whether to perform this with a tonsillectomy can be debated. I don't see anything wrong with a unit performing pharyngoscopy, tonsillectomy, access for BoT mucosectomy, and if negative then sending to another unit to perform the BOT mucosectomy if they do not do so. This would be a step forward than not offering the HPV related patients a mucosectomy.
- I think my issue with MALT ectomy is that is avoids the notion of BOT mucosectomy being a specialist diagnostic intervention (by linking it with tonsillectomy in one word) - which it is given the necessary MDT discussions that go with it and overall management plans.
- I'm not sure why anyone would feel strongly enough to object to the term "MALTectomy" - it is logical!
- 2fi - No - We would suggest bilateral TBM

3: Surgical management of patients diagnosed as HNSCCUP

Round 1

- These are all consider statements and represent the nuances of MDT discussions. They don't have the weight to produce practice change that the offer statements do. None of these deserve Offer status - agree with that.
- I don't see why 3b shold be different from other disease stages
- 3e - difficult one. I think there is a balance to be struck. Is the morebidity from your neck dissection worse than that from the additional RT field?? Controversial
- How about '3b consider US surveillance' - CT/ MRI would be a waste of resource
- 3e surgical contralateral neck staging - too morbid
- Pittsburgh study showed a pick up rate of only 13% with tongue base mucosectomy for HPV negative CUP . There is no good evidence to justify contralateral neck dissection to allow omission of contralateral neck RT
- Late radiation dysphagia and other late toxicities have a strong association with surgery. Therefore the use of surgery should be reserved for those patients with a poor prognosis with non- surgical management. This includes those with HPV and EBV negative disease and recent SEER data suggests those with locally advanced (T3/T4) HPV +ve disease
- Strongly disagree with therapeutic neck dissection at same time as a staging diagnostic procedure. If positive, which is about 1/3, then subjects patient to multimodality treatment with surgery then radiotherapy which for a excellent prognostic cancer comes with morbid toxicity effects and is unnecessary treatment as seen in PET NECK
- 3b - not sure evidence on effect on outcomes to suuport this? 3e. We would believe modern ct and pet and us neck as enough staging to exclude contralateral disease and allow ipsilateral treatment
- Omission of contralateral neck RT is a valid option for patients without a staging neck dissection
- for statement 22 - in HPV-ve disease the oropharynx is not necessarily the most likely primary site, so the added morbidity may be difficult to justify. for statement 20 - would follow PET neck protocol for statement 22 - concerned about the significant increase in morbidity associated with bilaterla neck dissection followed by bilater neck radiotherapy, if disease is discovered in contralateral neck. FO T0 tumours, our practice is to irradiate unilateral neck only, with salvage treatment at relapse if needed.
- 3aii some confusion in- HPV negative HNSCCUP-role of TBM and Tonsillectomy+/- ND
- 3a1 we would do bilateral Ts
- 3b we would do single post treatment PET, further imaging only if indicated
- We would consider a neck dissection for 3ai, but would usually try to find the primary first as otherwise neck dissection unnecessary as RT needed anyway.
- 3b We do 3-4 month PET, same as the RT and CRT patients
- 3ai- this is suggesting that a neck dissection should be performed with the MALTectomy where this is still part of the diagnostic process. Surely this is one option. Treatment with neck dissection may not be required if the patient were to choose RT. Also - this complicates things of a primary is found and further resection with a messed ligation is needed.
- For investigation of an unknown primary, as a bare minimum we would perform a bilateral and not just an ipsilateral tonsillectomy. I have had a couple of patients presenting with bilateral tonsil SCC. Traditionally, when our oncologists say the radiotherapy given to the neck will cover the base of tongue, a tongue base mucosectomy has not been performed in order not to delay treatment. In addition, limited access to the robot means that we cannot do a tongue base mucosectomy at the same sitting as an EUA with tonsillectomy.
- Do not agree with MALTectomy term, 3c/d a bit controversial ? conflicts with PET neck trial data
- 3b - whilst regular imaging, may have a place here I feel this statement is too vague to be useful and without evidence base to support the implications on service delivery. What imaging? What does regular mean? What evidence do we have to support this over close clinical surveillance?
- 3e - whilst this seems a potentially attractive proposition we do not believe there is sufficient evidence to support this in terms of improved patient morbidity/experience. This surely needs to be subject to RCT before adopting into national guidance
- 3ai and 3aii Whilst the neck disease would be treated with neck dissection we would recommend bilateral tonsillectomy prior to this. These statements would stand if "ipsilateral tonsillectomy and tongue base mucosectomy (ipsilateral oropharyngeal MALTectomy) and" is removed.
- 3c and 3d Surgery or radiotherapy can both be considered primary treatments and each can be considered or recommended after primary treatment based on imaging or pathology reports. If radiotherapy is chosen as primary modality neck dissection should not occur before.
- Agree with 'consider' but MDT not convinced of evidence for p16 negative disease- this remains a case by case discussion
- This may be better addressed in a consensus meeting about 'management of the neck', regardless of CUP or identifiable primary site.

- 3ai there was no majority answer it was split 50/50 agree/disagree

Round 2

- Use ultra sound scan to follow up contolateral neck
- Contra lateral staging neck dissection adds morbidity and unnecessary for well-lateralised tonsil SCC unless there are guarantees oncology will omit contra lateral RT.
- TBM in HPV negative tumours has low diagnostic yield so will advocate mainly for HPV positive unknown cancers.
- 3aii: agree only as "consider" used.
- There was a suggestion to core neck lumps before FNA. I would not agree, provided FNAs reported quickly. Our pathologists will FNA in clinic and then we will get an immediate result and plan accordingly.
- Whilst we would not get a PET-CT as a first investigation, we have a low threshold to early diagnostic PETs and have found them very helpful (eg "branchial cyst" in right age group will get PET after USS and FNA (both done in the neck lump clinic). We have easy access to PET with a short turnaround. If other centres do not have this facility then surely this is something we should recommend so the resources are made available to all that need it.
- I remember from the consensus day a few year years ago we agreed bilat tonsillectomy for all HNSCCUP, (in the days before HPV). Currently we certainly would if P16+ on core. In most instances we remove contralateral tonsil in P16+ patients even when primary identified.
- 3e could read "Consider contralateral staging neck dissection - following MDT discussion - where there is no clinical or radiological evidence of disease - for patients in whom a pN0 contralateral neck dissection would permit the omission of prophylactic dose radiotherapy"
- 3aii - why do we need this in here? There are so many potential "considers" for possible surgical interventions - where do we stop? This looks like more of a justification for considering this intervention for this patient group. I think the only contentious element to this statement is the role of BoT mucosectomy in the HPV negative neck node scenario - that gets crowded out by the management of the neck question in the same statement.
- 3aii agree that small primary with small neck disease (T1N1) can be treated with surgery alone. 3e excessive morbidity
- MDT just wanted to reiterate that all patients should be offered access to high quality clinical trials that will address the current lack of evidence to guide future decision-making.
- I think this depends on the primary stage and site
- Our MDT was divided on 3aii, but consensus decision is as above.
- Same comments as mentioned in the previous round
- Diagnosis and treatment should be separate
- Is HPV status on p16 or PCR? Will influence decision making if p16 only is used. Why only ipsilateral tonsillectomy for 3aii?

Round 3

- 3e I would think most centres would offer DXT rather than surgery but having consider is the correct way to leave this.
- 3aii agree - minimal morbidity and offers a reasonable chance of cure
- 3e disagree - unnecessary surgical morbidity
- 3aii - I feel this should only be included if the plan is to treat with surgery alone
- For 3aii: Disagree on the basis of the demographic representation of this group. Usually older less fit patients. Seems to much to consider all this treatment as they would likely be best served with non surgical treatment, Very different to the P16+ group.
- For 3e: Disagree on basis would offer a lot of unnecessary morbidity if PET negative. PET is a good NPV test as long as the primary lesion is PET Avid
- 3aii: Not clear from the question, but this would be with the expectation of RT as well.
- Agree with 'consider' as this allows treatment to be individualised to patient.
- The problem with recommending ipsilateral tongue base mucosectomy for all patients is that this is a diagnostic procedure; while it will yield a higher rate of identification of the primary tumour it has not demonstrably improved oncological outcomes. Recommending an invasive diagnostic modality, with significant resource implications, in the absence of clear evidence of benefit is not responsible in a 3rd party payer healthcare system. The correct setting for this procedure is a trial designed and powered to determine whether or not it confers benefit w.r.t loco regional control, disease specific, and overall survival.
- In our MDT we would not offer CL RT to these patients - as long as well-lateralised.
- In an unknown primary HPV negative SCC with small volume nodal metastasis and no ECS, radical radiotherapy should be considered. If there is large volume disease in the neck then surgery and adjuvant treatment as such HPV negative disease do not do as well oncologically with only RT.
- Contra lateral staging neck dissections add extra morbidity and more evidence is required.

- Both statements are reasonable practices for MDTs to discuss. "Consider" would be appropriate and recognises that alternative management plans are also reasonable.
- Contralateral neck dissection represents an acceptable rationale to obviate the need for radiation therapy: particularly in the context of treating the patient either: 1. solely with surgery or 2. through obviating bilateral neck radiation, if ipsilateral radiation is required post treatment.
- 3aii - No – This should be worked up as unknown primary and therefore bilateral TBM +/-bialteral tonsillectomy before ND

4: Non-surgical management of patients diagnosed as HNSCCUP

Round 1

- 4c to 4g need to be taken into context with what has been done surgically. If a full MALTectomy has be done and is negative, then these statements could be considered but may not be followed. What is suggested may be common practice. What about turning them the other way round and considering NOT treating the opposite neck etc if a full MALTectomy has been done?
- - 4b - this is too broad based - majority of patients will fall within this. It would be beneficial to stratify this group and offer different treatment option based on 1. >3 cm 2. Multiple nodes 3. Extracapsular extension. The clinical outcome is not same in all these three group of patients.
- 4h- consider? I think HPV+ N2b disease does not mandate CRT after surgery, but if primary treatment is RT I would agree offer chemo too.
- Not sure about 4i either. In HPV+ disease and "minor" ENE there may be no compelling reason for chemo in addition to RT. Perhaps should be a consider?
- 4j would depend whether there's any radiological evidence of RP nodal involvement, in which case I would recommend RT is given.
- Not sure where there is evidence to justify such a blank statement as this. Lots of papers out there with N2b disease treated ipsilateral showing a very low rate of primary and contralateral recurrence and for those who recur high rates of salvage. Think it weighing up the patient, toxicity, burden of disease and having informed discussion with patient. Don't think you should be pushing oncologists routinely treat a patient with 2 or 3 nodes bilaterally with a statement like this There is only a point in increasing diagnostic scans and degree and complexity of diagnostic biopsies if it then changes what oncologists are willing to cover. With modern diagnostic techniques the certainty it is an unknown primary is high and therefore ipsilateral treatment without mucosal coverage and contralateral neck might be appropriate and justify the lengthy and morbid staging procedures and improved long term toxicity and functional outcomes without compromising survival. Xrt has always been based on 20% risk of microscopic disease and don't think with modern staging the chance of primary or contralateral nodes is as high as that to continue justifying bilateral and mucosal xrt in unknown primary scc apart from very high risk (but could justify as they are at as much risk of distant mets or local failure than regional recurrence) or bilateral involved (rate) cases
- 4b - these 'inclusion criteria' for post op RT are quite wide - I'd suggest 'consider RT for 1 node >3cm' whereas the stronger 'offer RT' is more appropriate for the multiple LNs, ENE
- We do not routinely give RT to potential primary sites. Where it is given, we would stick to 50Gy equivalent - thise dose should be adequate for micropscopic disease. Note - for statement 33, updated RCR guidance being published soon
- Please note these responses incorporate the west of scotland regional mdts including NHS Greater Glasgow and Clyde, Ayreshire and Arran and NHS Lanarkshire
- 4a we would not omit RT if a primary has not be identified, we would omit RT to the neck in that scenario though
- 4(c). Radiotherapy to the contralateral neck (provided N0) can be avoided by performing a contralateral selective neck dissection under the same GA if the ipsilateral neck is being operated on prior to giving ipsilateral (C)RT.
- 4f - our MDT favoured TMI V no primary Site RXT considered on a case by case basis. Partial treatment may be incorrect and result in reduction of subsequent treatment options should a primary present.
- 4j - we would actually like to abstain from this as our 2 oncologists have respectfully differing opinions here
- 4b Offer rather than cosider if multiple nodes or extranodal extension. Consider if solitary node over 3cm with no extranodal extension.
- 4c and 4d We generally offer unilateral treatment unless there are multiple levels of nodes involved.
- 4c and 4d: although this is discussed and considered, the MDT wouldn't recommend this unless there are other features to indifcate contra lateral treatment.
- 4g: some debate in the MDT. This is commonly out practise but some question as to evidence
- 4j: our practise is to include this when there is bulky level 2 disease. Feel 'include' is too strong with current wording.
- 4j needs more detail - is it p16+ disease, is it bulky nodal disease?

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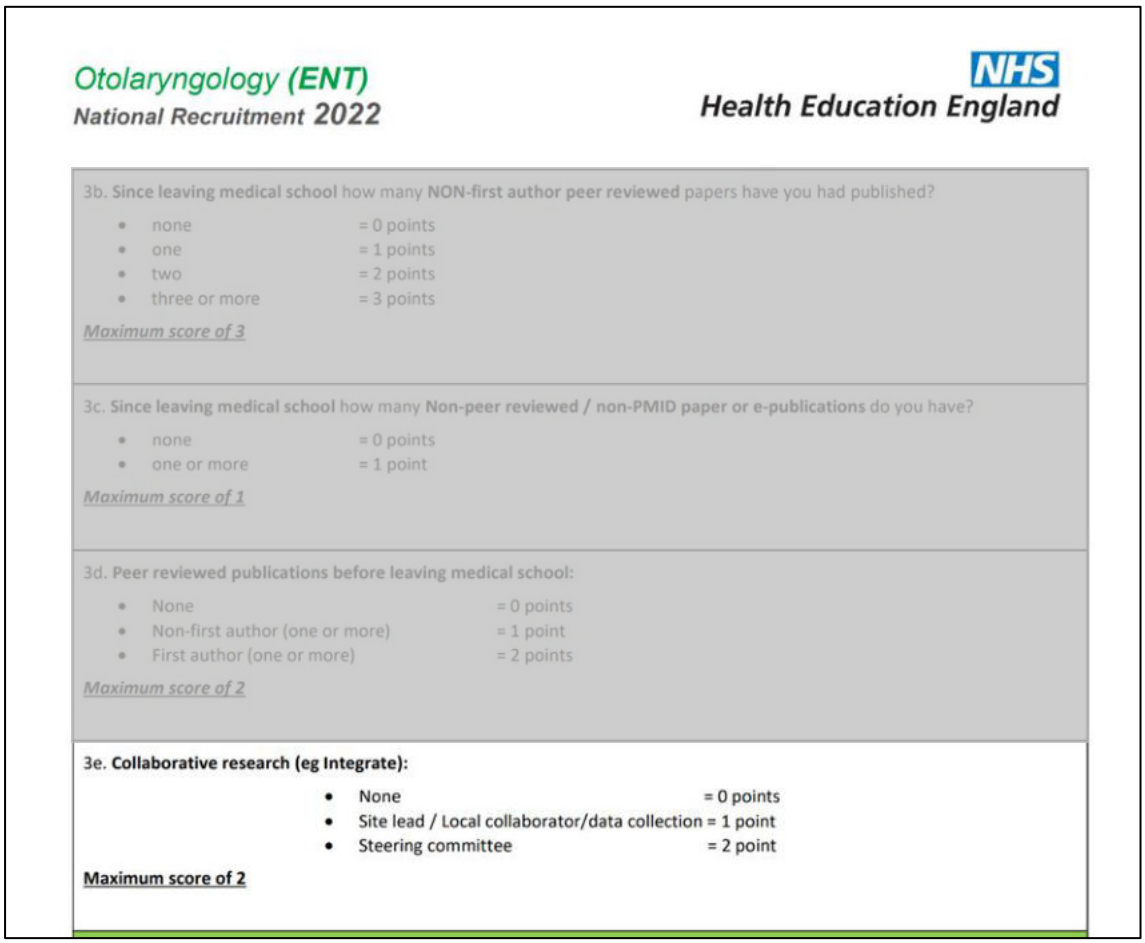
Justin W Roe	Speech and language therapist	Department of Speech, Voice and Swallowing, The Royal Marsden Hospital, London, UK.
Kevin Harrington	Project Management Team	Head and Neck Unit, The Royal Marsden Hospital, London, UK.
Vinidh Paleri	Project Management Team lead Site primary	Head and Neck Unit, The Royal Marsden Hospital, London, UK.

Correct at time of submission

Appendix 27: ENT National Recruitment 2022 Collaborative Research Criteria



Otolaryngology (ENT)
National Recruitment 2022

NHS
Health Education England

3b. **Since leaving medical school** how many **NON-first author peer reviewed** papers have you had published?

- none = 0 points
- one = 1 points
- two = 2 points
- three or more = 3 points

Maximum score of 3

3c. **Since leaving medical school** how many **Non-peer reviewed / non-PMID paper or e-publications** do you have?

- none = 0 points
- one or more = 1 point

Maximum score of 1

3d. **Peer reviewed publications before leaving medical school:**

- None = 0 points
- Non-first author (one or more) = 1 point
- First author (one or more) = 2 points

Maximum score of 2

3e. **Collaborative research (eg Integrate):**

- None = 0 points
- Site lead / Local collaborator/data collection = 1 point
- Steering committee = 2 point

Maximum score of 2