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

Protocol version:	v1.1
Date:	9th July 2019
Sponsor:	The Royal Marsden NHS foundation Trust Fulham Road London SW3 6JJ
CCR number:	CCR5065
IRAS number:	256047
Funders:	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 in Otorhinolaryngology, 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
Contact:	info@MOSESstudy.co.uk
URL:	www.MOSESstudy.co.uk

This protocol follows the format recommended by WHO found at "Recommended format for a Research Protocol" found at http://www.who.int/rpc/research_ethics/format_rp/en/ and the template provided by the Health Research Authority at https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/.

Table of contents

1 Version history

Protocol version no.	Date	Version
0.1	9/1/19	Sponsor application
1.0	5/4/19	Amendments following CCR review
1.1	9/7/19	Amendments following REC review

2 Project summary

2.1 Rationale

Cancer of the unknown primary (CUP) in the head and neck (H&N) affects around 1-2% of all head and neck cancers seen each year in the UK[1]. The oropharynx is thought to be a common site of the primary cancer, even when it cannot be identified with current standard care. Tongue base mucosectomy (TBM) offers a further opportunity to remove oropharyngeal mucosa to try and identify the primary but conventional histology (CH) may not be adequate to identify small or multiple cancers.

2.2 Objectives

Primary objective:

To establish if step serial sectioning, compared to and conventional histology, improves identification of a primary site in tonsillectomy and tongue base mucosectomy specimens in cancer of the unknown primary in the head and neck.

Secondary objectives:

1. Compare the pick-up rate of primary cancers in tongue base mucosectomy specimens between surgical methods (robotic vs laser vs endoscopic).
2. Prospectively evaluate functional recovery of swallow and pain scores after tongue base mucosectomy.
3. Conduct qualitative research encompassing patient interviews and thematic analysis of patients with cancer of unknown primary in the head and neck who have had tongue base mucosectomy.

2.3 Methods

Evidenced based standard operating protocols will be generated for TBM and SSS. Centres performing TBM to investigate CUP will be asked to participate. After CH the tonsillectomy and TBM specimens will undergo SSS. Patients will be asked to record pain scores relating to their procedure and MDADI questionnaires to record swallowing outcomes. A cohort of patients will also be interviewed to establish their views on the unknown primary, TBM and SSS, undergoing thematic analysis.

2.4 Populations

H&N patients with CUP undergoing TBM in the UK.

2.5 Timeframe

Prospective identification of patients will take place over 1 year.

2.6 Expected outcomes

Increased identification of single and multi-focal primary cancers. Acceptance of TBM and SSS amongst CUP patients. Consensus on management of the unknown primary with greater diagnostic information gained from TBM and SSS.

3 Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Print Name: _____

Signature: _____

Date: _____

Chief Investigator:

Print Name: Vinidh Paleri

Signature: 

Date: 09.07.2019

4 Rationale & background information

Approximately 5% of H&N cancer present with a neck metastasis with no clinically evident primary site.[1,2] Patients undergo clinical examination and cross-sectional imaging to attempt to identify this primary site.[3] 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 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.[4]

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.[4,5]

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 it's 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.

5 Study goals and objectives

5.1 Goals:

To establish the role of TBM and SSS in management of CUP in H&N.

5.2 Primary objective:

To establish if SSS, compared to conventional histology, improves identification of a primary site in tonsillectomy and TBM specimens in CUP in H&N.

5.3 Secondary objectives:

1. Compare the pick-up rate of primary cancers in TBM specimens between surgical methods (robotic vs laser vs endoscopic).
2. Prospectively evaluate functional recovery of swallow and pain scores after TBM.
3. Conduct qualitative research encompassing patient interviews and thematic analysis of patients with CUP in H&N who have had TBM.

6 Study Design

6.1 Type of study

Prospective descriptive observational cohort study.
[Qualitative descriptive study with thematic analysis].

6.2 Population

Patients diagnosed with squamous cell cancer of the head and neck, through positive biopsy of a cervical lymph node metastasis, whom have not had the primary site identified by either clinical examination or cross-sectional imaging (CT/MRI) including PET CT.

6.3 Sampling frame

12 months, or until 60 cases are recruited to the prospective cohort study.
[Until saturation of thematic analysis for qualitative study].

7 Patient Selection Criteria

7.1 Inclusion criteria

- Aged over 18
- Both sexes
- Cervical metastatic SCC, confirmed with cytology or biopsy, undergoing TBM for identification of primary site

7.2 Exclusion criteria

- Primary site identified by any means prior to being indicated for TBM
- Patients undergoing targeted biopsies or resections

8 Methodology

8.1 Identification of patients

Patients will be identified from the MDT lists from participating centres which will be screened weekly by local leads. Those satisfying inclusion and exclusion criteria will be approached to take part.

Additionally, for the patient interview qualitative component, local teams may mention the study to patients who have been previously treated with tongue base mucosectomy during their routine follow up appointments. The MOSES study team will not approach any of these patients directly. Adverts will also be places at peopleinresearch.org and at mosesstudy.co.uk for people to self-refer.

8.2 Consent

Eligible patients will be approached by the usual care team at their next scheduled outpatient appointment. No additional outpatient appointments or patient contacts will be required. A series of 'MOSES patient packs' will be supplied to each participating centre. The packs will include a bespoke consent form which will remain in the local patient record. They will also include a patient information leaflet for the patient to keep. Appropriate time will be given to patients to read and digest the information on the Patient Information Sheet. Written consent will be taken by a delegated clinician most likely the Principal Investigator at each site.

8.3 Functional outcomes and pain scores.

The patient packs will also include 6 sets of questionnaires, to be completed pre-operatively and at 3 weeks, 6 weeks, 3 months, 6 months and 12 months post-operatively. These are to assess pain scores and swallowing function. Patients will be asked to record their pain score at its worst, at its least and most of the time, on a Numeric Rating Scale. They will be asked to assess their swallow function by completing a M. D. Anderson Dysphagia Inventory (MDADI). At each stage, Stamped Addressed Envelopes (SAE) will be supplied to the patients to be able to return the questionnaires to a central MOSES address at the Royal Marsden Hospital, London.

8.4 Dataset and case report form (CRF)

The following fields will be recorded on the CRF:

- Demographics: Age at presentation, sex, study ID, date of referral
- Medical history: Smoking and alcohol history
- Surgical history: Timings of tonsillectomy and TBM, TBM method (robotic/laser/endoscopic)
- Investigations: Nodal staging, HPV status, EBV status, MRI/CT/PETCT performed
- Conventional histology result, including foci and margin status

- SSS histology result, including foci and margin status
- Pain and swallowing function scores

Data collected on the CRF can be used as source data.

8.5 Pseudonymisation

Each site will generate a unique study ID and use a 'key' to reference this to the NHS and hospital medical record number. This key will be stored locally at contributing trusts on an excel file on the hard drive of a secure NHS computer. The study key will be stored for the duration of the study and then destroyed in line with local processes for handling patient identifiable data. No patient identifiable data will leave the contributing trusts.

A case report form (CRF) will be created for each patient to record the above dataset including the unique study ID. This information will be shared with the central MOSES team via nhs.net mail to a central MOSES computer held at the Royal Marsden Hospital in the H&N office.

The central MOSES team will only receive and process pseudonymised data associated with the study ID. The central MOSES database will not record contributing sites by name so that individual cases are not linkable to their site of origin. The key to this information will be kept separately to the MOSES database.

Study ID will be formed from a three letter hospital code followed by a three digit consecutive number, eg RMH001, RMH002, etc.

8.6 Surgical technique

All centres known to be performing TBM in the UK will be invited to take part. The surgery will take part at the contributing centre adhering to their usual practices. This will encompass techniques using laser resection, endoscopically assisted techniques and resections using robotic systems. There is currently no standardised method for performing TBM. An affiliated project will look to generate a standard operating protocol (SOP) for TBM for potential future studies. The technique used in each case will be recorded on the CRF.

8.7 Histological processing

All tonsillectomy and TBM specimens will undergo conventional histological processing at the local site. Information from this will be presented to the local MDT and influence local management in the usual way. Once the specimens have been utilised, and the management plan established, the tissue specimens will be centralised to laboratories at the Royal Victoria Infirmary (RVI) in Newcastle under the care of Dr Max Robinson.

To simplify the Material transfer agreements (MTAs), specimens will first be centralised to the Human Tissue Bank at RMH before being sent onto the RVI. Appropriate tissue handling practices will be observed. RMH uses FreezerPro Laboratory Management Software to facilitate handling and tracking of tissue specimens.

The paraffin blocks supplied will undergo step serial sectioning using the following method: Steps every 0.5mm with five serial 4μm sections taken. Each block will be processed in this way until the material is consumed. Slides will be stained with haematoxylin and eosin stain (H&E) and examined for signs of SCC.

If an SCC is identified, then serial sections 2 and 4 will be submitted for HPV testing (p16 immunohistochemistry and high-risk HPV DNA in situ hybridisation). Serial sections 1 and 5 will be retained for repeat tests if required. The pathologist will compose a report and complete the relevant sections of the CRF.

Unused material will be returned to the contributing centres if desired. Some material may be retained for further study, as detailed in the patient information sheet and informed consent form.

8.8 Qualitative methods and data outcomes

Patients eligible for inclusion in the prospective cohort study will also be asked on the consent form if they would be happy to be contacted by a trained member of the MOSES team to be interviewed about their views on the following topics:

- Their views on the patient pathway to date.
- Their views on TBM.
- Their views on CUP in H&N and the psychological impact of not knowing the origin has been identified.
- Their views on the potential diagnostic improvements brought by SSS
- Their views on the possible escalation of treatment brought about by identification and incomplete removal of a primary
- Their views on robotic surgery in general

There is a separate patient information sheet and informed consent form for this qualitative component. Patients not consenting to be contacting regarding the above interviews will not be precluded from participation in the remainder of the study.

After appropriate training in qualitative research methodology, a core committee will meet to agree a final methodology, form a provisional topics list and suggest interview questions. We will then engage with a PPI group to assess topic list and questions and to hold practice interviews with appropriate feedback. Patients will be recruited for one-to-one interviews at various stages of their treatment.

The one-to -one interviews will be recorded on a trust Dictaphone, and a transcription of the conversation made. The transcription will be reviewed and coded using appropriate software. There

will be interval thematic analysis and further recruitment/interviews until saturation (as per Francis method) before final thematic analysis [8]. No patient identifiable data will be recorded as per the methods above. Basic treatment information will be recorded alongside demographics to give context to the answers.

9 Assessment timings

The following tables summarises the time points at which respective data fields will be gathered and returned:

Procedure		Screening /day 0	3 weeks	6 weeks	3 months	6 months	12 months
PI	Eligibility	x					
	Informed Consent	x					
	Medical and surgical history	x					
	Investigation results	x					
	Conventional histology result		x				
	CRF Completion	Page 1	Pages 2 &3				
Patient	Pain questionnaire	x	x	x	x	x	x
	MDADI questionnaire	x	x	x	x	x	x
MOSES	CRF Completion			Pages 4&5	Pages 4&5	Pages 4&5	Pages 4&5

Return of data:	Screening /day 0	3 weeks	6 weeks	3 months	6 months	12 months
PI to return CRF and week 0 questionnaires		x				
Return of questionnaires in SAE		x	x	x	x	x
Histology result from Royal Victoria Hospital, Newcastle			x			
Qualitative interviews			Various time points			

10 Statistical Considerations

10.1 Study endpoints

For the Primary objective:

Identification of cancer in the tonsillectomy or TBM specimen on histology.

For the Secondary objectives:

1. Compare the pick-up rate of primary cancers in TBM specimens between surgical methods (robotic vs laser vs endoscopic).
    - Identification of cancer in the tonsillectomy or TBM specimen on histology.
    - We anticipate no significant disparity in pick up rate between methods with the limited number of cases in this study.
2. Prospectively evaluate functional recovery of swallow and pain scores after TBM.
    - We anticipate no significant change in means from pain and MDADI scores between 0 and 6 week questionnaires. Results at 3 weeks are anticipated to be different as still recovering from surgery. Results up to 12 months will evaluate effects of any subsequent treatments and future recovery.
3. Conduct qualitative research encompassing patient interviews and thematic analysis of patients with CUP in H&N who have had TBM.
    - Qualitative thematic analysis therefore no quantitative end point.

10.2 Sample size

We are limited by our funding to 60 specimens being processed at our Newcastle Laboratory. Meta-analysis shows a pickup rate of 58% for this cohort. We anticipate a potential increase pick up rate of around 10%. Using the 60 specimens the 95% confidence interval boundaries around the pickup rate will be +/- 12.5% for 58% or +/-11.8% for 68%.

10.3 Study duration

Recruitment of patients will be open for 12 months. If the 60 patients are recruited within this timeframe then the study will close early. If the 60 patient target is not achieved by 12 months then the co-investigators will agree by consensus whether or not to extend the study duration.

10.4 Analysis methods

Descriptive analysis only is anticipated. The rate of CH and SSS pick up will be reported in the overall specimens and separately in the sub-group of surgical methods with 95% confidence intervals. The pain

scores and swallow recovery with MDADI scores will be reported using mean/median and standard deviation or range as appropriate at each time point of 0, 3 weeks, 6 weeks, 3 months, 6 months and 12 months. Similarly, score change between time points will be summarized in the same way. The primary and secondary analysis will be done when the complete sample size is recruited and last patient on the study completed all follow-ups.

10.5 Database management

The study will require database to store pseudonymised data. Data to be collected can be found in the attached Case Report Form (CRF) template. Data will be entered into the MACRO online data storage tool by Elsevier (https://www.elsevier.com/en-gb/solutions/macro). Data from the CRFs will be entered onto the MACRO database by the MOSES team.

10.6 Safety Considerations

There are no immediate safety implications anticipated due to the observational and non-interventional nature of the study.

There is potential for primary cancers to be identified in some tissue specimens where it had been missed at the local site when undergoing conventional histology. These updated results from the pseudonymised specimens will not be available in a timeframe that could influence patient treatment.

10.7 Follow-Up

Beyond the questionnaires finishes at 12 months post operatively, there is no follow up planned for the patients. Outcome data is derived from the tissue specimens. As above, results from SSS of the tissue specimens will not be fed back to the individual MDT as it will have no potential to influence management which will already have been enacted.

10.8 Quality Assurance

The core MOSES team handling the pseudonymised data have all undergone GCP training with valid contemporary certification.

10.9 Expected Outcomes of the Study

TBM is a relatively new surgical procedure with little data relating to patients experience and recovery from this operation. The pain and MDADI questions will go some way to showing the acceptability of this procedure to patients. It is expected that by 6 weeks the pain and MDADI scores will have returned to near baseline. Most patients will go on to receive radiotherapy to their pharyngeal mucosa, which is

known to worsen swallowing function. This data will go some way to clarifying that any subsequent difficulties may not be attributable to the TBM procedure.

Any increased pick up rate resulting from SSS could lead to wider adoption of this process in the management of CUP in the H&N. The size of any primary sites identified through SSS over conventional histology will also be recorded and could influence the size of histological levels employed for future TBM and tonsillectomy specimens in the future management of CUP in H&N.

Data from the patient interviews and thematic analysis should help to guide patient goals for any further research in CUP and H&N. Of particular note will be the patients' wishes regarding timing of the tonsillectomy and TBM procedures, which can occur separately, particularly if initial investigation is performed in a peripheral hospital that does not offer TBM. The potential changes in management from identification of primary sites using SSS, and potential for escalation of treatment through the addition of concomitant chemotherapy will also be novel.

Results from this descriptive prospective observational study will form the foundation of a potential phase III trial investigating the roles of TBM and SSS in management of CUP in H&N. The precise research question is yet to be established.

10.10 Dissemination of Results and Publication Policy

Findings from the study will be submitted for publication in relevant H&N peer reviewed journals. JH will be lead author and VP will be last author on papers, with MR and KH also included as senior authors. The Principal Investigators at each site will be included as authors, as per journal policy and following review and approval of the final manuscripts.

10.11 Duration of the Project

Date	Activity
Dec 2018	First draft of protocol
	First contact with potential sites
Jan 2019	Protocol submission to sponsor
Feb 2019	CCR meeting
	Submission of IRAS
March 2019	Confirmation of approval of RMH sponsorship
	Proportionate review ethics approval
	Qualitative research training for clinical research fellow JH
April 2019	Opening of first sites at RMH and Imperial Trust
May 2019	Opening of further sites
June 2019	Identification of patients for qualitative interviews
May 2020	Completion of recruitment
June 2020	Analysis
July 2020	Draft Manuscript

11 Problems Anticipated

11.1 Slow recruitment of TBM centres

Early contact with the TBM centres across the UK should improve timely recruitment.

11.2 Slow recruitment of TBM patients

It is very unlikely that any eligible patients will be missed by the MDTs and clinicians involved in recruitment. It is also felt to be unlikely that patients will not consent to being involved in the study as, by design, there has intended to be minimal burden from the questionnaires.

12 Project Management

Name	Vinidh Paleri
Role(s)	Chief investigator
Responsibilities	Oversight of project design, conduct and reporting. Liaison with Research Ethics Committee (REC), and other review bodies, during the application process, and where necessary during, the conduct of the research. Ensure adherence to protocol.

Name	Max Robinson
Role(s)	Co-investigator Chief pathologist
Responsibilities	Coordination of processing of pathology specimens once received at Newcastle laboratories and reviewing of slides for diagnosis of primary outcome of MOSES trial.

Name	John Hardman
Role(s)	Co-investigator Clinical research fellow
Responsibilities	Recruitment of contributing centres. Coordination of centralising pathology specimens to Newcastle laboratories Coordination of data governance and control of the MOSES database. Tabulation of data from questionnaires. Analysis and write up of MOSES findings

13 Ethical considerations

The protocol will be submitted for ethical review to the Human Research Authority's 'Integrated Research Application System' (IRAS). It is believed the application will be suitable for a 'proportionate review' which allows fast tracking of the process.

Having undergone SSS, the tissue specimens may have new or additional carcinomas identified. This information will not be available to the treating MDT in a timeframe that could influence patient care. Their treatment plans will have been enacted. The results of the pathological processing will not be fed back to the contributing centres but will only be held in a pseudonymised central MOSES database.

Patients will be asked to complete pain score questionnaires and swallowing function questionnaires. Many centres collect swallow function scores for head and neck cancer patients routinely. These questionnaires will be an additional burden to these patients. However, it is also acknowledged that by asking for these data it may prompt closer attention and better care for these patients.

Patients approached to take part in one to one interviews have potential to discuss their perceptions regarding their cancer and cancer management. This could be potentially distressing for some patients. They will be provided with appropriate contact information for Clinical Nurse Specialists throughout the process. They are also eligible to withdraw from the process at any stage without any impact on their care. It is likely that the majority of the patients will have completed their treatment and be in surveillance by the time they are approached to be involved in the interviews.

14 Informed consent process

14.1 Informed Consent Forms

Please see appendix for patient information sheets and informed consent forms.

There are two versions of each form. Firstly, for inclusion in the main portion of the MOSES study, and secondly for those agreeing to take part in the qualitative interviews.

15 Budget

15.1 Approved funding

This study has been funded by a grant from Oracle Cancer Trust. The following is a summary of the costings for the grant application that were revised and approved on 3rd December 2018:

	Item	Total	Comment
TOTAL COST OF PROJECT	Pathological processing	£ 30,937.50	(£475.96/case)
	Clinical research fellow	£ 50,538.09	Total for 2 yrs
	MD registration fees (ICR)	£ 9,220.00	(£4,610 /yr)
	Qualitative Research Methods Course	£ 1,525.00	https://bit.ly/2DXIbxY
	Supervising PI (Prof Vin Paleri)	£ 11,567.00	(2hrs/wk)
	Dr. Max Robinson (pathology lead)	£ 9,203.80	(2hrs/wk)
	Consensus meeting	£ 5,000.00	
ORACLE GRANT REQUESTED	TOTAL	£ 117,991.39	
	Per Annum	£ 58,995.70	over 2 yrs

This study received a further grant from the Biomedical Research Centre TPT Pump Priming fund. This award of £20,000 will cover Human Tissue Bank costs at RMH and the receipt and transfer of tissue from the contributing units to the laboratory at the RVI in Newcastle. It will also cover reimbursement of patient travel costs, room hire, basic catering/tea/coffee, interview transcription and a licence for the NVIVO coding analysis software for the qualitative interviews.

Statistics and database costs were expected to be around £10,000. However, these costs are no longer applicable, following the award of the TPT Pump Priming grant above.

15.2 Outstanding funding

There is currently no outstanding funding anticipated.

15.3 Other support for the Project

We are grateful for the support from Oracle Cancer Trust, the Royal Marsden Hospital, the Institute for Cancer Research and Newcastle upon Tyne Hospitals NHS Foundation Trust.

The salary for the Clinical Research Fellow has also received contributions from the Royal College of Surgeons of England and ENT UK.

16 Collaboration with other scientists or research institutions

16.1 Curriculum Vitae of investigators

The CV of the Principal investigator will be provided.

16.2 Other research activities of the investigators

Current research projects that the principal investigator is involved in are listed in the appended CVs, including the source of funding of these projects, the duration of those projects and the percentage of time spent on each.

17 Financing and Insurance

Financing has been outlined in the 'Budget' section above.

Insurance is as per Sponsors arrangements.

18 Table of acronyms

Acronym	Meaning
CCR	Committee for clinical research
CH	Conventional histology
CRF	Case report form
CT	Computed tomography
CUP	Cancer of unknown primary
EBV	Epstein Barr virus
FNAC	Fine needle aspiration cytology
GCP	Good clinical practice
H&E	Haematoxylin and eosin stain
H&N	Head and neck
HPV	Human papilloma virus
IRAS	Integrated research application system
MDADI	M. D. Anderson Dysphagia Inventory
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
MTA	Material Transfer Agreement (Part of HRA Statement of Activities)
PET CT	Positron emission tomography and computed tomography
REC	Research ethics committee
RMH	Royal Marsden Hospital
RVI	Royal Victoria Infirmary, Newcastle (laboratories)
SAE	Stamped addressed envelope
SCC	Squamous cell carcinoma
SOP	Standard operating protocol
SSS	Step serial sectioning
TBM	Tongue base mucosectomy

19 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;130:S170–5.

2. Galloway TJ, Ridge JA. Management of Squamous Cancer Metastatic to Cervical Nodes With an Unknown Primary Site. J Clin Oncol. 2015;33:3328–37.

3. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over | Guidance and guidelines | NICE [Internet]. [cited 2018 Dec 3]. Available from: https://www.nice.org.uk/guidance/ng36/chapter/Recommendations#investigation

4. Winter SC, Ofo E, Meikle D, Silva P, Fraser L, O'Hara J, et al. Trans-oral robotic assisted tongue base mucosectomy for investigation of cancer of unknown primary in the head and neck region. The UK experience. Clin Otolaryngol. 2017;42:1247–51.

5. Wallis S, O'Toole L, Karsai L, Jose J. Transoral endoscopic base of tongue mucosectomy for investigation of unknown primary cancers of head and neck. Clin Otolaryngol. 2018;

6. Black CC, Ogomo C. Does pTis exist in HPV-driven tonsillar carcinomas? An ultrastructural review and examination of two cases. Ultrastruct Pathol. 2017;41:55–61.

7. Genden EM. The role for surgical management of HPV-related oropharyngeal carcinoma. Head Neck Pathol. 2012;6 Suppl 1:S98-103.

8. Francis JJ, Johnston M, Robertson C, Glidewell L, Entwistle V, Eccles MP, et al. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. Psychol Health. 2010;25:1229–45.