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Finding/identifying primaries with neck disease (FIND) clinical trial protocol: a study integrating transoral robotic surgery, histopathological localisation and tailored deintensification of radiotherapy for unknown primary and small oropharyngeal head and neck squamous cell carcinoma

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ABSTRACT

Introduction Carcinomas of unknown primary site (CUP) of the head and neck have historically been worked up and managed heterogeneously. Failure to identify a primary site may result in large radiotherapy mucosal volumes. Transoral approaches such as Transoral Robotic Surgery (TORS) may improve the yield of identifying hidden primaries. We aim to assess the oncological and functional outcomes of a combined treatment approach with TORS and tailored radiotherapy.

Methods and analysis Twenty-five patients with metastatic squamous cell carcinoma to the neck without clinical or radiographic evidence of a primary site will be enrolled in a phase II trial. Patients will undergo a diagnostic or therapeutic approach with TORS based on specific algorithms incorporating tailored radiotherapy according to the location and laterality of the primary tumour. The primary outcome is to evaluate the out-of-field failure rate over a 2-year period. Secondary outcomes include identification rates, survival outcomes, patient reported outcomes and functional swallowing outcomes.

Ethics and dissemination The University Health Network Research Ethics Board approved this study (ID 15–9767). The results will be published in an open access journal.

Trial registration number NCT03281499.

Strengths and limitations of this study

- This is the first prospective study to integrate the role of transoral robotic surgery into the diagnostic evaluation of patients presenting with cancers of unknown primary site (CUP).
- A strength of this study is that it will prospectively evaluate the role of transoral robotic surgery in deintensifying treatment for CUP patients.
- Another strength of the study is that it includes patient-reported outcomes and functional swallowing outcomes as secondary measures.
- A limitation of this study is that participants are not randomised to intervention or control arms.
- Another limitation of this study is that following intervention, management decisions are at the discretion of the treating physician.

INTRODUCTION

Carcinomas of unknown primary site (CUP) of the head and neck account for 1.5%–9% of all head and neck cancers.[1–3] Historically, CUP tumours were believed to originate from one of several putative sites in the upper aerodigestive tract including the oropharynx, nasopharynx or hypopharynx.[4] In the era of the human papillomavirus epidemic however, recent literature now demonstrates that 89% of all patients who present with CUP and ultimately have a tumour identified have a primary in the oropharynx (45% in the palatine tonsils and 44% in the tongue base).[5] Given that roughly two-thirds (64%) of patients presenting with cervical lymphadenopathy have an oropharyngeal primary tumour, the rising incidence of oropharyngeal carcinomas will likely be reflected in the unknown primary cancer population.[6]

Traditional techniques for identification of primary tumours in CUP involves a PET/CT scan followed by examination under anaesthesia with biopsies of the nasopharynx, tongue base, piriform sinuses in conjunction with a tonsillectomy. This has been shown to identify at most 44% of primary tumors.[7] This low yield may be related to small primary tumours hidden within the lingual tonsil of the tongue base which escape identification with deep biopsy alone. Complete resection of the mucosal lining of the tongue base and lingual tonsils may improve the diagnostic yield, yet surgical access for a tongue base lingual tonsillectomy has traditionally been precluded due to difficult access. Transoral Robotic Surgery (TORS), however, allows for this resection through the mouth with the use of angled instruments, high-definition endoscopes and articulated instrumentation arms.[8] When traditional methods of finding a primary are unsuccessful, several groups have demonstrated that TORS may identify a primary tumour site in 71% of cases.[9–16]

Accurate diagnostic evaluation of patients who present with CUP tumours is critical as management depends on whether or not the primary tumour is identified. Small primary tumours identified in the oropharynx, nasopharynx and hypopharynx after a diagnostic workup are typically managed with radiotherapy to the primary site and high-risk nodes. Unidentified tumours, however, are treated with mucosal irradiation to all high-risk mucosal sites, at the expense of added morbidity.

We propose to integrate TORS into the diagnostic evaluation of patients presenting with metastatic squamous cell carcinoma to the neck of unknown primary origin. We aim to localise small hidden oropharyngeal carcinomas, determine their laterality and, based on the laterality of the tumour and neck nodes and completeness of resection, offer reduced radiotherapy to the primary site and/or to the neck. We hypothesise that this approach to unknown primary carcinomas will be both safe and effective. Herein, we propose a trial to investigate this new diagnostic and therapeutic approach.

METHODS/DESIGN

We are conducting a phase II clinical trial at the Princess Margaret Cancer Center/University Health Network (Toronto, Ontario, Canada). The trial schema is outlined in figure 1. An overview of trial registration data is provided in table 1. This protocol was prepared using the SPIRIT reporting guidelines.[17]

Objectives

The primary objective for the study is to determine the rate of out-of-field failures following treatment as determined by use of morphological imaging (contrast enhanced CT or MRI of the neck) and confirmed by biopsy. We will determine the proportion of patients who experience a failure out of their radiotherapy treatment volumes in order to proceed with larger phase II or phase III prospective studies. We hypothesise that, in order to be considered safe, we should have an out-of-field and marginal failure rate of less than 15%, which includes both local (mucosal) and regional (neck node) failures.

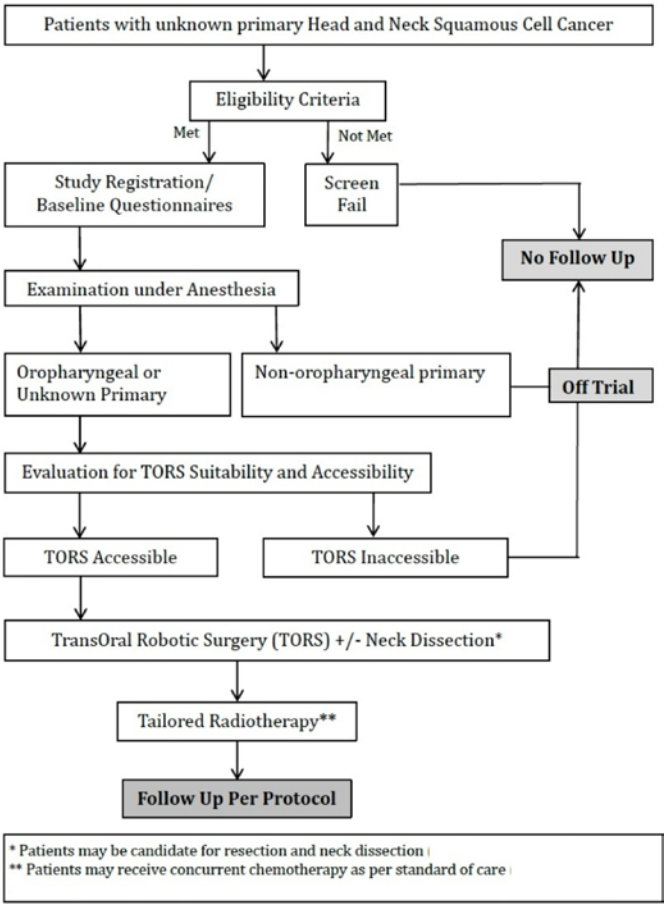

Figure 1 Study schema.

As secondary objectives, we will examine:

1. The profile of TORS-related adverse events within 30 days following surgery using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC-AE v.4.0)
2. The proportion of patients with occult oropharyngeal cancer and the location of those primary tumours, the proportion of patients with completely resected primary oropharyngeal carcinomas and the proportion of patients amenable to deintensified treatment defined by avoidance of radiation to the primary site or at least one side of the neck.
3. Patient reported swallowing related quality of life outcomes using the MD Anderson Dysphagia Inventory (MDADI)
4. Objective measures of swallowing impairment using videofluoroscopic swallowing studies rated using the Modified Barium Swallow Impairment Profile (MBSImP), the Penetration-Aspiration Score (PAS) and the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST).
5. Patterns of failure (local, regional, distant) and (out-of-field, marginal and in-field).

Table 1 Trial registration data

Primary registry and trial identifying number	ClinicalTrials.gov NCT03281499
Date of registration in primary registry	21 August 2017
Secondary identifying numbers	N/A
Source(s) of monetary or material support	Innovation Fund for Surgical Oncology (IFSO), Department of Surgical Oncology, Princess Margaret Cancer Centre
Primary sponsor	University Health Network, Toronto
Secondary sponsor(s)	N/A
Contact for public queries	John R de Almeida
Contact for scientific queries	John R de Almeida
Public title	Transoral Robotic Surgery and Tailored Radiotherapy in Unknown Primary and Small Squamous Cell Head and Neck Cancer
Scientific title	Finding/Identifying Primaries with Neck Disease (FIND) Clinical Trial Protocol: A Study Integrating Transoral Robotic Surgery, Histopathologic Localization, and Tailored De-Intensification of Radiotherapy for Unknown Primary and Small Oropharyngeal Head and Neck Squamous Cell Carcinoma
Countries of recruitment	Canada
Health condition(s) or problem(s) studied	Head and Neck Squamous Cell Carcinoma
Intervention(s)	Tailored radiotherapy regimen following transoral robotic surgery
Key inclusion and exclusion criteria	Inclusion: ► Age ≥18 ► Metastatic squamous cell carcinoma (T0,N1-3,M0) to at least one regional lymph node of the neck based on fine needle aspiration biopsy, core biopsy, excisional biopsy, or neck dissection Exclusion: ► Evidence of a nasopharyngeal carcinoma, non-cutaneous head and neck squamous cell carcinoma or lymphadenopathy unlikely to originate from a primary oropharyngeal carcinoma. ► Prior radiotherapy
Study type	Interventional
Date of first enrolment	14 September 2017
Target sample size	25
Recruitment status	Recruiting
Primary outcome(s)	► Determination of the rate of out-of-field failures following treatment
Key secondary outcomes	► Adverse events (AE) monitoring ► Determination of proportions of occult oropharyngeal cancers identified ► Determination of the proportion of patients amenable to deintensification treatment ► Exploration of speech and swallowing performance status

6. 2-year locoregional control, progression-free survival and overall survival.
7. Observer rated speech and swallowing using the Performance Status Scale for Head and Neck (PSS-HN).
8. Patient reported neck impairment using the neck dissection impairment index (NDII) .
9. The diagnostic properties of 18-FDG PET/CT for patients with CUP.
10. Acute and late toxicities after treatment as measured by the CTC-AE v.4.0.

Inclusion criteria

► Age ≥18

► Newly diagnosed metastatic squamous cell carcinoma (T0, N1-N3, M0, AJCC seventh edition) to at least one regional lymph node of the neck based on fine needle aspiration (FNA) biopsy, core biopsy, excisional biopsy or neck dissection with no clinical or radiographic evidence on morphological imaging of a primary site

Exclusion criteria

► Evidence of a nasopharyngeal carcinoma which includes a positive nasopharyngeal biopsy or core lymph node biopsy staining for Epstein Barr Encoded RNA (EBER) by in situ hybridisation.

► Prior non-cutaneous head and neck squamous cell carcinoma.

- History of neck dissection—contralateral to the side of nodal disease.
- Presence of lymphadenopathy on CT unlikely to originate from a primary oropharyngeal carcinoma (eg, parotid lymphadenopathy or isolated lower neck adenopathy in level IV/V without level II/III involvement).
- Radiologically abnormal/enlarged retropharyngeal adenopathy.
- Poor performance status (ECOG status 3–5).[18]
- Severe comorbidity or uncontrolled intercurrent illness.
- Not a surgical candidate.
- Pregnancy.

Evaluation

Prior to study entry

A full history, physical examination and fiberoptic laryngopharyngoscopy will be completed by both a Head and Neck Surgeon and a Radiation Oncologist. Any clinically apparent tumour will be biopsied and the participant will be excluded if positive. All patients will undergo axial imaging with a contrast-enhanced CT scan or contrast or non-contrast-enhanced MRI of the head and neck. Patient will also undergo a PET/CT scan using fluorodeoxyglucose (18-FDG PET/CT). A core biopsy of metastatic cervical lymph nodes will be obtained prior to examination under anaesthesia. All lymph nodes measuring >1 cm on the contralateral side of the neck that do not have any features suggestive of metastatic lymph node involvement will undergo an FNA biopsy. Specimens/cell blocks will be stained using immunohistochemistry for p16. Epstein-Barr Virus Encoded RNA (EBER) in situ hybridisation of the node biopsy is recommended but not required. Patients who are positive for EBER will be excluded from the study.

After study registration

All patients will complete the MD Anderson Dysphagia Inventory (MDADI),[19] the Neck Dissection Impairment Index (NDII),[20] the Performance Status Scale for Head and Neck (PSS-HN)[21] as well as a videofluoroscopic swallow study (VFS). VFS studies will be rated by a trained speech language pathologist using: the Modified Barium Swallow Impairment Profile (MBSImP),[22] the Penetration-Aspiration Score (PAS), Pharyngeal Constriction Ratio (PCR) and the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST).

TREATMENT

Operative examination under anesthesia

All recruited participants will be taken to the operating room for an examination under anaesthesia with biopsies. All putative mucosal sites for harbouring an occult malignancy will be directly visualised endoscopically. Biopsies will also be obtained from abnormal lesions guided by preoperative imaging (CT, MRI and PET/CT). Patients with positive intraoperative biopsies of non-oropharyngeal lesions will be excluded. Patients with positive intraoperative biopsies on frozen sections of oropharyngeal lesion may be considered for resection and neck dissection or tailored radiotherapy depending on the extent of nodal disease (see online supplementary appendix 1). Specifically, patients with no radiographic extranodal extension and with N1-N2b nodal disease may undergo definitive resection and neck dissection during the same general anaesthetic.

The approach for identifying a primary site will be based on findings of the preoperative PET/CT study. In patients with no suspicious primary site on PET/CT, the surgical evaluation begins with an ipsilateral palatine tonsillectomy followed by intraoperative pathologic frozen section analysis of the tonsil using a 'bread-loafing' technique. The palatine tonsil will be bread-loafed into sections approximately 2–3 mm thick from superior to inferior and evaluated in toto for the presence of tumour by frozen section analysis. If a primary tumour is identified in the palatine tonsil, a resection and neck dissection may be performed to facilitate clearance of the margins in patients with favourable disease (no radiographic extranodal extension and with N1-N2b disease). In patients with unfavourable disease, patients will be treated with definitive (chemo)radiotherapy. If no primary site is identified in the ipsilateral palatine tonsil, a TORS lingual tonsillectomy will be performed in addition to three deep biopsies from the contralateral palatine tonsil (superior, middle and inferior pole). The lingual tonsillectomy will comprise a mucosal and lymphoid tissue resection from the circumvallate papillae to the vallecula anteroposteriorly and from glossotonsillar sulcus to glossotonsillar sulcus. The lingual tonsillectomy can be done as a single excision or divided into two hemi-compartments. A neck dissection may be performed in patients with favourable neck disease.

In patients with a PET/CT showing a suspicious primary site in the oropharynx, the TORS procedure will aim to remove the suspicious primary site. If the suspicious site is in the palatine tonsil, a palatine tonsillectomy will be performed as above followed by intraoperative pathologicl frozen section analysis of the 'bread-loafed' tonsil. Resection and neck dissection may be performed during the same general anaesthetic if a primary site is identified and in patients with favourable disease (no radiographic extranodal extension and with N1-N2b disease). If the suspicious site on PET/CT is in the lingual tonsil, a lingual tonsillectomy will be performed with three deep biopsies from the contralateral palatine tonsil. Given the size of the lingual tonsil, no intraoperative bread-loafing will be done on this specimen. Concurrent neck dissection may then be offered in patients with favourable disease. In cases with radiographic evidence of ENE or advanced nodal disease, patients will be treated with primary radiation and possibly chemotherapy.

In patients undergoing a definitive resection and neck dissection, prophylactic ligation of branches of the

external carotid artery including the lingual artery at a minimum and possibly the facial artery and ascending pharyngeal artery will be performed to reduce the risk of severe post-operative haemorrhage.

Post-TORS study procedures

Complications will be reported in the 30 days following the final surgical procedure. The MDADI, NDII and PSS-HN will be administered prior to commencement of radiotherapy and after completion of TORS.

Histopathological localisation

Identified primary tumours will be classified as lateralised if they are located in the ipsilateral palatine tonsil or ipsilateral tongue base with at least a 1 cm distance from the midline. Margin status will be determined on tonsillar and tongue base tumours and measured in millimetres and will be reported as clear (≥3 mm), close (<3 mm) or microscopically positive if cancer extends to the edge of resection.[23] Additional adverse pathological features will be reported such as perineural invasion, lymphovascular invasion as well as positive nodal count and the presence of extra nodal extension for those patients who underwent neck dissections.

Radiation therapy

In general, patients with unfavourable nodal disease (radiographic extranodal extension or N2c-N3 nodal disease) will undergo definitive radiotherapy with or without cisplatin chemotherapy after diagnostic surgery (see online supplementary appendix 1 and 2) and will not undergo definitive resection. Two exceptions apply to this general rule: (1) in certain cases, a contralateral incidental primary may be identified at the time of TORS procedure with neck dissection and upstage the patient to N2c; (2) in patients with advanced nodal disease (N3), a neck dissection and resection of the primary (if identified) may be offered upfront if this patient is felt to require neck surgery in order to achieve disease control.

Patients with favourable nodal disease (N1-N2b without radiographic extranodal extension) on study may be treated with TORS resection and neck dissection. Radiotherapy will be given in the adjuvant setting for patients with adverse risk features including the following:

- Close (<3 mm) or positive margins at the primary site
- Pathological extranodal extension
- Single node >3 cm or multiple unilateral positive nodes

In patients who undergo TORS procedures, radiotherapy will be avoided at the primary site if a primary site is identified and the margins are ≥3 mm or if no primary site is identified after the TORS workup. The rationale for avoidance of primary site radiation in patients in whom no primary site is identified is that the entire oropharyngeal axis has been examined thoroughly and that likely no primary site exists (see online supplementary appendix 3).

For nodal disease, the GTV represents grossly involved nodes. Grossly positive nodes are defined as those greater than 1 cm in axial dimension, any size with evidence of necrosis, PET positive or biopsy proven carcinoma. For patients who have undergone initial neck surgery, sites of preoperative gross nodal disease as well as adjacent structures may be considered high risk. Clinical Target Volumes CTVs are contoured in relation to the gross targets and regions of potential subclinical spread. In scenarios where a primary site is not identified, patients will undergo active surveillance of the primary site. In scenarios where a primary site is identified, and not completely excised with wide margins, the entire subsite will be treated. Study specific nodal region contouring will be done according to online supplementary appendix 4. The planning target volumes (PTVs) are geometric expansions of the CTVs to account for internal motion and residual setup error. All CTVs will have a corresponding PTV which will represent at least a 5-mm expansion of the CTV in all planes.

All patients will undergo CT-based treatment planning, and intensity-modulated radiotherapy (IMRT) will be used. IMRT planning is volumetric with dose volume histogram assessments to ensure PTV coverage and organs at risk avoidance. Patients will be treated in the supine position and immobilised in a thermoplastic mask.

Chemotherapy

The administration of concurrent chemotherapy (IV cisplatin) with radiotherapy after transoral robotic surgery will be at the discretion of the treatment team as per their institutional practices. Patients with positive margins at the primary site do not necessarily require chemotherapy unless deemed necessary by the treatment team for other reasons. Eligible patients with pathological ENE or positive nodal margins will receive adjuvant chemoradiotherapy as per current international guidelines.

FOLLOW-UP TEST AND PROCEDURES

All patients will undergo a CT head and neck with contrast 3 months after the completion of radiotherapy and every 3 months for the first 2 years. A CT chest will be performed at 1 and 2 years post treatment. Patients will complete the MDADI, NDII and PSS-HN after completion of TORS, after the completion of radiotherapy as well as 3 months, 1 year and 2 years post completion of treatment. A repeat VFS will be completed 2 years after completion of treatment. Patients who move to standard of care after surgery will be followed for any subsequent therapies and relapses. The study will make every reasonable effort to follow patients for the entirety of the trial period. We anticipate loss to follow-up will be <10% over the 2-year period.

Identifying and classifying failures

Nodal/ regional failures

The radiographic definition of a complete response for nodal disease that has been treated with radiotherapy

is defined as a total resolution or involution of previous lymphadenopathy to <1.0 cm without any suspicious features (eg, central necrosis, rounded borders, radiographic evidence of extracapsular extension, three borderline size nodes). All patients with HPV-negative disease or advanced HPV-positive nodal disease (N3) without a radiographic complete response and have not received upfront neck dissection will undergo a consolidation neck dissection as per institutional protocol.[24] Patients with less advanced HPV-mediated nodal disease (N1-N2c) and without complete radiographic response may undergo serial imaging surveillance (every 6–8 weeks) to watch for continued involution or progression, in which case a consolidation neck dissection would be performed. Any post-treatment neck dissections with positive nodal disease will be considered a regional failure.

Primary site failures

Patients with clinically or radiographically concerning areas within the upper aerodigestive tract will undergo a biopsy of the primary site with salvage surgery if possible.

Distant failures

Patients will undergo annual CT scans of the chest. Patients with radiographic evidence of metastatic disease will be classified as distant failures. Those with indeterminate lesions will undergo biopsy and classified as failures when positive.

In-field, marginal and out-of-field failures

Local or regional failures will be classified as in-field, marginal or out-of-field relative to their radiotherapy treatment volumes. Recurrent or persistent tumour volume (Vf) on CT will be coregistered with pretreatment scans. In-field failures are defined as those with >95% of the Vf in the original treatment or prophylactic volumes; marginal as those with 20%–95% of the Vf in the original treatment or prophylactic volumes; and out-of-field as those with <20% of the Vf in the original treatment or prophylactic volumes.[25]

Patient recruitment

Patient recruitment in FIND began on 14 September 2017. Participants will be followed for 2 years following end-of-treatment. A study table with complete follow-up details is included (table 2). The primary completion date is projected for August 2020 and the study completion date is projected for August 2021.

STATISTICAL CONSIDERATIONS

Sample size calculation

We hypothesise that to provide a safe approach, the rate of out-of-field and marginal failures should be less than 15%. The institutional out-of-field failure rate is 1%. Using a one-sided test, with an alpha of 0.05 and power of 0.8, the estimated sample size is 19. We estimate 15% of patients will fail screening procedures (ie, patients excluded at EUA) and 10% will be lost to follow-up yielding a sample size of 25 patients.

Primary objective

The primary outcome for the study is to determine the rate of out-of-radiation field biopsy proven failures following treatment. Morphological imaging (contrast enhanced CT or MRI of the head and neck) will be obtained to delineate local and regional failures. The volume of recurrent disease (Vf) (both local and regional recurrence) will be delineated on the morphological imaging study and coregistered with the pretreatment morphological imaging study. If the >95% of the Vf is within the treatment (otherwise known as CTV1) and prophylactic (CTV2) treatment volumes, the failure will be considered an in-field failure.[25] If between 20% and 95% of the Vf is within the treatment and prophylactic volumes, the failure will be considered a marginal failure.[25] If <20% of the Vf is within the treatment and prophylactic volumes, the failure will be classified as an out-of-field failure.[25]

Secondary objectives

1. Complications from EUA/TORS – Complications from EUA and TORS will be collected, graded and reported using the CTCAE v4.0 tool.[26]
2. Proportions and location in patients with occult tumours identified – The proportion of primary tumours identified and their respective locations will be reported.
3. Proportion of patients with an oropharyngeal cancer resected with negative margins (≥3 mm) – The proportion of patients in whom a primary oropharyngeal cancer is resected with negative margins will be reported.
4. Proportion of patients amenable to deintensification of the neck and primary site – The proportion of patients who will receive a deintensified radiotherapy regimen defined as a lower dose or volume to the primary site or neck will be determined.
5. Patient reported swallowing and quality of life - Swallowing will be assessed using the MDADI. Swallowing scores at various time points will be reported with mean summary scores and SD. Post-treatment (2 years) and baseline scores will be compared. Independent predictors for mean change in scores for the MDADI global score and each of the three MDADI subscales will be explored using multiple linear regression.
6. Objective swallowing impairment - VFS assessment will be conducted at two time points: at baseline and at the end of study (2 years post completion of treatment). Two SLPs, blinded to each other and patient medical status, will rate the VFS findings using the MBSImP oral and pharyngeal rating profiles. Post-treatment (2 years) and baseline scores will be compared. Independent predictors for mean change in scores MBSImP two subscales will be explored using linear regression. Similar analysis will be conducted looking at Pharyngeal Constriction Ratio (PCR), Penetration-Aspiration Score (PAS), Pharyngeal Constriction Ra-

Table 2 Study requirements prior to study entry, after study registration and prior to follow-up

Test and procedures	Screening	Presurgery	Surgery	After TORS	Radiotherapy (weekly)	End of Treatment (EOT)*	Follow-up (q3 months)†	End of study (24 months post EOT)‡
Informed consent	X							
Physical examination including height and weight	X						X	X
Fibreoptic laryngo-pharyngoscopy	X							
ECOG Performance status assessment	X							
PET/CT scan	X							
CT Chest							X§	X
Contrast enhanced CT or MRI—head and neck	X						X	X
FNA of lymph node	X							
Operative examination under anaesthesia			X					
TORS			X					
Core biopsy of lymph node for EBER and HPV status	X							
Pregnancy test	X							
Performance status for head and neck (PSS-HN) questionnaire		X		X¶–		X	X**–	X
Video-fluoroscopic swallow study and MBS-ImpTM, DIGEST, PCR, & PAS ratingX		X						X
MDADI questionnaire		X		X¶–		X	X**–	X
NDII questionnaire		X		X¶–		X	X**–	X
Adverse events evaluation				X	X	X	X	X
Disease evaluation		X				X	X	X
Dental evaluation				X				

*End of Treatment assessments are completed on the day of last radiation treatment±5 business days.
†Follow-up assessments are done every 3 months±2 weeks.
‡End of Study assessments are done at 24 months after the last radiation treatment ± 4 weeks.
§CT Chest at follow up phase is done at 12 months and 24 months post end of treatment.
¶PSS-HN, MDADI and NDII questionnaires are completed within 2–4 weeks from TORS date.
**In the follow up phase, the PSS-HN, MDADI and NDII questionnaires are completed at 3, 12 and 24 months after the last radiation treatment.

tio (PCR) and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST).

7. Patterns of failure and survival - Patterns of failure will be classified as local, regional or distant with specific emphasis on location of failure. Failures will be further classified as in-field, marginal or out-of-field based. Local, regional and locoregional control as well as disease-specific survival will be determined using competing risk methods. Progression-free survival and overall survival will be determined using Kaplan Meier methods.
8. Patient reported neck impairment outcomes - PSS-HN and NDII scores will be summarised. Post-treatment (2 years) and baseline scores will be compared with paired Wilcoxon tests. Mean change from baseline scores for the PSS-HN and NDII will be compared between patients treated with unilateral and bilateral neck irradiation and between patients with primary site irradiation and no primary site irradiation using Kruskal-Wallis test. Independent predictors for mean change in scores PSS subscales will be explored using linear regression.
9. PET/CT diagnostic properties - Sensitivity, specificity, positive predictive values and negative predictive values of PET/CT will be determined with histopathological confirmation of cancer as the gold standard.

All outcomes will be reported with 95% CI.

PERSPECTIVE/CONCLUSION

Patients who present with carcinomas of unknown primary site (CUP) of the head and neck represent a challenging problem for clinicians both from a diagnostic and therapeutic perspective. Traditional techniques for identification of primary tumours are successful less than half the time. The remaining unidentified tumours are treated with mucosal irradiation to all high-risk mucosal sites, which may be associated with significant functional and quality of life implications.

The addition of transoral robotic surgery techniques have been shown to identify up to 70% of primary tumours that have otherwise escaped initial identification at this timepoint. By integrating TORS into the diagnostic evaluation of patients presenting with CUP through a prospective study, we suspect we will be in a position to deintensify treatment and reduce morbidity without impacting overall survival for a significant number of individuals.

DATA COLLECTION, RETENTION AND MANAGEMENT

All data obtained in the clinical trial will be reported on an electronic case capture form (Medidata). The investigator will review the data and electronically sign it to acknowledge agreement. All study documents will be retained at the UHN for 25 years in accordance with section C.05.012 of the Health Canada Food & Drug Regulations.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

Patients and members of the public were not involved in the study design. We will however invite patients to help us develop our dissemination and knowledge translation strategy.

DATA SAFETY MONITORING BOARD

An independent data safety monitoring board (DSMB) has been assembled through the Princess Margaret Cancer Centre. The DSMB contains a surgical oncologist, radiation oncologist, medical oncologist, and a statistician. The DSMB meets every 3 months and discusses target accrual and morbidity related to the trial. The DSMB will review any adverse events related to the surgical procedure and to radiotherapy and make recommendations. Given that this is a small study with a sample size of 25 patients and a short accrual timeframe, we will not perform an interim analysis.

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Contributors JD oversaw all aspects of this study. All authors have provided input into the study design (JD, CN, MV, RM, DC, SB, DG, AH, EY, UM, IW, BP, WX, JK). Many of the investigators are also active in participant recruitment (JD, DG, DC, SB, JK). WX is the statistician overseeing the analysis of the study results. All authors will have access to the final data set (JD, CN, MV, RM, DC, SB, DG, AH, EY, UM, IW, BP, WX, JK). JD and CN wrote the original draft of the manuscript and the remaining authors were involved in the revision and editing process. All authors have approved the final manuscript and agree to its publication in BMJ Open (JD, CN, MV, RM, DC, SB, DG, AH, EY, UM, IW, BP, WX, JK).

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study protocol has been approved by the University Health Network Research Ethics Board (REB#-159767). Informed written consent will be obtained from all participants by a clinical research coordinator (online supplementary appendix 5 – Consent Form). All protocol amendments will be confirmed in writing and submitted for review to the ethics board. Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff.

Provenance and peer review Not commissioned; externally peer reviewed.

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