THE RECUT STUDY

transoral Robotic surgery for rECurrent tumours of the Upper aerodigestive Tract

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Sponsor:	The Royal Marsden NHS foundation Trust Fulham Road, London SW3 6JJ
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1 VERSION HISTORY

Protocol version no.	Date	Version
0.1	2019/02/11	First draft, as distributed for feedback
0.2	2019/03/21	Updated co-investigators
1.0	2019/04/02	Approval from chief investigator
1.1	2019/05/31	Prepared for submission to the Committee for Clinical Research
1.2	2019/07/22	Following review by the Committee for Clinical Research
1.3	2019/08/08	Minor changes to affiliations, dataset and Gantt chart
1.4	2019/09/06	Final CCR submission
1.5	2019/11/15	RECUT+ Sub-study amendment
1.6	2020/01/14	Following review by the Committee for Clinical Research
1.7	2020/04/16	Removal of RECUT+ sub-study (moved to separate project) Provision for anonymised data submission
1.8	2021/07/29	End of Study definition updated

2 PROPOSED CO-INVESTIGATORS

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Christian Simon	MD	Department of Otolaryngology - H&N Surgery Lausanne University Hospital Lausanne, Switzerland	Consultant

First name, middle initial, surname	Highest earned degree	Department, section, institution, city and state or country	Role
John C Hardman	MBChB MSc	Head and Neck Unit The Royal Marsden Hospital London, UK	Clinical Research Fellow
Grainne Brady	BSc MRes	Head and Neck Unit The Royal Marsden Hospital London, UK	Speech and language therapist
Justin Roe	BA(Hons) MSc PhD	Head and Neck Unit The Royal Marsden Hospital London, UK	Speech and language therapist
Sarah Stephen	BSc	Department of Otolaryngology - H&N Surgery Newcastle upon Tyne Hospitals Newcastle, UK	Speech and language therapist

3 PROJECT SUMMARY

Rationale

Recurrent head and neck cancer (HNC) is being increasingly been managed by surgical resection with good outcomes. The emerging role of transoral robotic surgery (TORS) has not been fully assessed in this context.

Objectives

Primary objective:

To report disease-free survival at 2 years for patients with HNC recurrence treated with TORS.

Secondary objectives:

In patients with HNC recurrence treated with TORS:

- To report overall and disease-specific survival at 2 years.
- To report rates of close and involved surgical margins.
- To report rates of gastrostomy and tracheostomy use at 1 year.

Methods

Retrospective observational cohort study from international centres.

Timeframe

Patients undergoing TORS for recurrence up to the July 31st 2018.

Submission of data after July 31st 2020.

Expected outcomes

- Disease free survival rates of around 75% 2 years
- High incidence of close surgical margins.
- Low rates of tracheostomy and gastrostomy usage at 1 year.

4 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: _____

5 RATIONALE AND BACKGROUND INFORMATION

Head and neck cancer (HNC) is the 6th most common type of cancer in the world and is increasing in incidence.[1,2] Squamous cell carcinomas (SCC) account for the majority of these HNCs. An increasing number of these SCCs are being found to be associated with the Human Papilloma Virus (HPV) which has also been shown to be associated with a more favourable outcome. These HPV related cancers tend to affect younger patients with fewer comorbidities. As such, we are finding a larger cohort of patients are surviving for longer after treatment for their primary cancers.

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 (SIR 11.2, 95% CI [10.6–11.8]).[3] 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, cancer at the same site identified within 5 years.[4] Treatment for all of these cancers, which we will broadly term 'recurrent' cancers for the purposes of this study, can be complex. Commonly, radiotherapy will have formed part of the treatment regime at either the primary site or to the neck for these patients. Radiotherapy causes fibrosis in the irradiated tissues, reducing tissue pliability, contributing to trismus and reducing healing potential at the effected sites.[5] This can pose significant challenges to any further surgical intervention, which may form the mainstay of any subsequent management if re-irradiation is not an option or not indicated.[6] Surgery must then look to be as minimally invasive as possible in order to maximise functional outcomes and reduce disruption of affected tissues.

Options for surgery have traditionally involved transmandibular and transcervical routes.[5] More recently transoral routes have been adopted as endoscopic instruments become more widely available and adopted. Transoral Robotic Surgery (TORS) is the latest development in the field which confers some significant advantages to the surgeon and to the patient.[6–8] For the surgeon, the endoscopic view is 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 oral stoma. For the patient, there is less disrupted tissue if access incisions are avoided, reducing the volume of tissue that would be susceptible to scarring which can affect swallowing function or lead to fistula formation.

However, there are little data to show oncological and functional outcomes are acceptable following TORS surgery for recurrent cancers. This is in part as it is a relatively new technology and in part because whilst increasingly common, the absolute number of surgeries performed remains relatively low at individual centres. Published outcomes have shown 2 year disease-free survival rates around 75%.[6,9,10] The RECUT study aims to use a collaborative methodology to document the outcomes from TORS for recurrent HNC being performed at a number of high volume centres across the globe.

6 AIM, OBJECTIVES AND OUTCOME MEASURES

6.1 Aim

To establish the effectiveness of TORS in treating recurrent HNC.

6.2 Objectives

Primary objective:

To report disease-free survival at 2 years for patients with HNC recurrence treated with TORS.

Secondary objectives:

In patients with HNC recurrence treated with TORS:

- To report overall and disease-specific survival at 2 years.
- To report rates of close and involved surgical margins.
- To report rates of gastrostomy and tracheostomy use at 1 year.

6.3 Outcome measures

Primary outcome measure:

Disease-free survival at 2 years.

Secondary outcome measures:

- Overall survival at 2 years.
- Disease-specific survival at 2 years.
- Rates of close and involved surgical margins.
- Rate of gastrostomy use at 1 year.
- Rate of tracheostomy use at 1 year.

7 STUDY DESIGN AND SETTING

7.1 Study design

Retrospective cohort study

7.2 Study setting

- Multicentre.
- Tertiary referral units managing recurrent HNC.
- International centres, who are active in the academic literature, and have performed at least 20 primary TORS resections will be invited to be involved.

8 PARTICIPANT ELIGIBILITY CRITERIA

8.1 Inclusion criteria

- Aged over 18
- Previous HNC treated with radiotherapy
- Undergoing TORS as part of their management for recurrent disease
- Surgery performed on or before July 31st 2018.

8.2 Exclusion criteria

- TORS used in a diagnostic setting only
- Nasopharyngeal and thyroid cancers

9 STUDY PROCEDURES AND METHODOLOGY

9.1 Patient identification

This will likely vary by centre. Some centres may keep a prospective log of all recurrent cancers and/or TORS cases. Other centres may have to re-screen their MDT or patient lists to identify patients. It is assumed that each centre contributing data will enter all consecutive eligible patients into the study.

9.2 Sampling timeframe

Start date

The start date of identification will vary by centre, relating to when the centre began performing TORS. There will be no restriction on the earliest date for a case to be eligible for submission.

End date

Surgery performed up until the July 31st 2018 inclusive.

Submission of data will be requested after July 31st 2020 to allow 2 years minimum follow up from time of surgery.

End of Study will be defined by resolution of all data queries and completion of database entries in preparation for final statistical analysis. Once this stage has been reached, a 'Declaration of End of Study Form' will be sent to RMH R&D and the Research Ethics Committee (REC) notifying them that the study is now concluded. A summary of the final research report will be provided to the Committee within 12 months of the conclusion of the study. This will report on whether the study achieved its objectives, summarise the main findings, and confirm arrangements for publication or dissemination of the research.

9.3 Consent

Consent from individual patients will not be sought. This study will report on the outcomes of management that has already taken place. There will be no impact on the management of patients as a result of inclusion in the study.

9.4 Anonymisation of patients

The project management team will not collect the names, addresses or medical record numbers (MRN) of any patients.

Dates of birth, surgery recurrence, death and last follow up will be used to generate durations. Durations only, not dates, will be submitted to the project management team.

Given the relative rarity of TORS for recurrent HNC, reporting and analysis will not identify individual cases in any subsequent reports, presentations and publications.

Pseudonymised data submission

Where possible, centres will be asked to assign each case contributed with a local study ID. This will allow the project management team to query any incomplete or noncoherent data that is submitted with the local team. As there is traceability from the project management team's database to a local study ID and then from that local study ID to a medical record number (MRN), this data would be considered pseudonymised.

Anonymised data submission

Where required, local teams may opt instead to submit fully anonymised data. In this instance, the local site will not keep a local study ID related to medical record number (MRN) and there will be no traceability from the project management team's database to a local record. The submission of anonymised data will be reflected in the Data Sharing Agreement signed between the Data Discloser and the Data Receiver (RMH).

The number of centres submitting pseudonymised and anonymised data will be reported.

9.5 Dataset

The full dataset is available in an associated excel file. The dataset is divided into the following areas:

1. **General patient details**: Demographics, smoking/alcohol and co-morbidities
2. **First cancer:** Involved sites, staging, procedures and adjuvant treatment
3. **TORS for recurrence:** Involved sites, staging, procedures, complications and adjuvant treatment
4. **Post-operative histology:** Staging and margins
5. **Outcomes:** Survival, recurrence, follow-up, diet/gastrostomy and tracheostomy status

Co-morbidities

The co-morbidity score will be taken using the Adult Co-morbidity Evaluation-27 (ACE-27) index, which is validated for use in HNC patients[11,12]. This rates the grade of decompensation affecting the various body systems, as well as presence of obesity and the status of any cancer or substance abuse. The grade of decompensation ranges between none (Grade 0) through mild, moderate and severe decompensation (Grades 1 to 3). The result is an Overall Comorbidity Score of 0 to 3, taken as the highest grade of decompensation in any one system/category, unless the patient scores grade 2 in two more different systems/categories, in which case they are designated Overall Score 3.

Functional outcomes

Functional outcome will be recorded using the 'Normalcy of Diet' rating from the Performance Status Scale for HNC patients (PSS-HN). This an 11 point scale giving a score between 0 and 100 ranging from complete gastrotomy tube dependence to an unrestricted diet.

Gastrostomy tube use at 1 year will be recorded.

Tracheostomy tube use at 1 year will be recorded.

Classification of 'recurrent' disease

The following timeframes will be used to classify tumours treated after management of the original primary:

- <12 months: Residual disease
- ≥12 months, <5 years: Recurrent disease
- <5 years: New primary disease, separate site
- ≥5 years New primary disease

9.6 Data collection

Data will be entered into an Excel spreadsheet with restricted data fields and data validation to improve data completeness and homogeneity. The Excel spreadsheet will be shared via secure email to observe appropriate data governance. The project management team will amalgamate databases from each centre for a pooled analysis.

9.7 Data storage

John Hardman, the Clinical Research Fellow, will be the custodian of the data submitted to the Royal Marsden Hospital.

Data will be stored on a named computer in the Head and Neck office at the sponsoring organisation, the Royal Marsden Hospital, Fulham Road, London, SW3 6JJ and held for 5 years.

10 STATISTICS AND DATA ANALYSIS

10.1 Pooled analysis

All cases will be entered into a pooled analysis. No individual centre will be identifiable from the analysis.

10.2 Study end points

Please see Outcome measures above.

10.3 Sample size

The final sample size will be dependent on the number of centres enrolled and the number of cases submitted by each centre. The expected number of patients recruited ranges between 50 to 150 patients.

The table below shows the widths of the confidence intervals (95% CI) given a 75% DFS at 2 years.

Table1

Width of interval	0.25	0.17	0.14
DFS rate	0.75	0.75	0.75
95% CI	0.63-0.88	0.67-0.84	0.68-0.82
Number of patients needed	47	100	147

10.4 Data analysis

Data analysis methods will include description of the participants at each centre for demographics, diagnosis and surgery using counts/number of patient and percentages for categorical data and mean/medium and standard deviation/range for continuous data.

There is no control group for comparative analysis.

Frequencies and percentages of all secondary endpoints will be reported. 95% confidence interval will be calculated where appropriate.

Surgical margin will be used for subgroup analysis of survival. The disease-free survival at 2 years will be used to identify an optimal cut-off for the surgical margin in order to divide the cohort into two comparable groups. If sufficient data are available, a maximally selected rank statistic will be used to estimate the optimal cut off point for surgical margins. If insufficient data are available then the categorical variables will be positive margin, close margin (less than 3mm) and clear margin (≥3mm).

The Clinical Research Fellow (JH) will be responsible for the database and analysis. Statistical support will be provided by the Research Data Management and Statistics Unit at The Royal Marsden NHS Foundation Trust.

Statistical analysis will be conducted with Microsoft Excel, SPSS and R Studio software.[13–15]

10.5 Survival analysis

Survival probability will be estimated with Kaplan Meier survival (KM) curves. Disease-free survival (DFS), overall survival (OS), and disease-specific survival (DSS), based on the pooled data, will be presented with 95% prediction intervals.

Survival will be measured from date of TORS procedure. Overall survival will be measured until date of death. Disease-free and disease-specific survival will be measured until residual disease, recurrent disease (locoregional or distant) or new primary disease is identified or has caused death respectively.

The Cox proportional hazards regression model will be used to define the impact of prognostic factors on overall survival. Factors to be included in this model will include: Stage at recurrence (1/2 or 3/4, according to TNM 7), close or negative margin (as determined by the method below), co-morbidity score (nil/mild or moderate/severe), p16 status and timing of recurrence (residual disease or recurrent/second primary).

Sub-group analyses

Survival analysis will be presented separately for: SCCs and other histological types; for oropharyngeal SCCs (HPV positive and negative); and by tumour timing and location as set out in Classification of 'recurrent' disease.

10.6 Censoring

Patients will be censored in the survival analysis at the following time points:

1. At their most recent follow up, if still under active surveillance, or
2. At the point at which they were lost to follow up.

We do not anticipate any events occurring that would require early withdrawal or further follow up impossible.

11 PROBLEMS ANTICIPATED

11.1 Slow recruitment of centres

Issue:

Resistance to sharing data from individual centres for potential comparison with other international centres.

Possible solutions:

It is explicitly outlined that we will not be reporting outcomes from individual named centres. Our intention is not to see which centres are better or worse, as there may be large variation in case selection and treatment intent. Some centres are much more likely to offer palliative surgery and others may be more constrained by resources outside of the departments' and/or surgeons' control.

11.2 Slow recruitment of patients

Issue:

Busy centres may be willing to contribute data but may not be able to dedicate clinician time to collect the primary data in a reasonable time frame

Possible solutions:

The Gannt chart outlines the project timeline to guide progress. We will use international meeting deadlines to help dictate deadlines and keep momentum in the project.

12 ETHICAL CONSIDERATIONS

12.1 Ethical review

The study was reviewed and approved by the Health Resource Authority on 5th November 2019 IRAS 268830. It is assumed that centres submitting cases will have secured the necessary local approvals for their locality.

12.2 Patient contacts

No additional patient contacts are required as part of this study.

12.3 Patient consent

As this is a retrospective cohort study, no explicit consent for involvement will have been sought from the included cases. In the majority of cases, the treating surgeon will not be the researcher. Data to be analysed will be submitted by the treating surgeon to the researchers on the project management team. In order to maintain patient confidentiality, no patient identifiable data will be transmitted to the researchers.

12.4 Potential identification of patients

Please see Anonymisation of patients above.

13 PROJECT MANAGEMENT TEAM

Name	John Hardman
Role(s)	Co-investigator Clinical research fellow First author
Responsibilities	Design of dataset and analysis strategy. Data analysis. Drafting of manuscript(s). Submission of manuscript(s).

Name	Vinidh Paleri
Role(s)	Chief investigator Senior author
Responsibilities	Oversight of project design, conduct, analysis and reporting. Liaison with ethics committees and other review bodies, as appropriate. Final review of drafted manuscript(s). Publication strategy.

This study will contribute towards the pursuit of a Doctorate at the Institute for Cancer Research by John Hardman, the Clinical Research Fellow. Some of the data collected from this study may be used in the relevant thesis, prior to ultimate submission for publication or presentation.

14 AUTHORSHIP POLICY

14.1 Criteria for inclusion in authorship

All contributing centres will be included in any subsequent presentations and publications. All contributing authors will have:

- Contributed to the acquisition of data, and
- Contributed to the revising of any manuscripts, and
- Given final approval of the submitted manuscripts, and
- Agreed to be accountable for the integrity of the work.

This is in accordance to the International Committee of Medical Journal Editors guidance for contributing authors.[16]

Each site may have a lead contributor and associated contributors included, as long as criteria above are satisfied.

14.2 Acknowledgements

All individuals contributing to the data collection will be acknowledged in any subsequent presentations and publications.

15 FUNDING

Salary for the Clinical Research Fellow is provided by a grant from the Oracle Cancer Trust and the Royal College of Surgeons of England and ENT UK.

16 TABLE OF ACRONYMS

Acronym	Meaning
ACE-27	Adult Co-morbidity Evaluation-27
ASA	American Society of Anesthesiologists
AWD	Alive with disease
CCR	Committee for Clinical Research (Royal Marsden Hospital)
CT	Computed tomography
DFS	Disease-free survival
DOC	Died of other causes
DOD	Died of disease
DSS	Disease-specific survival
H&N	Head and neck
HNC	Head and neck cancer
HPV	Human papilloma virus
HRA	Health Research Authority
IRAS	Integrated Research Application System
IRB	Institutional review board
KM	Kaplan Meier
MDADI	M. D. Anderson Dysphagia Inventory
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
MRN	Medical record number
NED	No evidence of disease
OS	Overall survival
PET CT	Positron emission tomography and computed tomography
PSS-HN	Performance status scale for head and neck cancer patients
RMH	Royal Marsden Hospital
ROC	Receiving operating characteristic curve
SCC	Squamous cell carcinoma
SIR	Standardised incidence ratio
TORS	Transoral robotic surgery

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