QMUS-HNC-RT

An investigation of the feasibility, reliability and acceptability of using of ultrasound to assess muscle echogenicity and size in key speech and swallowing tissues before and after radiotherapy in a head and neck cancer population

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Name & Role	Date	Signature

Study Management Group

Chief Investigator: Dr Gemma Clunie

Co-investigators: Ms Jodi Allen, Dr Margaret Coffey, Mr Jonathan Bernstein, Dr Dorothy Gujral, Professor Alison McGregor

Statistician: Professor Caroline Alexander has acted as statistical advisor

Study Management: as above

Clinical Queries

Clinical queries should be directed to Dr Gemma Clunie (gemmaclunie@nhs.net) who will direct the query to the appropriate person

Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 9480**
Imperial College - Research Governance and Integrity Team (RGIT) Website

Funder

There are two funding sources for the study:

- Senior Clinical and Practitioner Research Award (NIHR304447) National institute of Health and Care Research (NIHR)
- Seed Fund Grant, Department of Surgery and Cancer, Imperial College London

This protocol describes the QMUS-HNC-RT study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

US	Ultrasound
SLT	Speech and Language Therapy
HNC	Head and Neck Cancer
ENT	Ear, Nose and Throat
ICHT	Imperial College Healthcare NHS Trust
PPIE	Patient and Public Involvement and Engagement
OM	Outcome Measures
CROM	Clinician Reported Outcome Measures
PROM	Patient Reported Outcome Measures
AE	Adverse Effect
SAE	Serious Adverse Effect
QOL	Quality of Life
MDADI	MD Anderson Dysphagia Inventory
FOIS	Functional Oral Intake Scale
PSS H&N	Performance Status Scale – Head & Neck
SHI	Speech Handicap Index
MDT	Multidisciplinary
SLTs	Speech and Language Therapists
VAS	Visual Analogue Scale
IDDSI	International Dysphagia Diet Standardisation Initiative
QMUS	Quantitative Muscle Ultrasound

KEYWORDS

Speech, swallowing, muscles, ultrasound, head and neck cancer, feasibility study

STUDY SUMMARY

TITLE	An investigation of the feasibility, reliability, and acceptability of using of ultrasound to assess muscle echogenicity and size in key speech and swallowing tissues before and after radiotherapy in a head and neck cancer population
DESIGN	Feasibility, reliability, and acceptability study to use an ultrasound assessment protocol in clinical practice with a head and neck cancer population with an embedded pilot observational study.
AIMS	1. To undertake a feasibility, reliability, and acceptability study of ultrasound assessment of muscles in HNC patients 2. To undertake a descriptive, observational study of ultrasound pre and post radiotherapy
OUTCOME MEASURES	Measurement of visibility Measurement of echogenicity Measurement of muscle size and thickness Inter- and intra-rater reliability measures MD Anderson Dysphagia Inventory Performance Status Scale – Head & Neck Speech Handicap Index Functional Oral Intake Scale International Dysphagia Diet Standardisation Initiative (IDDSI) diet and fluids level
POPULATION	People with a head and neck cancer diagnosis due to be treated with radical radiotherapy or chemoradiotherapy as primary curative treatment plan
ELIGIBILITY	People over 18 with a head and neck cancer diagnosis due to be treated with radical radiotherapy or chemoradiotherapy as primary curative treatment plan
DURATION	1 year

1. INTRODUCTION

1.1. BACKGROUND

Head and neck cancer (HNC) represents a significant cause of morbidity and mortality globally. It is the seventh most common cancer globally, with more than 556,701 new cases per year, and 293,711 deaths (1, 2). By the year 2030, a 30% expected increase in global incidence of HNC is expected, partly driven by a rise in human papillomatosis viral (HPV) infection (2-4). Incidence is known to be higher in those living in more socioeconomically deprived areas (2). The costs of HNC are significant, with an estimated cost of £309 million across a five-year period in 2011, and a recent systematic review reporting a cost of £25,311 per patient in oral cancer patients (5).

Treatment modalities vary, but radiotherapy is often the sole option, or is used adjuvant to chemotherapy and surgical approaches. Unfortunately, cumulative injury to tissues caused by radiotherapy, fibrosis and surgical scarring to skin and muscles are common side effects that deteriorate over time. For HNC patients this can cause significant morbidity relating to both swallowing and speech function (6-8). At present there is limited understanding of the mechanisms of fibrosis, its progression, quantification, or the treatment options for swallowing and speech (9, 10). Ultrasound has been used as a modality to quantify altered skin and muscle structure in the neck and has the potential to assess other anatomical structures such as the muscles of speech and swallowing using similar parameters (11, 12). Quantitative muscle ultrasound (QMUS) includes metrics such as muscle thickness, cross-sectional area, and echogenicity as an indirect measure of muscle structure.

Utilitisation of QMUS to assess the muscles involved in speech and swallowing is particularly interesting to Speech and Language Therapists (SLTs) (13, 14). SLTs are the members of the HNC multidisciplinary team whose role is to assess and manage those patients with swallowing and speech difficulties because of their cancer diagnosis and treatment (15). They provide prophylactic and reactive rehabilitation programs to HNC patients following detailed assessment of their difficulties (16, 17). The two key instrumental assessment methods to help inform treatment are Flexible Endoscopic Evaluation of Swallowing (FEES) and Videofluoroscopic Swallowing Study (VFSS). FEES is invasive and VFSS necessitates exposure to radiation. Importantly, neither provide morphometric information on muscles related to speech and swallowing. QMUS could offer an additional tool that is cost-effective and timesaving (18), without being intrusive or risking radiation dose (19). In addition QMUS provides information on underlying muscle pathophysiology, for example detail on muscle mass and quality(20). This expands on and complements the biomechanical and symptom profile of swallowing provided by FEES or VFSS (21).

In clinical areas such as neuromuscular disorders, QMUS is being explored as an assessment of muscle echogenicity and function (22, 23) with the feasibility of this approach recently considered in relation to a post-surgical HNC cohort with promising results (24). Examination of these muscles in a HNC population undergoing radiotherapy could provide SLTs with valuable information about

underlying muscle pathophysiology to enable them to develop tailored and specific rehabilitation protocols.

The aim of the current study is to carry out a feasibility, reliability, and acceptability project to investigate the use of QMUS in a head and neck cancer population pre- and post-radiotherapy.

1.2. RATIONALE FOR CURRENT STUDY

Rationale: To explore the use of QMUS as an outcome measure for therapeutic assessments and interventions for the muscles related to speech and swallowing in a head and neck cancer population undergoing radiotherapy.

Research Question: Is use of ultrasound assessment in a pre- and post-radiotherapy head and neck cancer population a feasible and reliable approach to visualise and quantify muscle echogenicity and size, and are such assessments acceptable to patients?

Hypothesis: It is feasible, reliable, and acceptable to use ultrasound assessment to assess muscle echogenicity and size in a pre- and post-radiotherapy head and neck cancer population.

2. STUDY OBJECTIVES

Primary objective
To determine the feasibility of using ultrasound to assess the echogenicity and size of the muscles involved in speech and swallowing pre- and post-radiotherapy with HNC patients in clinical practice.

Secondary objectives

1. To investigate the inter- and intra-rater reliability of size and echogenicity measurement from ultrasound data acquired from HNC patients.
2. To investigate the acceptability of using QMUS to assess echogenicity and size to HNC patients undergoing radiotherapy.
3. To complete a pilot observational study to begin to explore change in muscle echogenicity and size pre- and post-radiotherapy, depending on success of the primary objective and including patient and clinician reported outcome measures used in current clinical practice.

3. STUDY DESIGN

Type of Study: Feasibility
Duration: 12 months
Number of participants: 20
This is an initial pilot “proof of concept” study, with no comparative statistical analysis or attempt to identify standard deviation of the mean therefore a sample size calculation has not been completed.

Types of participants: Adult patients with a diagnosis of squamous cell carcinoma of tongue, tongue base, tonsil, oropharynx, hypopharynx or larynx, radical radiotherapy or chemoradiotherapy as primary curative treatment plan

3.1. STUDY OUTCOME MEASURES

Appendix 1 shows the "Schedule of events during study".

Feasibility

This is a feasibility study, therefore there is no primary outcome measure. The outcome measurements will be taken from protocols defined in previous studies (24, 25) to assess the following muscles:

- Anterior belly digastric (left and right)
- Mylohyoid
- Geniohyoid
- Masseter
- Temporalis
- Tongue (superior longitudinal, transverse, genioglossus)
- Sternocleidomastoid

Feasibility parameter	Measure	Feasible for clinical practice	Not feasible for clinical practice
1. Visibility of each muscle	Three-point scale of visibility – clear, questionable, not visible (24)	At least 3 of the above muscle groups are visible so that a recording can be made for measurement	Less than 3 of the above muscle groups are visible to make a recording.
2. Measurement of muscle structure (echogenicity)	This is an assessment of image brightness using greyscale analysis (25)	Able to identify region-of-interest to express echogenicity in each muscle group	Unable to identify region-of-interest to express echogenicity in each muscle group
3. Measurement of size (thickness and cross-sectional area)	Muscle thickness will be calculated using electronic callipers positioned at the standard locations defined in the protocol. Cross-sectional area will be calculated using continuous trace calipers to outline the muscles of interest which will automatically	Able to measure thickness and cross-section in each muscle group.	Unable to measure thickness and cross-section in each muscle group

	generate a cross-sectional area (cm2).		

Reliability

Reliability parameter	Measure	Feasible for clinical practice	Not feasible for clinical practice
1. Inter-rater measurement reliability of thickness, cross-sectional area and echogenicity	Two blinded raters will independently extract and measure muscle thickness & cross-sectional area according to a pre-agreed protocol	Intra-class correlation coefficient (ICC) of >0.7 (assessed for each muscle measured)	Intra-class correlation coefficient (ICC) of <0.7 (assessed for each muscle measured)
2. Intra-rater measurement reliability of thickness, cross-sectional area and echogenicity	Individual raters will repeat assessment of size at two timepoints	Cronbach's alpha measure of internal consistency of >0.7	Cronbach's alpha measure of internal consistency of <0.7

Acceptability

Acceptability parameter	Measure	Acceptable for clinical practice	Not acceptable for clinical practice
Is use of US acceptable to patients?	Survey responses indicating acceptability % of participants indicating the US is not burdensome using a visual analogue scale	>70% participants indicating that US is not burdensome using visual analogue scale; survey responses supporting this	<70% participants indicating that US is not burdensome using visual analogue scale; survey responses supporting this

Patient-reported outcome measures
MD Anderson Dysphagia Index (MDADI) (26)

Speech Handicap Index (SHI) (27)

Clinician-reported outcome measures
Performance Status Scale Head and Neck (PSS-H&N) (28)
Functional Oral Intake Scale (FOIS) (29)
International Dysphagia Diet Standardisation Initiative (IDDSI) diet and fluids level (30)

4. PARTICIPANT ENTRY

4.1. PRE-REGISTRATION EVALUATIONS

Confirmation of histopathology and oncological treatment plan per gold standard Head and Neck Cancer multidisciplinary team meeting. This will not differ from the standard clinical protocol for HNC patients. Patient characteristics (age, sex, height, weight, BMI, ethnicity, diagnosis, tumour location and staging, treatment plan including radiotherapy dose thresholds to different structures) will be collected from the medical notes and a case report form (see Appendix 2). Potential participants will not be approached to take part in the study at the same appointment they have been told their diagnosis, including staging, and treatment plan.

4.2. INCLUSION CRITERIA

- Over 18
- Diagnosis of squamous cell carcinoma of tongue, tongue base, tonsil, oropharynx, hypopharynx or larynx
- Radical radiotherapy/chemoradiotherapy as primary curative treatment plan
- Able to give written consent

4.3. EXCLUSION CRITERIA

- Under 18
- Other primary carcinoma site
- Surgery as primary treatment plan
- Unable to give written consent
- Unable to complete patient reported outcome measures due to cognitive impairment

4.4. WITHDRAWAL CRITERIA

A participant will be withdrawn early if they no longer wish to participate in the study. Participants will be made aware of their right to withdraw at any time during the study period, regardless of reason. Participants need only communicate their wish to be withdrawn from the study to any of the investigators and the participant would be withdrawn from the study. Identifiable data already collected with consent would be retained and used in the study. No further data would be collected or any other research procedures carried out on or in relation to the participant.

5. ADVERSE EVENTS

5.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2. REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded- it should be specified if only some non-serious AEs will be recorded, any reporting should be consistent with the purpose of the trial end points.

5.3.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to existing diagnosis of head and neck cancer, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
g.clunie@imperial.ac.uk

Please send SAE forms to: Dr Gemma Clunie g.clunie@imperial.ac.uk or gemmaclunie@nhs.net
Tel: 020 3311 1492 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

HNC patients remain under the care of the Imperial College Healthcare NHS Trust (ICHT) Head and Neck Cancer multidisciplinary team, including Speech and Language Therapy (SLT) for at least five years following completion of their oncology treatment. It is highly unlikely that the ultrasound scan will identify any incidental findings due to the number of diagnostic scans (including ultrasound) the patient will have to be given their diagnosis. However, any incidental findings during the study will be identified by the SLTs and reported to the treating surgeon and Oncology teams for management.

During and following the end of the trial, participants will continue to be followed by SLT at ICHT. Routine data will be used when possible. Should any participant come to harm during this study, the relevant medical and/or surgical teams will be alerted. Adverse events will be recorded and reported to the ENT Surgical Clinical Team or the Medical Oncology Clinical Care Team as appropriate.

End of study – date of last subject and last data collection

7. STATISTICS AND DATA ANALYSIS

Professor Caroline Alexander has provided support to guide the statistical analysis for this study.

Patient characteristics (age, sex, height, weight, BMI, ethnicity, diagnosis, tumour location and staging, treatment plan including radiotherapy dose thresholds to different structures) will be summarized using descriptive statistics and a narrative synthesis of the treatment plans.

Feasibility

1. **Visibility of muscles**

Descriptive statistics will be used to describe the visibility for each muscle with a percentage specified for each criterion (clearly, questionable, not visible) for each muscle.

2. **Measurement of muscle structure (echogenicity)**

Using specialist software, the echogenicity (greyscale) of a defined region of interest for each muscle will generate a numeric value between 0 and 255 (24). The overall echogenicity of the muscles will also be described according to their treatment timeline, for example pre- and post-radiotherapy means, medians, histograms, QQ plots and boxplots. Variability will also be explored, for example echogenicity will also be converted into a z score (number of standard deviations from normal).

3. **Measurement of muscle size (thickness and cross-section)**

Measures of muscles e.g., cross sectional area and thickness, will be described. For example, pre- and post-radiotherapy means, medians, histograms, QQ plots and boxplots. Variability will also be explored, for example muscle size will also be converted into a z score (number of standard deviations from the mean). Reliability (both inter- and intra-rater reliability) of the assessment of muscle size will be explored using Cronbach's alpha and intraclass correlation coefficient (ICC) or similar.

Acceptability
A survey based on the constructs of acceptability described in the theoretical framework of acceptability model (TFA) (31) will be undertaken with patient participants at a time convenient to them within the study period (see Appendix 3). The survey will be developed using Qualtrics software and shared via email. For those participants who do not have an email address, or would prefer a paper copy this will be provided at an existing clinical appointment. Descriptive statistics will be used to analyse quantitative fields from the survey with inductive thematic analysis (32) used on open text responses. This will help to understand whether ultrasound is acceptable.

Descriptive statistics will be used to summarize the visual analogue score (VAS) rating of acceptability for patients (this will be an embedded question within the survey.)

Observational study
The changes of muscle echogenicity and size pre- and post-radiotherapy will be explored using descriptive statistics to gain an understanding of the variability of these measures. It is not the aim of this pilot study to power this to explore change over time.

Patient and clinician reported outcome measures.
The outcome measures will be reported using appropriate descriptive statistics depending on normality of distribution.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Solihull Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2. CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3. CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Data will be pseudonymised.

Data will be transferred to Imperial College London.

8.4. INDEMNITY

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Resolution for NHS Trusts in England, which apply to this study.

8.5. SPONSOR

Imperial College Healthcare NHS Trust will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6. FUNDING

This protocol details independent research arising from a National Institute for Health and Care Research Senior Clinical and Practitioner Research Award (NIHR SCPRA 304447) and a Seed Fund grant from the Department of Surgery and Cancer, Imperial College London. The Chief Investigator will not receive any personal payment over and above normal salary and will not receive any other benefits or incentives for taking part in this research. Participants are not being paid to take part in the study..

8.7. AUDITS

The study may be subject to audit by Imperial College Healthcare NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Gemma Clunie. Research management will be provided by Ms Jodi Allen, Professor Alison

McGregor, Dr Margaret Coffey, Dr Dorothy Gujral and Mr Jonathan Bernstein. A patient advisory group support and guide the research.

10. PUBLICATION POLICY

A final study report will be produced summarising the data collected. All data used will be anonymised. This will be sent out to patient charities, forums and social media and published on the Imperial College website. We will ask each participant if they would like to receive the report. These will be worded using lay terminology and supported by the patient advisory group. The information will also be available on the chief investigator's website https://profiles.imperial.ac.uk/g.clunie

The work will be submitted to conferences such as the UK Swallow Research Group (UK SRG), Dysphagia Research Society (DRS) and the British Association of Head and Neck Oncologists (BAHNO) as well as peer reviewed journals. The results of the study will also be reported internally to the Speech and Language Therapy and Head and Neck Cancer multidisciplinary teams at Imperial College Healthcare NHS Trust

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Appendix 1. Schedule of events during study

	Exam		
	Pre-treatment	At least 6 weeks post treatment	Timepoint according to participant choice within study period
Informed consent	X		
Demographic collection	X		
Ultrasound assessment	X	X	
Patient reported outcomes	X	X	
Clinician reported outcomes	X	X	
Survey and VAS assessment			X

Appendix 2: Case Report Form (see separate document)

Appendix 3: Survey (see separate document)