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Are there genetic markers that can help to predict which patients who have had radiotherapy or chemotherapy for head and neck cancer will be more or less likely to have problems with swallowing or opening their mouth?

Submission date
12/11/2018

Recruitment status
No longer recruiting

Registration date
28/11/2018

Overall study status
Ongoing

Last Edited
14/01/2025

Condition category
Signs and Symptoms

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Many of the 7,000 patients in England and Wales who develop head and neck cancer each year are treated with radiotherapy (targeting cancer cells using radiation) or chemo-radiotherapy (targeting cancer cells using a combination of drugs and radiation). We want to find out whether genetics can predict who will suffer from severe radiation damage. In the future, patients at high risk could be offered alternative treatments including lower doses of radiation, radiation that targets only cancer cells or alternative treatments such as surgery.

Patients who have had radiotherapy to the head and neck region often have problems with swallowing or mouth opening. These problems may make it difficult to eat certain foods. Some patients are unable to eat enough and have to be fed through a tube. High doses of radiation can also decrease the blood supply to the jawbone. If this happens, the bone gets less oxygen than it needs, which may result in the death of bone tissue. This relatively rare condition is called osteoradionecrosis or ORN. All of these problems can have a negative impact on patients' quality of life.

Research suggests that one or more genes may be linked to the risk of post-radiation complications in the head and neck. In this study we want to test a much larger collection of genes. We want to find out whether we can predict swallowing and mouth opening problems. DNA is made up of chemical compounds and contains the genetic instructions needed for a plant or animal to develop, survive and reproduce. DNA provides a unique genetic fingerprint for each person. Nearly every cell in a person's body has the same DNA. Genetic tests are done using DNA that has been extracted from a sample of blood or saliva. The tests allow researchers to see which genes are more frequently present among those patients with severe complications and /or which genes are present among patients with fewer problems. We will compare the genes from all patients.

Who can participate?
Adults who have had radiotherapy or chemo-radiotherapy in the last 1 to 6 years for head and neck cancer

What does the study involve?
The study has 2 phases. Phase 1 is for up to 1,000 patients who have had radiotherapy or chemo-radiotherapy in the last 1-6 years and wish to take part in this study. You will fill in one questionnaire that asks about your swallowing. It will also ask you about tube feeding, mouth opening and ORN. The questionnaire will take about 10 minutes to complete. You will be asked to post it back to the study centre using the Freepost envelope provided.
Phase 2 is for the same 1,000 patients who took part in phase 1. We will send you a letter inviting you to take part in the genetic testing. This may be several months after you complete your questionnaire, as we need to know everyone's scores. We will ask you to come to a special research clinic.
At the clinic, we will collect a small amount of saliva and about 2 teaspoons of blood. We will also assess your swallow ability. After wetting your mouth with a little cold water we will ask you to swallow air. We will measure how many swallows you can make over 30 seconds by either watching you or gently feeling your neck area. If you are able, there will also be another swallow test where you will be asked to drink 100 ml of water as quickly as possible. The number of swallows and the time taken will be measured. During your visit to the clinic we will also ask you to complete a 2-page questionnaire that asks about how you feel about your own swallowing ability. The questionnaire will only take a few minutes to complete. We will also measure how wide you can open your mouth and assess the level of any tissue damage after your radiotherapy treatment.
The whole process will take about 30 minutes plus some waiting time, which we will try to keep to a minimum. We will reimburse your reasonable travel and childcare costs. If you are unable or do not wish to attend a research clinic in person, we will give you an opportunity to provide a saliva sample and complete the questionnaire by post.

What are the possible benefits and risks of participating?
This study will not help you directly, but the information we get from this study may help improve the treatment of people with head and neck cancer in the future. Some patients will need to attend a research clinic to donate blood and saliva. This appointment will be in addition to any other appointments you have. Some patients may experience mild pain or bruising at the blood sample site.

Where is the study run from?
The study is run from Saving Faces – The Facial Surgery Research Foundation which is based at Barts Health NHS Trust. There are 16 sites throughout England taking part in this study.

When is the study starting and how long is it expected to run for?
January 2014 to December 2026

Who is funding the study?
The British Association of Oral and Maxillofacial Surgeons, Saving Faces – The Facial Surgery Research Foundation and John Anderson Cancer Research trust will pay for the study.

Who is the main contact?
Mr Andrew Lyons, info@savingfaces.co.uk

Contact information

Type(s)
Public

Contact name
Mr Andrew Lyons

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
105648

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
GRAD

Study information

Scientific Title
Can genomics predict dysphagia after head and neck radiotherapy?

Acronym
GRAD

Study objectives
We will conduct a genome-wide association study (GWAS) pilot comparing the genomic profiles of patients who do and do not suffer from severe swallowing difficulties (dysphagia) and mouth opening difficulties after radiotherapy or chemoradiotherapy for head and neck cancer, and identify all genetic factors associated with a higher risk of developing severe complications. This is a case controlled cohort study involving up to 1000 patients who have been treated with radiotherapy or chemoradiotherapy for head and neck cancer, within the last 1-6 years. There are no clinical risks associated with the study, and patients will be given a telephone number and email address that they can use to contact a clinician who will address any concerns. Patients will

be asked to give blood and saliva samples from which genomic DNA will be extracted for analysis. Some mild pain or bruising from the venepuncture is possible. Patients will be warned beforehand that they may experience some mild discomfort.

There is no direct benefit to the patients who participate in this study, however the identification of candidate radiotoxicity biomarkers from this pilot will lead to further validations studies, which if successful, could enable clinicians to screen head and neck cancer patients in the future and offer those who are most likely at risk of developing fibrotic complications, including dysphagia, trismus and ORN, some alternative treatments.

If SNPs that can predict for severe radiation complications in head and neck cancer patients can be identified, then in the future treatments for head and neck cancers may be tailored to the patients' genetic profiles. A significant number of patients who receive successful surgery for head and neck cancer have only marginal indications for adjuvant radiotherapy after analysis of their tumour's histopathology. Radiation could be avoided in these marginal cases.

For those patients who need radiotherapy, the radiation dose could be personalised according to the patient's genotype to maximize tumour control while reducing damage to normal tissues. Patients with HPV related cancer could be offered a lower dose of radiation as they have lower risk of recurrence than other patients. Additionally advances in radiotherapy technology may inform dose tolerance for swallowing musculature. Patients who cannot be offered alternative treatments could be given intense therapies by a speech and language therapist both before and after treatment to minimise the effects of radiotherapy.

If these strategies can reduce the incidence of radiotoxicity-related morbidities without affecting survival, there will be a reduction in healthcare costs incurred for the supportive care required for patients with severe radiotherapy morbidity. Lastly, this study has the potential to demonstrate that genetic tests can be performed on DNA obtained from a simple saliva test, which would be of great benefit to head and neck cancer patients. It may be practical in the future to produce an inexpensive blood or saliva test for every patient prior to treatment.

A retrospective case controlled cohort study using Genome Wide Association (GWAS) to compare genomic differences between head and neck cancer patients who do and do not suffer from severe swallowing and mouth opening difficulties after radiotherapy or chemoradiotherapy.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 20/03/2014, NRES Committee South East Coast - Surrey (HRA, Bristol Research Ethics Committee Centre, Whitefriars, Level 3, Block B, Lewins Mead, Bristol, BS1 2NT, United Kingdom; +44 207 104 8131; surrey.rec@hra.nhs.uk), ref: 14/LO/0429

Study design
Multicentre retrospective case-controlled cohort study

Primary study design
Observational

Study type(s)

Diagnostic

Health condition(s) or problem(s) studied
Dysphagia following radiotherapy or chemotherapy for head and neck cancer

Interventions
In the first phase of this study, patients will be asked to complete self-assessment using the Sydney Swallow Questionnaire and return it with their signed consent form. This will allow researchers to classify them as either cases or controls, whom we will match to each other according to the following factors: tumour stage, tumour site, type of radiotherapy, chemotherapy regimes. As patients will not have the opportunity to discuss the study in person with any member of the study team, the patient information sheet contains details of a clinician whom patients can contact by phone or e-mail if they want to. If they have any questions that need to be directed to their care team, the surgeon will ensure that they receive a response from an appropriate person. Patients who do not wish to participate in this study will be able to complete a short 'tick box' form and return it in the prepaid envelope. In this case they will not be contacted again about the study.

In phase two of this study, patients who have given informed consent will be invited to attend a research clinic where they will be asked to complete a dysphagia-specific quality-of-life questionnaire; the M. D. Anderson Dysphagia Inventory (MDADI), and a repeat of the self assessment Swallowing Questionnaire. 10 ml of blood and 5 ml of saliva will be collected by a clinic nurse, doctor or qualified clinical researcher. The saliva will be collected using kits that require the patient to spit into a tube, those who have difficulty in producing saliva have the option of using an assisted kit, or providing a sample by gargling.

Additionally, patients attending the research clinic will be asked to complete a Repetitive Saliva Swallowing Test (RSST). This test is intended to check the patient's ability to voluntarily swallow repeatedly. During the test, patients will be in a resting position. The inside of their mouth will be wet with cold water using a sponge, and the patient will be instructed to repeatedly swallow air. A trained doctor or qualified clinical researcher will count the number of swallows achieved by the movement of laryngeal elevation, either visually or by palpating. Three or more dry swallows within 30 seconds is considered normal. They will also be asked to complete the 100 ml water swallow test where patients are asked to drink 100 ml of water as quickly as is comfortably possible and the time taken and number of swallows will be recorded.

The blood and saliva samples will be sent to the Genome Centre at Barts and the London Medical School, where genomic DNA will be extracted using standard procedures before being analysed using an Illumina Infinium SNP genotyping array, according to the manufacturers recommendations.

Patients will also have their inter-incisal distance measured to assess limited mouth opening and be graded as per the fibrosis scale to grade the level of oedema/fibrosis after radiotherapy. If patients are unable to attend a research clinic, or if suitable clinics cannot be organised, the patients will be asked to give a saliva sample that can be sent through the post and also to complete and return the self assessment questionnaires.

Intervention Type
Genetic

Primary outcome(s)

The association between genetic variants and severe radiotoxicity in head and neck cancer patients, with the association between common SNPs and radiation-induced dysphagia (which determines case/control status) assessed using the PLINK suite of genetic analysis programs from Harvard University.

Key secondary outcome(s))
1. Prevalence and degree of dysphagia as determined by scores on the Sydney Swallowing Scale at the two visits
2. The proportion of saliva samples that are suitable for GWAS analysis

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. Aged 18 years and over (no upper limit)
2. Treated for primary head and neck cancer with radiotherapy or radio-chemotherapy
3. Between 1 and 6 years post-treatment at the time of recruitment

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
1076

Key exclusion criteria
1. Not deemed able to give informed consent
2. Thyroid cancer
3. Head and neck surgery

Date of first enrolment
06/08/2015

Date of final enrolment
03/10/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
Whitechapel Road
London
United Kingdom
E1 1BB

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
Guy's Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
University College London Hospitals NHS Foundation Trust
University College Hospital
235 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre
North Middlesex University Hospital NHS Trust
North Middlesex University Hospital NHS Trust
Sterling Way
London
United Kingdom
N18 1QX

Study participating centre
East and North Hertfordshire NHS Trust
Mount Vernon Cancer Centre

Mount Vernon Hospital
Rickmansworth Road
Northwood
Middlesex
United Kingdom
HA6 2RN

Study participating centre
The Pennine Acute Hospitals NHS Trust
North Manchester
General Hospital
Delaunays Road
Crumpsall
Manchester
United Kingdom
M8 5RB

Study participating centre
Portsmouth Hospitals NHS Trust
Queen Alexandra Hospital
Cosham
Portsmouth
United Kingdom
PO6 3LY

Study participating centre
Royal Surrey County Hospital NHS Foundation Trust
Royal Surrey County Hospital
Egerton Road
Guildford
United Kingdom
GU2 7XX

Study participating centre
Walsall Healthcare NHS Trust
Manor Hospital
Moat Road
Walsall
United Kingdom
WS2 9PS

Study participating centre
The Shrewsbury and Telford Hospital NHS Trust
Royal Shrewsbury Hospital
Mytton Oak Road
Shrewsbury
United Kingdom
SY3 8XQ

Study participating centre
Norfolk and Norwich University Hospitals NHS Foundation Trust
Norfolk and Norwich University Hospital
Colney Lane
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NR4 7UY

Study participating centre
Barking, Havering and Redbridge University Hospitals NHS Trust
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Rom Valley Way
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RM7 0AG

Study participating centre
East Kent Hospitals University NHS Foundation Trust
Kent and Canterbury Hospital
Ethelbert Road
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CT1 3NG

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Weston Park Hospital
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S10 2SJ

Study participating centre

Nottingham University Hospitals NHS Trust
QMC
Derby Road
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NG7 2UH

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Addenbrooke's Hospital
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Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Other

Funder Name
British Association of Oral and Maxillofacial Surgeons

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes