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A study to investigate HPV-detect, a new way to measure the response to treatment in patients with Human Papilloma Virus (HPV) positive head and neck cancer

Submission date
25/11/2019

Recruitment status
No longer recruiting

Registration date
03/03/2020

Overall study status
Completed

Last Edited
21/10/2025

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
Following curative chemo-radiation (CRT), about 20-30% of patients with locally advanced human papillomavirus related (positive) oropharyngeal cancer (HPV+OPC) undergo unnecessary neck dissection or biopsies based on positive or equivocal post-CRT 18F-FDG PET-CT (PET-CT). As the positive predictive value of such PET scans is sub-optimal, a more reliable marker of 'true' residual disease is required as a means of guiding management decisions. The newly developed ultra-sensitive and specific assay 'HPV-detect' can non-invasively measure the post-CRT plasma HPV DNA levels, and can be used to guide management decisions potentially avoiding unnecessary surgical procedures. The aim of this study is to find out whether HPV DNA measured using HPV-detect is a predictor of the absence of residual disease following primary RT/CRT for HPV+ positive oropharyngeal cancer.

Who can participate?
Patients aged 18 or over with squamous cell carcinoma of the oropharynx undergoing curative RT/CRT

What does the study involve?
This is a sample and data collection/analysis study only. Diagnostic tumour biopsy blocks are required for all patients. Blood samples will be collected from consenting HPV+ patients at baseline, weekly during CRT, weekly for 4 weeks after treatment, at 6 weeks, 3, 6, 9 and 12 months after CRT. HPV negative patients will donate samples at baseline, at 6 weeks, and at 3, 6, 9 and 12 months only. In HPV+ patients an additional tissue sample will also be collected after any surgical procedures and/or biopsies and additional blood samples will also be obtained before and after any surgical procedure or biopsy.

What are the possible benefits and risks of participating?
There is no direct benefit for individual patients participating in this study. It is hoped that the information gained from this study will help to improve the treatment options and/or quality of

life for patients with HPV-positive locally advanced head and neck cancer in the future. Patients will be asked to donate blood samples during the study, which may be associated with some degree of discomfort, risk of bleeding or infection. However, it is anticipated that the risks associated with these procedures will be minimal. Blood samples collected up to the 3-month timepoint will be taken at the same time as routine blood samples. Blood sampling at the routine follow up appointment after 3 months may be in addition to standard practice at some centres. Tissue blocks will be requested from tissue taken routinely at diagnosis and after any surgery or biopsies performed post (chemo)radiotherapy.

Where is the study run from?
Cancer Trials and Statistics Unit, Institute of Cancer Research (UK)

When is the study starting and how long is it expected to run for?
May 2019 to September 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Marie Emson
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Integrated Research Application System (IRAS)
237168

Central Portfolio Management System (CPMS)
42229

Study information

Scientific Title
Investigation of novel plasma Human Papilloma Virus DNA assay for treatment response estimation in head and neck cancer

Acronym
INOVATE

Study objectives
Approximately 2000 patients are diagnosed annually in the UK with oropharyngeal (throat) cancer caused by human papillomavirus (HPV) infection. The standard treatment is chemotherapy and radiotherapy followed by surgical removal of any cancer left behind. The surgery is undertaken based on results of a scan (18F-FDG PET-CT). However, approximately 20-30% of patients will receive unnecessary surgical intervention, as residual cancer is not confirmed on pathological examination post-surgery. Following surgery approximately 25% of patients will have immediate complications and all will suffer significant permanent side effects (pain, shoulder dysfunction, altered quality of life). Therefore a more reliable marker of true residual disease is required as a means of guiding management decisions.
As HPV positive(+) oropharyngeal cancers release HPV-DNA into the blood stream its presence can serve as a detection marker of residual cancer after treatment. HPV-detect, an assay developed and tested in a single-centre, prospective pilot study at the Royal Marsden Hospital /Institute of Cancer Research, is a way to measure HPV-DNA levels using a blood test. Further validation of HPV-detect is now required in a prospective multi-centre study. The study is needed to establish its usefulness in patient care and evaluate its potential to predict the absence of residual disease and avoid unnecessary surgery. INOVATE is a multicentre study which aims to collect biological samples from 143 HPV+ and 48 HPV negative patients with oropharyngeal cancer. Patients will be asked to donate archival diagnostic tumour tissue samples and blood samples taken at specified time points up to 1 year following treatment. HPV-DNA levels will be measured using HPV-detect and the results correlated with the 18F-FDG PET-CT results at 12 weeks. In addition, barriers to adoption of the test and how to address these will be studied. A health economic analysis will study the cost benefits of implementing the test in the UK.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/10/2019, London - Bloomsbury Research Ethics Committee (HRA RES Centre Manchester, Barlow House 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; Tel: +44 (0)207 104 8127; Email: nrescommittee.london-bloomsbury@nhs.net)ref: 19/LO/1558

Primary study design
Observational

Study design
Non-randomized observational cross-sectional

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Head and neck cancer

Interventions

INOVATE is a multicentre prospective biological sample collection and analysis study which aims to validate circulating Human Papilloma Virus (HPV) DNA as a marker of residual disease in patients with HPV+ oropharyngeal cancer. The study will be open to newly diagnosed patients with HPV+ and HPV- tumours (negative controls) who are due to receive radical radiotherapy alone or chemotherapy and radiotherapy (RT/CRT). The study will comprise the collection and analysis of tissue and blood samples. For tissue samples, the researchers will request and use the archival formalin-fixed paraffin-embedded blocks from biopsies obtained for the diagnosis of cancer or at surgery. Therefore, no additional biopsies will be required. Venous blood samples will be collected before treatment and at regular intervals during and following completion of treatment.

Patient suitability for the study will initially be assessed at the multidisciplinary team's (MDT) assessment meeting. Any patient who expresses an interest and is technically suitable for the study will be informed about the INOVATE study.

Following the discussion patients will be given the patient information sheet. It is proposed that as this is not a treatment study any patient who requests to consent to the study on the same day will be allowed to do so. Patients who wish to consider their participation in the study will be invited to return to the hospital at least 24 hours later to confirm participation and to sign the consent form.

SCREENING ASSESSMENTS

There are no additional screening assessments specific to the INOVATE study. It is anticipated that patients will be screened prior to standard treatment with RT/CRT as per local practice. Consenting patients will be registered into the study after diagnosis, routine screening and confirmation of HPV status. All patients will be required to donate a blood sample at baseline ie after registration but before any standard treatment commences.

HPV negative patients will be requested to donate further blood samples at 6 weeks post-RT /CRT and at 3, 6, 9 and 12 months after treatment.

HPV positive patients will be requested to donate blood samples weekly during RT/CRT and weekly for 4 weeks thereafter, at 6 weeks, 3, 6, 9 and 12 months post-CRT. If the patient's RT treatment is extended into week 7 an additional blood sample will be taken to ensure that a sample is collected at the end of treatment. Additional tissue and blood samples will also be requested for HPV+ patients before and after any surgical procedures or biopsies performed post-RT/CCRT. Tissue collected at this time is part of the centres' routine practice and the study will request access to these tissue blocks.

Blood samples collected up to the 3-month timepoint will be taken at the same time as routine blood samples. Blood sample donation at the routine follow up appointment post-3 months may be in addition to standard practice at some centres. Centres are advised to inform patients that some samples may be in addition to standard practice during the informed consent process and this is also detailed in the patient information sheet.

FOLLOW UP

There are no scheduled follow up visits for INOVATE. However, data will be collected from the patients' routine follow up visits following treatment according to local practice.

Approx 12 weeks after the completion of RT/CRT all patients will be routinely required to have an 18F-FDG-PET-CT scan to assess response to treatment. All centres who have expressed an interest in taking part in INOVATE have confirmed that this scan is used routinely at 12 weeks at their centres. ICR-CTSU will collect data from 18F-FDG PET-CT scans performed as part of routine practice. Sites are requested to send a copy of the report for the 3 month 18F-FDG PET-CT scan to the ICR-CTSU office. This report should be redacted to protect the patient's personal

data.
ICR-CTSU may request redacted reports of other 18F-FDG PET-CT scans carried out during the lifetime of the study.
It is anticipated that patients with equivocal PET-CT and a lymph node greater than 1cm or a positive PET-CT will be routinely recommended to have a biopsy and/or neck dissection. The type of surgery will be at the discretion of the local MDT.
Clinical data will be collected by ICR-CTSU from routine follow up appointments until 12 months post-RT/CCRT but this will not require any additional visits or action from the participants in the study. Sites will be requested to report any confirmation of residual disease at 12 weeks or later confirmation of disease progression/recurrence to the ICR-CTSU Trials Office on eCRFs. If HPV+ patients are required to progress to surgery/biopsies sites are asked to notify ICR-CTSU in an expedited manner on the appropriate eCRF. This will enable ICR-CTSU to prompt sites about the additional tissue and blood sample collection for HPV+ patients who will be scheduled for surgery.

STAKEHOLDER ANALYSIS AND HEALTH ECONOMICS STUDY
The National Institute for Health Research London in vitro Diagnostics Cooperative (NIHR London IVD) at Imperial will undertake stakeholder analyses to understand risks, adoption barriers and assess the potential impact of HPV-detect in the NHS. This study will involve members of the research team at participating sites who may be selected to be interviewed on a one-to-one basis about current use of HPV-detect and to identify user needs, user experience, perceived trust and acceptance of the use of HPV-detect.
PLEASE NOTE: The details of the health economics study will be added to the protocol by amendment prior to initiation.

The patient information sheet (PIS) will inform the patient about the clinical data collection for the study. The PIS will also clearly state that patients, their research doctors and other members of the patient's clinical care team at the site will not be informed of their HPV-detect test result and that the result will not affect their future treatment.

Intervention Type
Other

Primary outcome(s)
The specificity of HPV-detect (using plasma HPV DNA levels) in correctly identifying those with no residual disease, at 3 months following completion of primary RT/CRT; defined as the proportion of patients who are HPV-detect negative among those with no residual disease according to 18F-FDG PET at the same timepoint.

Key secondary outcome(s)
1. The sensitivity of HPV-detect (using plasma HPV DNA levels) in correctly identifying those with residual disease at 3 months following completion of primary RT/CRT; defined as the proportion of patients who are HPV-detect positive among those with residual disease according to 18F-FDG PET-CT at the same timepoint
2. The proportion of patients who have no residual disease on biopsy/neck dissection amongst those with residual disease according to 18F FDG PET-CT but HPV-detect negative at 3 months after primary RT/CRT
3. Repeated measures of plasma HPV DNA levels up to a period of 12 months post RT/CRT (timepoints defined in the Interventions field) will be associated with the clinical and radiological response
4. Sensitivity and specificity of HPV-detect in measuring plasma HPV DNA levels compared with

HPV DNA levels from diagnostic tissue at baseline; defined as the proportions of true positives and the proportions of true negatives, respectively
5. The pattern of plasma HPV DNA responses to RT/CRT presented by calculating the percentage change in HPV DNA level at each assessment timepoints from baseline (timepoints defined in the Interventions field)

Completion date
15/09/2025

Eligibility

Key inclusion criteria
1. Aged 18 years or above.
2. Newly diagnosed patients with T1-T2/N1-3 or T3-T4/ N0-3 squamous cell carcinoma of the oropharynx
3. Availability of tissue from one archival diagnostic tumour tissue block
4. Confirmed HPV status (p16InK4A IHC/ISH)
5. Patients must be candidates for and willing to undergo curative RT/CRT
6. Written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
191

Key exclusion criteria
1. Previous or concurrent illness or situation, which in the investigator’s opinion would interfere with collection of the complete sample collection
2. Any invasive malignancy within previous 5 years (other than non melanomatous skin carcinoma or cervical carcinoma in situ
3. Clinical evidence of metastatic disease

Date of first enrolment
10/01/2020

Date of final enrolment
11/05/2022

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
The Royal Marsden NHS Foundation Trust
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
Royal United Hospitals Bath NHS Foundation Trust
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
James Cook University Hospital
South Tees Hospitals NHS Foundation Trust
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Southampton General Hospital
University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
United Kingdom
SO16 6YD

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

Study participating centre
University Hospital Aintree
Aintree University Hospital NHS Foundation Trust
Fazakerley Hospital
Lower Lane
Liverpool
United Kingdom
L9 7AL

Study participating centre
Queens Medical Centre
Nottingham University Hospitals NHS Trust
Trust Headquarters
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Colchester District General Hospital
East Suffolk And North Essex NHS Foundation Trust
Turner Road
Colchester
United Kingdom
CO4 5JL

Study participating centre
University Hospitals Bristol NHS Foundation Trust
Marlborough Street
Bristol
United Kingdom
BS1 3NU

Study participating centre
Queen Alexandra Hospital
Portsmouth Hospitals NHS Trust
Southwick Hill Road
Portsmouth
United Kingdom
PO6 3LY

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
Clatterbridge Cancer Centre
Clatterbridge Hospital
Clatterbridge Road
Wirral
United Kingdom
CH63 4JY

Study participating centre
Velindre Hospital
Velindre Road
Cardiff
United Kingdom
CF14 2TL

Sponsor information

Organisation
The Institute of Cancer Research, London

ROR
https://ror.org/00xmdg797

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council; Grant Codes: MR/R015589/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from inovate-icrctsu@icr.ac.uk.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 2.0	27/09/2021	19/05/2022	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes