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A phase III trial of intensity-modulated proton beam therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer

Submission date
20/01/2020

Recruitment status
No longer recruiting

Registration date
27/01/2020

Overall study status
Ongoing

Last Edited
25/03/2026

Condition category
Cancer

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

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-proton-beam-radiotherapy-for-oropharyngeal-cancer-torpedo

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
268843

Protocol serial number
CPMS 43839, IRAS 268843

Study information

Scientific Title
A phase III trial of intensity-modulated proton beam therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer

Acronym
TORPEdO

Study objectives
The number of cases of cancers arising from the tonsil and back of the tongue is rising worldwide. Even when this type of cancer is large or has spread to lymph nodes in the neck (called locally advanced cancer), it usually responds well to treatment and most people are cured. However, treatment with radiotherapy combined with chemotherapy can cause severe side effects during treatment. In the long term, this has the potential for significant harmful impact on quality of life.

This study includes patients with locally advanced cancers of the tonsil and back of the tongue. It will focus on whether proton beam therapy (a newer form of radiotherapy) can reduce side effects and improve patient-reported quality of life compared with standard radiotherapy (called intensity-modulated radiotherapy). Proton beam therapy can be directed more precisely than standard radiotherapy. This reduces the amount of normal tissue receiving radiation that isn’t wanted. It is known from international use of proton beam therapy (e.g. the USA) that it is a safe treatment and is thought to cause less damage to normal tissues.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/12/2019, North West - Greater Manchester West Research Ethics Committee (Barlow House 3rd Floor, 4 Minshull Street, Manchester M1 3DZ, UK; Tel: +44 (0)207 104 8021; Email: nrescommittee.northwest-gmwest@nhs.net), REC ref: 19/NW/0700

Study design
Randomised; Interventional; Design type: Treatment, Radiotherapy

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Oropharyngeal cancer

Interventions
Participants will be recruited from selected sites across the UK. Potential participants will be identified by their clinical care teams and their suitability will be discussed at local multidisciplinary team meetings. Participants will have locally advanced oropharyngeal squamous cell carcinoma prostate cancer and have opted to have chemo-radiotherapy as radical treatment.

Participants will be approached by a member of their clinical care team and will receive a verbal explanation of the trial, together with a Patient Information Sheet which they will take home with them. They will be given sufficient time to make a decision about whether they would like to participate and will be able to discuss their options with friends, family or their GP. They will have the opportunity to raise any questions about TORPEdO with their clinical care or research team and these will be addressed prior to their decision about whether to participate. Should they chose to participate they will be asked to sign a consent form to record their informed consent.

All participants will be randomised via the central randomisation service provided by the Clinical Trials and Statistics Unit at The Institute of Cancer Research (ICR-CTSU). Participants will be randomised using a computer-generated minimisation technique which ensures balance between the treatment groups. Using this technique, the treatment allocation for each participant depends on the characteristics of the participants already involved, thus minimising imbalance across any factors that might predict outcome.

The following assessments will be performed prior to randomisation into TORPEdO:
a) Complete medical history, physical examination (including weight and height), WHO performance status (PS)
b) Pre-radiotherapy dental assessment (may be conducted at randomising centre or proton centre)
c) Blood to be taken for full blood count, renal function (calculated GFR/isotope depending on local hospital policy)
electrolytes and liver function tests
d) Completion of baseline Patient Reported Outcomes (PRO) questionnaires
e) Swallowing function assessments
f) Feeding tube status (including type or tube e.g. nasogastric vs gastrostomy and tube use)

g) Radiological assessment of oropharyngeal cancer: all patients will be clinically assessed and radiologically staged in line with standard practice. Radiological assessment should include as a minimum: MRI neck & CT thorax preferred, however CT neck + CT thorax is acceptable
h) Histology report
i) ECG/BSA (concurrent chemotherapy assessments) considered as per local hospital policy

TORPEdO pre-treatment assessments (after randomisation):
a) Dental assessment - for patients who did not have this done as part of the screening assessments
b) NM isotope GFR (depending on local hospital policy as this is not mandated by the trial protocol) - for patients who did not have this conducted as part of the screening assessments (however calculated renal function should have been conducted to ensure eligibility for the trial)
c) Audiometry assessment
d) Maximum interincisal distance to assess for trismus
e) Baseline assessment of symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5.0.
f) DW-MRI (for patients taking part in the optional DW-MRI sub-study at The Christie Hospital)

TORPEdO during treatment assessments:
Treatment will be given over 6.5 weeks, patients will be seen at the end of each week and the following assessments will be performed:
a) Patient weight (to assess any weight loss) and WHO PS
b) Blood to be taken for full blood count, electrolytes, liver function tests
c) Feeding tube status (including type or tube e.g. nasogastric vs gastrostomy and tube use)
d) Assessment of symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5.0
e) DW-MRI (for patients taking part in the optional DW-MRI sub-study at The Christie Hospital) during week 3 of treatment
For IMPT patients all on treatment assessments will take place at the Proton centre.

TORPEdO end of treatment assessments (end of week 7):
a) Patient weight (to assess any weight loss) and WHO PS
b) Blood to be taken for full blood count, electrolytes, liver function tests
c) Completion of PRO questionnaires
d) Feeding tube status (including type or tube e.g. nasogastric vs gastrostomy and tube use)
e) Assessment of symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5.0

TORPEdO post treatment assessments:
At 6 weeks post treatment:
a) Patient weight (to assess any weight loss) and WHO PS.
b) Completion of PRO questionnaires.
c) Feeding tube status (including type or tube e.g. nasogastric vs gastrostomy and tube use).
d) Assessment of symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5.0.
e) Clinical response assessment.

At 3, 6, 12, 18, 24 post treatment:
a) Patient weight (to assess any weight loss) and WHO PS
b) Completion of PRO questionnaires
c) Swallowing function assessments
d) Feeding tube status (including type or tube e.g. nasogastric vs gastrostomy and tube use)

e) Audiometry assessment (3 months, 12 months, 24 months)
f) Maximum interincisal distance to assess for trismus (3 months, 12 months, 24 months)
g) Assessment of symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5.0 and LENT SOMA
h) All patients will undergo clinical and radiological assessment to determine their response to treatment 12-14 weeks after completion of radiotherapy. Radiological assessment will be in line with standard practice: PET-CT is preferred, however MRI neck + CT Thorax acceptable. Imaging may be performed earlier if clinically indicated, e.g. if there is a clinical suspicion of residual disease
i) Clinical response assessment at 6, 12, 18 and 24 months to determine disease response. Further radiological review should be carried out as per standard practice if clinical assessment raises the suspicion of recurrent disease
j) Healthcare resource-use (3, 6, 12 months).

At 3, 4, 5 years post treatment:
a) Completion of PRO questionnaires
b) Assessment for recurrence and survival only

Annual visits after 60 months:
Patients will not be required to undergo any trial-specific investigations, however, data will be requested annually from standard follow visits relating to patients disease status, survival and health resource usage assessment.

Patient-reported outcomes
TORPEdO participants will take part in the QL study. They will be asked to complete a patient-reported outcomes questionnaire before radiotherapy, at the end of radiotherapy (week 7) and at week 6. Further questionnaires will be at 3, 6, 12, 18, 24, 36, 48 and 60 months. The initial questionnaires will be handed to patients at clinic visits and those from 3 months onwards will be posted directly to patients' homes. The questionnaires should take no more than 30 minutes to complete.

Translational sub-studies (optional)
Patients will be asked to gift archival tumour tissue and blood samples as part of optional sub-studies. Blood sampling will coincide with collection of routine clinical bloods (no separate needle sticks):
EDTA blood (10 ml) for genomics (taken at 1 timepoint)
Streck bloods (40 ml on first occasion; 30 ml thereafter) for liquid biopsies (taken at 4 timepoints)
EDTA bloods (30 ml) for immune markers (taken at 4 timepoints).
EDTA bloods (10 ml) for proteomics (taken at 10 timepoints)
MRI substudy (for The Christie patients only - optional)
One MRI scan before treatment starts and a second MRI scan during the third week of treatment.

Quality assurance, training and patient safety
Detailed technical radiotherapy planning and delivery guidelines will be in place for TORPEdO. These will set out exactly how the radiotherapy should be given. They will include details of the safety margins to be added around the treatment area, mandatory limits relating to the proportion of the total radiotherapy dose to which normal tissue can be exposed (dose constraints) and how participants should be prepared to receive treatment.

In addition to the technical radiotherapy guidelines, a comprehensive quality assurance programme led by the National Clinical Research Institute Radiotherapy Clinical Trials Quality

Assurance (NCRI RTTQA) group will be put in place to ensure quality and consistency of radiotherapy delivery to participants within and between TORPEdO centres. Centres will have to pass components of this programme before they are approved to recruit TORPEdO participants. TORPEdO trial teams at participating sites will also receive training from the TORPEdO trial manager on the trial protocol and logistics at a site initiation meeting prior to commencing recruitment. Only when a centre has satisfactorily completed the pre-trial quality assurance and training, will they be able to invite patients to participate in TORPEdO. Quality assurance processes will be ongoing throughout TORPEdO.

Patient safety will be monitored by the Independent Data Monitoring Committee (IDMC) who will review all safety and efficacy data by treatment group.

Central trial management will be conducted by the ICR-CTSU, a UKCRC registered NCRI cancer clinical trials unit.

Participants will be recruited to TORPEdO at participating sites for approximately 33 months. Where possible, follow up data will continue to be collected for all trial participants from routine clinic visits until their death, to contribute to the planned secondary endpoint analyses which will be published as data becomes available. Analysis of all primary and secondary endpoints will be conducted by ICR-CTSU. A Trial Management Group (TMG) will be set up and will have responsibility for day to day management of the trial. It will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups membership will include a lay/consumer representative.

The independent Trial Steering Committee (TSC) will meet annually throughout TORPEdO to oversee the study's progress on behalf of the sponsor and funder. The IDMC will meet in confidence, at least annually, to review the data and make recommendations as appropriate to the TSC and TMG.

Intervention Type
Other

Primary outcome(s)
Co-primary endpoints:
1. University of Washington Quality of Life Questionnaire (UW-QoL) physical composite score
2. Gastrostomy dependence or CTCAE grade 3 weight loss (i.e. ≥ 20% weight loss from baseline)
Timepoint(s): 12 months after completion of chemoradiotherapy

Key secondary outcome(s))
1. Health-related quality of life (HR-QoL) evaluated using the PRO questionnaires at baseline, end of treatment, 6 weeks post-treatment and at 3, 6, 12, 18, 24, 36, 48, and 60 months post-treatment
1.1. University of Washington Quality of Life (UW-QoL)
1.2. EORTC QLQ-C30 and QLQ-H&N43
1.3. M.D. Anderson Dysphagia Inventory (MDADI)
2. Tube feeding status evaluated at 3, 12, 18 and 24 months after completion of treatment
3. Acute and late severe toxicity assessed by physician recorded CTCAE v 5.0 and physician-rated dysphagia scores at baseline, week 1, week 2, week 3, week 4, week 5, week 6 (during treatment) week 7 (end of treatment), 3, 6, 12, 18 and 24 months post-treatment

4. Swallowing function evaluated using the 100-mL Water Swallowing Test at baseline, and at 3, 6, 12, 18 and 24 months following completion of study treatment
5. Performance Status Scale for Head and Neck Cancer (PSS-HN) Normalcy of Diet and Place of Eating scores reported at baseline, and at 3, 6, 12, 18 and 24 months following completion of study treatment
6. Hearing measured by audiometry at baseline, and at 3, 12 and 24 months post-treatment
7. Trismus evaluated using change in maximum interincisal distance at baseline, and at 3, 12 and 24 months post-treatment
8. Resection rate, defined as the proportion of patients proceeding to surgical treatment (including neck dissection) after the completion of radiotherapy treatment
9. Loco-regional tumour control, defined as time from randomisation to loco-regional recurrence i.e. recurrence at the primary site or in the neck
10. Overall survival, defined as time from randomisation to death from any cause
11. Cost-effectiveness analysed using the healthcare resource use questionnaire developed for the trial, Work Productivity Assessment Index (WPAI-SHP) and EuroQol five-dimensional questionnaire (EQ-5D-5L) at baseline, end of treatment, 6 weeks post-treatment and at 3, 6, 12, 18, 24, 36, 48, and 60 months post-treatment

Completion date
01/09/2028

Eligibility

Key inclusion criteria
1. Histologically confirmed oropharyngeal squamous cell carcinoma
2. HPV positive TNM8: T1-2 N1-2 (excluding T1-2 with a single ipsilateral node < 3cm), T3-4 N0-2
3. HPV negative TNM 8: T1N2, T2N1-N2, T3-4N0-2
4. Local MDT decision for concurrent chemoradiotherapy with bilateral neck treatment
5. Age >=18 years
6. WHO performance status 0-1
7. Adequate renal function, glomerular filtration rate (GFR) > 60ml/min calculated using Cockcroft-Gault formula
8. Adequate cognitive ability (in the opinion of the local PI) to complete PRO assessments
9. Willingness to comply with the protocol, including travel to the proton centre for IMPT treatment
10. Written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
120 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Feeding tube insertion required for nutrition due to dysphagia prior to treatment [Note: patients who have prophylactic feeding tube insertion, with or without tube use to top up nutrition prior to starting treatment, remain eligible for the study]
2. N3 disease
3. Upfront neck dissection
4. Use of induction chemotherapy
5. Previous head and neck radiotherapy
6. Major surgery within 6 months of trial entry
7. Permanent pacemaker or implantable cardioverter-defibrillator
8. Any invasive malignancy within previous 2 years (other than non-melanomatous skin carcinoma or cervical carcinoma in situ)
9. Previous or concurrent illness (e.g., active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis), which in the investigator's opinion would interfere with completion of therapy, trial assessments or follow up
10. Pregnancy; lactating women or women of childbearing potential unwilling or unable to use adequate non-hormonal contraception (male patients should also use contraception if sexually active)
11. Pre-existing speech or swallowing problems unrelated to the diagnosis of cancer

For patients taking part in the optional DW-MRI study at The Christie Hospital the following additional exclusion criteria apply:
1. Any contraindication to MRI scanning, including metallic heart valve replacement, permanent pacemaker, implantable cardiac defibrillator, non-MRI compatible metal implants, neuro-stimulators
2. A history of allergy/reaction to Gadolinium contrast

Date of first enrolment
15/02/2020

Date of final enrolment
01/09/2023

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
England
M20 4BX

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
England
LS9 7TF

Study participating centre
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle-upon-Tyne
England
NE7 7DN

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Northern General Hospital
Herries Road
Sheffield
England
S5 7AU

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

Study participating centre

Royal United Hospitals Bath NHS Foundation Trust
Combe Park
Bath
England
BA1 3NG

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
England
NW1 2PG

Study participating centre
University Hospitals Coventry and Warwickshire NHS Trust
Walsgrave General Hospital
Clifford Bridge Road
Coventry
England
CV2 2DX

Study participating centre
Portsmouth Hospitals NHS Trust
De La Court House
Queen Alexandra Hospital
Southwick Hill Road
Portsmouth
England
PO6 3LY

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

Study participating centre
Worcestershire Acute Hospitals NHS Trust
Worcestershire Royal Hospital
Charles Hastings Way

Worcester
England
WR5 1DD

Study participating centre
University Hospital Southampton NHS Foundation Trust
Mailpoint 18
Southampton General Hospital
Tremona Road
Southampton
England
SO16 6YD

Study participating centre
Abertawe Bro Morgannwg University LHB
One Talbot Gateway
Seaway Drive
Seaway Parade Industrial Estate
Baglan
Port Talbot
Wales
SA12 7BR

Study participating centre
Torbay and South Devon NHS Foundation Trust
Hengrave House
Torbay Hospital
Newton Road
Torquay
England
TQ2 7AA

Study participating centre
Velindre NHS Trust
Unit 2
Charnwood Court
Heol Billingsley
Cardiff
Wales
CF15 7QZ

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
Queen Elizabeth Medical Centre
Edgbaston
Birmingham
England
B15 2TH

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

Study participating centre
York Teaching Hospital NHS Foundation Trust
York Hospital
Wigginton Road
York
England
YO31 8HE

Sponsor information

Organisation
Institute of Cancer Research

ROR
https://ror.org/00dpztj76

Funder(s)

Funder type
Charity

Funder Name

Cancer Research UK; Grant Codes: C58459/A27172

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

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 (TORPEdO Trial Manager, TORPEdO-icrctsu@icr.ac.uk). Formal responsibility for all data collected within this trial lies with the trial sponsor (ICR). ICRCTSU's Data and Sample Access Policy, available on external-facing web pages, details eligibility criteria for access and how access to collections will be prioritised. Priority will be given to projects from within the original trial proposal and access will usually be reserved for trial purposes until those studies are concluded. Data will not be released where this could impact on the reporting of the primary research questions of the trial.
The policy defines the application process. In the first instance, applicants are encouraged to approach ICRCTSU and/or the Chief Investigator (CI) informally to discuss the feasibility of the proposal including the suitability of the collection for the proposed research. Once feasibility has been established, formal applications are made using the ICRCTSU Sample and Data Access Request Form. Applications should include a clear statement of the study hypothesis, objectives and proposed methodology and details of the responsible person or persons who will carry out

the work. A statistical analysis plan and a power calculation are also required. A preliminary review of complete applications is performed by the CI and ICRCTSU Scientific Lead to ensure that the proposal is achievable and is scientifically sound. If both agree, the application is forwarded to the TMG for review and prioritisation. Once an application has been agreed in principle by the TMG it is submitted to the TSC for final approval. If approved, the applicant must agree to the conditions of access in writing under an access agreement between the applicant's host institution and the sponsor. Identifying data is not made available to applicants. Data must be stored in a secure location with access strictly controlled and overseen by those named on the application. Applicants are asked to provide a lay summary of their research project, as well as an end of project report or publication of the results to the TMG.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		21/11/2022	29/12/2022	Yes	No
HRA research summary			28/06/2023	No	No
Interim results article		21/03/2026	25/03/2026	Yes	No
Participant information sheet	v4.0	28/04/2021	29/12/2022	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol (other)	v5	09/02/2022	29/12/2022	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes