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Can proton beam therapy improve survival and reduce late side effects compared with standard-of-care intensity-modulated radiotherapy in patients with sinonasal cancer?

Submission date
18/12/2023

Recruitment status
Recruiting

Registration date
26/03/2024

Overall study status
Ongoing

Last Edited
24/02/2026

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
Cancer of the sinuses (the air spaces in our nose and facial bones) is a rare disease, which is often found to be quite advanced by the time it is noticed. The treatment for sinus cancer usually involves surgery followed by radiotherapy, but radiotherapy may also be used without surgery. In some cases, chemotherapy may also be used to treat the cancer. Radiotherapy is an important part, either to treat the cancer itself (where surgery has not been done) or to treat the cancer cells that remain after surgery (without radiotherapy these cells would grow back). The current treatment is intensity-modulated radiotherapy (IMRT). Proton beam therapy (PBT) is a newer form of radiotherapy, which may be more effective at treating cancer or cancer cells to improve the chance of cure. It may also cause less damage to nearby normal structures, resulting in fewer side effects. However, this is unknown and it is also possible that some side effects may be increased by protons. PROTIS aims to compare PBT with IMRT, to see whether or not there is an improvement in cure rates and a difference in long-term side effects.

Who can participate?
Patients aged 25 years old and over diagnosed with sinus cancer, histologically confirmed by the hospital to be either sinonasal squamous cell carcinoma (SNSCC) or sinonasal adenocarcinoma (SNAC).

What does the study involve?
The study aims to recruit 276 patients, and each participant will be involved in the study for up to 5 years after treatment. When taking part in PROTIS, there is a 50:50 chance (which is decided randomly) that participants will be allocated to receive either IMRT (standard of care) or PBT. Regardless of which treatment participants receive, radiotherapy will be delivered daily (excluding weekends) for up to 7 weeks. If participants are receiving IMRT, it will be delivered at their local hospital as if they were not taking part in the trial. If they are to receive PBT, this will be delivered at one of the two NHS proton beam centres in the UK (The Christie, Manchester or University College London Hospital (UCLH), London). Usually, this will be the centre closest to

the participants' home but other factors are considered for example capacity at the centres. This will mean travelling to the specialist unit and staying away from home during treatment (up to 7 weeks). Reasonable travel expenses are reimbursed, and the NHS provides apartment accommodation for the patient and one family member or carer. The doctor or nurse will provide further information about this.

Before starting treatment, participants will need to attend a planning visit at the treating hospital. This may be at the proton beam centre if allocated to PBT in the trial. They will meet the members of the team and will attend some clinical appointments. During this time, they will have a mould/mask made which will be worn during all the radiotherapy treatments. These appointments are likely to occur across several days.

There are several other treatments/assessments involved in the trial as well as the radiotherapy. Some of these are the same as standard of care but others are additional. To treat the cancer some participants will be offered surgery before radiotherapy; others may be offered chemotherapy. The decisions about what is required will be the same whether they are taking part in the trial or not. If they are having surgery, the team would like to take some biopsies, which can be used to answer some important research questions. To understand potential long-term side effects the clinical team will perform some tests/ assessments. The first set will be before starting radiotherapy, these are called baseline assessments. These tests include clinical assessment, blood tests, hearing tests, eye examinations, and tests to check the sense of smell and brain function including attention, memory, language, reaction time and perception, thinking and memory. Participants will also be asked to complete a few questionnaires about their quality of life. These same tests will then be repeated at different time points after their radiotherapy so that any changes can be tracked.

What are the possible benefits and risks of participating?
The results from this study will be used to help us improve treatments for patients with sinus cancer. It is known that most patients having radiotherapy will experience some side effects. Part of the PROTIS trial is to understand whether PBT can reduce the side effects of radiotherapy. At the moment we do not know if this is the case.

Where is the study run from?
The Christie NHS Foundation Trust are the sponsor and lead clinical site. The day-to-day running of the trial is via the Liverpool Clinical Trial Centre (LCTC)

When is the study starting and how long is it expected to run for?
October 2022 to September 2031

Who is funding the study?
Cancer Research UK (Taylor Family Foundation)
National Institute for Health and Care Research (NIHR)

Who is the main contact?
PROTIS@liverpool.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-proton-beam-radiotherapy-for-sinus-cancer-protis#undefined

Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
325882

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 56569, IRAS 325882

Study information

Scientific Title
PROton beam Therapy versus Intensity-modulated radiotherapy for Sinonasal cancer

Acronym
PROTIS

Study objectives
Treatment with proton beam therapy can improve disease-free survival rate compared with standard-of-care IMRT for non-metastatic sinonasal cancer

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 13/12/2023, London-Surrey Research Ethics Committee (2 Redman Place Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8088, (0)207 104 8131; surrey.rec@hra.nhs.uk), ref: 23/LO/0933

Study design
Open-label phase III multi-centre prospective randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Non-metastatic sinonasal cancer

Interventions
PROTIS is an open-label phase III multi-centre prospective randomised controlled trial. The overall aim is to assess whether proton beam therapy (PBT) compared with standard-of-care intensity-modulated radiotherapy (IMRT) improves cure rates for patients with sinonasal cancer. Secondary to this is to assess the long-term side effects and impact on quality of life.

The trial aims to recruit 276 patients with non-metastatic sinonasal cancer from 20 UK sites. Patients have a 50:50 chance of being allocated to receive either standard of care IMRT or PBT. Treatment will be given over 6-7 weeks. Following treatment patients will enter a follow-up phase of up to 5 years (2 years minimum) where they will attend regular clinical visits.

Participant identification
Potential participants will be identified during multi-disciplinary team (MDT) meetings at their local hospital. During these meetings which include various clinical teams, diagnostic scans (MRI or CT-chest) and biopsies will be reviewed and decisions on patient treatment will be documented.

Depending on the size and location of the tumour a patient may require surgery to try and remove the cancer or induction chemotherapy to reduce or shrink the cancer. These treatments will need to be delivered before beginning radiotherapy treatment (as standard of care). The decision for these treatments will be the same whether a patient is taking part in the trial. Depending on which treatment is recommended participants will enter the trial either via a surgical or oncology pathway.

If a patient is identified as potentially eligible for the study, they will be approached by the clinical team (either surgical or oncology) and provided with information about the trial.

Surgical
It is expected that approximately 80% of patients will require surgery before radiotherapy. Informed consent will be taken and eligibility will be confirmed by appropriate members of the surgical team. The surgery itself is part of standard care for treating this disease and is not under investigation in this trial.

Participants requiring surgery and attending either Liverpool or Manchester ONLY will also be asked to participate in a sub-study which will involve collecting tumour biopsies and additional blood collections (six in total).

Oncology
For participants who have not undergone surgery informed consent will be taken and eligibility will be confirmed by appropriate members of the oncology team. Participants will proceed straight to baseline tests.

Participants who have undergone surgery will then attend oncology visits. The oncologist will reconfirm eligibility and the participant's consent. There is a small chance that following surgery this study is no longer suitable for the participant. If this is the case, the clinical team will discuss treatment options with the participants and withdraw them from the study. Otherwise, patients will continue to baseline tests.

The oncology team may also advise that concurrent chemotherapy is needed at the same time as radiotherapy.

Baseline tests
These tests include clinical assessment, blood tests, hearing tests, eye examinations, tests to check sense of smell and paper-based brain function tests, as well as the completion of quality of life questionnaires. Tissue taken from cancer at diagnosis is requested to be sent to the labs.

These assessments will require the participant to attend clinic and some, such as eye and hearing tests, are performed in different departments. These may need to be performed on different

days depending on scheduling and potentially different locations depending on local hospital departmental set-up.

Randomisation
Participants are randomised on a 1:1 basis to receive either IMRT or PBT. Randomisation will be performed using minimisation to take account of the multiple stratification factors, including subsite (maxilla vs other), pathology (SNSCC vs high-grade SNAC vs low-grade SNAC), surgery (yes/no), use of chemotherapy (yes/no), stage (T2/3 vs T4a vs T4b) and recruiting centre. Once randomisation is confirmed the participant will be informed on the form of radiotherapy they will receive. Standard of care IMRT will be delivered at the local recruiting hospital.

However, PBT can only be delivered at one of two NHS proton beam centres in the UK (The Christie, Manchester or UCLH, London). Upon randomisation, the clinical team will input data into the proton beam referral portal. Patients will be assigned to one of the centres based on factors including but not limited to availability and distance. During treatment, the team at the proton beam centre will assume all care responsibilities for the patient and will complete all on-treatment CRFs.

Allocation to PBT will mean travelling to the specialist unit and staying away from home during treatment. Reasonable travel expenses would be reimbursed, and the NHS provides apartment accommodation for the patient and one family member or carer.

Radiotherapy planning Visit
Before starting radiotherapy treatment, participants will need to attend a planning visit at the treating hospital (proton beam centre if allocated PBT). During this visit, a special mould called a “mask” or “shell” will be made which will support the patient to be able to lie still and in the same position for each treatment. This is followed by diagnostic scans (performed while wearing the radiotherapy mask), which will be used to plan the radiotherapy treatment.

Induction chemotherapy (if required)
If the clinical team decides that chemotherapy is required to shrink the cancer before radiotherapy (induction) then this will be performed at the local recruiting hospital before starting radiotherapy. It is expected that 2 rounds of chemotherapy will be administered with the participant attending the radiotherapy planning session between rounds.

Concurrent chemotherapy (if required)
The clinical team may also decide that the participant requires chemotherapy delivered while receiving radiotherapy (concurrent chemotherapy). If this is to happen, chemotherapy will be provided at the hospital providing the radiotherapy.

Radiotherapy Treatment
Radiotherapy treatment will be delivered in 30-35 fractions. One fraction will be delivered once daily (excluding weekends) every week, for up to 7 weeks.

During treatment, the clinical team will monitor symptoms and any side effects. At the immediate end of treatment, there will be a health status assessment and participants will be asked to complete some questionnaires.

If attending a proton beam centre the participants will be discharged back to the care of the local recruiting hospital.

After Treatment (follow-up)
After treatment, participants will need to attend follow-up visits at the local recruiting hospital.

Follow-up visits are timed to be aligned with routine care visits for MRI scans (3, 12, 24, 36, 48, 60m). Data from some of these scans will be sent to a radiologist to review for any signs of injury to the brain.

The treating physician may request additional surveillance scans in line with local practice.

As part of the trial follow-up, there will be some additional tests relating to long-term side effects and participants will be asked to complete quality-of-life questionnaires. The first visit is 6 weeks after finishing treatment. Then 3, 6, 12, 18 and 24 months after treatment, then once a year for the next 3 years.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Disease-free survival (DFS) measured using a biopsy; a biopsy with pathological confirmation will define a DFS event. Where a biopsy is not possible, correlative imaging can be used as a surrogate to define a DFS event from randomisation to cancer recurrence, death from any cause, or 5-year follow-up.

Key secondary outcome(s))
1. Loco-regional tumour control measured using a clinical evaluation post-treatment. Additional non-trial visits will be carried out as per local policy and standard of care, from randomisation to tumour growth or 5 years follow-up.
2. Distant failure measured during follow-up via imaging if prompted by participants having symptoms of concern and as per standard of care from randomisation to distant failure or 5 years follow-up.
3. Overall survival measured using all deaths reported from randomisation to death or 5 years follow-up.
4. Acute severe (grade 3-5) toxicity events measured by physician recorded CTCAE v5.0 up to 12 weeks from completion of treatment.
5. Late severe (grade 3-5) toxicity events measured by physician recorded CTCAE v5.0 from 12 weeks to 5 years from completion of treatment.
6. Neuro-cognitive decline measured using EORTC core tests conducted and scored at sites and compiling the corresponding scoring manuals/algorithms at baseline, 12 weeks, 52 weeks, 2, 3, 4 and 5 years.
7. Visual function measured using visual acuity, visual fields, Lens exam, IOP, fundus exam, media clarity, levator function, pupil function, colour vision, ocular alignment/movement assessment, lid/lash/ocular surface exam and Optical Coherence Tomography (OCT) at baseline, 2 and 5 years.
8. Olfactory function measured using UPSIT at baseline and 2 years.
9. Pituitary function measured using blood tests collected as per standard of care Growth hormone (IGF-1), Adrenal (ACTH/cortisol (9am)), and Thyroid (TSH fT4 fT3), Gonadotrophins/ sex steroids (FSH/LH/SHBG testosterone or oestradiol, prolactin) at baseline, 52 weeks, 2 and 5 years.
10. Auditory function measured using pure tone audiometry +/- extended high frequencies at baseline and 2 years.
11. Trismus measured using maximum interincisal distance at baseline, 12, 52 weeks and 2 years.
12. Brain injury/necrosis measured using central review of MRI scans (collected as standard of

care sinus/neck) at baseline, 52 weeks, 2, 3, 4 and 5 years.
13. Quality of Life measured using participant completed questionnaires; EORTC-QLQ-C30, EORTC-QLQ-BN20, EuroQoL EQ5D5L, ASBQ at baseline, end of treatment, 6, 12, 24, 52, 78 weeks, 2, 3, 4 and 5 years.

Completion date
30/09/2031

Eligibility

Key inclusion criteria
Current inclusion criteria as of 31/10/2024:

1. Written and informed consent obtained from participants
2. Agreement of participant to comply with the requirements of the trial, including travel and residential stay at the proton centre if allocated to PBT
3. Histologically confirmed:
3.1. Sinonasal squamous cell carcinoma (SNSCC) or
3.2. Sinonasal adenocarcinoma (SNAC)
4. Primary tumour (T) staging (AJCC 8th edition):
4.1. T3-4 all subsites (maxillary, ethmoid, sphenoid or frontal sinuses, and/or nasal cavity) or
4.2. T2 nasal cavity involving ethmoid sinus
5. Age >=25 years old
6. WHO performance status 0-1
7. Multidisciplinary team (MDT) decision for curative intent treatment
7.1. with surgery or
7.2. without

_____

Previous inclusion criteria:

1. Written and informed consent obtained from participants
2. Agreement of participant to comply with the requirements of the trial, including travel and residential stay at the proton centre if allocated to PBT
3. Histologically confirmed:
3.1. Sinonasal squamous cell carcinoma (SNSCC) or
3.2. Sinonasal adenocarcinoma (SNAC)
4. Primary tumour (T) staging (AJCC 8th edition):
4.1. T3-4 all subsites (maxillary, ethmoid, sphenoid or frontal sinuses, and/or nasal cavity) or
4.2. T2 nasal cavity involving ethmoid sinus
5. Age > = 16 years old
6. WHO performance status 0-1
7. Multidisciplinary team (MDT) decision for curative intent treatment
7.1. with surgery or
7.2. without

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Mixed

Lower age limit
25 years

Upper age limit
110 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Distant metastatic disease, as determined by routine pre-operative radiological staging investigations
2. Previous head and neck radiotherapy
3. Any invasive malignancy within the previous 2 years (other than non-melanomatous skin carcinoma or cervical carcinoma in situ)
4. Previous or concurrent illness that would interfere with completion of therapy, trial assessments or follow-up (in the opinion of PI)
5. Pregnant or breastfeeding women
6. Participants unwilling or unable to use adequate non-hormonal contraception

Date of first enrolment
16/09/2024

Date of final enrolment
01/04/2029

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
Cambridge University Hospitals NHS Foundation Trust
Cambridge Biomedical Campus
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
Nottingham University Hospitals NHS Trust - Queen's Medical Centre Campus
Nottingham University Hospital
Derby Road
Nottingham
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NG7 2UH

Study participating centre
Manchester University NHS Foundation Trust
Cobbett House
Oxford Road
Manchester
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M13 9WL

Study participating centre
Liverpool University Hospitals NHS Foundation Trust
Royal Liverpool University Hospital
Prescot Street
Liverpool
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L7 8XP

Study participating centre
Northern General Hospital
Northern General Hospital NHS Trust
C Floor, Huntsmnan Building
Herries Road

Sheffield
England
S5 7AU

Study participating centre
University Hospitals Southampton NHS Trust
Southampton General Hospital
Tremona Road
Southampton
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SO16 6YD

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

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
England
B15 2GW

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

Study participating centre
East and North Hertfordshire NHS Trust
Lister Hospital
Coreys Mill Lane

Stevenage
England
SG1 4AB

Study participating centre
Gloucestershire Hospitals NHS Foundation Trust
Cheltenham General Hospital
Sandford Road
Cheltenham
England
GL53 7AN

Study participating centre
The Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Hospital
Clatterbridge Road
Bebington
Wirral
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CH63 4JY

Study participating centre
Mount Vernon Cancer Centre
Rickmansworth Road
Northwood
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HA6 2RN

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

Study participating centre
Gloucestershire Hospitals NHS Foundation Trust
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Sandford Road
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Sponsor information

Organisation
The Christie NHS Foundation Trust

ROR
https://ror.org/03v9efr22

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

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 and Care Research

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

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?
Participant information sheet	version 2.0	11/12/2023	08/03/2024	No	Yes
Participant information sheet	version 5.0	30/01/2025	24/02/2026	No	Yes