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A clinical trial to investigate if proton beam therapy with chemotherapy given before surgery for patients with oesophageal cancer that has spread to the surrounding tissues, significantly reduces the severe side effects to the heart and lungs and allows immunotherapy to be started sooner after surgery when compared with standard radiotherapy and chemotherapy before surgery, and whether this delivers value to the NHS and patients

Submission date 27/12/2023	**Recruitment status** Recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 15/02/2024	**Overall study status** Ongoing	
Last Edited 08/11/2024	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims

Although the optimal treatment strategy in oesophageal (food pipe) cancer has been the subject of research for several decades, overall outcomes are very poor, with a 5-year survival of 15%. In the UK there are 9100 new cases of oesophago-gastric cancer diagnosed and approximately 7925 deaths every year (Cancer Research UK Oct 2019). Oesophageal cancer is a strategic priority for CRUK and a serious health problem world-wide. Pre-surgery treatment consists of chemotherapy or chemoradiation, but the optimal treatment is unknown. Over 60% of patients experience severe side-effects from their treatment and this impacts their outcomes. Proton beam therapy is a new radiotherapy treatment; there are currently only 2 centres in England with Proton beam therapy machines. Proton beam therapy may help to reduce side-effects and is an important avenue of research. This trial has been funded by CRUK.

This study aims to investigate if Proton beam therapy and chemotherapy given before surgery for oesophageal cancer significantly reduces the risk of severe toxicity and prevents delay of post-operative immunotherapy when compared with standard photon radiotherapy.

Who can participate?
Patients over 16 years old with resectable oesophageal cancer.

What does the study involve?
Patients will be randomised 1:1 into the experimental arm (Proton beam therapy, chemotherapy + surgery) and control arm (photon radiotherapy, chemotherapy + surgery). Patients suitable for immunotherapy will then receive up to 12 months of treatment as per standard of care. This UK trial will recruit patients from 15 NHS sites; all patients randomised to receive Proton beam therapy will be treated at either UCLH/Christie. Patients will receive treatment for 5 weeks before surgery, and for up to 1 year after surgery. Patients will be followed up at NHS sites for up to 1 year, and then survival data will be collected from NHS Digital for a further 2 years.

What are the possible benefits and risks of participating?
The potential risks and burden will only be applicable to patients randomised to the experimental arm to receive Proton-beam therapy over a period of 3 weeks. Patients on the control arm will be treated as per standard of care. There is a risk of financial burden on patients allocated proton beam therapy who will need to travel to one of the two proton beam centres for their specialised radiotherapy treatment. Patients will be required to organise the travel themselves with the help of their 'key worker' from the relevant Proton beam therapy centre. Patients may also be required to stay away from home for 3 weeks if they live far away from one of the 2 proton beam centres. As with any radiotherapy there may be some long-term side effects. The study doctor or nurse will go through these with trial patients and this information is included in the patient information sheet. The adverse events from Proton beam therapy are considered to be low risk, as the concept of Proton beam therapy is to negate the effects of radiation to the healthy tissues surrounding the tumour, mainly healthy lung and heart tissue. The treating team will be monitoring patients for any side effects during and after treatment and will be taking care of any long-term adverse events for up to a year after surgery.

There may be no direct benefit to research participants and this is explained in the patient information sheet. Research participants enrolled in the trial will have a 50% chance of receiving PBT for their oesophageal cancer, which is not currently available off trial, which may or may not improve their survival and quality of life from potentially fewer side effects than standard photon based radiotherapy. With 2 proton beam centres now in England, patients will no longer have to travel overseas for their PBT treatment. Patients in this study will have access to this new treatment, possibly increasing the chances of a long-term cure. Proton beam therapy may make immunotherapy easier to tolerate and possibly more effective. However, none of this is proven and there is no guarantee that individual patients will benefit directly from taking part in this study. We hope the information we gain from the study will benefit people who develop oesophageal cancer in the future. If the trial is a success and shows PBT treatment is better than photon beam radiotherapy then the standard of care may change in future.

Where is the study run from?
University College London (UK)

When is the study starting and how long is it expected to run for?
January 2024 to June 2032

Who is funding the study?
Cancer Research UK
The Taylor Family Foundation (UK)

Who is the main contact?
ctc.protieus@ucl.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-proton-beam-radiotherapy-for-oesophageal-cancer-and-gastroesophageal-junction

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
329646

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 58475, IRAS 329646

Study information

Scientific Title
A randomised phase 2 trial comparing proton versus photon-based neoadjuvant chemoradiation, followed by adjuvant immunotherapy, in oesophageal cancer

Acronym
PROTIEUS

Study objectives
Proton beam therapy given concurrently with chemotherapy before surgery significantly reduces the risk of severe toxicity and prevents delay of post-operative immunotherapy when compared with standard photon radiotherapy for oesophageal cancer.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 23/01/2024, The London - Camden & Kings Cross Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8086; CamdenandKingsCross.REC@hra.nhs.uk), ref: 23/LO/0964

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet.

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

Interventions

Eligible patients will be allocated by a computer devised programme into one of the treatment groups: A) a group receiving proton beam radiotherapy (PBT) or B) a group receiving standard of care treatment photon radiotherapy. All patients will receive 3 weeks of daily radiation and 5 courses of chemotherapy once weekly, followed by surgery. Patients in PBT group will travel to one of the proton beam centres either in Manchester or London. After chemoradiotherapy, all patients will have surgery and if they have a small amount of remaining cancer cells (residual disease) after surgery, they will receive immunotherapy for up to 1 year after their surgery, approximately 4 to 12 weeks after surgery. The frequency when the patient should receive immunotherapy, for example, once every 2 or 4 weeks, will depend on the local hospital's policy.
After finishing surgery, all patients will be seen at clinic (follow-up visits) at the first month after the surgery, then every 3 months for up to a 1 year. Further follow-up data will be collected remotely via a data collection service called NHS Digital (NHS England data registries).
There is also a translational research component where extra blood and tissue samples will be taken from patients.

Intervention Type
Procedure/Surgery

Primary outcome measure
Frequency and percentage of patients that experience severe post operative complications prior to or at the follow-up assessment 3 months after surgery measured using adverse event data entered on the database by sites which is graded using both the CTCAE and the Clavien Dindo Scale

Secondary outcome measures
Preliminary data on longer term efficacy outcomes following 1 year of adjuvant immunotherapy for patients that do not achieve pathologic complete response at surgery measured using survival data and the number and percentages of different types of disease recurrences

Overall study start date
23/01/2024

Completion date
01/06/2032

Eligibility

Key inclusion criteria
1. 16 years of age or older
2. Histologically confirmed diagnosis of oesophageal adenocarcinoma (OAC) or squamous cell carcinoma (OSCC)
3. Tumour of the thoracic oesophagus or gastroesophageal junction with distal maximum extension no more than 3 cm beyond the gastroesophageal junction
4. cT stage > = 2 and/or cN stage > = 0-2 defined by AJCC 8th edition
5. ECOG performance status 0–1
6. Suitable for and fit to receive curative neoadjuvant Chemoradiotherapy followed by surgery by an Upper GI MDT
7. Suitable for and fit to receive adjuvant Immunotherapy according to local guidelines
8. Adequate cardiovascular and respiratory function for surgery in the opinion of the surgical

team within 4 weeks prior to randomisation
9. Willing and able to give written informed consent and able to comply with treatment and follow up schedule
10. Willing and able to undergo treatment at a PBT centre (i.e. UCLH or The Christie) if randomised to Proton Arm

Participant type(s)
Patient

Age group
Adult

Lower age limit
16 Years

Sex
Both

Target number of participants
Planned Sample Size: 170; UK Sample Size: 170

Key exclusion criteria
1. Metastatic disease or extensive nodal disease (N3).
2. Patients who have had previous treatment for invasive oesophageal carcinoma or gastro-oesophageal junction carcinoma (including Photo Dynamic Therapy or laser therapy for high grade dysplasia/carcinoma in-situ).
3. Patients with > 3cm mucosal extension of tumour into the stomach beyond the GOJ or where the superior extent is in the cervical oesophagus
4. Total length of disease (primary tumour and involved lymph nodes) length > 8 cm
5. Patients with unstable angina, uncontrolled hypertension, cardiac failure or arrhythmia and other clinically significant cardiac disease.
6. Patients with an oesophageal stent (patients requiring a PEG/RIG/feeding jejunostomy for nutritional purposes ARE eligible).
7. No relevant co-morbidities, including Usual Interstitial Pneumonia (UIP) pulmonary fibrosis and connective tissue disorders.
8. History of other malignancy likely to interfere with the protocol treatment (e.g. patients with previously treated malignancy who have been disease-free for < 1 year, or patients with active malignancy undergoing treatment). Exceptions:
8.1. Subjects who have been successfully treated and disease-free for > 3 years,
8.2. A history of treated non-melanoma skin cancer,
8.3. Successfully treated in situ carcinoma,
8.4. CLL in stable remission, or indolent prostate cancer requiring no or only anti-hormonal therapy.
9. Any other situation, which in the opinion of the local PI, makes the patient unsuitable for this trial.
10. Women who are pregnant or breastfeeding.
11. Patients unable to adhere to the contraception guidance in the protocol.

Date of first enrolment
11/06/2024

Date of final enrolment
01/07/2029

Locations

Countries of recruitment
England

United Kingdom

Wales

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

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

Study participating centre
The Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Hospital
Clatterbridge Road
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Study participating centre
Guys and St Thomas' NHS Foundation Trust
249 Westminster Bridge Road
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SE1 7EH

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

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
Swansea Bay University Local Health Board
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Tonna Uchaf
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SA11 3LX

Study participating centre
Leeds Teaching Hospitals NHS Trust
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Beckett Street
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LS9 7TF

Study participating centre
The Christie NHS Foundation Trust
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Study participating centre
University Hospitals Birmingham NHS Foundation Trust
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Study participating centre
University Hospitals Coventry and Warwickshire NHS Trust
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Study participating centre
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Study participating centre
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Sponsor information

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Sponsor type
University/education

Website
http://www.ucl.ac.uk/

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

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

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
The Taylor Family Foundation

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal

Intention to publish date
01/06/2033

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

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