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Study protocol: PreOperative Brain Irradiation in Glioblastoma (POBIG) – A phase I trial

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ABSTRACT

Background: Glioblastoma is a high-grade aggressive neoplasm whose outcomes have not changed in decades. In the current treatment pathway, tumour growth continues and remains untreated for several weeks post-diagnosis. Intensified upfront therapy could target otherwise untreated tumour cells and improve the treatment outcome. POBIG will evaluate the safety and feasibility of single-fraction preoperative radiotherapy for newly diagnosed glioblastoma, assessed by the maximum tolerated dose (MTD) and maximum tolerated irradiation volume (MTIV).

Methods: POBIG is an open-label, dual-centre phase I dose and volume escalation trial that has received ethical approval. Patients with a new radiological diagnosis of glioblastoma will be screened for eligibility. This is deemed sufficient due to the high accuracy of imaging and to avoid treatment delay. Eligible patients will receive a single fraction of preoperative radiotherapy ranging from 6 to 14 Gy followed by their standard of care treatment comprising maximal safe resection and postoperative chemoradiotherapy (60 Gy/30 fr) with concurrent and adjuvant temozolomide). Preoperative radiotherapy will be directed to the part of the tumour that is highest risk for remaining as postoperative residual disease (hot spot). Part of the tumour will remain unirradiated (cold spot) and sampled separately for diagnostic purposes. Dose/volume escalation will be guided by a Continual Reassessment Method (CRM) model. Translational opportunities will be afforded through comparison of irradiated and unirradiated primary glioblastoma tissue.

Discussion: POBIG will help establish the role of radiotherapy in preoperative modalities for glioblastoma.

Trial registration: NCT03582514 (clinicaltrials.gov).

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Introduction/rationale

Glioblastoma is the most common primary brain tumour with dismal progression-free and overall survival, the latter averaging 15–18 months [1,2]. There is an urgent need for novel strategies to improve treatment efficacy. The standard treatment protocol comprises maximally safe surgical resection followed by chemoradiotherapy, delivered 4–6 weeks post-surgery [3]. However, postoperative remnant foci of neoplastic cells can grow and manifest before commencing radiotherapy. A meta-analysis by our group demonstrated that 40–50 % of glioblastoma patients experience disease progression in the time interval between surgery and post-operative treatment [4].

In >80 % of patients relapse occurs around the surgical cavity [5,6] despite maximal resection and efforts to improve the efficacy of radiotherapy with dose escalation [7]. As complete tumour resection is not possible, pre-operative treatment intensification may be effective as it targets the disease at an earlier and potentially more vulnerable stage [8].

There is great interest in early timepoint therapies for glioblastoma that target the pre-, intra- or early post-operative tumour microenvironment [8]. Preoperative radiotherapy is of particular interest given the encouraging results in other tumour types [9,10]. The preoperative time point has more favourable treatment characteristics compared to the postoperative tumour microenvironment, with less tumour hypoxia/molecular heterogeneity, which could therefore increase the treatment response [8]. Intensified pre-operative radiotherapy could be delivered to patients with glioblastoma in addition to the standard of care using contemporary external beam approaches [8]. Data on the safety profile of radiotherapy dose escalation studies [7] suggests that dose that is additional to the standard postoperative regime (60 Gy in 30 fractions), can be safely delivered, but it remains unclear how more dose can improve patient outcome. Preoperative radiotherapy has not been trialled, despite its strong rationale.

In this phase I study – PreOperative Brain Irradiation in Glioblastoma (POBIG), we will evaluate the safety and feasibility of a single dose (fraction) of radiotherapy delivered before surgery in patients with a new diagnosis of glioblastoma. POBIG is a dose escalation study to determine the maximum tolerated dose (MTD) and maximum tolerated irradiated volume (MTIV) of preoperative radiotherapy that can be safely delivered. We will utilize biologically effective doses ranging from 6 Gy to 14 Gy.

POBIG will recruit patients based on a radiological rather than a tissue diagnosis. This approach is justified by the proven sensitivity of historic, and more recently developed, multi-modal MRI techniques [11,12]. In addition, we only will enrol those patients whose imaging is independently reported as diagnostic of glioblastoma by at least two neuroradiologists with a subspecialty interest in neuro-oncology, that are part of our weekly MDT. Notably, the radiotherapy planning scan within POBIG will employ multiple advanced physiological MRI sequences, including perfusion (arterial spin labelling, dynamic susceptibility contrast and dynamic contrast-enhanced MRI) and diffusion imaging (diffusion-weighted MRI and diffusion tensor imaging), to further increase the diagnostic yield. This strategy offsets the need for an initial brain biopsy, which is associated with a 1–2 % risk of mortality and could introduce a further delay within the treatment pathway [13]. The main differential is a brain metastasis, in whom preoperative radiation is well described [14]. To minimise the possibility of recruiting an IDH mutant and/or 1p19q co-deleted tumour, we will consider characteristics such as age and radiological appearance whilst screening for eligibility, which are strongly correlated with these mutations [12,15,16].

POBIG will evaluate the feasibility of selecting patients in whom preoperative radiotherapy can be safely employed after clinical and radiological assessment. Patients requiring urgent surgery will be excluded [17].

POBIG will deliver additional radiotherapy dose to normal anatomical structures (OAR, organs at risk), which must be accounted for. The structures considered in POBIG treatment are the brainstem, ipsilateral optic nerve and chiasm, that have radiotherapy dose constraints (Dmax) of 57 Gy, 55 Gy and 54 Gy, respectively. These dose constraints are historically established from older radiotherapy delivery techniques and as such can be regarded as conservative when considering that newer radiotherapy techniques can reduce the high dose volume delivered to the OAR [18,19]. POBIG therefore accepts an additional dose of up to 4 Gy (Dmax), including a 2 mm safety margin around the OAR (creating a Planning Risk Volume, PRV), with careful patient monitoring. Our internal radiotherapy planning exercises have shown advantages for proton radiotherapy for tumours located close to the brainstem and/or optic apparatus. We are currently in the process of applying for treatment commissioning to enable the use of protons as a treatment modality in POBIG for selected patients (e.g. those with tumours located close to the brainstem).

In addition to its unique design, POBIG will offer the first in-human translational opportunity to evaluate the early effects of radiation on glioblastoma tissue. This is because part of the tumour will be excluded from the irradiation field to safeguard some tissue for pathological diagnosis and molecular profiling (cold spot). Irradiation will be preferentially administered to the tumour components that are unlikely to be removed and are therefore at high risk to recur (hot spot). Both of these regions will be differentially sampled in POBIG to characterize the irradiation profile of glioblastoma. Such data can help guide preoperative combined treatment strategies such as immunotherapy [20].

POBIG is a contemporary trial designed to intensify early time point therapy for glioblastoma. It will help establish the role of radiotherapy in preoperative modalities for glioblastoma, using advanced treatment and imaging techniques.

Design

POBIG is an open-label, dual-centre, prospective, single-arm phase I dose escalation trial. The trial is currently recruiting at two sites comprising Greater Manchester's regional brain tumour centre:

- Manchester Centre for Clinical Neurosciences, Northern Care Alliance NHS Foundation Trust, Salford Royal, Stott Lane, Manchester, UK.
- The Christie NHS Foundation Trust, Wilmslow Road, Manchester, UK (also trial sponsor).

Inclusion and exclusion criteria are shown in Table 1.

Endpoints

Primary objective

To determine MTD and MTIV of a single fraction of preoperative radiotherapy, given in addition to standard treatment, in patients with a new diagnosis of glioblastoma. MTD and MTIV will be determined by monitoring for dose-limiting toxicities (DLTs), defined as:

- Radiotherapy related swelling leading to a change of the scheduled date of surgery.
- Post-operative radiotherapy commencement delayed to beyond 6 weeks after surgery due to radiation-related symptoms and/or complications from surgery.
- Interruption of post-operative radiotherapy >5 days due to radiation related symptoms that could be attributable to the preoperative treatment.

Adverse events and DLTs will be scrutinised by the trial management group, dose escalation committee, sponsor and relevant clinicians from the neuro-oncology MDT.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria and justifications
• Age ≥35 years. • Male or female. • New radiological diagnosis of glioblastoma. • Performance status judged by World Health Organisation, Eastern Cooperative Oncology Group [ECOG] score = 0–1. • Case has been reviewed by Neuro-oncology multidisciplinary team (MDT – neurosurgeon, clinical oncologist, radiologist and pathologist); MDT consensus that offering study entry is clinically appropriate and safe i.e. patient unlikely to come to harm (e.g. hydrocephalus) from delayed surgery and pre-operative radiotherapy based on available clinical information and imaging. • Confirmation at first clinic visit that study entry is clinically appropriate and safe (e.g. lack of severe and debilitating symptoms of raised intracranial pressure). • Intention to treat with surgical resection and postoperative adjuvant therapy as per current standard of care (Stupp regimen). • Tumour size, location and configuration meet radiotherapy treatment planning criteria (e.g. to secure cold spot/hot spot, meets dose constraints for organs at risk when accounting for post-operative radiotherapy). • Adequate haematological and biochemical parameters for surgery and contrast agent administration (full blood count and coagulation profile deemed acceptable by clinical team, eGFR >30 ml/min). • Mental capacity to consent for treatment. • Able and willing to give informed consent.	• Planned biopsy procedure only. Suspicion of other tumour on CT body scan or known malignancy except non-melanoma skin cancer, completely resected cervical or prostate cancer (with Prostate Specific Antigen of less than or equal to 0.1 ng/ml) within the past 3 years. Contraindications to contrast-enhanced MRI scanning (e.g. claustrophobia, gadolinium allergy).

Secondary objectives

- To evaluate the accuracy of MRI to select patients with glioblastoma for preoperative radiotherapy without pathological confirmation.
- To evaluate the effect of preoperative radiotherapy on tumour growth between surgery and postoperative chemoradiotherapy (Rapid Early Progression, REP).
- To evaluate the effect of preoperative radiotherapy on survival: overall survival will be measured in months from the date of surgery to the date of death. Progression-free survival will be measured in months from the date of surgery to the date of first neuroimaging evidence of progression confirmed by consensus at the neuro-oncology multidisciplinary team meeting.
- To evaluate the effect of preoperative radiotherapy on the pathological and molecular profile of glioblastoma and relate these to clinical outcome. This objective will be assessed through a translational sub-study.

Treatment description

A flow diagram describing the study pathway and timelines is shown in Fig. 1.

Prior to preoperative radiotherapy

Our centres act as a single referral centre for brain tumours from the Greater Manchester region. Our weekly neuro-oncology MDT meeting (tumour board meeting) is attended by all clinicians involved in the treatment of patients with brain tumours including neurosurgeons and neuroradiologists with a subspecialty interest in neuro-oncology, neuro-oncologists, neuropathologists, neurologists, clinical nurse specialists and allied health professionals.

New referrals of suspected glioblastoma are screened at the MDT and potentially eligible patients are approached to confirm eligibility and provide study information. Patients that express an interest will be followed-up at a separate consent appointment the following week where study consent will be formally obtained. A separate study consent appointment is incorporated in our study design following feedback from both local and national patient and public involvement focus groups who participated in the study design. We observed that patients and relatives specifically requested a few days to process information before deciding to enrol in POBIG. Information presented to patients will follow recommendations from our patient focus groups and patient representative.

After enrolment, patients will undergo a computed tomography (CT) and MRI scan for preoperative radiotherapy planning. All MRI scans will include standard structural sequences (T1 pre/post contrast, T2 and FLAIR) and physiological sequences (diffusion and perfusion weighted imaging).

Preoperative radiotherapy

Preoperative radiotherapy will be delivered as photon-based Volumetric Modulated Arc Therapy (VMAT).

Preoperative radiotherapy treatment plans will be designed by consensus of the neuro-oncologist, neurosurgeon and clinical physicist to delineate an area of tumour that does not receive radiation (cold spot) and an area that receives the full dose of irradiation (hot spot), whilst meeting dose constraints for anatomical structures at risk when accounting for postoperative radiotherapy. The cold spot will receive less than 2 Gy and have a volume of at least 2 cm^3 with a 3 mm safety margin. Less than 0.2 cm^3 of the cold spot will receive a dose greater than this. The hot spot is defined as the area of the tumour that is deemed to be the highest risk for remaining as postoperative residuum and will only include tumour defined on T1 with contrast ± T2/FLAIR MRI sequences. An example of a radiotherapy treatment plan from the first patient is given in Fig. 2.

The preoperative radiotherapy treatment plan must meet dose constraints for OAR when accounting for postoperative adjuvant radiotherapy. OAR include the optic pathway and brainstem. Dose parameters of the OAR will be recorded prospectively by a qualified member of the research team or treatment team. Doses to OAR will be kept as low as possible during preoperative radiotherapy with a maximum dose of 4 Gy to the Planned Risk Volume (PRV = OAR + 2 mm; see Table 2). Patients who do not fulfil this criteria are excluded from the study.

POBIG is a dose/volume escalation trial with 5 radiotherapy dose levels (6 Gy, 8 Gy, 10 Gy, 12 Gy and 14 Gy) and three treatment volumes (<30 cm^3, 30–60 cm^3 and >60 cm^3). These dose levels represent the prescribed doses within the hot spot, and the volumes represent the hot spot planning treatment volume (i.e. no additional margins are considered). The minimum dose within the hot spot is 75 % of the prescribed dose level.

The study will commence with lower doses delivered to smaller treatment volumes. These lower doses are still clinically significant to exert cytotoxic/cytostatic effects as found in preclinical studies [22]. The dose levels follow the experience of preoperative radiosurgery for brain metastases, where studies have achieved doses of up to 14 Gy, albeit for smaller tumour volumes [14].

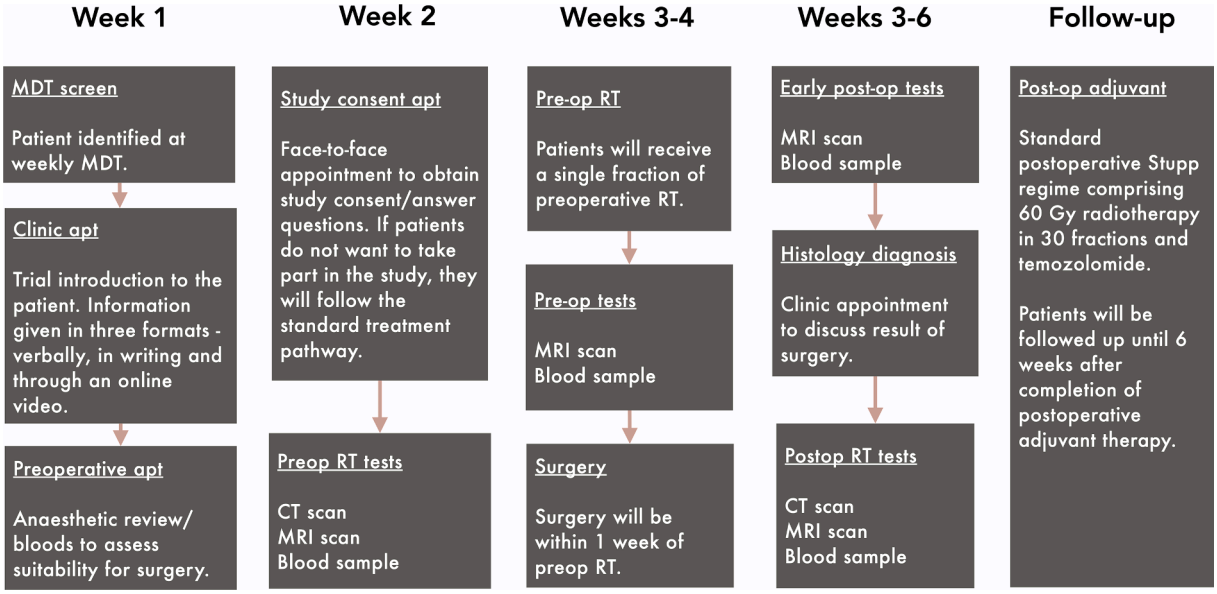

Fig. 1. Trial pathway. POBIG is a phase I dose/volume escalation trial that is testing the safety and feasibility of providing a single fraction of preoperative radiotherapy in patients with a new radiological diagnosis of glioblastoma. Our trial pathway has been developed in collaboration with local and national patient focus groups. Abbreviations: MDT = multidisciplinary team; preop = preoperative; RT = radiotherapy.

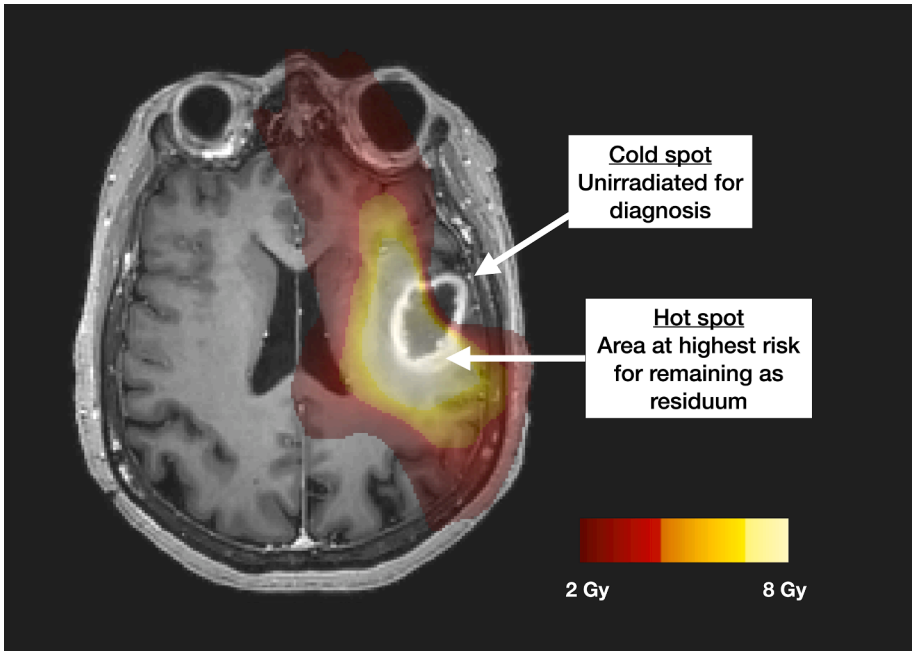

Fig. 2. Example of a POBIG preoperative radiotherapy treatment plan. A unique aspect of this trial is that part of the tumour is excluded from the radiation field for diagnostic sampling (cold spot). The area that is deemed highest risk of residual disease is given the full dose of radiation (hot spot). The preoperative radiotherapy dose delivered to the hot spot will vary from 6 to 14 Gy.

Outcome data for patients at a given dose level will be entered into a Continual Reassessment Method (CRM) model and the model output will guide dose and volume escalation.

Patients will also be administered prophylactic steroids alongside preoperative radiotherapy to reduce the risk of treatment related side effects. The dose of steroids will be at the discretion of the treating team (including the clinical oncologist and neurosurgeon) and judged on patient signs and symptoms.

Tissue and sample collection

Surgery

Patients will undergo neurosurgical resection within 7 days of preoperative radiotherapy aiming for maximal safe resection. Neurosurgical resection will employ conventional techniques including 5-ALA, intraoperative ultrasound, neurophysiology monitoring and neuronavigation. Intra-operatively, the radiotherapy treatment plan will be available to allow mapped sampling from the cold and hot spots. Image-guided biopsies will be obtained, and biopsy coordinates will be annotated on the corresponding preoperative MRI scan. Tissue from the cold

Table 2
Dose constraints for organs at risk in POBIG.

Organ at risk	Margin (PRV), mm	Max Dose (Gy)	Volume (cm^3)
Brainstem	2	4	0.2
Optic Nerve	2	4	0.01
Chiasm	2	4	0.01

spot will be used for diagnostic purposes.

Tissue

Tissue will be kept on ice until transport to pathology. A neuropathologist will assess the viability of each study sample and divide samples to be snap frozen and formalin-fixed, paraffin-embedded (FFPE) for future research purposes.

Blood samples

Patients will have trial blood samples taken at several points noted in Fig. 1.

Postoperative course and monitoring

If a tissue diagnosis of glioblastoma is established, patients will receive postoperative chemo-radiotherapy. This comprises 60 Gy postoperative radiotherapy delivered over 6 weeks with concomitant and adjuvant temozolomide.

Patients will be monitored at each visit for the development of DLTs and adverse events. Patients will be followed-up up to 6 weeks after completion of postoperative chemoradiotherapy. This time period for monitoring should allow adequate time to assess DLTs attributable to preoperative radiotherapy. Follow-up imaging after completion of postoperative treatment will utilise physiological MRI sequences (perfusion and diffusion) where possible to aid differentiation between disease progression versus pseudoprogression.

Patients will be monitored for the occurrence of dose-limiting toxicities, as outlined above. Other adverse events, such as those relating to the surgery, will also be recorded. Radiation toxicity will be scored according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [23].

A patient will be withdrawn from the study if the MRI scan performed for radiotherapy planning purposes raises doubts about the imaging diagnosis, if a histological diagnosis of glioblastoma is not established or if they lose mental capacity at any stage.

Patients can participate in other studies unless they could affect the DLTs described in POBIG. This means that patients cannot participate in studies evaluating dose modifications or systemic treatment during or before radiotherapy. Patients can participate in studies evaluating treatments in the adjuvant or recurrent setting.

Statistics

We will use a Continual Reassessment Method (CRM) model to inform our dose escalation and determine the MTD and MTIV. This is a Bayesian statistics-based model. It uses all available data from previous doses to guide dose escalation. The model uses the estimated rates of DLTs at each dose level and a target toxicity, which is the percentage risk of DLT that patients would be willing to accept. This data is used to guide dose escalation. The CRM has advantages over traditional approaches such as 3 + 3. Dose escalation will occur in increments from 6 Gy to a maximum dose of up to 14 Gy. Treatment levels in the CRM are shown in Fig. 3. The sample size depends on the MTD and MTIV achieved but is estimated to be around 18 patients according to CRM estimates.

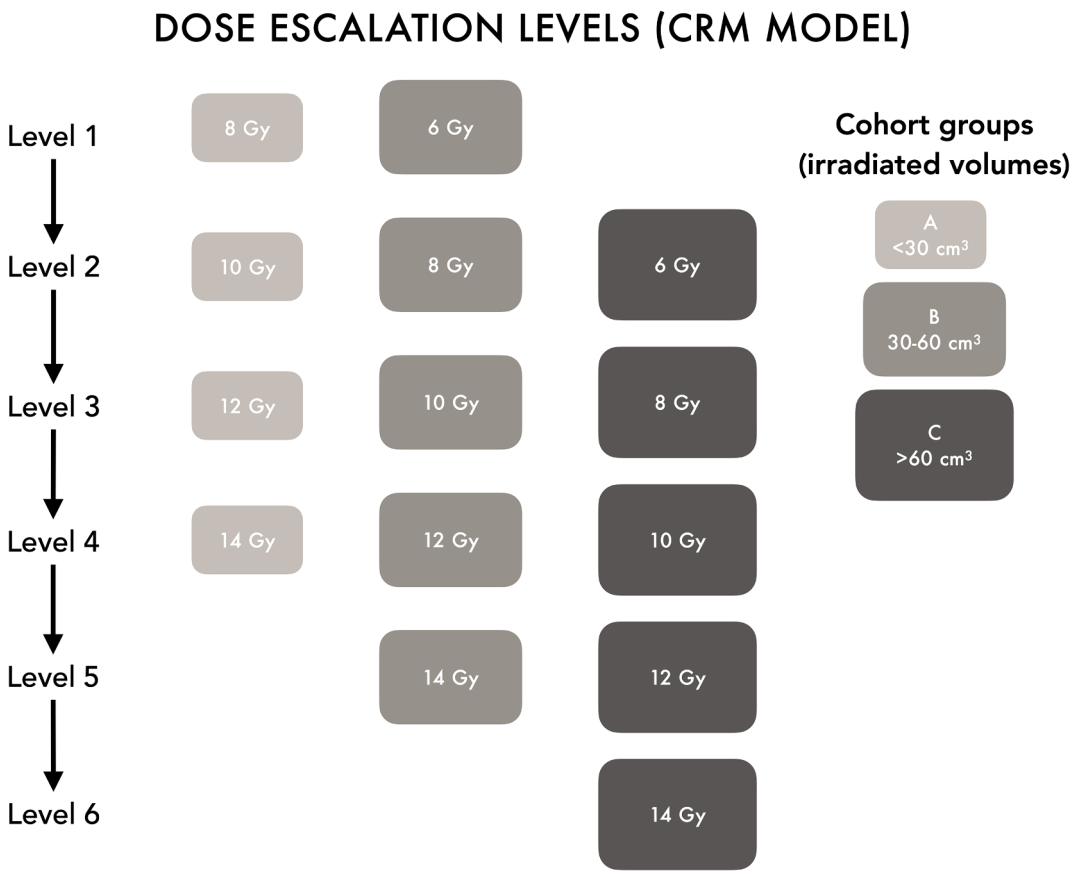

Fig. 3. Treatment levels in the Continual Reassessment Method (CRM) model. Cohorts will be opened dependent on radiotherapy dose and irradiated volume. We will firstly progress down treatment levels in the <30 cm^3 category before opening larger radiotherapy treatment volume categories.

The primary outcome will be reported in terms of MTD and MTIV. Secondary clinical outcomes will be reported as defined in the outcomes section – including OS, PFS and REP. For each of these outcomes, Kaplan-Meier survival curves will be plotted to ascertain survival statistics. A trial statistician (RJ) will aid in statistical analysis.

Planned timeline

The estimated duration of recruitment is 24 months with a completion date between 2024 and 2025. A premature discontinuation of the trial is possible in case of unforeseen toxicity or insufficient recruitment. An internal feasibility study at our centres suggests our recruitment target and timeline is feasible with an expected accrual of 1–2 patients per month.

Ethical and legal considerations

POBIG has received ethical approval (Greater Manchester South Research Ethics Committee, reference 21/NW/0121). Amendments are currently ongoing. Patients will be informed of the potential benefits and risks of taking part in this trial (including the risk of misdiagnosis, delay in surgery and preoperative radiotherapy itself). Informed consent will be taken from patients after they have had adequate time to read through study information and watch an online video [24] at a dedicated consent appointment.

Data will be collected by study investigators and stored pseudonymized electronically in a study specific database. All Investigators and site staff involved with the study will comply with the requirements of The Data Protection Act 2018 and General Data Protection Regulations 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The research team have completed Good Clinical Practice (GCP) and trial monitoring is being performed independently by a Clinical Trials Unit (Liverpool Clinical Trials Unit). Any personal data recorded will be regarded as confidential, and any information which would allow individual participants to be identified will not be released into the public domain.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: POBIG is funded by UK Research and Innovation Medical Research Council (UKRI MRC). The research program of GB (Chief Investigator, senior author) is supported by Cancer Research UK RadNet Manchester.

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