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UK Neuro-Oncologists and multidisciplinary colleagues are developing a trial for patients with good prognosis glioma comparing quality of life (QOL) and the long term effects of radiotherapy between patients treated with proton beam therapy (PBT) and modern, state of the art image guided intensity modulated photon radiotherapy (IMRT). Patients with glioma differ in important ways from other oncology patients and this may have important implications for this and other studies. Patients frequently report symptoms including headaches, seizures, personality and memory changes and often have complex neurological deficits affecting language, cognition and motor function [1,2]. These can have significant practical implications impacting on daily activities, communication and driving and patients are often reliant on carers and public transport for travelling [3,4]. Furthermore, patients are often young, in employment and with caring responsibilities of their own. The feasibility of running randomised studies evaluating PBT in patients with glioma is an important consideration, particularly in respect of participants' views of a randomised design and the requirement for treatment at national centres. The value of patient and public involvement at an early stage in the development of research studies is well recognised in helping shape research proposals, making them more patient-centred and supporting recruitment [5,6].

Patients with good prognosis 1p19q co-deleted oligodendroglioma have relatively favourable outcomes following radiotherapy and chemotherapy. A recent randomised study in low grade glioma (LGG) demonstrated a median overall survival of around 13 years, with significantly better survival in the subgroup of 1p19q co-deleted oligodendroglioma [7]. Similar survival has been shown for grade III 1p19q co-deleted oligodendroglioma with combined modality treatment [8,9]. Radiotherapy remains a key component of the treatment of these tumours but is associated with long-term side effects including neurocognitive decline and endocrinopathies [10–12], which adversely affect QOL [13]. Exposure of normal brain tissue even to low doses of radiation has been shown to affect neurocognitive function in patients with LGG [14,15] and radiotherapy dose comparison studies have demonstrated superior sparing of normal brain structures with PBT compared with IMRT [16,17]. Small numbers of prospective non-randomised cohort studies have demonstrated proof of concept for PBT in patients with glioma but there is no randomised research evidence favouring PBT over conventional photon radiotherapy [18–20]. Significant capacity is available within the UK NHS PBT clinical service for clinical trials and with its track record in leading practice-changing clinical trials in radiotherapy, there is an expectation that the UK will be at the forefront of expanding the evidence-base for the use of PBT [21].

To ensure our trial is sensitive to the needs of participants and provides research outcomes that are relevant to patients, we have involved patients and their carers in the design of our trial at the outset. We conducted a focus group, the main aims of which were to explore acceptance and

willingness for randomisation and patient and carer equipoise, as distinct from medical or societal equipoise. The treatment pathway within our trial will mirror that of the phase III randomised trial of PBT in oropharyngeal cancer (TORPEdO), whereby patients randomised to photon radiotherapy will receive this at their local treatment centre but those randomised to PBT will travel to Manchester or London [22]. Patients who had completed radiotherapy treatment for WHO grade II or III oligodendroglioma at least two years previously, and their carers, were invited to our focus group in Manchester in November 2018 and 15 patients and carers participated in total. The workshop consisted of a series of discussions and presentations centred around 5 questions based on those used by the recently reported TORPEdO trial focus group [22]. Information sheets about our proposed study design, neurocognitive assessments and the EORTC QOL questionnaires were also discussed (Table 1).

We encountered fewer pre-conceptions relating to PBT than we expected. Many patients had seen stories about PBT in the media and explained that their views on PBT had been shaped by these. Patients demonstrated an awareness that PBT was a more targeted form of radiotherapy but were uncertain whether PBT was more effective than standard radiotherapy at treating tumours. There was also an awareness that some patients and children in the UK are currently treated with PBT overseas.

Patients and their carers expressed clear support for the trial, and its clinical rationale. Patients positively highlighted the opportunity to access PBT within a clinical trial and demonstrated a clear understanding and appreciation for the need to randomise individuals between two treatments to allow a comparison of the treatments in an unbiased fashion. The group clearly stated that randomisation should give an equal chance of obtaining one treatment or the other, specifically favouring 1:1 randomisation. Patients suggested that equal randomisation would reinforce clinical equipoise and to do otherwise was unfair and may give the impression that one treatment was favoured over the other. The primary endpoints of this trial will be comparisons of QOL measurements using standard EORTC QOL questionnaires (C30 and BN20) [23,24] and neurocognitive assessments between PBT and photon radiotherapy. Participants agreed that these were important measures and considered these outcomes to correspond closely with their own priorities.

We discussed terminology and participants considered that the word ‘trial’ indicates uncertainty in the quality or standard of the treatment being offered and implied an element of experimentation, both of which they knew not to be the case. Participants also disliked the word ‘tests’, considering that this implied a right or a wrong answer with a requirement to pass or succeed in the assessment, which may increase anxiety. Overall, patients’ preferred terms were ‘comparison’, ‘research study’ and ‘cognitive assessments’ and we will use these in all patient-facing literature related to this work.

Participants made the important observation when reviewing the C30 and BN20 QOL questionnaires that these did not adequately reflect some important aspects of daily wellbeing and fatigue. For example, there was a specific observation that questionnaires did not address "difficulty getting going in the morning, which causes frustration and impacts significantly on family life, work and mood". The fact that assessments currently considered as gold standard do not always address areas that patients consider important is worthy of further reflection. We will incorporate these suggestions by including additional questions in our QOL assessments, strengthening the trial and adding validity to the key QOL endpoint. Patients stated they would be happy to complete questionnaires "for as long as necessary" and participants asked whether questionnaires should also be given separately to carers for their perspective, which we will incorporate.

Travelling for PBT and the potential requirement for accommodation during PBT was clearly identified by the focus group as the biggest potential barrier to trial recruitment. Whilst some participants would have been prepared to travel and stay over for their treatment, it was acknowledged that individual personal circumstances would dictate the ability of patients to do this. This could exclude certain groups from trial participation, which participants identified as a potential source of bias. Patients highlighted concerns that travelling for treatment may impact work and family life, and disrupt support networks during treatment.

Specific concerns about fatigue and expense of travel were expressed and participants voiced that reimbursement of travel costs is essential because without this some patients may find it impossible to undertake PBT, introducing lack of equitable access and the possibility of biasing the trial results. The need for adaptability and flexibility with choices of accommodation, travel and treatment times, particularly around holiday times, at the PBT site were highlighted. Patients considered it important for trial participants to be made aware of potential contingency plans for machine breakdown and the potential requirement for weekend treatments at the outset. There was also a concern that when patients are staying away from home at the PBT site, they may prefer, and need, a carer to stay with them, potentially creating difficulties for couples with children at home.

Patients strongly endorsed and supported our proposed trial and participants positively highlighted the opportunity to access PBT within a clinical trial providing a mandate from patients and their carers to continue developing this trial. Patients with brain tumours often have complex neurological deficits that can affect cognition and ability to drive, making patients dependent on their support network, particularly at the time of treatment. It is therefore important to acknowledge and discuss the specific needs of patients with brain tumours separately as these differ from those of patients with other types of cancer. This focus group was an invaluable opportunity to help guide our

trial design and we believe our trial will be stronger and more relevant to patients, carers and health professionals as a result of this engagement.

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