Patient involvement in the design of a phase III trial comparing IMPT and IMRT for oropharyngeal cancer

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For patients with favourable risk human papilloma-virus associated oropharyngeal cancer, local control and survival outcomes are excellent [1]. However, despite the use of highly conformal intensity-modulated radiotherapy (IMRT) severe acute and late side effects are common, adversely impacting quality-of-life. Compared with photons, the superior dosimetric properties of protons with sharp lateral penumbra and distal fall-off reduce the radiation dose beyond the target volume and may lessen treatment-related toxicities such as: oral mucositis, dryness, taste disturbance, swallowing dysfunction and osteoradionecrosis. However, there are only preliminary observational data to support the clinical advantage of proton beam therapy for oropharyngeal cancer [2–5], and prospective randomised trials are needed. An on-going phase II/III study (NCT01893307) from the MD Anderson primarily aims to compare rates of late grade 3-5 toxicities between IMRT and intensity-modulated proton therapy (IMPT) for oropharyngeal cancer (https://clinicaltrials.gov/ct2/show/NCT01893307, accessed December 2017). The UK proposes to open a multi-centre phase III study (TORPEdO, TOxicity Reduction using Proton bEam therapy for Oropharyngeal cancer) to assess the benefit of IMPT in terms of patient reported toxicities and quality-of-life and, as a secondary objective, cost-effectiveness.

Approximately 700 of the 1500 funded annual capacity for two planned NHS UK proton beam centres (The Christie Hospital in Manchester opening August 2018, and University College London Hospital opening 2020) will be available for either clinical trials or evaluative commissioning. The UK, with an established strong track record in delivering major practice

changing clinical trials in radiotherapy e.g., PARSPORT, START and CHHiP [6–8] aims to be at the forefront in establishing the evidence-base for the use of proton beam therapy.

Patient and public involvement in the early stages of trial design increases the success of a study in terms of its feasibility and acceptability to patients, thereby supporting recruitment [11–13]. We conducted three focus groups in Manchester, Leeds and Sheffield to understand patients' views about the proposed TORPEdO trial, including acceptability of randomisation, the patient pathway when enrolled in the trial, willingness to travel and stay in Manchester or London for proton beam therapy and the trial design and endpoints. Fifteen patients with favourable risk oropharyngeal cancer who had completed radiotherapy ≥1 year ago were identified and invited to participate from each centre. Overall 33 out of the 45 invited patients and eight relatives attended the focus groups between September and October 2017. Each session lasted two hours and consisted of presentations and discussions structured around a series of questions (Table 1). Information was recorded on pre-prepared laminates, patient questionnaires, audio recordings and by telephone or email contact with a sample of patients following each meeting. Data were interpreted using thematic analysis.

Table 1. Questions asked during the focus group

All Centres	Additional questions for Leeds and Sheffield
What do you think are the differences between standard radiotherapy and proton therapy?	What are your views on travelling and staying in Manchester if you are offered proton beam therapy as part of the trial?
How do you feel about entering a study where there is a 50% chance of getting standard radiotherapy and a 50% chance of getting proton therapy?	
What are your views on the trial pathway?	
What are your views on the trial outcomes?	

Opinions were sought on the name of the proposed study in Manchester. 'TORPEdO' was thought to be concise, easy to remember and would not deter trial participation. Existing knowledge about proton beam therapy was variable. Some described protons as a more targeted therapy with less toxicity, whilst others knew very little but had heard the term protons described in the media. In general, people considered protons to be a superior treatment and had some understanding of the differences compared with standard photon

radiotherapy. There was enthusiasm to participate and be randomised in the study, to both help future patients (inform future treatments) and have a 50% chance of receiving IMPT (the patients were informed that proton beam therapy would not be available as an NHS treatment outside the clinical trial). Some expressed that they would be disappointed if randomised to IMRT, but this would not deter them from considering the trial. Reassurance was provided that it remains uncertain in this situation whether any potential dosimetric superiority achieved with proton planning translates into clinical benefit for patients i.e., the presence of clinical equipoise. The patient pathway and trial layout were viewed positively. In Sheffield and Leeds, the timings at each stage of the pathway were discussed e.g., the timings from study enrolment to randomisation. To allow sufficient preparation for those receiving IMPT in Manchester or London, people felt the time interval between each stage of the patient pathway should be minimised (e.g., time from clinic to outcome of randomisation; time from randomisation to travel to Manchester or London). Patients reported that they would need information about the proton centres and provision of support when considering taking part in the trial.

We sought to understand peoples' views on the logistical challenges in relation to travel and accommodation if randomised to IMPT. This was particularly pertinent for those living in Sheffield and Leeds. There was a general willingness to travel to Manchester for treatment planning and delivery, which was balanced against missing family and established social networks. Feelings were mixed in relation to staying in Manchester for the duration of treatment with IMPT. The preferred option was to stay in Manchester in apartment based accommodation close to the hospital during the week with the option of returning home at the weekends. This preference was thought to be achievable with adequate family, clinical and nursing support. Some raised the possibility and feasibility of daily travel if continuing to work or due to childcare responsibilities. Many patients felt it important for a relative or carer to stay during treatment to provide both emotional and social support. Participants felt that, as far as possible, the accommodation should be tailored to individual's needs e.g., providing reliable / fast internet access to be able to contact family or equipment / toys for children. Easy access to shuttle transport between the apartment and the hospital was highlighted to avoid potential unnecessary anxiety caused by inadequate hospital parking. All patients and relatives emphasised the importance of ensuring adequate support for those randomised to IMPT which included: telephone or face-to-face contact with a clinical nurse specialist, speech and language therapist and dietician.

Patients' views of toxicity as the primary outcome measure were discussed. In general participants felt this to be an appropriate and useful measure. We sought to understand the

side effects experienced by patients six weeks and one year post treatment. Following this, we explored views on the patient reported outcome questionnaires that we plan to use in the study. We asked opinions about the University of Washington questionnaire as a tool to collect outcome data at different time points. The questionnaire consists of 15 single domains divided into six physical, six socio-emotional and three global questions, which have been validated for use in head and neck cancer trials [14]. To understand if the six physical questions that make up the composite score for the primary outcome measure of the trial were relevant, we compared the side effects that patients reported as the most important to them with those measured by the University of Washington questionnaire. Of those reported four of the six physical symptoms (loss of taste, oral dryness, swallowing dysfunction and problems chewing) on the University of Washington scale, were described as the most important side effects one year after treatment. The acceptability of the questionnaire was assessed using a written feedback form, which was completed by 30/33 (91%) patients. Twenty-eight (93%) of the patients thought the six physical questions were a good primary outcome measure for the trial. All patients stated the questionnaire and the scale were clear. Twenty-eight patients (93%) thought the areas covered were relevant. Hearing loss was the most common missing symptom, highlighted by 5/30 (17%) patients. Other reported missing symptoms (for the primary outcome composite score) were: psychological issues (n=2) fatigue (n=1) and bone damage (n=1). Nine patients (30%) thought free text boxes were needed. All considered the frequency of completion of questionnaires over five years follow up to be appropriate and feasible. The favoured method of completion of the questionnaire varied: on paper in clinic (12/37; 32%), on paper at home (11/37; 30%), on a tablet in clinic (8/37; 22%) and online (6/37; 16%).

This was an important piece of work to understand patients' and carers perceptions about the first proposed proton trial in the UK. The feedback on the patient pathway and logistics was encouraging for the feasibility of the study and is invaluable in shaping the trial design.

Conflict of Interest

There are no conflicts of interest.

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