Response to ‘Position statement on ethics, equipoise and research on charged particle therapy’

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ABSTRACT
In August 2011, a group of medical doctors, ethicists, academic and medical physicists were asked to debate and reach consensus on the potential need for randomised control trials to test charged particle radiation therapy (CPRT) for treating tumours. The outcome of the meeting was a paper recently published in the Journal of Medical Ethics entitled “Position statement on ethics, equipoise and research on charged particle therapy” by Sheehan et al. However, 6 of the 30 meeting participants withdrew from authorship of the ‘position statement’ because their views were not adequately represented. The ‘position statement’ did not state our reasons for withdrawing from the statement, which is a considerable omission. We had two principal objections: (1) the case for the benefits to patients and society of randomized trials to test CPRT was not adequately represented, and (2) the complexities and potential harms of CPRT were not clearly stated. In this response we explain and justify our objections. Patients, doctors and policymakers seeking to make independent judgments about whether equipoise exists for the relative benefits of CPRT should therefore read this document alongside the ‘position’ statement.

In total, 6 of the 30 meeting participants withdrew from authorship of the ‘position statement’ because their views were not adequately represented. The Sheehan et al paper did not mention the reasons for our withdrawal, which is an important omission. We had two principal objections (see Box 1 for complete list). First in the “Methodological and evidential considerations”, Sheehan et al omitted our key point: unless sufficiently large benefits relative to conventional photon radiotherapy (X-rays) can be demonstrated empirically, randomised trials comparing CPRT with conventional radiotherapy are warranted. Such trials should involve clinically important outcomes such as survival and morbidity. Our views are informed by the fact that many promising new medical interventions, even those with persuasive rationales, have turned out to be disappointing or harmful when subjected to randomised trials. Potential harms of CPRT include the danger of missing a target (potentially damaging other tissues) and lack of robustness. Perhaps more importantly, the randomised trials that have been conducted failed to show a benefit of CPRT over conventional radiotherapy.

In the body of the text, Sheehan et al addressed the issue of whether randomised trials are necessary in the following way:

Where the dose distribution with CPRT is substantially improved and suggests substantial superiority to other treatments and existing clinical results suggest significant superiority, a RCT would be neither necessary nor appropriate... where predicted differences [between CPRT and conventional therapy] are small... a RCT may be clinically unrewarding and a poor use of resources.

The term ‘significant’ in this context is misleading given the common use of the term to denote statistical significance. More importantly, neither statistical significance in an observational study nor observational evidence about different dose distributions is sufficient to preclude the usefulness of randomised trials. In addition, contrary to what they state, randomised trials are beneficial precisely when predicted differences are small. If CPRT had a small apparent benefit compared with conventional radiotherapy in an observational study, a less biased test (such as a randomised trial with allocation concealment and blind outcome assessment) could reveal no differences, or indeed a small benefit of conventional radiotherapy. This is because well-documented biases (especially selection bias) in observational studies can influence the size and direction of apparent effects.

Confusing the case for equipoise further, Sheehan et al misrepresent the evidence for CPRT. They state: “Published clinical series suggest some clinical benefit from CPRT in a number of conditions when compared with current conventional X-ray techniques”. They then use this statement to conclude (later in the same paragraph) that “the available clinical results have important implications in that they may influence the judgment of individual clinicians and could disturb clinical equipoise, while also possibly influencing patients’ views”. It is true that available evidence should influence patient and physician judgements about whether equipoise exists. However, they only cite a single study for their conclusion (Terasawa

Box 1 Key omissions and misrepresentations in Sheehan et al “Position statement on ethics, equipoise and research on charged particle therapy”

▶ In the key methodological recommendations, the following point was omitted: unless sufficiently large benefits relative to conventional X-ray radiotherapy are demonstrated, randomised trials are warranted.
▶ Relevant technical details and complexities of charged particle radiation therapy were inadequately stated (see online supplementary appendix).
▶ Relative harms of particle therapy were not mentioned: potential gains can be offset by (a) the danger of missing a target (and damaging other tissues) and (b) lack of robustness.
▶ The Sheehan et al paper does not specify the need for rigorous (non-randomised but carefully controlled) international studies comparing particle therapy with conventional therapy.
et al)\(^6\); a single cited study does not represent ‘available clinical results’. Moreover, the conclusion Sheehan et al draw from the cited study does not match what the study itself reports. In fact Terasawa et al conclude that

several studies of charged-particle radiation therapy for cancer have been published. However, these studies do not document the circumstances in contemporary treatment strategies under which radiation therapy with charged particles is superior to other modalities. Comparative studies in general, and randomized trials in particular (when feasible), are needed to document the theoretical advantages of charged-particle radiation therapy in specific clinical situations.\(^6\)

The Sheehan et al paper also states: “In rare tumour entities, low patient numbers may limit the practicalities of RCTs”. They do not proceed to specify the need for rigorous (non-randomised but carefully controlled) international studies comparing particle therapy with conventional therapy.

The need for rigorous evaluation in randomised trials is also salient given the far greater cost (to individuals and society) of CPRT compared with conventional radiotherapy.

The second main reason for our disagreement with the Sheehan et al paper is that CPRT is more complex and less certain than their paper reveals (see online supplementary appendix for a detailed list of these complexities). These complexities need to be understood to develop and optimise particle therapy further so that clinical benefits can be realised, and to make decisions about what kind of research is required.

Inclusion of our points would have represented a true consensus document. As it stands the Sheehan et al paper does not provide an adequate ‘platform for future research’ and represents the position of a select group of authors. Patients, doctors and policymakers seeking to make independent judgments about whether equipoise exists for the relative benefits of CPRT should therefore read this document alongside the ‘position’ statement.

CPRT is an incredible technology with the potential to improve the treatment of malignant tumours. Only rigorous empirical research and evaluation will help identify the diseases, patient groups and circumstances in which such potential can be realised.

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