Editorial

Methodological Considerations in the Evaluation of Radiotherapy Technologies

N.G. Burnet *, L.J. Billingham †, C.S.K. Chan ‡, E. Hall §, J. Macdougall †, R.I. Mackay ††, T.S. Maughan ‡‡, C.M. Nutting ‡***, J.N. Staffurth ‡‡‡, T.M. Illidge ‡‡‡ on behalf of the National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group Executive Group

* University of Cambridge, Department of Oncology, Addenbrooke’s Hospital, Cambridge, UK
† MRC Midland Hub for Trials Methodology Research and Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, UK
‡ National Cancer Research Institute, London, UK
§ Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, UK
¶ Christie Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, UK
|| Gray Institute for Radiation Oncology and Biology, University of Oxford, Oxford, UK
*** The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK
**** Institute of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, UK
††† School of Cancer and Imaging Science, University of Manchester, Manchester, UK

Received 28 May 2012; accepted 18 June 2012

Introduction

Radiotherapy is a high technology discipline and this is increasingly the case in the modern era. In keeping with other technology-dependent treatment modalities, radiotherapy is constantly evolving, often by small but discernible increments. It is important to adopt developments that will improve patient outcomes, as over 90,000 patients receive radiotherapy with curative intent in the UK each year. However, there are major challenges around the best ways to evaluate such developments, which have parallels in other specialties, such as surgery [1]. The challenges relate partly to the complexity of the radiotherapy process, with multiple inter-related steps, the stepwise nature of technological innovation and the complex dose–effect relationships of tumours and normal tissue. Thus, there are important differences in the way radiotherapy research and development needs to take place compared with the well-established research pathway for an investigational drug [2].

The need to consider how to evaluate new radiotherapy technology motivated a workshop on ‘Approaches to the Evaluation of Rapidly Evolving Radiotherapy Technologies’, delivered by the Clinical and Translational Radiotherapy Research Working Group (CTRad) and supported by the Medical Research Council in 2010 [3]. This workshop highlighted a number of key issues and themes, summarised below, with many of the solutions requiring further work.

The Approach to Radiotherapy Research and Evaluation

The more complex a treatment or intervention, the more difficult evaluation becomes, and the more imaginative the approach to choosing methodologies for effective evaluation must be. The randomised controlled trial (RCT) has been the cornerstone of clinical evaluation over a long period, and remains the best method for avoiding bias and providing methodological and intellectual rigour in the results if powered correctly. RCTs have provided important clinical results for new radiotherapy technology, including conformal radiotherapy [4] and more recently intensity-modulated radiotherapy [5], proving that a reduction of a high dose to normal tissues reduces toxicity, and endorsing the concept that dose can be a biomarker for outcome.

Concerns are sometimes raised about the need or appropriateness of using RCTs as a tool to evaluate developing radiotherapy technology. The first common point of discussion is that differences observed in the new technology are deemed by the community to be so large that an RCT would be inappropriate and unnecessary. However, the size of such an effect must be large enough to reliably exclude bias from confounding factors. A relative difference of 10 times in the rate of an effect has been suggested as...
comfortably large enough [6]. This difference is unrealistically large in the context of clinical radiotherapy. For example, the improvement in 5 year biochemical local control comparing 74 Gy with 64 Gy in the RT01 trial gives a ratio of only 1.2, for a clinically worthwhile gain (71% versus 60%) [7]. Similarly, the reduction in 2 year xerostomia from the use of intensity-modulated radiotherapy in the PARSPORT trial (83% reduced to 29%) achieves a ratio of only 2.9, despite providing a valuable clinical gain for patients [5].

The second point relates to clinical equipoise. In order to conduct an RCT ‘ equipoise’ must be considered to exist, whereby there is reasonable, professional uncertainty about the outcomes of different treatments [8]. Two important philosophical aspects of equipoise are relevant: first, it is entirely possible for there to be strongly polarised views between individual clinicians, but that overall there is equipoise within the broader community. Second, lack of evidence can be grounds for reasonable disagreement, and therefore equipoise, because of society’s moral and financial interests in high-quality evidence [9]. This last consideration may be important in the approach to evaluating new technologies, such as proton beam therapy, and argues that RCTs may be more ‘possible’ than sometimes appreciated.

However, there are genuine limitations with RCTs, as explained eloquently by Rawlins [10] and others [11] and there is a need to diversify, develop and embrace alternative approaches to evaluation. Observational studies or decision modelling may be more appropriate and cost-effective in certain situations. The Medical Research Council has also identified that alternative methodologies to the RCT may be necessary and appropriate for evaluating interventions considered to be complex [12]. Radiotherapy can be considered to fit the definition of a ‘complex intervention’, with the complexity arising from the multiple interacting components requiring feedback between them, the need for expertise from different professional groups, the variable effect from changes in total dose, dose per fraction, overall treatment time, and the relative biological effectiveness (RBE) for protons or other light ions. This needs to be better understood by funders and decision makers, as well as the professionals involved in developing evaluation studies.

Since the earliest use of radiotherapy, some key advances have been made based on an engineering paradigm. For example, megavoltage equipment was clearly seen to achieve vastly greater depth penetration and skin sparing than orthovoltage X-rays, and the change was made without the need for an RCT. Other examples include the improvements seen with replacement hips, metal heart valve replacements and the use of computed tomographic imaging. Nevertheless, it is entirely appropriate and good practice to evaluate developments in techniques or technologies. If we accept that the RCT is not always the correct methodology, the challenge is to find the best approach, and this requires further work.

Radiotherapy-specific Trial Design

For maximum value, radiotherapy trials need two separate end points, arguably co-primary end points, to define the rates of tumour control and late toxicity, and hence the therapeutic ratio [13]. For trials of radical radiotherapy in potentially curable tumours, it is usual to need 10 years of follow-up to ensure robust estimates for both end points. The requirement for such longevity to collect late outcome data is currently poorly addressed, seems to have low priority with research funders, and may also present a tension with primary care trusts, who are arguing for early discharge from oncology clinics [14].

Trials testing new technology can be designed to use a single end point of toxicity. Large reductions in sample size might be expected, but such trials are typically underpowered to look for equivalence or non-inferiority in tumour control. This illustrates a genuine dilemma, as the reduced toxicity end point can be proven with small numbers, but equivalence in tumour control may require hundreds or thousands of patients. With careful design, a technology question can be embedded in a large RCT, which is addressing different questions, to make use of the detailed toxicity data collected in the trial. A good example to illustrate this point is the image-guided radiotherapy substudy embedded in the CHHiP trial.

In all radiotherapy trials, quality assurance is vital, as the quality of the radiotherapy can affect the trial outcome. In a recently reported head and neck trial [15], the effect on outcome of poor adherence to strict protocols overwhelmed the effect of the drug being tested. It is enormously important that the Radiotherapy Trials Quality Assurance group has successfully obtained centralised funding to underpin radiotherapy research activity.

Phase I studies including radiotherapy can be frustratingly slow to complete recruitment. In part, this is because acute toxicity does not necessarily predict late toxicity, so there is a need to wait between study cohorts to exclude serious complications. An imaginative approach is to conduct parallel studies in which a second novel agent is assessed, while awaiting outcomes from the first combination, the so-called flip-flop design. This has been done for drug–radiotherapy combinations using different novel agents [16], but has thus far not been applied to phase I radiotherapy trials alone. Alternatively, the time-to-event continual reassessment method is designed for late-onset toxicities, making it an efficient design for phase I radiotherapy trials [17].

Conclusions

The complexity and pace of technological advances in radiotherapy make careful choice of methodologies essential. Although the RCT remains the cornerstone of evaluation, developing additional approaches not only has academic value, but is also necessary if we are to make progress in improving outcomes for patients. Currently, the UK has unprecedented opportunities to develop and deliver international leading radiotherapy trials under the auspices of the National Cancer Research Institute CTRad group.
Acknowledgements

Many of the concepts described here resulted from the Methodology Workshop on ‘Approaches to the Evaluation of Rapidly Evolving Radiotherapy Technologies’ delivered by CTRad and supported by the Medical Research Council, 27 May 2010 in London. Our thanks to all those involved in the workshop (listed on the website [3]). We are grateful to Dr Charlotte Coles, Dr Simon Thomas and Ms Kate Burton for helpful discussions. Dr Neil Burnet is supported by the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre. Professor Lucinda Billingham is supported by the Medical Research Council (grant number G0800808).

References