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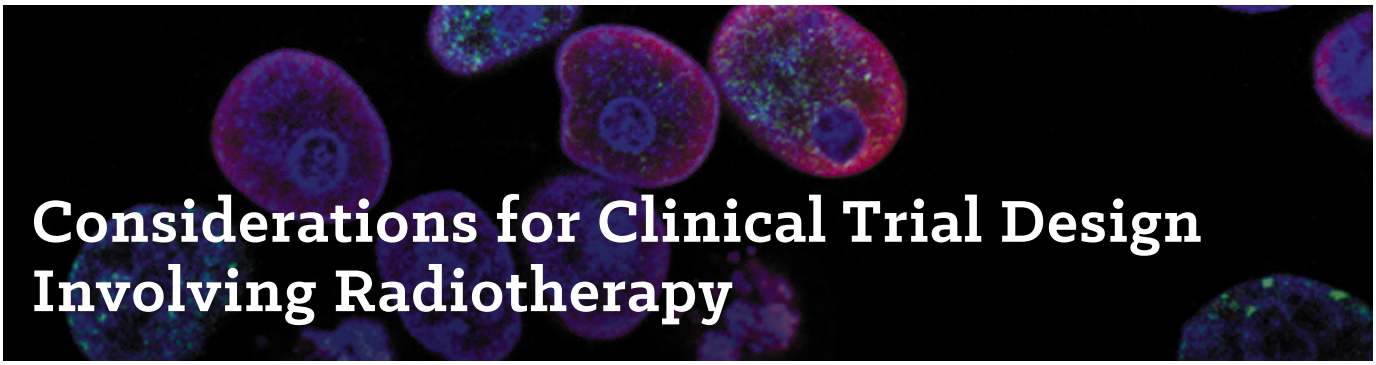

Considerations for Clinical Trial Design Involving Radiotherapy

Radiation therapy has been used for many years as an effective form of treatment against many cancer types; yet it remains less well researched and utilised than other well-known cancer therapies such as chemotherapy.

Radiotherapy works to shrink or completely eradicate cancer cells with the aim of reducing the risk of recurrence or to cure the cancer completely. When used in this setting, the intent is known as "radical" or "curative" treatment. Radiotherapy can also be given in the palliative setting when a cure is not possible to relieve symptoms caused by the cancer.

Radiotherapy can be used alone or in combination with other treatments such a chemotherapy, which is known as chemo-radiation. It is also often given prior to (neoadjuvant) or post (adjuvant) surgery. It is a very versatile treatment coming with its own nuances compared to other commonly used cancer therapies such as chemotherapy, surgery, and immunotherapy.

The amount or dose of radiotherapy delivered is measured in grays (Gy) per fraction. For example, a patient treated with 62Gy in 28 fractions would receive 2.2Gy of radiotherapy per fraction/administration. Typically, patients would receive one fraction per day, Monday to Friday.

These differences need to be well understood when it comes to designing and conducting clinical trials of radiotherapies, meaning trials for radiotherapy, can require unique strategies and methodologies, and can often present challenges not faced in other settings.

This article will focus on some of these challenges faced in general across all clinical trials involving radiotherapy, followed by a closer look at the different trial phases.

General Considerations for Radiotherapy Trial Design

When designing radiotherapy clinical trials, there are some general considerations to be aware of, among them:

- **Access to treatment**
  Radiotherapy machines are not always available on a local level. This is particularly the case for newer forms of radiotherapies such as intensity modulated radiotherapy (IMRT) and proton beam therapy (PBT). Therefore, feasibility of recruitment and the generalisability of the trial results need to be considered, particularly when it comes to conducting large scale definitive trials. More novel and efficient trial designs need to be considered to optimise the availability of patients.
- **Assessment of adverse events and duration of follow-up**
  Side-effects from radiotherapy come in the form of short-term and late/long-term effects. The definition of these will differ between cancer types, but short-term side-effects are typically those experienced during and up to 6 weeks after the end of treatment. Whereas late/long-term side effects can present or still be present years later depending on the type of radiotherapy given and cancer being treated. Therefore, it's important that clinical trials incorporate sufficient follow-up for toxicities and patient reported outcomes to fully capture the extent of the incidence and duration of these side-effects. A variety of methods for data capture should be considered including the use of electronic devices and follow-up phone calls to try and maintain compliance throughout the duration of the study.
- **Bias**
  Minimisation of bias (e.g., selection, attrition, and assessment bias) is a key consideration for all clinical trials. However, radiotherapy can bring some additional challenges. Radiotherapy technology is continuously advancing, and newer forms of treatment such a PBT, have been subject to much interest in the media. External biases such as these could impact the equipoise of a patient when considering participation in a trial and feasibility of randomisation should the patient have a strong treatment preference. This must be carefully addressed through unbiased patient-facing material and training of participating site staff.

  Another consideration is the feasibility of 'blinding'. Unlike many cancer drugs, depending on the comparator, it may be more difficult to blind a patient to treatment allocation with radiotherapy, again increasing the risk of bias within the study. This could be minimised by ensuring assessments are conducted independently and blind to treatment allocation where feasible.

Considerations for Phase I Trials

The main aim of Phase I trials (sometimes known as "first-in-human trials") are to establish the safety of a treatment and recommended dose level for further evaluation at Phase II. This will usually involve treating small cohorts of patients in escalating doses until the 'maximum tolerated dose' (MTD) is determined i.e., the highest dose of a drug or treatment that does not cause unacceptable side-effects. These unacceptable side-effects are known as dose limiting toxicities (DLTs) and require patients to be followed up for long enough to be able to observe any DLTs, which may prevent escalation to the next dose level. Typically for drug trials, patients are usually observed for DLTs during their first cycle of treatment e.g., 4–6 weeks. But radiotherapy trials require a longer period of follow-up to ensure DLTs, many of which will occur post-treatment, are observed.

Many Phase I 'rule-based' designs, such as the Standard 3+3 Design and Accelerated Titration Design, require all patients within a cohort to be followed up for the same length of time before assessing the potential for dose escalation. In the radiotherapy setting, this could lead to lengthy Phase I trials, which is not desirable.

Model-based Phase I designs can provide a more efficient way of assessing patients within each dose level. For example, the Time-to-Event Continual Reassessment Method (TITE-CRM) design allows dose decisions to be made without the need for all patients to be fully followed-up and faster entry of patients into the study based on the accumulating toxicity data. The downside of this approach is that these types of designs are more complex and intensive from

both a statistical and practical perspective compared to the more conventional methods.

Considerations for Phase II Trials

The main objectives of Phase II trials are to further establish the safety profile of an intervention and generate preliminary evidence of short term efficacy to determine if the intervention is worthy of taking forward for a definitive assessment within a Phase III trial. Importantly, a Phase II trial should act as a screening tool for Phase III, for example, selecting an optimal dose to take forward out of a number of "acceptable" doses.

Phase II trials require a larger number of patients than Phase I, anywhere between 10s–100s patients. Depending on the type of radiotherapy being delivered and accessibility to treatment, recruiting large numbers of patients within a timely manner might pose challenging. Therefore, strategies are needed to try and reduce the overall numbers of patients required whilst still generating sufficient data on the experimental treatment(s).

Phase II trials provide the opportunity to be more flexible with certain statistical design parameters, to address these recruitment challenges, whilst at the same time, still being statistically robust. Three approaches could be:

- Inflation of the type 1 error rate
- 1-sided test for statistical significance
- 2:1 randomisation

The type 1 error rate or significance level is the probability of observing a 'false-positive' result. It is typically set at 5% for Phase III and many Phase II trials, which represents the probability that you are willing to accept of observing a false positive result. But since the Phase II trial is not the end of line when it comes to evaluating a treatment, and a promising intervention will undergo further rigorous testing during Phase III, inflating the type 1 error at Phase II (for example to 10%) is considered an acceptable approach. In turn, if all other statistical parameters are kept constant, this will reduce the overall required sample size, as effectively you are saying you would be willing to accept more uncertainty around the result.

Another approach to reduce the overall sample size could be to perform a 1-sided test for statistical significance, as opposed to a standard 2-sided test. By doing this you would be seeking to demonstrate a difference in a specific direction i.e., experimental > control, as opposed to any difference between the two groups, positive or negative. A 1-sided test gives you more statistical power than a 2-sided one, which in turn reduces your sample size if all other parameters are kept constant. It is however a less conventional approach and may come under scrutiny for not allowing effects to be demonstrated in either direction. It may be considered acceptable, however, at Phase II if there is strong case to believe the direction of the effect will be in one particular direction and there is little interest in the alternative.

Finally, if there is already sufficient prior evidence and knowledge on the control arm, a 2:1 randomisation ratio could be employed, giving patients twice as much chance of receiving the experimental treatment. Whilst this will not lead to a reduction in sample size, it will increase the amount of data and evidence for the treatment of interest, and potentially have a positive effect on recruitment into the trial.

Master Protocols – Challenges and Benefits

Master protocols incorporate multiple trials and/or interventions into one single overarching clinical study protocol and are designed to answer multiple research questions. Trial designs which could make use of a master protocol could be platform, basket, and umbrella trials, the latter of which will be the focus here.

Umbrella trials are designed to study multiple therapies in parallel for a single disease, which may be divided into different subgroups based on the presence of a specific biomarker or mutation, stage of disease, or risk group.

When treating patients with radiotherapy in the past, it was standard practice to treat all patients with a particular type of cancer with the same dose and schedule of radiotherapy, regardless of the stage of the disease or presence of known prognostic factors. This could mean that patients with early-stage disease may be being over-treated, and patients with more advanced, later-stage disease who might benefit from an increased dose of radiotherapy, may be being undertreated. Advances in radiotherapy technology now means that different doses of radiotherapy can be delivered to different parts of the tumour and surrounding tissues, allowing for a more personalised medicine approach.

Umbrella trials are particularly suited for personalised medicine approaches as they allow the study of multiple therapies within a single disease, targeted at patients who are most likely to benefit i.e., patients with the same stage of disease, or with a particular genetic mutation.

For example, a study of patients with anal cancer, might divide patients into three groups, i.e., those with low, medium and high risk disease, where risk is determined by how advanced the cancer is. Three separate trials may be run under a single clinical protocol, where three different experimental doses of radiotherapy are studied alongside the standard control. This type of design is not only efficient compared to running three separate individual studies but also increases the likelihood of a positive result by personalising treatment towards those patients who are most likely to benefit.

As with any new approach, there are both challenges and benefits. Challenges may include more complex designs and methodology, more upfront investment to design and set-up the trial, a single independent data monitoring committee (IDMC) for the duration of the trial, and multiple IDMC reports to be delivered at one time.

The benefits of the umbrella approach, however, are significant. Multiple research questions can be answered more efficiently, and it allows for a more personalised medicine approach potentially leading to greater interest by patients in participating. It optimises infrastructure across trials resulting in cost savings vs. running individual trials and allows patients with potentially rarer disease types to take part in a trial which may not have been feasible to conduct on its own, outside of the setting of a master protocol.

In Summary

Design of clinical trials for the evaluation of radiotherapies can bring up some unique challenges not seen with other cancer therapies. These nuances need to be well understood, and novel or less conventional approaches may need to be employed to try and overcome them.

Lucy McParland

Lucy McParland is a Principal Statistician at PHASTAR (www.phastar.com), a contract research organization (CRO). Lucy joined the company in 2019, following a move from the University of Leeds where she was involved in leading the late phase oncology portfolio for radiotherapy research. Lucy has over 13 years of experience working in clinical trials, in both the academic research setting and for CROs. She also provides statistical consultancy for key industry partners.