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Rediogenomics

Optimal design and patient selection for interventional trials using radiogenomic biomarkers: A REQUITE and Radiogenomics consortium statement

Dirk De Ruysscher [a,b,*], Gilles Defraene [b], Bram L.T. Ramaekers [c], Philippe Lambin [a], Erik Briers [d], Hilary Stobart [e], Tim Ward [f], Søren M Bentzen [g], Tjeerd Van Staa [h], David Azria [i], Barry Rosenstein [i], Sarah Kerns [j], Catharine West [k]

[a] Maastricht University Medical Center, Department of Radiation Oncology (MAASTRO Clinic), The Netherlands; [b] KU Leuven, Radiation Oncology, Belgium; [c] Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, The Netherlands; [d] Patient Advocate, Hasselt, Belgium; [e] Patient Advocate, Cambridge; [f] Patient Advocate, Manchester, UK; [g] University of Maryland, School of Medicine, USA; [h] The University of Manchester, Manchester Academic Health Science Centre, UK; [i] Department of Radiation Oncology and Medical Physics, Institut Regional du Cancer Montpellier, France; [j] University of Rochester Medical Center, USA; [k] The University of Manchester, Translational Radiobiology Group I Institute of Cancer Sciences, The Christie NHS Foundation Trust, UK

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ABSTRACT

The optimal design and patient selection for interventional trials in radiogenomics seem trivial at first sight. However, radiogenomics do not give binary information like in e.g. targetable mutation biomarkers. Here, the risk to develop severe side effects is continuous, with increasing incidences of side effects with higher doses and/or volumes. In addition, a multi-SNP assay will produce a predicted probability of developing side effects and will require one or more cut-off thresholds for classifying risk into discrete categories. A classical biomarker trial design is therefore not optimal, whereas a risk factor stratification approach is more appropriate. Patient selection is crucial and this should be based on the dose–response relations for a specific endpoint. Alternatives to standard treatment should be available and this should take into account the preferences of patients. This will be discussed in detail.

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Introduction

Radiotherapy is used to treat more than 50% of cancer patients with either curative or palliative intent. In general, there is an assumed dose–effect relationship for local tumour control [1], i.e., higher radiation doses increase the probability of local tumour control. However, the risk of late side effects hampers dose escalation, and so-called "tolerance" doses to organs at risk (OAR) have been determined as those considered acceptable. Typically, a 5–10% chance of developing side effects with a severity of grade 3 or more is regarded as "acceptable". This is of course a subjective percentage. Some patients may consider a higher probability of side effects acceptable to achieve an increased probability for cure, whereas others might favour a lower risk of side effects despite a reduced probability for cure. Moreover, the level of risk considered acceptable also depends on the type of side effect [1,2].

Currently, comparable patients with a similar type and stage of disease receive the same radiotherapy regimen (dose and fractionation schedule), with adjustments made according to dose and volume parameters of the organs at risk [3,4]. The ability to predict an individual's risk of side effects would enable an informed decision and a move to personalised treatments [5]. Such treatment individualisation requires predictive models that are accurate enough to estimate a risk percentage for a certain side effect and its grade for each individual patient. Unfortunately, this is not the case for existing predictive models. Most models are essentially based on dose–volume parameters, with some including a few clinical factors, and have an area under the curve (AUC) of less than 0.70 [3]. However, they are often used in clinical practice to set the "threshold doses" for OAR because of their high negative predictive value (NPV), typically above 0.80. This "threshold" is set conservatively in order to achieve a low proportion of patients experiencing severe side effects. The consequence is that most patients could receive a higher radiation dose and hence theoretically a better probability of local tumour control without undue toxicity while the same "acceptable" proportion of individuals develop severe side effects. This concept has been used in individualised "isotoxic" radiotherapy schedules [4].

* Corresponding author at: MAASTRO Clinic, University Maastricht, GROW Research Institute, Dr. Tanslaan 12, 6229 ET Maastricht, The Netherlands.
E-mail address: dirk.deruysscher@maastro.nl (D. De Ruysscher).

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More recently, studies have revealed a role for genetic variation in influencing response to radiotherapy [5]. The field of "radiogenetics/genomics" investigates the relationships between the genes/biologic pathways involved in cellular/tissue responses to radiation and risk of radiotherapy toxicity. In the future, this will lead to the development of risk models that can be used to stratify patients according to their genetic risk for radiotherapy-induced damage and hence to more optimal personalised radiotherapy schedules [6]. Radiogenomic studies have already identified loci that influence late radiation damage, such as those in *TANC1* [7]. It is very likely that in the coming years, many genetic variants will be identified that individually contribute small increased risks for radiation damage, but together represent an actionable polygenic risk profile of sensitivity. These radiogenomic profiles would be used in combination with physical and clinical parameters to increase the accuracy of models predicting radiation toxicity. Targets that are suitable for a therapeutic intervention may be identified as well.

Radiogenomic models including genetic, physical and clinical parameters would underpin future personalised/precision radiotherapy. However, prior to clinical implementation these new models would need to be validated in clinical trials to test whether they can improve outcomes for patients [8]. In the past, models have mainly been developed and tested on retrospective series and few if any have passed the criteria for biomarker validation and implementation [9].

With an increasing number of predictive models being published it is of interest to consider if there could be an optimal design for testing whether they have a clinical impact. This review, therefore, considers possible interventions, endpoints and trial designs for testing the benefit of predictive models of radiotherapy toxicity. The design should be not only scientifically sound and practice changing, but also acceptable to patients. For that reason, patient representatives were invited to contribute to this work.

Interventions

Interventions that can be considered are: alternative treatment, dose modification, altered radiotherapy, mitigation/amelioration and the omission of postoperative radiotherapy in patients with a low risk for tumour recurrence.

For some cancers, there can be a choice of surgery or radiotherapy. An example, for breast cancer patients where those identified as having a high risk of toxicity could consider a mastectomy versus a breast conserving lumpectomy followed by radiotherapy. Surgery versus organ preserving radiotherapy can also be an option for some prostate and bladder cancers. Of course important questions remain about the relationships between susceptibility for normal tissue damage following surgery and radiotherapy. It is possible that some individuals have a high susceptibility to damage irrespective of the type of treatment. It is assumed that toxicities with the strongest radiation dose response relationship will be more specific for radiotherapy, but we are not aware of any evidence to support or refute this suggestion. For some cancer types, the toxicity profile may differ depending on the treatment type, and this could be a deciding factor in selecting the optimal treatment.

Individualised dose prescriptions could be considered. Perhaps the preferred option here would be dose escalation in those identified as having a very low risk of toxicity. However, elderly patients with cancers with poor overall survival rates, e.g., lung cancers, might choose palliative rather than potentially curative regimens.

Altered radiotherapy could be considered, such as hyperfractionation that can reduce toxicity for equivalent local control [10]. With the availability of stereotactic radiotherapy and increasingly proton therapy, defined patient groups at risk for toxicity based on their genetic profile and not only on dosimetric parameters [11,12] may be considered for these modalities.

Another option is for a therapeutic intervention. This may include radio-protectors (agents that reduce the incidence and/or the severity of acute and/or late toxicity as they reduce the initial extent of normal tissue damage) or radiation mitigators (agents that act after radiotherapy has been given but prior to the manifestation of toxicity) [13]. The largest amount of data comes from trials with amifostine, a thiol that scavenges free radicals. Although amifostine is the only FDA-approved radio-protector and that some trials did show a slight reduction of side effects, it is not widely used because there remains doubt about potential protection of the tumour as well. Moreover, neither amifostine nor newer radio-protectors have been tested in selected patients at high risk for radiation injury, e.g. identified by their radio-genomics profile [14]. As will be discussed later, the selection of the appropriate patients is essential to study radio-protectors or -mitigators. As many patients are treated with concurrent chemotherapy and radiotherapy, protectors and mitigators should also be investigated in this setting.

Adjuvant radiotherapy is frequently applied in, for instance, patients with breast or prostate cancer, aiming to diminish the chance of local recurrence. In breast cancer, postoperative radiotherapy decreases the chance of local recurrence by 50% and increases the survival by one sixth [15]. However, the absolute benefit differs greatly between the risk groups, with the lowest risk group only showing an increase in 15-year survival of 0.1%. Also in prostate cancer, postoperative radiotherapy improved the clinical progression-free survival at 5-years, but only in subgroups of patients [16]. Patients with a low risk of local recurrence but with a higher risk for toxicity could be omitted from postoperative radiotherapy.

Endpoints

The selection of the appropriate endpoints for clinical trials is essential. For interventional trials using radio-genomic biomarkers, this is difficult. Both acute and late radiotherapy toxicity have profound effects on the quality of life of cancer patients, particularly when the toxicity is severe [1,2]. Acute toxicity in one organ (e.g. the oesophagus) does not predict late damage in another site (e.g. the lung), but late consequential damage bridges acute and late toxicity in the same organ [17,18]. In clinical studies a primary endpoint may need to involve multiple toxicities occurring at different time-points. Statistical methods have been developed for this purpose [19,20]. Not only toxicity, but also quality of life, local control and survival following any intervention must be taken into account. Recommendations for the reporting of radio-genomics research were described in the STROGAR guidelines and should be addressed [21]. Surrogate endpoints for late radiation damage would increase the speed of the assessment, but these are not validated at present [22].

There is clearly no simple endpoint or time point that can be selected when designing a clinical trial. Composite endpoints should be considered.

Study designs

Randomised clinical trials

Randomised clinical trials (RCTs) are frequently considered to be the gold standard to obtain level I clinical evidence for interventional studies [23,24]. RCTs control for heterogeneity of the participants and allocation bias to a certain treatment arm, and because