Personalising Non-Small-Cell Lung Cancer Radiation Therapy: an RTT research perspective.

Background

I am an assistant professor in radiation therapy working at Trinity College Dublin. I am currently half way through my PhD studies, having spent 10 years working clinically as a radiotherapist (RTT), examining the personalisation of Non-Small-Cell Lung Cancer (NSCLC) radiation therapy. My research aims to investigate the potential to personalise the radiotherapy process from a number of perspectives, with a particular focus on using routine clinical imaging to evaluate pre-treatment growth dynamics and to model early tumour response to inform an optimised, personalised dose fractionation schedule. This article gives a brief introduction to some of my research topics.

Literature review

Current radiotherapy practice consists of standardised treatment protocols for the vast majority of our patients. In the case of NSCLC, all steps of the radiation therapy process from treatment planning and dose fractionation schedules to on-set geometric verification are carried out using population protocols rather than tailoring each step to the specific patient or the specific tumour. A long-established dose fractionation schedule of 60-66Gy in 30-33 fractions remains the radiotherapy standard of care [1] for patients with locally advanced NSCLC (LA-NSCLC). I am interested to find out whether this could be better tailored to the individual patient.

My first step was to thoroughly review the literature on this topic. This review identified that a variety of methodologies had been proposed and investigated to personalise radiotherapy prescriptions for patients with LA-NSCLC; however, most have not yet been tested in the clinical setting [2].

Five studies were identified which looked at the feasibility of dose modification in LA-NSCLC by carrying out retrospective dosimetric evaluations. While all five planning studies reported that dose modification was feasible in most patients with NSCLC Stage IB-III, this was a small cohort of patients (n = 101). Furthermore, the overarching aim of these studies was to escalate the dose for all patients rather than to ascertain differences between those that may or may not have benefited from a modified dose prescription. The NSCLC dose escalation trial, RTOG 0617, has demonstrated that this may not be beneficial to all patients [3].

Next, I reviewed published clinical data. Five prospective clinical trials were identified that utilised isotoxic treatment planning techniques to prescribe radiotherapy individually for LA-NSCLC. There was sizeable heterogeneity between these trials and, as a result, any direct comparative analysis between these studies is difficult and potentially unreliable. An increase in overall survival was associated with an increase in dose in three of the five studies. However, significant toxicity was reported in all studies, with Grade 5 adverse events also reported in four of the five studies.

Finally I identified nine novel concepts that might provide a future basis for personalised radiotherapy prescriptions. These approaches ranged from targeting hypoxic regions or sub-volumes of disease to incorporating models of tumour control probability (TCP)/normal tissue complication probability (NTCP) into the treatment planning process. One approach utilised mathematical modelling of tumour-volume changes over time to predict on-treatment regression, and clinical evaluation of this model became the basis of the remainder of my PhD research.

The literature review found that one reason for a lack of clinical progression in testing these novel approaches to personalised prescriptions was the lack of robust in silico evidence. Many of the proposed models or methods have been tested on mathematically generated populations in an academic setting. Further pre-clinical work is required before we can begin to translate these models into clinical practice.

The reviewed retrospective planning studies have shown that dose modification is feasible, and hence implementation of this concept in the clinic is possible. Some clinical evidence has been gained from a small number of trials that look at alternative dose fractionation schedules. These trials are largely focused on dose escalation, and mainly exploit the spatial relationship between targets and organs at risk (OARs). To an extent, this approach is personalised to the individual's gross anatomy. However, to personalise the treatment truly we should also aim to target disease features that are identifiable at a cellular level.

Furthermore, a true person-centred approach is lacking in much of this research, as the majority of studies and proposals aim simply to escalate dose without a focus on patient characteristics. The vast heterogeneity within this patient population highlights the myriad of factors that are not yet considered in our treatment approach [4]. This may provide a starting point for improved patient stratification and thus personalisation. While our efforts should not move away entirely from personalisation of the radiotherapy plan, we cannot continue to do this without also giving equal consideration to patient-related factors.

One potential barrier to the implementation of personalised radiotherapy prescriptions is the resource burden of such approaches. Clinical departments do not have unlimited resources available at present to deliver an entirely personalised approach to every patient. Those concepts and theories that have a minimal impact on workflow and resources are most likely to be the first that are introduced to clinical practice, if they are shown to be beneficial.

Predictive modelling of tumour regression during radiotherapy

As mentioned, my upcoming research focuses on one such approach, and is a clinical evaluation of a mathematical model proposed by Prokopiou et al. [5]. This model endeavours to predict early tumour regression over the course of radiotherapy. The model uses tumour volume changes over time to calculate a patient-specific Proliferation Saturation Index (PSI), and uses this index to predict the patient's response to radiotherapy. Evaluation on real-life, modern imaging datasets is required to test the accuracy of the PSI model in NSCLC to ensure the accuracy of the tumour volume inputs [6]. My research aims to address this deficit and assess the PSI model on a clinical dataset of 150 LA-NSCLC patients who are treated using conventionally fractionated radiotherapy. The PSI model predicts early tumour regression during radiotherapy and not clinical outcomes such as overall survival. However, early response during radiotherapy has the potential to be a relevant biomarker to predict clinical outcomes [7, 8]. We will also test this hypothesis in this research. The appeal of the PSI model is that it can predict tumour response to radiotherapy, potentially in advance of treatment commencement or at an early time point during the treatment. Additionally, we can simulate response to a variety of dose fractionation schedules and select the optimal prescription based on this simulated response.

If early tumour regression and PSI values are found to be reliable predictive markers, then we will ascertain whether a PSI-optimised radiotherapy prescription can improve predicted outcomes for patients by modelling alternative personalised dose-fractionation schedules.

Several studies have demonstrated that tumour volume regression measured on cone beam computed tomography (CT) during radiotherapy is a predictive biomarker of treatment outcome [9-12]. However, all of these studies assessed volume regression retrospectively and correlated observed regression with clinical outcomes. This research aims to predict that regression prospectively and adapt our treatment accordingly.

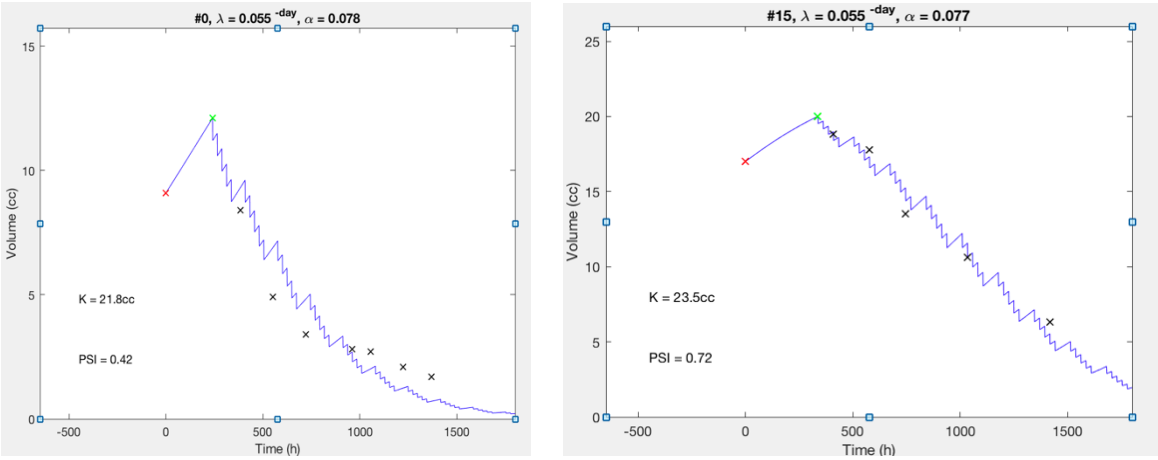

Figure 1.
Two individual patient plots display the measured tumour volume pre-treatment in red, the tumour volume at the start of radiotherapy in green, and the tumour volume over the course of radiotherapy delivery in black. The blue line is the PSI-model-simulated outcome for 2Gy per fraction prescription. It indicates good agreement between the modelled and actual volume changes. Note that these figures are preliminary as they are taken from a training dataset and not from a validation cohort.

Clinical applications

If this research proves that the model is useful, it will have clinical relevance not only for prescription modification, but also for adaptive radiotherapy. Accurate modelling of tumour regression during radiotherapy will enable us to select patients that will require adaptive replanning due to large volume regression. A recent audit [13] has highlighted that up to 40% of lung cancer treatment plans require adaptive assessment based on cone beam CT anatomical changes, and the ability to predict this requirement in advance would be invaluable to RTTs working clinically.

The overarching aim of my research is to make a meaningful contribution to the ongoing work in personalising and adapting radiotherapy for NSCLC patients. In turn this could lead to the increased use of predictive modelling for other treatment sites.

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