Combining Dosimetry & Toxicity: Analysis of two UK Phase III Clinical trials

Sarah L Gulliford
Joint Department of Physics, The Institute of Cancer Research & Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

sarahg@icr.ac.uk

Abstract. There are many advantages to performing a clinical trial when implementing a novel radiotherapy technique. The clinical trials framework enables the safety and efficacy of the “experimental arm” to be tested and ensures practical support, rigorous quality control and data monitoring for participating centres. In addition to the clinical and follow-up data collected from patients within the trial, it is also possible to collect 3-D dosimetric information from the corresponding radiotherapy treatment plans. Analysing the combination of dosimetric, clinical and follow-up data enhances the understanding of the relationship between the dose delivered to both the target and normal tissue structures and reported outcomes & toxicity. Aspects of the collection, collation and analysis of data from two UK multicentre Phase III radiotherapy trials are presented here. MRC-RT01 dose-escalation prostate radiotherapy trial ISRCTN47772397 was one of the first UK multi-centre radiotherapy trials to collect 3-D dosimetric data. A number of different analysis methodologies were implemented to investigate the relationship between the dose distribution to the rectum and specific rectal toxicities. More recently data was collected from the PARSPORT trial (Parotid Sparing IMRT vs conventional head and neck radiotherapy) ISRCTN48243537. In addition to the planned analysis, dosimetric analysis was employed to investigate an unexpected finding that acute fatigue was more prevalent in the IMRT arm of the trial. It can be challenging to collect 3-D dosimetric information from multicentre radiotherapy trials. However, analysing the relationship between dosimetric and toxicity data provides invaluable information which can influence the next generation of radiotherapy techniques.

1. Introduction

Radiotherapy in the 21st century allows a carefully shaped dose-distribution to be accurately directed to a tumour with either radical or palliative intent. However it is impossible to completely avoid targeting normal tissue surrounding the tumour. This is partly to ensure that all potential clonogens are included in the irradiated region but largely due to the entrance and exit path of each radiotherapy beam. As the ability to optimise and deliver more complex dose-distributions evolves, it will be possible to be much more prescriptive about the amount and distribution of radiation to normal tissue structures. In order to capitalise on this possibility the dose-response of each normal tissue must be characterised.
The process of characterisation is complex. Analysis requires clinical data including accurate and specific toxicity data and complete dosimetric information on specific organs at risk. Each normal tissue is associated with a number of different toxicities and heterogeneity in the treatment population will influence the side effects each patient will experience. Much of the information currently available on the response of normal tissues is summarised in the QUANTEC report [1]. Each of the organ specific papers is structured to include relevant endpoints, review dose-volume data and summarise recommended dose-volume constraints. The application of mathematical and biological models such as Normal Tissue complication Probability (NTCP)[2] are also considered.

2. Data Collection

The MRC-RT01 dose-escalation prostate radiotherapy trial ISRCTN47772397 [3] was one of the first UK multi-centre radiotherapy trials to collect 3-D dosimetric data. The trial randomised 843 men with localised prostate cancer between a standard radiotherapy dose of 64 Gy or an escalated dose of 74Gy achieved with a 10Gy boost to the prostate only. Although comprehensive follow-up data was available for most patients, it was only possible to combine the toxicity and dosimetric data for 388 patients. The deficiency in dosimetric data was partly attributable to difficulties in retrieving the data from treatment planning systems with non-proprietary export formats. These technical issues have been largely overcome with the wide-scale implementation of DICOM-RT and development of treatment plan analysis software [4,5]. However diligent prospective archiving of data is fundamental to the creation of comprehensive data sets.

3. Analyses

Data sets which combine toxicity and dosimetric data are valuable resources in the effort to further the understanding of the response of normal tissues. They can be used to derive dose-volume constraints using statistical methods [6,7], derive parameters for NTCP models such as the classic Lyman Kutcher Burman model [8,9] or develop novel models [10]. They are also invaluable as independent datasets on which to test potential models.

The initial analysis of the RT01 data took the form of an independent validation of dose-volume constraints for the rectum already proposed in the literature [11]. Two sets of rectal dose-volume constraints were tested; those proposed by Fiorino et al [6] of 40Gy/65%, 50Gy/55%, 60Gy/40%, 70Gy/25% and 75Gy/5% and those proposed for the CHHiP trial [12] of 30Gy/80%, 40Gy/70% 50Gy/60% 60Gy/50% 65Gy/30%, 70Gy/15% and 75 Gy/3%. Each constraint was tested independently on 7 different late rectal toxicity endpoints; Rectal Bleeding (RMH), Proctitis (RTOG) Subjective Sphincter control, Subjective stool frequency and Management of sphincter control (LENT/SOM) and Loose stools and rectal urgency (UCLA PCI).

The effect of retrospectively applying the constraints was tested by calculating Odds ratios defined as the odds of reporting a specified late rectal toxicity as a result of the treatment plan failing to meet a suggested constraint relative to the odds of reporting the specified late toxicity if the constraint had been met. It was demonstrated that some constraints were more effective for some endpoints than others; potentially due to underlying differences in patho-physiology. However, overall there was a clear picture that the more constraints failed (when considering the lowest volume constraint at each dose level) the more likely a patient was to experience toxicity. In addition, it was observed that in the group of patients whose treatment had met all of the constraints, approximately a third of patients reported toxicity graded as either moderate or severe.
4. Deficiencies in Current Methodology

There are several explanations for the failure of dose volume constraints and NTCP models to accurately predict toxicity. Firstly it is important to acknowledge that dose-volume constraints, models and model parameters are derived from a dataset which will represent one or more treatment types (e.g. fractionation, beam arrangement). It cannot be presumed that results can be generalised to another treatment type. However there are more fundamental reasons why the incidence of toxicity is not fully predicted by current approaches.

4.1 Deficiencies in Toxicity Reporting/Definitions.

Although standardised scales for toxicity reporting are used there are still challenges in the representation of side effects. Analysis is either performed cross-sectionally (i.e. toxicity reported at 2 years) or cumulatively using the maximum grade reported over the available follow-up period. Both definitions are sensitive to spurious results and neither fully characterises the experience of the patient[13]. An alternative approach is to use an area under the curve approach where the time and severity of toxicity are integrated over the follow-up period[7]. Figure 1 represents 2 idealised examples of follow-up history. Using standard definitions both patients would report grade 2 toxicity. However it is clear that the overall toxicity profile is quite different. Dose-volume constraints for the rectum were derived using both definitions and were shown to provide complimentary information.

![Figure 1 Illustrative examples of the time course of reported toxicity.](image)

4.2 Treatment plan not representative of the dose received by the normal tissue.

Treatment plans are calculated using a CT scan taken prior to treatment and therefore the dose accumulated by normal tissues is unlikely to be accurate. Changes in patient anatomy over the course of radiotherapy treatment are not uncommon. In addition intra- and inter- fraction motion will compound these uncertainties. In the era of IGRT it is possible to improve the estimate of dose received by a specific organ or tissue by recalculating the dose distribution on cone beam CT acquired over the course of treatment. Accumulating this dosimetric information should result in a more accurate representation of the dose distribution received[14].

4.3 Lack of spatial information

The dose distribution to a normal tissue is usually presented as a dose-volume-histogram (dvh). The dvh allows for comparison of the main features of the dose distribution however if the organ or tissue has a heterogeneous dose response then information regarding the location of the dose is also important. An alternative representation of the dose to a tubular structure such as the rectum is a dose surface map (figure 2) where the dose distribution to the rectum surface is unfolded and spatial integrity is preserved. Using dose surface maps to analyse the RT01 trial cohort it was possible to
demonstrate that loose stools was most correlated with the longitudinal (superior-inferior) extent of doses in the range of 20-30 Gy, in contrast rectal bleeding was best characterised by the lateral (left-right) extent of doses between 40 and 60Gy[15].

4.4 Patient & Genetic factors

Finally we consider that there are many patient specific factors that contribute to and confound the dose response of normal tissues. These factors may include co-morbidities and concomitant treatments. It is also important to consider inherent genetic differences. Single Nucleotide Polymorphisms (SNPs) are rearrangements of a single pair in a gene. These variations continue to be tested as potential candidates for radiation response although the large number of potential variations has so far led to inconclusive results[16].

5. The benefits of Clinical trials for the implementation on new radiotherapy techniques.

In addition to the comprehensive data collected within a clinical trial, there are other advantages to using data collected within this structured framework. The trial protocol ensures that all aspects of the radiotherapy are considered and acceptable techniques are defined. In addition rigorous quality assurance programs ensure that patients recruited to the trial are treated according to protocol. Overall this reduces the heterogeneity of data in the cohort available for analysis.

The importance of using clinical trials to implement new technology was highlighted by the results of the Phase III PARSPORT trial ISRCTN48243537 [17]. This trial was unique in comparing conformal radiotherapy and intensity modulated radiotherapy for head and neck cancer in a fully randomised setting. The use of IMRT allowed for sparing of the contra-lateral parotid gland and trial findings confirmed a decrease in Xerostomia in the group of patients who received IMRT.

An unexpected finding from the trial was that acute fatigue was more prevalent in the IMRT arm of the trial. It was hypothesised that the difference in the incidence of fatigue was related to differences in dosimetry to a number of CNS structures [18]. The dose distributions to the structures were compared to the incidence of fatigue and it was demonstrated that the maximum and mean dose to the posterior fossa, cerebellum and brainstem were correlated with acute fatigue. Subsequent analysis characterised the dose distribution using the dose-volume atlas method proposed by Jackson et al [19]. This method allows the dvh to be summarised in combination with a specific toxicity endpoint. Each box in the atlas represents a small region of dose and volume. The dvh are overlayed and the boxes through which the dvh passes are recorded (denominator). Also recorded in each box...
are the number of patients whose dvh pass through the box AND reported the toxicity under investigation (numerator). An example atlas generated for the cerebellum is shown in figure 3.

Figure 3. Dose-volume atlas summarising dvh of the cerebellum and incidence of grade 2 fatigue.

Using an atlas approach allowed the analysis of the relationship between the whole dvh and toxicity and has potential for both the derivation of constraints and generation of models. Use of the atlas method is encouraged within the QUANTEC report as it facilitates the combination of data from different patient cohorts. Combining datasets allows for development of generalisable models and independent testing.

6. Summary

Clinical trials are vital to validate and introduce new radiotherapy techniques. The framework of clinical trials facilitates the development of databases of carefully audited information providing valuable information on the response of normal tissues to radiation. Deficiencies in the characterisation of normal tissue response to radiation and confounding factors are acknowledged but ongoing research and feedback will improve future characterisation of the response of normal tissues.

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