

DESIGN AND METHODOLOGY OF A PROSPECTIVE TRIAL TO IMPROVE THE UNDERSTANDING OF KIDNEY RADIATION DOSE RESPONSE

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INTRODUCTION: The kidneys are a principal dose-limiting organ in radiotherapy for upper abdominal cancers. Our current understanding of kidney dose response and tolerance is limited and this is hindering efforts to introduce advanced radiotherapy techniques for upper-abdominal cancers. More precise dose-volume response models that allow direct correlation of delivered radiation dose with spatio-temporal changes in kidney function may improve radiotherapy treatment planning for upper-abdominal tumours [1]. The aim of this study is to utilise radiotherapy and combined anatomical/functional imaging data to allow direct correlation of radiation dose with spatio-temporal changes in kidney function. The data can then be used to develop a more precise dose-volume response model which has the potential to optimise and individualise upper abdominal radiotherapy plans.

METHODS: The Radiotherapy of Abdomen with Precise Renal Assessment with SPECT/CT Imaging (RAPRASI) is an observational clinical research study being conducted at Sir Charles Gairdner Hospital (SCGH) in Perth, and the Peter MacCallum Cancer Centre (PMCC) in Melbourne. Eligible patients are those with upper gastrointestinal cancer, without metastatic disease, undergoing conformal radiotherapy that will involve incidental radiation to one or both kidneys. For each patient, total kidney function is being assessed before commencement of radiotherapy treatment and then at 4, 12, 26, 52 and 78 weeks after the first radiotherapy fraction, using two procedures: a Glomerular Filtration Rate (GFR) measurement using the ⁵¹Cr-ethylenediamine tetra-acetic acid (EDTA) clearance; and a regional kidney perfusion measurement assessing renal uptake of ^{99m}Tc-dimercaptosuccinic acid (DMSA), imaged with a Single Photon Emission Computed Tomography / Computed Tomography (SPECT/CT) system. The CT component of the SPECT/CT provides the anatomical reference of the kidney's position. The data is intended to reveal changes in regional kidney function over the study period after the radiotherapy. The SPECT/CT scans, co-registered with the radiotherapy treatment plan, will provide spatial correlation between the radiation dose and regional renal function as assessed by SPECT/CT. From this correlation, renal response patterns will likely be identified with the purpose of developing a predictive model.

DISCUSSION & CONCLUSIONS: The project has commenced recruitment and a limited amount of patient data has been collected. Recruitment has been challenging due to patients typically being at an advanced stage, combined with the challenge of repeated hospital visits for follow-up studies. Tools are under development to derive the correlation of regional functional kidney changes with planned radiotherapy dose. There are no conclusions yet, but the data obtained from this project will guide decision making in treatment planning for upper-abdominal radiotherapy.

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A PROCESS FOR ADEQUATELY COMBINING HIGH-DOSE RATE BRACHYTHERAPY AND EXTERNAL BEAM RADIOTHERAPY DATA USING DEFORMABLE IMAGE REGISTRATION

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INTRODUCTION: Patients receiving conventional external beam radiotherapy (EBRT) followed by a ‘boost’ dose using high dose-rate brachytherapy (HDR-BT) present new challenges for registering CT planning images and combining doses. The time between the HDR-BT and EBRT planning CTs can be months. Consequently, there can be considerable differences in anatomy shape and location, including changes due to bowel gas and rectal fillings. The HDR-BT CT also includes catheters, artefacts and rectal packing materials. This study examines the image processing and deformable image registration (DIR) tasks that are required to adequately combine EBRT and HDR-BT data with a focus on the results of contour propagation.

METHODS: This preliminary study is based on 30 prostate cancer patients from the RADAR trial. All patients received EBRT followed by a ‘boost’ dose using HDR-BT, and a treatment planning CT scan at the start of EBRT and the start of HDR-BT. The rectum was manually contoured in all CT scans. The EBRT CT scan was retrospectively registered to the HDR-BT CT scan with rigid registration. Image processing was undertaken on the EBRT CT rigid registered image and the HDR-BT CT image to reduce the impact of features on the DIR. Image processing tasks included modifying the image intensities of features (rectal packing beyond the contour, HDR-BT catheters etc.), applying Gaussian filters and masking the rectum contour. DIR was applied with and without image processing using different algorithms from the DIRART code [1]. The resulting rigid, rigid plus DIR (rigid+DIR), rigid plus full image processing plus DIR (rigid+FIP+DIR) and rigid plus basic image processing plus DIR (rigid+BIP+DIR) vector fields were used to propagate the EBRT rectum contours. The four propagated EBRT rectum contours per patient were compared with the HDR contour using the Dice similarity coefficient (DSC) [2]. The DSC has a range of zero to one where one is perfect agreement.

RESULTS: Table 1 provides the DSC results for four registration methods where the DIR component was implemented via the Horn–Schunck optical flow algorithm (HSDIR). The differences between the DSCs for different methods were statistically significant except for rigid versus rigid+HSDIR.

Registration Method	Average DSC (Standard Deviation)	Median DSC (Interquartile Range)
Rigid	0.643 (0.116)	0.661 (0.148)
Rigid+HSDIR	0.640 (0.0889)	0.647 (0.112)
Rigid+BIP+HSDIR	0.855 (0.0399)	0.863 (0.0691)
Rigid+FIP+HSDIR	0.862 (0.0380)	0.864 (0.0673)

Table 1: Dice similarity coefficients (DSC) for various registration methods.

DISCUSSION & CONCLUSIONS: Combined rigid and DIR improved the contour propagation for the rectum relative to rigid registration if appropriate image processing was undertaken to remove artefacts near or within the rectum. The results are consistent with other studies where DIR was applied to CT imaging study sets from patients treated with EBRT only [2].

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AUTOMATED ANALYSIS OF DYNALOG FILES FOR ADVANCED RADIOTHERAPY TREATMENT VERIFICATION

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INTRODUCTION: The increased complexity of modern external beam radiation therapy treatments has led to an increase in the probability of errors in treatment devices. As such it is essential to verify the accuracy of the delivered dose distributions which are most frequently formed by a multi-leaf collimator (MLC). Unfortunately conventional methods for pre-treatment verification involve time consuming setup and analysis procedures that are undertaken manually by medical physicists [1]. This project aims to provide an alternative, automated method for treatment verification, both before and during the treatment, using the dynamic log files (Dynalog files) created by modern linear accelerators during delivery.

METHODS: A series of code has been developed to read through Dynalog files and extract useful data. Numerous values were calculated including; the error in each individual MLC leaf position, the speed and acceleration of each leaf, dose segment errors per field and the gravity effect. A large number of Dynalog files were analysed.

RESULTS: The developed code is found to take 117.398 ± 8.550 s to run using a PC with 2.50GHz CPU and 4.00GB of RAM. The Dynalog file of a prostate treatment has been analysed as a sample with distribution of leaf deviations from expected position as a function of leaf speed illustrated in Fig 1, showing a linear positive trend. The maximum positional error of leaves on the left bank was found to be 0.53mm with a mean of 0.19mm. The maximum root mean squared error on the left bank was found to be 0.14mm with a mean of 0.90mm.

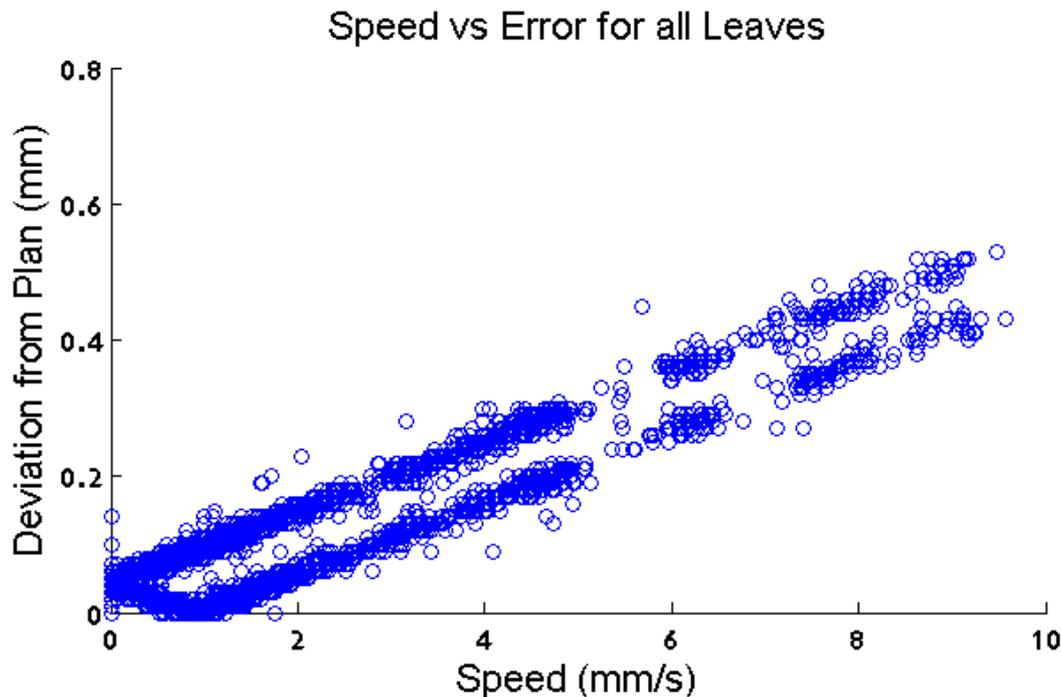


Fig. 1: Speed vs Positional Error for all Leaves

DISCUSSION & CONCLUSIONS: The developed code is a fast, alternative, automated method for treatment verification that is enabled by Dynalog files in performing quality assurance for external beam radiation therapy treatments.

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COMPARISON OF BLADDER DOSIMETRIC INDICES FOR MODELLING THE INCIDENCE OF ACUTE URINARY TOXICITY: AN ANALYSIS OF DATA FROM THE RADAR RADIOTHERAPY TRIAL

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INTRODUCTION: Normal tissue complication probability (NTCP) models are widely used to predict the incidence of toxicity. For a hollow organ like the bladder, methods used to quantify the dose received may affect model predictions. This study aims to compare the fits of NTCP models of acute urinary toxicity after radiotherapy using dosimetric indices derived from dose-volume (dv) which includes bladder content, dose-surface (ds) and dose-wall (dw) information for prostate cancer patients treated with three-dimensional conformal radiotherapy (3D-CRT).

METHODS: Digital treatment plans for 754 patients were available from the TROG 03.04 RADAR prostate radiotherapy trial. For dv, ds and dw (using 5 mm wall thickness), multiple indices (mean dose – dV_{mean} , dS_{mean} , dW_{mean} ; dose-%volume thresholds) were derived across all patients using scripting, with doses for individual treatment phases combined as equivalent dose in 2 Gy fractions (EQD₂ - $\alpha/\beta = 6$ Gy). These values were correlated with event incidence, being an increase of more than 5 in the International Prostate Symptoms Score (IPSS) at three months after the end of 3D-CRT. A bootstrap technique was used to determine model fit (loglikelihood, LL).

RESULTS: The considered indices derived from different methods are highly correlated (Spearman $R > 0.85$, $p < 0.0001$). Mean difference of dW_{mean} is significantly smaller than dV_{mean} and dS_{mean} ($p < 0.0001$, mean difference 3.27 ± 2.99 Gy and 3.39 ± 1.44 Gy respectively while dV_{mean} and dS_{mean} are not significantly different ($p = 0.08$, 0.12 ± 2.68 Gy). Dose threshold mean differences are shown in Fig. 1, with a maximum difference of 9.4% for dw-ds histogram. The bootstrap analysis shows significantly different fits ($p < 0.0001$) with $LL(dW_{mean}) > LL(dS_{mean}) > LL(dV_{mean})$. When specific dose-%volume thresholds are used, the dose-wall information provides higher log-likelihood across almost all doses.

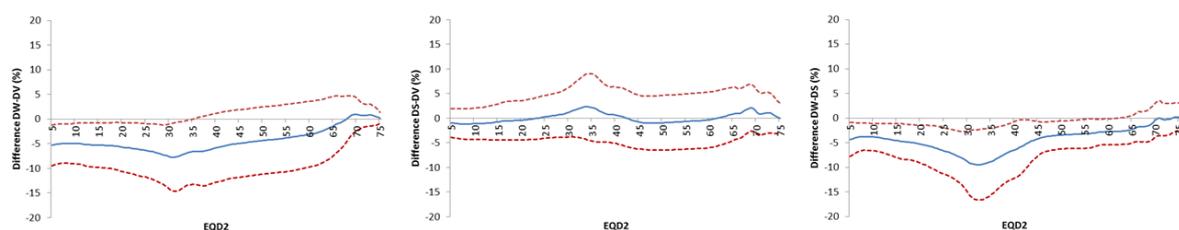


Fig. 1: Mean difference (solid) \pm 1 standard deviation (dashed) between the relative a) dose-wall and dose-volume, b) dose-surface and dose-volume c) dose-wall and dose-surface histogram as a function of EQD₂.

DISCUSSION & CONCLUSIONS: These results suggest the effect of dosimetric information derived from different methods may result in different model fitting with a better fit obtained when dose-wall information is used. This may affect the accuracy of the available toxicity models which use dose-volume information.

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VALIDATION OF A MONTE CARLO MODEL OF A FOD DETECTOR IN A STEREOTACTIC RADIOTHERAPY BEAM

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INTRODUCTION: Measurement of collimator scatter factors in stereotactic radiotherapy beams presents several challenges resulting from the need for small build-up and detector volumes. The main aim of this study was to validate a Monte Carlo (MC) model to investigate various beam characteristics and the effect that they have on in-air measured collimator scatter factors.

METHODS: Phase space files, produced for a Varian Novalis accelerator in stereotactic mode using BEAMnrc [1] and based on technical data supplied by Varian, were used as a source for a DOSXYZnrc MC dose calculation in a water phantom. Dose distributions were compared to measured data collected using Gafchomic film for cone sizes ranging from 4mm to 30mm diameter and the BEAMnrc model adjusted for optimal agreement. Collimator scatter factors (S_c) were then calculated using a Geant4 [2] MC model of a scintillator-based fibre-optic dosimeter (FOD) in air, using the optimised phase space files as input. These were then compared to S_c values measured using an equivalent physical FOD, as well as a variety of other detectors.

RESULTS: Good agreement was obtained between the Monte Carlo models and measured data for all stereotactic cone sizes ranging from 4mm to 30mm. Calculated and measured S_c values for the FOD agreed within measurement and calculation uncertainty for all cone sizes. However there was a variation between S_c factors measured with the FOD and that for all other detectors which decreased with increasing field size. These results are summarised in Fig. 1.

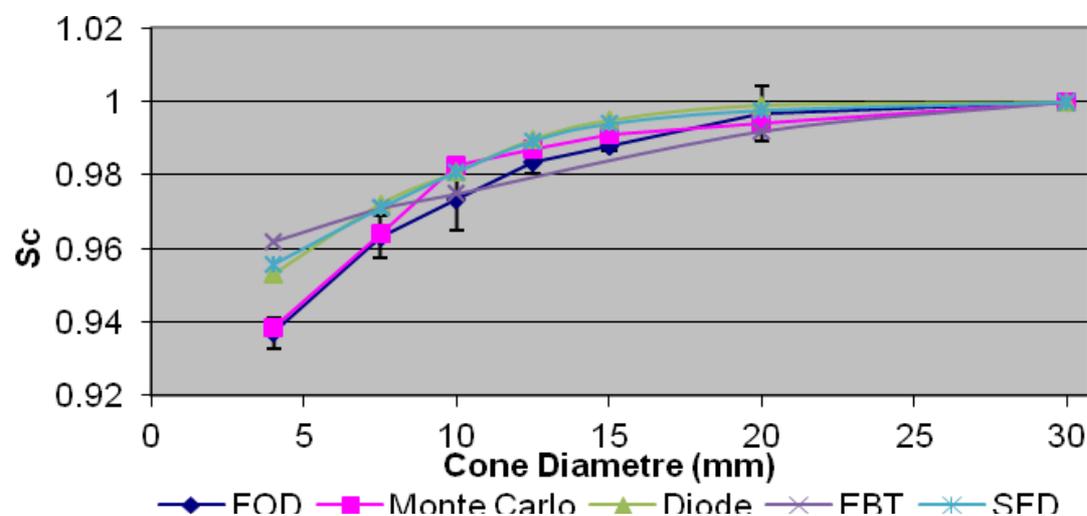


Fig. 1: Calculated and measured S_c factors as a function of cone diameter for a variety of detector types in a Varian Novalis Stereotactic 6 MV treatment beam.

DISCUSSION & CONCLUSIONS: The MC model of the FOD detector in a Novalis stereotactic beam showed good agreement with measured beam profile data as well as measured S_c factors. This validates the MC model and provides a platform to use MC simulations to further investigate and optimise FOD design and the physical processes influencing in-air beam measurements.

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THEORETICAL ESTIMATION OF RBE IN LOW-KV INTRAOPERATIVE RADIOTHERAPY: DERIVATION OF SECONDARY ELECTRON SPECTRA

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INTRODUCTION: Track structure simulation confirms that low energy electrons are the prime cause of double strand breaks (DSBs) and lethal cell damage in the treatments such as targeted intraoperative radiation therapy [1]. Higher relative biological effectiveness (RBE) has been attributed to low energy electrons compared to other high energy radiations (neutrons, photons and higher charged particles) [2]. Modelling the biological effect of targeted intraoperative radiotherapy involves simulation of lethal cell damage with these low energy electrons as the main cause of double strand breaks. While scoring the low energy electrons is an intricate issue of such a simulation, addition of low energy auger electrons (below 1 keV) is also important. We intend to understand the validity of this method through theoretical studies comparing the established Linear- Quadratic (LQ) model with experimental observations. The modelling of radiation dose delivered at a point is the starting point for subsequent Monte Carlo DNA damage [3] simulation.

METHODS: Direct spectral measurement of the Intrabeam source (Photoelectron corporation, CA) without an applicator attached was performed with a high resolution Schottky CdTe spectrometer (XR-100T, AMPTEK Inc., Bedford MA). Due to distortion by the response function of CdTe crystals, the measured spectrum was compared with a set of simulated or measured spectra at various grid energies by using stripping methods as discussed in Maeda et al [4]. Air corrections were made by using the mass attenuation coefficients using NIST data tables [5]. The corrected spectrum was used as an input for an EGSnrc Monte Carlo simulation [6] using realistic representation of the Intrabeam applicators. This simulation was used to score the spectra of secondary electrons generated in a 5 mm shell in breast tissue surrounding the applicator surface. Auger electron lines below 1 keV were manually added to the electron spectra as described in [7].

RESULTS: Measured Intrabeam X-ray spectra were comparable to those previously published (e.g. [8]). The stripping correction led to shifting of characteristic peak energies and had the most significant impact at low energies. Via the EGSnrc simulation we have been able to estimate Compton and photoelectron spectra in breast tissue as a function of device applicator size.

DISCUSSION & CONCLUSIONS: By combining measured spectra of X-rays from the Intrabeam source with Monte Carlo simulation of their subsequent transport in applicator and breast material, we have been able to derive the spectra of secondary electrons as generated in the region of breast tissue adjacent to the applicator. These spectra will be used to inform Monte Carlo damage simulation code in order to determine the relative RBE as a function of applicator size which, combined with theoretical DSB repair, will be compared with experimental measurements.

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DIMENSIONALITY REDUCTION OF DOSE-WALL HISTOGRAM VARIABLES USING PRINCIPAL COMPONENT ANALYSIS: ANALYSIS OF DATA FROM THE RADAR CLINICAL TRIAL

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INTRODUCTION: Dosimetric indices from dose-wall histograms (DWHs) are highly correlated to each other. To use the indices in toxicity prediction, the data needs to be reduced to smaller dimensions without losing important variance which may predict toxicity. Principal component analysis (PCA) has been used for this purpose without clear benefit. In this study, the principal components (PCs) of DWHs are used to construct toxicity prediction models for comparison with more routinely-derived indices. We aimed to validate this dimensionality reduction method using the extensive RADAR data set.

METHODS: Following review and archive to a query-able database, digital treatment plans for 754 patients were available from the TROG 03.04 RADAR prostate radiotherapy trial. The toxicity incidence for analysis was an increase of more than 5 of International Prostate Symptoms Score (IPSS) at three months after the end of three-dimensional conformal radiotherapy (3D-CRT). The variance of dose-wall histogram morphology of the bladder wall was summarized with principal components (PCs). We used logistic regression to measure the correlation between the first four PCs, mean dose, dose-received by the hottest 1cc (D1) and 2cc (D2), prescribed dose and relative volume of tissue receiving a dose threshold (V10, V20... V70).

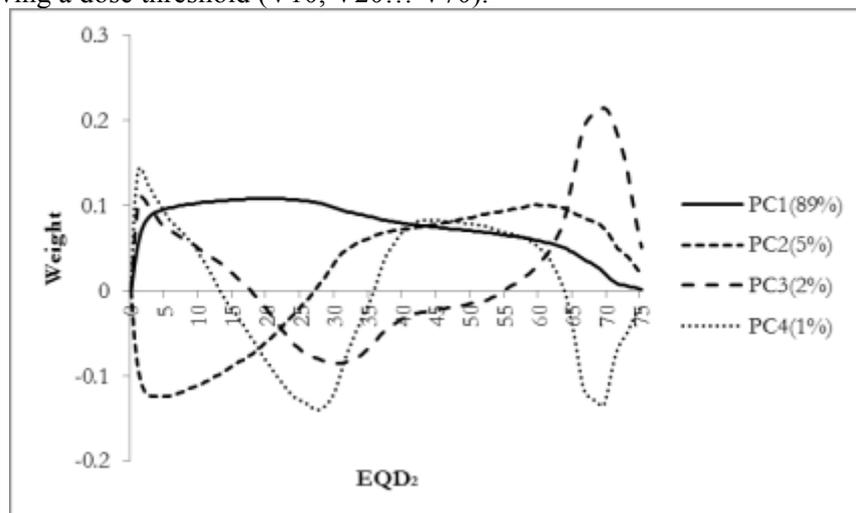


Fig. 1: Eigenvectors of PC1 to PC4. Percent variance described is shown in brackets.

RESULTS: The first PC describes 89% of the variation of DWH (Fig 1) and it is highly correlated to the mean dose (Spearman $r=0.998$). The second PC puts higher weight on V40 to V70 while the third PC has higher weight on dose between V65 to V75 and correlated to D2. Significant and borderline associations exist between PC1, mean dose, V10, V20, and V30 and acute urinary toxicity incidence. All non-PC indices associated with the incidence are highly correlated to PC1. The ORs expressed as a change of 1sd show similar result between PC1 and mean dose.

DISCUSSION & CONCLUSIONS: In our cohort of patients, the acute urinary toxicity can be best explained by the first PC. PCA can be used to reduce the dimensionality of DWH but without apparent advantage over simpler and widely-used indices like mean dose to capture the most variance.

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