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Validation of in-house knowledge-based planning model for predicting change in target coverage during VMAT radiotherapy to in-operable advanced-stage NSCLC patients

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Abstract

***Objectives*:** anatomical changes are inevitable during the course of radiotherapy treatments and, if significant, can severely alter expected dose distributions and affect treatment outcome. Adaptive radiotherapy (ART) is employed to maintain the planned distribution and minimise detriment to predicted treatment outcome. Typically, patients who may benefit from adaptive planning are identified via a re-planning process, i.e., re-simulation, re-contouring, re-planning and treatment plan quality assurance (QA). This time-intensive process significantly increases workload, can introduce delays and increases unnecessary stress to those patients who will not actually gain benefit. We consider it crucial to develop efficient models to predict changes to target coverage and trigger ART, without the need for re-planning.

***Methods*:** knowledge-based planning (KBP) models were developed using data for 20 patients' (400 fractions) to predict changes in PTV V_{95} coverage ($\Delta V95^{PTV}$). Initially, this change in coverage was calculated on the synthetic computerised tomography (sCT) images produced using the Velocity adaptive radiotherapy software. Models were developed using patient (cell death bio-marker) and treatment fraction (PTV characteristic) specific parameters to predict ($\Delta V95^{PTV}$)and verified using five patients (100 fractions) data.

***Results*:** three models were developed using combinations of patient and fraction specific terms. The prediction accuracy of the model developed using biomarker (PD-L1 expression) and the difference in 'planning' and 'fraction' PTV centre of the mass (characterised by mean square difference, MSD) had the higher prediction accuracy, predicting the ($\Delta V95^{PTV}$)within ± 1.0% for 77% of the total fractions; with 59% for the model developed using, PTV size, PD-L1 and MSD and 48% PTV size and MSD respectively.

***Conclusion*:** the KBP models can predict ($\Delta V95^{PTV}$)very effectively and efficiently for advanced-stage NSCLC patients treated using volumetric modulated arc therapy and to identify patients who may benefit from adaption for a specific fraction.

Introduction

Adaptive radiotherapy (ART) is an interactive process where treatment plans are modified to account for internal and/or external anatomical changes observed on volumetric images acquired prior to treatment delivery (Berkovic *et al.*, 2015; Li, 2011; Yan *et al.*, 1997; Britton *et al.*, 2007; Juhler-Nottrup *et al.*, 2008; Fox *et al.*, 2009). Anatomical changes, such as atelectasis, tumour baseline shift (0.5 cm (Tennyson *et al.*, 2017) to 1.5 cm (Mao *et al.*, 2017)), infiltrative changes, tumour progression, and pleural effusion, are inevitable during radiotherapy (Bosmans *et al.*, 2006; van Zwienen *et al.*, 2008; Fox *et al.*, 2009; Britton *et al.*, 2009; Britton *et al.*, 2007; Juhler-Nottrup *et al.*, 2008; Kwint *et al.*, 2014; Moller *et al.*, 2016). Significant anatomical changes could alter the planned dose distribution to an unacceptable level that could affect treatment outcome (Kataria *et al.*, 2014; Langendijk *et al.*, 2008). Work performed by Britton et al reported an average reduction in the dose to 95% of the planning target volume (PTV) and internal target volume (ITV) by – 11.9% ± 12.1% and – 2.5% ± 3.9% respectively compared to the original clinical plan distribution (Britton *et al.*, 2009; Britton *et al.*, 2007). Furthermore, several studies have also reported an increase in organs at risk (OAR) doses as a result of change in internal anatomy (Britton *et al.*, 2009; Britton *et al.*, 2007; Kataria *et al.*, 2014). These studies have showed that ART improves treatment outcome (Kataria *et al.*, 2014) for advanced stage non-small cell lung cancer (NSCLC) patients as prescription doses are delivered as planned, OAR doses are reduced and it allows dose escalation (Berkovic *et al.*, 2015; Li, 2011; Yan *et al.*, 1997; Britton *et al.*, 2007; Juhler-Nottrup *et al.*, 2008; Fox *et al.*, 2009; Sibolt *et al.*, 2015; Ramella *et al.*, 2017; Kataria *et al.*, 2014).

Different thresholds have been used to initiate adapting planning, including, an increase in OAR doses and/or reduction in ITV and PTV V_{95} coverage compared to the original clinical plans (V_{95}: volume of PTV or ITV receiving 95% of the prescription dose). Treatment plans were adapted for the patients where PTV and/or ITV volume(s) receiving 95% of the prescription dose reduced by ≥ 3% and/or ≥ 1% respectively (Britton *et al.*, 2009; Britton *et al.*, 2007; Spoelstra *et al.*, 2009; Moller *et al.*, 2016). In addition to the target coverage threshold, Moller et al investigated if ART could be triggered using surrogate volumes, using ring structures around the gross tumour

volume (GTV) and lymph nodes with margins of 2 mm and 5 mm respectively. ART was considered for the patients where the target volumes move outside the ring structures. They reported that the trigger criteria used, identified 98% of the patients correctly for adaptive planning with a false-positive rate of 20% (Moller *et al.*, 2016).

However, implementing ART clinically is challenging, especially identifying the patients who may benefit from ART in a timely manner. Some may not benefit where anatomical changes or tumour baseline shift is not sufficient enough to warrant plan adaption. The typical processes used for identifying the patients for adaptive planning are time-consuming and require the patients to undergo the full planning process (i.e., rescanning, re-contouring and re-optimising). This could significantly increase the clinical workload and also increase the radiation burden to these patients. Therefore, it is important to develop alternative methods to accurately identify patients for ART, without sending the patients through the full planning process for efficiency and convenience.

This study aimed to develop in-house knowledge-based planning (KBP) models for predicting change in planning target volume V_{95} coverage, compared to the original clinical plan, during the course of radiotherapy. A combination of patient-specific parameters and the change in PTV V_{95} coverage were used to build the models. Finally, the models were verified by comparing their prediction accuracy with the ones calculated on synthetic computerised tomography (sCT).

Method

Data collection

A total of twenty-five pre-existing patients' data were collected from the Eclipse treatment planning system and Lorenzo™ electronic patient record databases. A number of parameters, including, patient's demographics, histopathology, tumour staging, immune histology, PTV volume in a cubic centimetre (cc), and dose-volume histogram for PTV for each treated fractions were collected.

Treatment planning

In our clinic, for treatment planning, lung cancer patients capable of breathing regularly undergo four-dimensional computerised tomography scan (4DCT) and the patients with irregular breathing undergo a 3DCT scan. The 4DCT scans are binned into ten phases and the GTV contoured on at least three binned phases (e.g. max-inhale, max-exhale, and mid-phase) ensuring the full tumour motion is captured. The GTV contoured on each phased image was transferred onto the free-breath (FB) scan to accumulate with the others. For 3DCT patient, the GTV was contoured on the 3D scan. The internal target volume (ITV) for 4D patients and CTV for 3D patients were created by applying an isotropic margin (for microscopic spread) for squamous cell carcinomas (0.6 cm) and adenocarcinomas (0.8 cm) from accumulated GTV and 3D GTV respectively. The OAR volumes were contoured on FB scan and was used for treatment plan optimisation and dose calculations. The PTV was produced using a 0.5 cm isotropic margin from ITV for 4D patients, whereas, for 3DCT patients, PTV is produced by applying 0.9 cm circumferential and 1.2 cm superior and inferior margin.

All patients included in the study were planned with RapidArc®/VMAT (volumetric modulated arc therapy) within the Eclipse™ treatment planning system (Version 13.7, Varian Medical Systems, Palo Alto, CA) with 6 MV beams. Two partial arcs for both right- and left-sided tumours were used; direct beam entry through the contralateral lung was avoided in each case to minimise the dose received by it. Plan dose was calculated using the Acuros® XB algorithm (dose to water) with a uniform dose grid of 0.25 cm. The prescribed dose for patients included in the study was 55 Gy in 20 fractions. Treatment plans were optimised to meet the planning goals as described in Table 1. The normal tissue objective (NTO) function was used to limit the dose to healthy structures with the same priority as the PTV. The NTO is a function in the Eclipse planning system that reduces dose to healthy tissue as a function of distance from the PTV's outer boarder *(Olofssn, 2012)*. The default NTO settings were automatically applied (these being: distance from target boarder 1.0 cm, start dose 105%, end dose 60% and fall- off 0.05) with priority set the same as the PTV.

Assessment of adaptive planning

Production of synthetic CT (sCT): the cone-beam computerised tomography (CBCT) images acquired prior to each treatment fraction were imported in the Velocity 'adaptive radiotherapy' software (Velocity 4.0, Varian Medical System, Palo Alto, CA). To facilitate the image processing within the Velocity, the following was undertaken, 1) the planning CT (pCT) and CBCT images were initially rigidly registered using the same transformation obtained during a respective treatment session, to remove the impact of residual setup errors (Wang *et al.*, 2020).

2) The setup corrected using translational corrections only (6 degree of freedom correction is not available in our clinic). CBCT images were deformably registered to the treatment planning CT (pCT) images excluding the most superior and inferior slices to produce a synthetic image set (sCT).

3) A secondary structure data set was produced in the sCTs, including GTV and OAR volumes. The registration and volumes for each sCT were reviewed.

Evaluation dosimetric variations: sCTs produced within the Velocity were imported in the Eclipse treatment planning system. The GTV for each fraction was reviewed and edited where required by experienced clinical oncologists to account for tumour baseline shift and anatomical changes. Furthermore, clinical and planning target volumes were produced on each sCT by applying the same margin as the clinical plan. Then, doses were calculated on each synthetic CT using the same monitor units (MU) as the original clinical plan and the difference in PTV V_{95} coverage ($\Delta V95^{PTV}$) for each fraction was calculated (equation 1) and used to build the models.

Dose calculations in Eclipse V15.6: The planning system was upgraded to V15.6 prior to the experiment, so all the original clinical plans were recalculated in V15.6 using the same MUs as the original clinical plan (i.e. V13.7). Doses were calculated on sCT in V15.6 and compared with the clinical planned dose distribution calculated in V15.6. The PTV coverage by 95% of the prescription dose is denoted $V95^{PTV}$; the coverage planned on the planning scan is given a subscript 'planned' and the delivered dose calculated on synthetic scan is given a subscript 'delivered'.

$$\Delta V95^{PTV} = (V95^{PTV}_{Delivered} - V95^{PTV}_{Planned}) \quad \textbf{1}$$

Target volume baseline shift: the baseline shift of the centre of the mass (CoM) between the planning PTV (i.e. PTV from the original clinical plans) location and the adapted PTV (i.e. PTV produced on each sCT) was recorded. The Mean square difference (MSD) of the CoM shift was calculated for each fraction, being $[\frac{1}{3}\sum \Delta Xi^2]$ where *i* represents the x,y,z components of the shift-vector.

Immune-histology: in our clinic, immune histological (programmed death-ligand 1 (PD-L1) expression) testing for NSCLC patients started in 2017. Cell samples taken at biopsy were sent to immune-histology labs to assess PD-L1 expression using the Dako PD-L1 IHC 22C3 pharmDx test. These data were stored in the electronic patient record system, Lorenzo^{TM} and available for this study. Recent clinical trial results showed significant improvement in overall survival in patients who received consolidation treatment with durvalumab (immunotherapy) (Paz-Ares *et al.*, 2020; Brahmer *et al.*, 2018; Antonia *et al.*, 2018; Antonia *et al.*, 2017). In the trial, durvalumab was administered to patients who have had stable disease or treatment response following chemo-radiotherapy (Paz-Ares *et al.*, 2020; Brahmer *et al.*, 2018; Antonia *et al.*, 2018; Antonia *et al.*, 2017). Durvalumab is a human monoclonal antibody that selectively binds to programmed death ligand-1 (PD-L1), blocking its interaction with its receptor, programmed death-1 (PD-1) (Paz-Ares *et al.*, 2020; Antonia *et al.*, 2018; Antonia *et al.*, 2017).

Development of model

Three knowledge-based planning models were developed using multivariate analysis. Twenty patients' data were used to develop the models and that for five patients retained for verifying the model predictions. PTV V95 coverage calculated for each fraction; PTV volume, lungs-GTV (total lungs volume substracted from GTV) volume, Heart (cc) volume, as contoured at planning in a cubic centimetre (cc) and MSD, for each fraction, were calculated and used to develop the models. Three models were developed using MSD, PD-L1 and PTV volume parameters to predict the change in PTV V_{95} coverage for each fraction. Model 1 was developed using MSD (fraction term) and PTV (patient term) (see equation 2), Model 2 developed using all three parameters, fraction term (MSD) and patient term (PD-L1 and PTV) (see equation 3) and the Model 3 was developed using MSD and PD-L1 (see equation 4). The prediction accuracy of

each model was calculated using equation 5 (where j refers to model index) and assessed.

$$Model\_1 = [(m_{MSD} \times MSD) + (m_{PTV(cc)} \times PTV_{cc})] \quad \textbf{2}$$

$$Model\_2 = [(m_{MSD} \times MSD) + (m_{PTV(cc)} \times PTV_{cc}) + (m_{PDL1} \times PD - L1)] \quad \textbf{3}$$

$$Model\_3 = [(m_{MSD} \times MSD) + (m_{PDL1} \times PD - L1)] \quad \textbf{4}$$

$$Predict\ \Delta V95^{PTV} = m \times Model\_j \quad \textbf{5}$$

Verification of the model

The model was verified by predicting a change of PTV V_{95} coverage ($\Delta V95^{PTV}$) for five patients that were independent of those used for creating the models. The predicted change for each fraction (using all three models) was compared to the dose coverage calculated on each fraction's synthetic CT.

Statistical analysis

The KBP models were developed using multivariate analysis. The prediction accuracy of each model was assessed using the Student's paired t-test. p- values < 0.05 were considered as suggesting statistically significant differences.

Results

Development of models

The knowledge-based planning models were developed to predict the change in PTV V_{95} coverage ($\Delta V95^{PTV}$) using combinations of, PD-L1: biomarker, MSD: tumour baseline shift, PTV, lungs-GTV, and heart size (Figure 1). However, the models included OAR did not improve results. A total of 400 fractions (n = 20 patients) were used to develop the models (see Table 2 for patient demographics). The observed range of the data was: MSD 0.0 to 20.23, PD-L1 0.0% to 100.0% and difference in PTV V_{95} coverage -11.8% to 10.1%.

Accuracy models

$\Delta V95^{PTV}$ was predicted using all three models for 100 fractions (n = 5 patients) (Figure 2). Model 1 showed statistically significant differences (i.e. model 1 did not model the change in PTV coverage volume well) between the prediction and calculated PTV V_{95} coverage with p = 0.018, whereas the model 2 and 3 did not show significant differences with the p = 0.163 and 0.509 respectively.

Furthermore, the percentage of fractions with $\Delta V95^{PTV}$ between ± 0.5% and ± 1.0% was calculated (Table 3). The results show that model number three, developed using PD-L1 and MSD, predicted 77% of the total fractions within ± 1.0%. The percentage of such fractions was lower for models 1 and 2, 48% and 59% respectively. The numerical data for all three models are shown in Table 4.

This data is depicted over a broader comparison threshold is given in Figure 1 and plots of individual fraction prediction against measured difference, for all the test factions, are shown in Figures 2A-C.

Discussion

Anatomical changes, either internal (e.g. atelectasis, tumour shrinkage or growth, or shift tumour location) and/or external (patient weight loss), commonly occur during the course of radiotherapy for inoperable advanced-stage NSCLC patients. Significant changes in anatomy could alter planned dose distribution and affect treatment outcome for patients if treatment plans are adapted. Several studies have demonstrated the benefits of adaptive radiotherapy.

Furthermore, the frequency of adaptations is important especially when the patients are treated with fewer numbers of fractions (hypo-fractionated radiotherapy, e.g. 55 Gy in 20 fractions) as compared to the conventional fractionated radiotherapy (66 Gy or 60 Gy in 33 or 30 fractions respectively). Volumetric imaging and time-consuming re-planning are required to assess and to make treatment management decisions. This could significantly increase clinical workload and also increase the radiation burden to

the patients who do not benefit from adaptive planning. Therefore, more efficient methods are required to assess if the patients would benefit from adaptive planning or not and to assess the optimal time for adaption. This study was performed with prior approval from the local research and development department.

A percentage drop in PTV V95 coverage has been commonly used to trigger ART planning (Britton *et al.*, 2009; Britton *et al.*, 2007; Spoelstra *et al.*, 2009; Moller *et al.*, 2016). To reduce decision making time overheads we felt it was important to develop in-house knowledge-based planning models to efficiently estimate PTV dose coverage using patient-specific parameters with/without data available from patient set-up at the beginning for the fraction. The 'fraction data' considered were PTV characteristics, specifically the difference between the planned PTV and the PTV at the treatment fraction as represented by the MSD of the shift between their respective centre of mass. The results showed that relatively simple models can predict change in PTV V95 coverage efficiently *and* accurately, as compared to recalculations based on original clinical plans, which was the primary aim of this study.

It was interesting to observe that, the model developed using both PTV characteristics and PD-L1 data (patient term) combined had higher prediction than the model developed using the PTV characteristics only. However, the model built with PD-L1 data and the single 'fraction' PTV characteristic representing the relative change between plan and fraction presentation had higher accuracy compared to the model produced using these along with the 'planning' PTV size (patient term). This points towards the necessity or importance of having a term that represents the physical changes between the plan and the delivery fraction. A fourth model, unreported here, was investigated that used the planning PTV data and PD-L1 data, however extremely poor correlation or predictive potential was noted and this option was discarded early in our study.

Validation of the models indicated a superiority of the predictive benefit of a combination of the PD-L1 data and the shift of PTV centre of mass at very exacting comparison criteria; we note that for more forgiving thresholds (i.e., ≥ ± 2.0%) the three models converged. Compared to the study by Moller (Moller *et al.*, 2016), the prediction accuracy of the models 1 and 2 was higher at locally used trigger level of

3% for adaptive planning (i.e., 3% reduction in PTV coverage triggering the decision) whereas it is the same for the model 3. However, the approaches in that study and ours were very different; our study does not require to produce any addition structures which is the basis of their methodology. described by Moller (Moller *et al.*, 2016). At a 5% trigger level (suggested by Britton *et al.*, 2009; Britton *et al.*, 2007; Spoelstra *et al.*, 2009), the prediction accuracy is 100% for all three of the models presented herein. Furthermore, unlike other studies, the models presented in our study can predict trends and could help managing workload.

The parameters used in this study are readily available for all advanced stage inoperable lung cancer patients. The patient-specific (PTV volume and PD-L1) parameters are available before starting radiotherapy: PD-L1 is acquired for all advanced-stage NSCLC patients to decide if the patient is suitable for immunotherapy and the PTV volume is contoured for all radical lung patients prior to starting treatment. The treatment fraction specific information is available (in some form) for all patients who undergo volumetric image-guided radiotherapy and is obtained prior to delivering each treatment fraction. This means that our models can trigger adaptive radiotherapy using readily available information and more importantly prior to delivery of each fraction. We continue to consider and explore models that will help predict the likelihood a patient may benefit from adaption strategy, based on characteristics independent of radiotherapy planning/treatment.

In this study (reflecting our clinical capability) we only considered the use of 3 Degree Of Freedom (3DOF) registration and corrections. This requires that a greater translation in the registration may be needed, to offset the lack of rotational correction, and would be represented by a larger MSD term in our calculations. In our models this leads to a larger estimate of the predicted change in PTV coverage which, if greater than the trigger level for re-planning, may lead to a replan (adaption) that wouldn't have been required should a 6DOF correction have been available. However, we do not consider this to be a limitation of our methodology since the replanning is triggered in response to the capabilities of the treatment system under consideration.

Conclusion

This study showed that relatively simple KBP models can accurately *and* efficiently predict change in the PTV (V95) dose coverage without the need for full-dose calculations. We found that a model based on a parameter (MSD) representing the spatial shift of the PTV beween planning and treatment verification scan and a patient specific parameter (PD-L1) resulted in the better accuracy of prediction. The application of such methodologies will help to streamline the adaptive radiotherapy planning process for advanced stage in-operable non-small cell lung cancer patients. These models could be used in the context of on-table adaption or in a more conservative approach where a trend over 'fractions to date' are considered to predict a likely need for adaption on a 'near future fraction'. More importantly, in this study, a patient-specific biomarker (PD-L1), which is independent of the radiotherapy planning or treatment (verification) parameters, has been used for the first time and shown to be valuable in developing a model for predictively triggering Adaptive Radiotherapy.

Acknowledgement and conflict of interest

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The authors declare no potential conflicts of interest.

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Table 1: Treatment planning objective used for planning NSCLC patients at our clinic

Volume	Parameters	Clinical constraints
Spinal Cord PRV (Planning Organ at Risk Volume)	$D_{0.01cc}$	< 45Gy
Planning target volume (PTV)	V_{95}	≥ 99%
	V_{107}	< 1.8cc
Lungs-gross tumour volume (GTV)	V_{5Gy}	< 60%
	V_{20Gy}	< 35%
Heart	V_{30Gy}	< 45%
	Mean Dose	< 26Gy

Table 2: Patient demographics for the patients included to build and to verify the models.

	Mean/Frequency/Range Within Models	Mean/Frequency/Range Verification (outside models)
Age mean (+/- SD)	70.37 (6.72) Years	69.36 (6.83) Years
Gender		
Male	9	3
Female	11	2
Staging	T1aN0/T4N3	T1aN0/T4N3
PTV volume (cc)	325.6/164.0 – 507.2	269.7/97.8 – 476.41
Histology		
Adenocarcinoma	10	2
Squamous cell carcinoma	10	3

Table 3: Percentage of total fractions from the test data set against the different limits.

	±0.5%	±0.6%	±0.7%	±0.8%	±0.9%	±1.0%
Model1	24%	28%	34%	37%	43%	48%
Model2	32%	39%	42%	45%	53%	59%
Model3	58%	65%	71%	74%	75%	77%

Table 4: Coefficients of the models developed for predicting change in target coverage.

	Model1	Model2	Model3
Patient factor		**Coefficients**	
Intercept	-2.228	-1.342	0.237
MSD	-0.577	-0.669	-0.727
PD-L1	NA	-0.012	-0.017
PTV Vol (cc)	0.005	0.004	NA

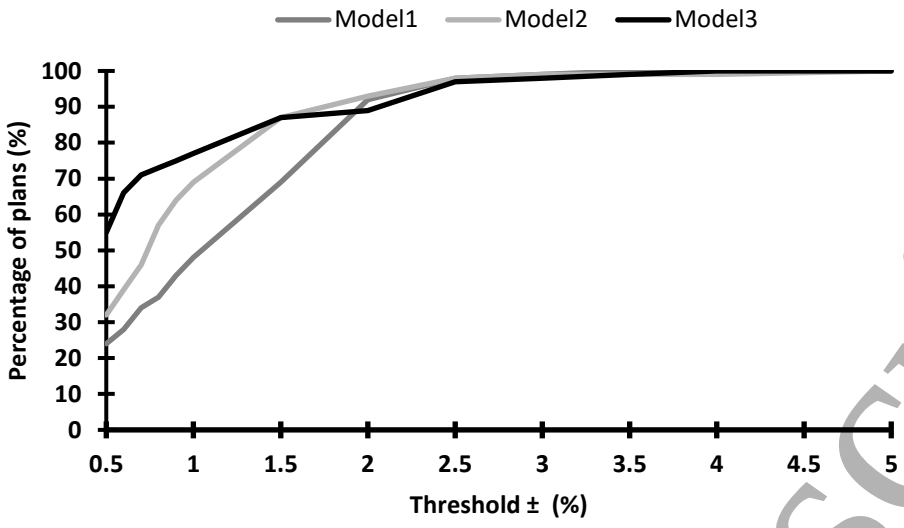

Figure 1: Percentage of total fractions within plus and minus the defined threshold.

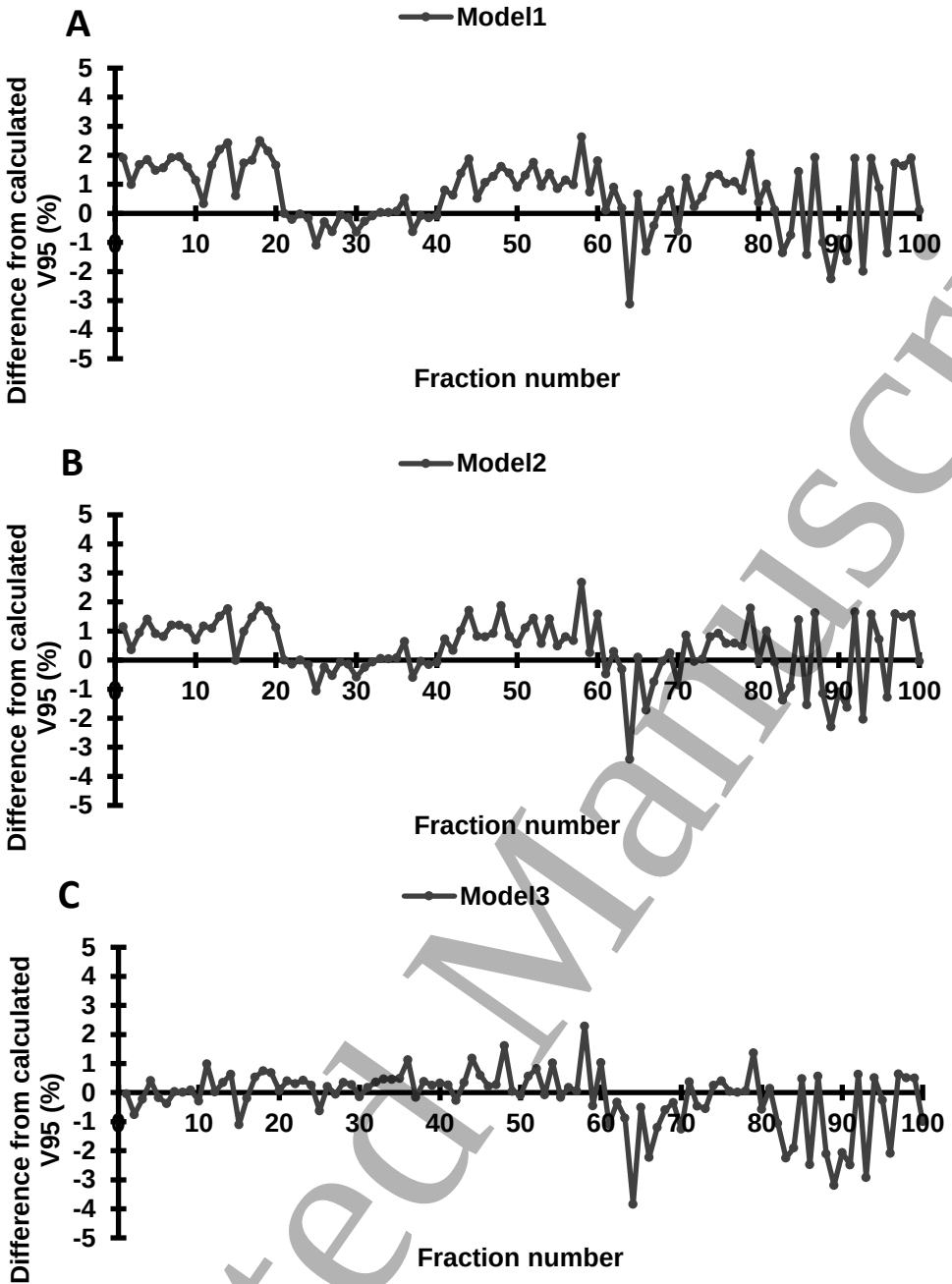

Figure 2: Verification data for all three models.

A) Results from the model developed using mean square difference (MSD) and PTV volume (cc); B Results from the model developed using MSD, PTV volume and PD-L1; C Results from the model developed using PD-L1 and MSD.