

# A Novel TPS Toolkit to Assess Correlation Between Transit Fluence Dosimetry and DVH Metrics for Adaptive Head and Neck Radiotherapy

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## Research Article

**Keywords:** Adaptive radiotherapy, Volumetric modulated arc therapy (VMAT), Transit dosimetry, RayStation scripting

**Posted Date:** May 25th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-541098/v1>

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**Version of Record:** A version of this preprint was published at Physical and Engineering Sciences in Medicine on August 31st, 2021. See the published version at <https://doi.org/10.1007/s13246-021-01048-5>.

# A Novel TPS Toolkit to Assess Correlation between Transit Fluence Dosimetry and DVH Metrics for Adaptive Head and Neck Radiotherapy

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## Abstract

Inter-fractional anatomical variations in head and neck (H&N) cancer patients can lead to clinically significant dosimetric changes. Adaptive re-planning should thus commence to negate any potential over-dosage to organs-at-risk (OAR), as well as potential under-dosage to target lesions. The aim of this study is to explore the correlation between transit fluence, as measured at an electronic portal imaging device (EPID), and dose volume histogram (DVH) metrics to target and OAR structures in a simulated environment. Planning data of 8 patients that have previously undergone adaptive radiotherapy for head and neck cancer using volumetric modulated arc therapy (VMAT) at the Royal Adelaide Hospital were selected for this study. Through delivering the original treatment plan to both the planning and rescan CTs of these 8 patients, predicted electronic portal images (EPIs) and DVH metrics corresponding to each data set were extracted using a novel RayStation script. A weighted projection mask was developed for target and OAR structures through considering the intra-angle overlap between fluence and structure contours projected onto the EPIs. The correlation between change in transit fluence and planning target volume (PTV) D98 and spinal cord D0.03cc with and without the weighting mask applied was investigated. PTV D98 was strongly correlated with mean fluence percentage difference both with and without the weighting mask applied ( $R_{\text{Mask}} = 0.69$ ,  $R_{\text{No Mask}} = 0.79$ ,  $N = 14$ ,  $p < 0.05$ ), where spinal cord D0.03cc exhibited a weak correlation ( $R_{\text{Mask}} = 0.35$ ,  $R_{\text{No Mask}} = 0.53$ ,  $N = 7$ ,  $p > 0.05$ ) however this result was not statistically significant. The simulation toolkit developed in this work provided a useful means to investigate the relationship between change in transit fluence and change in key dosimetric parameters for head and neck cancer patients.

**Keywords** Adaptive radiotherapy · Volumetric modulated arc therapy (VMAT) · Transit dosimetry · RayStation scripting

36 **Declarations**

37 **Funding** – No funding was received for conducting this study.

38 **Conflicts of interest/Competing interests** – The authors have no relevant financial or non-financial  
39 interests to disclose.

40 **Availability of data and material** – Not applicable

41 **Code availability** – Not applicable

42 **Ethics approval** – Approval was obtained from the Central Adelaide Local Health Network Human  
43 Research Ethics Committee (CALHN HREC). The procedures used in this study adhere to the tenets  
44 of the Declaration of Helsinki.

45 **Consent to participate** – Each participant has given consent to participate, via the statement “I do  
46 approve the use of my radiation therapy records for retrospective medical auditing and / or research.

47 **Consent for publication** – Not applicable

48

49

## 50 1.0 Introduction

51 Anatomical variations in head and neck (H&N) cancer patients can lead to clinically significant plan deterioration  
52 and adaptive radiotherapy (ART) may be required to restore an optimal dose distribution [1]. Past literature has  
53 explored the benefits of implementing ART workflows within a clinic for H&N cancer and has mostly been  
54 focused on improving dosimetry in parotid glands, which is crucial when lowering risk of xerostomia [1], [2].  
55 Monitoring the dose delivered to the spinal cord, via evaluation of kV cone-beam computed tomography (CBCT),  
56 has also shown to be beneficial in answering the golden question: *when* should we replan? [3]

57 Traditional methods to implement ART into the clinic are associated with a significant increase in the clinical  
58 workload to the radiotherapy department as a whole. As a result, there has been a recent push to develop an  
59 accessible and automated quantitative trigger for ART, with one common method being transit dosimetry with an  
60 electronic portal imaging device (EPID) [4]. Using relative EPID dosimetry, one can explore the gradual change  
61 in transit fluence over the course of treatment without necessarily needing to rely on the absolute precision and  
62 accuracy of the images themselves. Change in transit fluence is expected to be correlated with anatomical  
63 variations and patient setup errors, which has thus far been the main focus of research on this topic. Several groups  
64 have tried to correlate dosimetric impacts with change in transit fluence, where 2D relative gamma analysis is  
65 commonly utilised [5]–[8]. Through conducting gamma analysis on the transit EPID images acquired over the  
66 course of treatment, a variety of parameters can be extracted to help quantify change in dose to the patient.

67 Through utilising the mean gamma value,  $\gamma_{mean}$ , from a 2D 3%/3mm relative gamma analysis test on whole  
68 electronic portal images (EPIs), Piron et al. [5] concluded that change in transit fluence could be used as a predictor  
69 for plan deterioration for H&N cancer patients as a result of anatomical variations. Utilising the whole EPI,  
70 however, could result in misleading mean gamma values. If only a small area of pixels included large deviations,  
71 the EPI as a whole may still be similar to the baseline EPI and thus result in a score that is below the trigger  
72 threshold, ultimately decreasing sensitivity. By considering projections of regions of interest onto the EPIs, the  
73 sensitivity of the analysis may be improved.

74 By projecting planning target volume's (PTV's) onto EPIs obtained every fraction and correlating  $\gamma_{mean}$  with  
75 dosimetric changes (V95%), Piron et al. [6] found that projecting PTVs onto the EPIs and then conducting gamma  
76 analysis improved sensitivity to anatomical changes. However, projecting OARs onto the EPIs were not  
77 considered.

78 The same group then went on to establish an action threshold for H&N ART, and proposed a threshold of  
79  $\gamma_{mean} > 0.42$ , as evaluated using the whole EPI [7]. By considering a dosimetric threshold of V100% < 90% the  
80 group was able to analyse the sensitivity and specificity of the threshold proposed. Moreover, the group also  
81 explored the correlation between mean dosimetric differences of PTV and OARs with mean gamma values of the  
82 whole EPI for patients that did reach the action threshold, as well as patients that did not. A strong correlation  
83 between change in spinal cord dose and  $\gamma_{mean}$  was not observed, likely due to the inherent nature of the gamma  
84 analysis test conducted on whole EPIs - being more sensitive in high dose regions, such as PTVs, than lower dose  
85 regions, such as OARs.

86 Lim et al. [9] explored the correlation between change in transit fluence, in a generalised rectangular region  
87 surrounding the neck, and volumetric change of a ROI ( $\Delta V_{ROI}$ ) spanning from the Condylod process (jaw) to C6  
88 of the spinal cord. Volumetric change, which is a good predictor for grade 2 xerostomia [10], was found to be  
89 strongly correlated with change in transit fluence ( $R = -0.776, p < 0.001$ ). A 5% threshold in  $\Delta V_{ROI}$  could be

90 used as a trigger for ART, where the area under the receiver-operating characteristic curve (ROC) was determined  
91 to be 0.88. This study did not investigate the potential improvement in sensitivity by projecting the ROI onto the  
92 EPID.

93 When utilising linac-measured EPIs for relative gamma analysis, one of the largest sources of systematic error  
94 in these types of studies include the accuracy of the first fraction EPI. The results of these studies all rely on the  
95 assumption that the patient anatomy at the time of the first fraction EPI is representative of the patient anatomy at  
96 the time of the planning CT (pCT). A poor baseline could be misleading and yield results with  $\gamma_{mean}$  values  
97 significantly lower than actually representative of the change since pCT. The research presented in this study  
98 differs from previous studies by predicting transit EPIs using an in-house script developed in the RayStation  
99 treatment planning system (TPS) by RaySearch Laboratories, rather than analysing linac-measured EPIs. The  
100 advantage of this approach is in the removal of any patient set-up errors, as well as any anatomical variation in the  
101 patient between obtaining the pCT and first fraction baseline EPI. Rather than using weekly CBCTs to obtain  
102 multiple EPIs over the course of treatment, this study will also only consider the pCT and rescan CT (rCT) to  
103 avoid any uncertainties associated with deformable image registration of the pCT's to CBCT's, or dose calculation  
104 uncertainty on CBCT. Considering these factors, the developed tool allows for the investigation of correlation  
105 between change in transit fluence and change in patient DVH metrics in a more controlled environment.

## 106 **2.0 Methods**

### 107 **2.1 Patient selection**

108 Human research ethics and research governance approval was obtained for the study. The radiotherapy datasets  
109 (treatment plans, planning CTs and RT structure sets) of eight patients previously having undergone adaptive  
110 radiotherapy for H&N cancer at the RAH were collected and anonymized. Each patient consented to their data  
111 being used for research purposes and had at least 1 rescan CT acquired over the course of treatment.

### 112 **2.2 EPI Prediction in RayStation**

#### 113 *2.2.1 EPID Model*

114 The EPID model developed in this work was generated to represent EPI's measured with a Varian TrueBeam  
115 aS1200 MV imager in Portal Dosimetry mode. Square field Portal Dosimetry images were collected to provide  
116 beam profiles and output factors with and without solid water in place and the EPID at 150 cm source to detector  
117 distance (SDD).

118 A simple EPID model was constructed in RayStation to model the Varian TrueBeam aS1200 MV imager  
119 operating in Portal Dosimetry mode. The model consisted of a 40 cm × 40 cm × 5 cm water slab atop a  
120 40 cm × 40 cm × 4 cm lead slab. Dose planes were extracted at 3.6 cm depth in the water slab. The selected water  
121 slab thickness and extraction depth were guided by Varian Portal Dosimetry calibration settings. The thickness of  
122 the lead slab was selected based on a comparison of measured and computed output factors. Calculated EPIs  
123 simulated in RayStation at 150 cm SDD were first downscaled to 100 cm SDD, where flood field and beam profile  
124 corrections were applied, and subsequently scaled back to 150 cm SDD. This was done to mimic the major  
125 corrections applied in forming an EPI in portal dosimetry mode on the linac.

### 126 2.2.2 EPI Extraction

127 The RayStation EPID template model was imported as regions of interest into the original treatment plan of a  
 128 given patient within RayStation. By utilising a number of functions within the RayStation python scripting  
 129 environment, an automated sequence of steps was programmed to rotate the EPID model around isocenter for each  
 130 control point of a VMAT plan as outlined in Fig. 1. The EPID model was first positioned to have the 3.6cm  
 131 extraction depth positioned 50.0 cm below the origin. This was followed by rotation to a given control point, and  
 132 subsequent translation to be centred at the isocenter. Once positioned appropriately, the dose for that VMAT  
 133 control point was calculated. The dose delivered to the extraction plane within the EPID model was then stored  
 134 into a 200 x 200 pixel array, with a pixel size of 2.0 mm, and subsequently integrated over every control point of  
 135 the VMAT plan. To help optimise the time required to extract the EPIs from  $n$  beams, the dose from all beams at  
 136 a given gantry angle was calculated, rather than rotating the model around the patient  $n$  times. Thus, the generated  
 137 image is a sum of all beams in a fraction, rather than per-beam images. Once the original treatment plan had been  
 138 simulated using the pCT, the process was repeated using the rCT to obtain a second EPI.



139  
 140 **Fig. 1** EPID extraction process repeated along every control point for both the pCT and rCT. EPID first positioned  
 141 50.0 cm below origin, then rotated to a given control point angle, and translated to 50.0 cm from isocenter

### 142 2.2.3 VMAT Script Validation

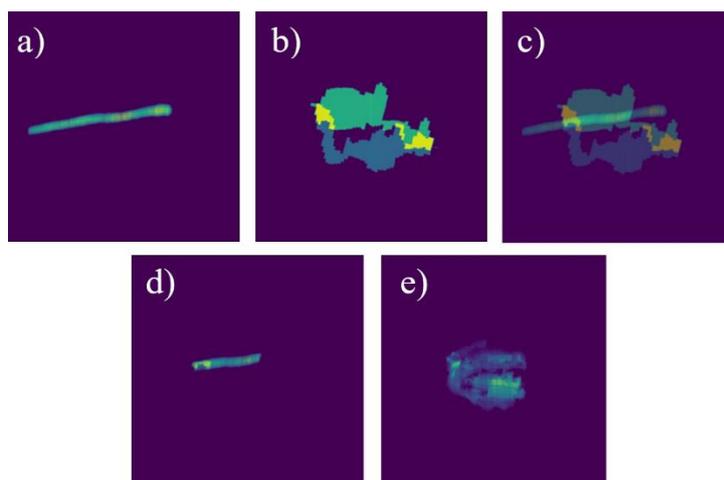
143 To validate our model, a 20.0 x 20.0 x 10.0 cm thick solid water slab was positioned at 90.0 cm SSD on a Varian  
 144 TrueBeam linac, with the EPID positioned at 150.0 cm SDD. A VMAT treatment plan was then delivered, and a  
 145 baseline EPI was extracted. To simulate change in patient anatomy, 2.0 cm of the solid water slab was removed  
 146 anteriorly and the same VMAT treatment plan was delivered to extract a second fraction EPI. The change between  
 147 the second EPI and the baseline was then calculated as a 2D percentage difference map, relative to dose maximum  
 148 of the baseline. This process was then repeated using the simulation toolkit developed in RayStation to obtain a  
 149 predicted 2D percentage difference map.

## 150 2.3 ROI Projection Mask

151 Past research has shown that projecting ROI's onto the EPIs can lead to improved sensitivity in using change in  
 152 transit fluence as a quantitative trigger for adaptive radiotherapy. The contours of the spinal cord and PTV's for  
 153 each patient included in the study were thus extracted through utilising DICOM RT structure files. These contours  
 154 could then be projected onto the extraction plane of the EPI with the use of modules within the dicompyler-core  
 155 Python package [11]. A ROI projection mask was then created, taking the thickness of the structure in the beam's-  
 156 eye-view into consideration to weight the mask by the path length through the structure as shown in Fig. 2.a).

157 In this work, the spinal cord was chosen as a significant ROI alongside the PTV's as plan adaption for H&N  
 158 patients at the Royal Adelaide Hospital is often triggered by the monitoring of spinal cord doses during on-course  
 159 plan dosimetry assessment. However, the methods outlined in this work can still be applied to a variety of different  
 160 structures, such as the parotid glands when considering toxicities such as xerostomia [9], [10]. If a plan contained  
 161 multiple PTV volumes with different dose levels, each was treated as an independent ROI in the correlation  
 162 analysis. The evaluation PTV contours (PTV\_EVAL), as calculated via subtracting the higher dose PTV's from  
 163 the lower dose PTV's, were utilised as these are the volumes that undergo DVH assessment during treatment  
 164 planning.

165 To further evolve the ROI projection mask, one can consider the overlap between the open field of the MLC  
 166 configuration and the projection of the structure of interest. Thus, the DICOM plan file was also used to extract  
 167 these coordinates on the EPI to create a 'fluence projection' mask. EPI pixels that lay within the open field  
 168 projection were given a value of 1, and those outside the open field were given a value of 0. The mask could then  
 169 further be weighted by the monitor units (MU's) delivered to the open field region for a given control point through  
 170 multiplying the mask through by the cumulative meterset value and beam MU's found in the DICOM RT plan file  
 171 as shown in Fig. 2.b). The resulting mask could then be integrated along each control point to obtain a final intra-  
 172 angle projection mask as shown in Fig. 2.e), which highlights the regions within the EPI for which dose was  
 173 delivered to a particular structure of interest, weighted by the structure's volume and MU's delivered.



174  
 175 **Fig. 2** Process used to derive an intra-angle ROI and fluence projection mask. For each control point, a) the  
 176 structure projection mask and b) fluence projection is used to obtain d) the overlap between the two, as visualised  
 177 by c). This process is repeated for each control point to achieve e) the final intra-angle ROI and fluence mask

## 178 2.4 DVH Parameters

179 Change in transit fluence alone cannot be used as a reliable trigger for adaptive radiotherapy without first  
 180 understanding how this quantity relates to dosimetric differences within the patient. Current workflows at the  
 181 Royal Adelaide Hospital involve an on-course dosimetry monitoring program to ensure target coverage does not  
 182 diminish by a certain amount and that serial organs at risk, such as the spinal cord, do not exceed tolerance values.  
 183 In this study DVH metrics considered for the spinal cord and PTV\_EVAL structures relate to the near maximum  
 184 and minimum doses received by the volumes, being the D0.03cc and D98 metric respectively. In this work, the  
 185 change in these metrics over the two CT datasets (original planning CT and rescan CT) was considered and any  
 186 correlation between them and change in transit fluence was explored.

## 187 2.5 Correlation

188 As previously mentioned, a correlation between change in transit fluence and change in D0.03cc or D98, for the  
 189 spinal cord and PTV's respectively, would show that change in transit fluence can be used as a trigger for adaptive  
 190 radiotherapy. There have been multiple approaches in quantifying this change in transit fluence to be used as a  
 191 trigger for adaptive radiotherapy, where gamma parameters are commonly utilised such as  $\gamma_{max}$ ,  $\gamma_{mean}$ , and  $\gamma_{1\%}$ .  
 192 One disadvantage of this approach is that gamma values are always positive and thus give no information regarding  
 193 the direction of such change. A second fraction EPI that has received a greater amount of dose than the baseline  
 194 may show similar corresponding gamma parameters to a second fraction EPI that has received less dose than the  
 195 baseline. It was thus decided that the mean percentage difference between the two EPIs should be calculated,  
 196 relative to the baseline, as this will also provide directional information. It should be noted, however, that signed  
 197 percentage differences in a region of interest may cancel and lead to lower-than-expected mean values. Care should  
 198 thus be taken when interpreting these values via first assessing the 2D percentage difference map.

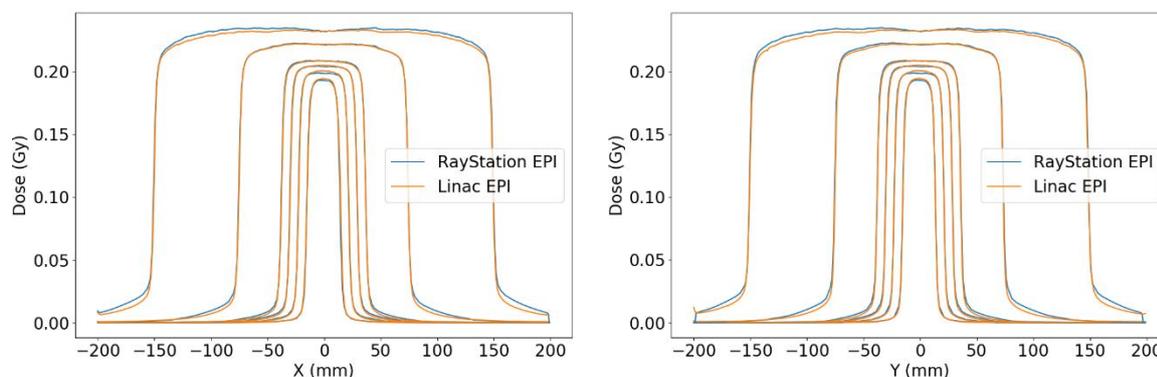
199 A correlation between the change in D0.03cc and D98, for the spinal cord and PTV\_EVAL's, and mean fluence  
 200 percentage difference with and without the respective masks applied was then explored. Noting that with no mask  
 201 applied, the entire 40x40 cm EPIs were utilised, whilst disregarding doses <10% of local maximum. Statistical  
 202 analysis was conducted through considering Pearson's correlation coefficient ( $R$ ), Spearman's rank correlation  
 203 coefficient ( $\rho$ ), and a linear regression with a 95% confidence interval. The statistical significance of the  
 204 correlation coefficients was also calculated for the given sample size, where the difference between the correlation  
 205 with and without the projection masks applied was also considered to explore any improvements in sensitivity that  
 206 the mask may supply.

## 207 3.0 Results

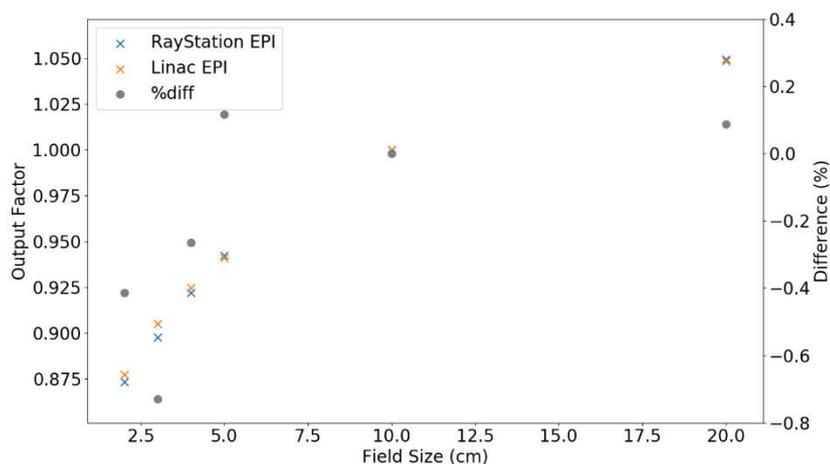
### 208 3.1 EPID Model

#### 209 3.1.1 Non-Transit Verification

210 The EPID model used in this work was developed through consideration of beam profiles, output factors, and  
 211 gamma analysis between predicted and measured EPIs. Fig. 3 shows beam profiles from linac-measured and  
 212 RayStation calculated EPIs after delivering 2.0 x 2.0, 3.0 x 3.0, 4.0 x 4.0, 5.0 x 5.0, 10.0 x 10.0, and  
 213 20.0 x 20.0 cm<sup>2</sup> square fields with the EPID positioned at 150 cm SDD. The output factors of these square fields  
 214 were also obtained, as shown in Fig. 4, showing percentage differences all less than 0.8%.



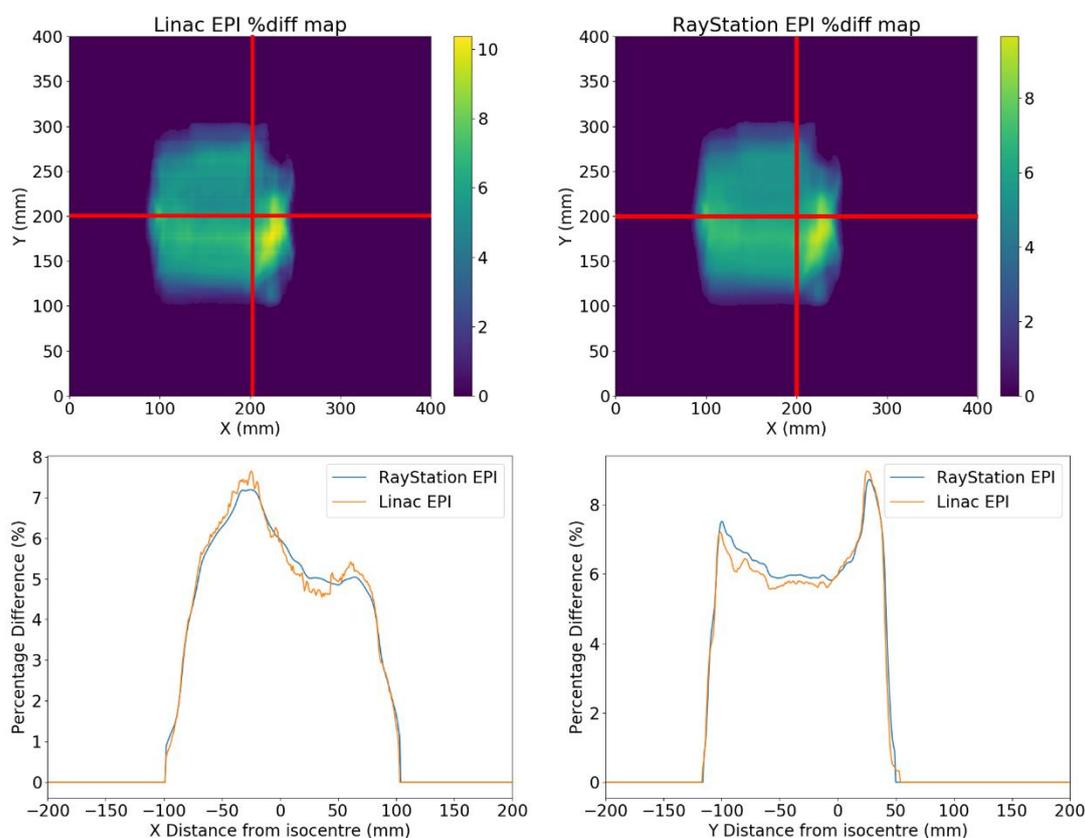
215  
 216 **Fig. 3** True (Linac) and predicted (RayStation) non-transit beam profiles with EPID positioned at 150 cm



217  
218 **Fig. 4** True (Linac) and calculated (RayStation) output factors from square fields, with percentage difference

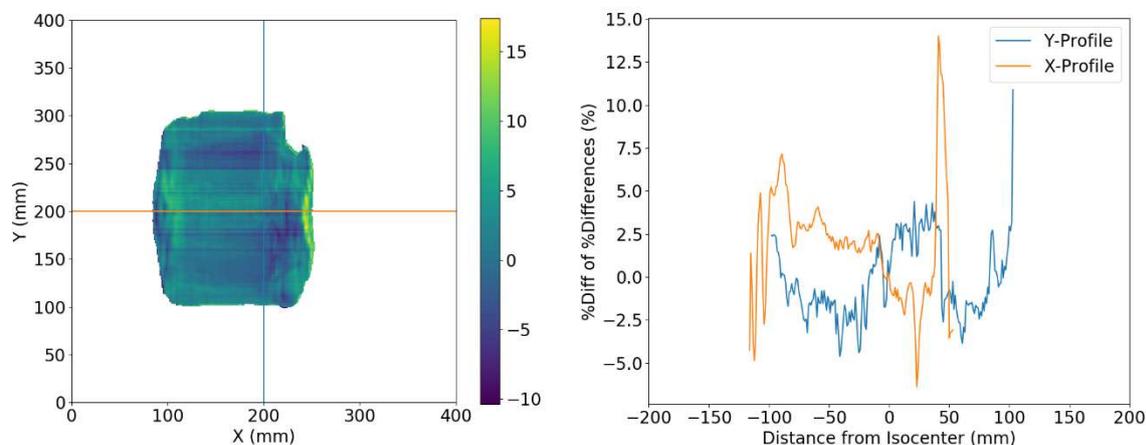
### 219 3.2 EPID Model Validation

220 The EPID model developed was first validated through simulating change in patient anatomy via anteriorly  
221 removing 2.0 cm of a solid water slab between two deliveries of a VMAT plan. Changes in the linac-measured  
222 EPIs were compared to changes in the TPS-calculated EPIs through comparing percentage differences,  $\Delta\phi_{\%}$ , in  
223 beam profiles between the two exposures as shown in Fig. 5. It can be seen that majority of the error lies within  
224 the field, where %difference in regions of high dose gradient between the predicted and measured changes  
225 adequately agree with one another. In the x-profiles shown, a maximum percentage difference of 7.2% and 7.7%  
226 was observed for the predicted and true changes in EPIs, respectively.



227  
228 **Fig. 5** True (Linac) and calculated (RayStation) 2D percentage difference maps used for model validation, with x  
229 and y-profiles

230 Similarly, for the y-profiles, a maximum percentage difference of 8.7% and 9.0% were observed for the predicted  
 231 and true change in EPIs. The mean percentage error between the true and predicted percentage differences was  
 232 1.49%, ranging between a maximum of 17.4% and a minimum of <0.01%. The 2D percentage error map between  
 233 the two percentage differences is shown in Fig. 6. The TPS simulation was thus considered as a good indicator of  
 234 what one would measure on a linac MV imager in the corresponding situation.



235  
 236 **Fig. 6** 2D percentage error map of the 2D percentage difference maps used for EPID model validation, with X-  
 237 and Y-profiles

### 238 3.3 Correlation of change in transit fluence and change in DVH metrics

#### 239 3.3.1 No Weighting Mask Applied

240 The correlation between change in transit fluence and change in DVH metrics for the 8 patient datasets was  
 241 explored. D98 PTVs and D0.03cc for the spinal cord was first explored with no weighting masks applied - utilising  
 242 the entire 40x40 cm EPIs whilst disregarding doses <10% of local maximum. Fig. 7.a) shows the relationship  
 243 between mean transit fluence percentage difference and change in D98 for the PTVs, with a linear regression band  
 244 fitted to a 95% confidence interval. Pearson's and Spearman's correlation coefficients were determined to be 0.79  
 245 and 0.82 respectively, indicating a strong correlation exists. Similarly, Fig. 7.b) shows the relationship between  
 246 change in D0.03cc for the spinal cord and mean transit fluence percentage difference, also with a linear regression  
 247 band fitted to a 95% confidence interval. Pearson's correlation coefficient of 0.53 indicates a moderate correlation  
 248 exists between the two parameters, as well as Spearman's correlation coefficient of 0.32.

#### 249 3.3.2 Weighting Masks Applied

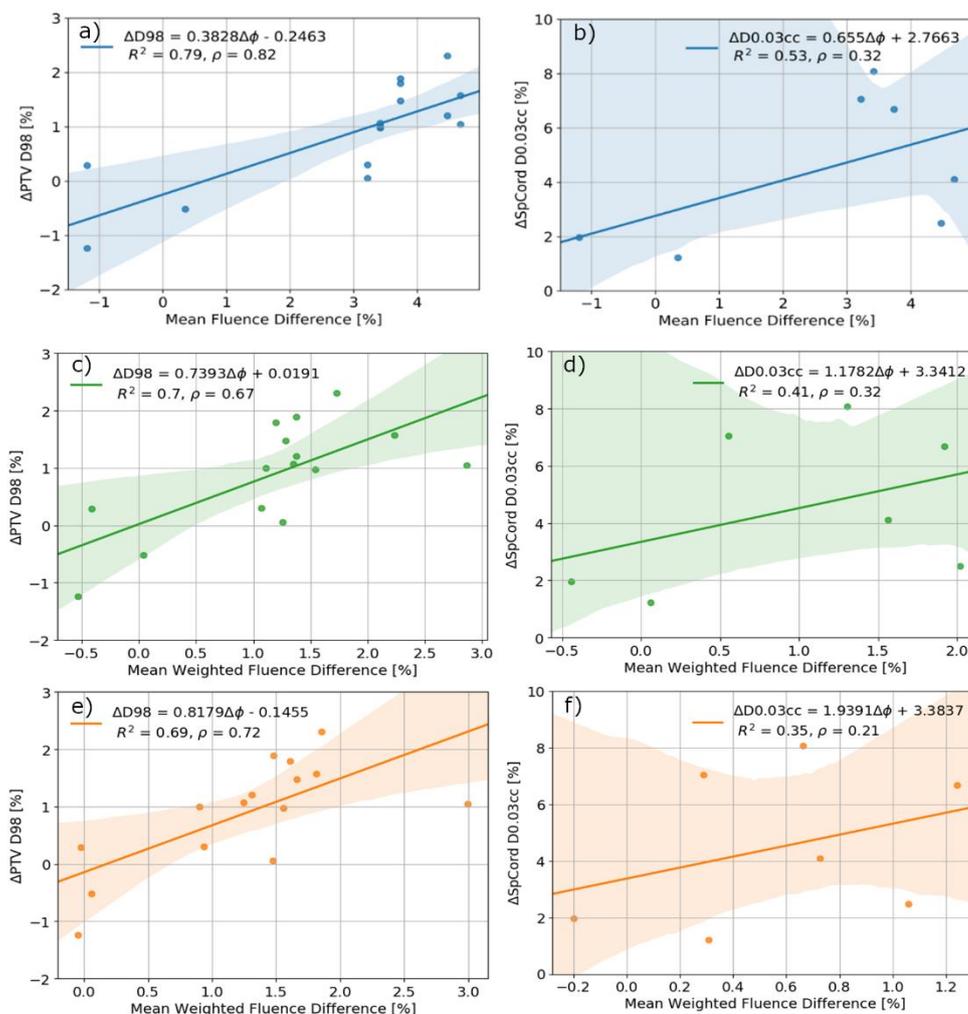
##### 250 ROI Projection Mask

251 To observe the individual benefits of various contributions to the overall weighting mask applied, the effects of  
 252 projecting the ROIs onto the EPIs were first considered. Fig. 7.c) and Fig. 7.d) show the correlation between  
 253 change in D98 and D0.03cc with mean weighted fluence percentage difference, respectively. Pearson's and  
 254 Spearman's correlation coefficients suggest that strong and moderate correlations exist for the PTVs and spinal  
 255 cords, respectively, yielding values of 0.70 and 0.67 for the PTVs and 0.41 and 0.32 for the spinal cords. The slope  
 256 of the linear regression fit for both the PTVs and spinal cords increase when utilising the ROI projection mask, in  
 257 comparison to no weighting mask applied. This result suggests that the weighting mask applied increases the  
 258 overall sensitivity of the fit, as expected.

### 259 Intra-angle ROI and Fluence Projection Mask

260 The final level of complexity added to the weighting projection mask includes an intra-angle convolution between  
 261 a fluence projection mask, through considering the MLC leaf configuration, and ROI projection mask, through  
 262 considering the position of some ROI on the EPI. By considering the overlap between the fluence and ROI  
 263 projections, one is able to consider the regions on the EPI for which some structure received dose at any point  
 264 during the treatment delivery.

265 Fig. 7.e) and Fig. 7.f) show the correlation between change in D98 and D0.03cc with mean weighted fluence  
 266 percentage difference for the PTVs and spinal cords, respectively. Pearson's and Spearman's correlation  
 267 coefficients of 0.69 and 0.72 for the PTVs, and 0.35 and 0.21 for the spinal cords, suggest that a strong correlation  
 268 exists for D98 and mean weighted percentage difference, and a weak correlation exists with D0.03cc and mean  
 269 weighted percentage difference. In comparison to the correlation data with the ROI projection masks applied,  
 270 Pearson's and Spearman's correlation coefficients increase for the cases of the PTV projections and decrease in  
 271 the case of utilising the spinal cord projections. All correlation coefficients decreased relative to the correlation  
 272 data with no mask applied, however the sensitivity of the correlation with the intra-angle ROI and fluence  
 273 projection mask applied significantly increased, as shown by the steeper slopes.



274  
 275 **Fig. 7** Correlation between change in D98 and D0.03cc with change in mean fluence percentage difference with  
 276 no mask applied for a) the PTV(s) and b) spinal cord; with the projection mask applied for c) the PTV(s) and d)  
 277 spinal cord; and with the intra-angle fluence projection mask applied for e) the PTV(s) and f) spinal cord.

## 4.0 Discussion

Change in transit fluence, as measured via mean percentage difference, was found to be strongly correlated with change in PTV D98 and moderately correlated with change in spinal cord D0.03cc with no weighting mask applied. Pearson's and Spearman's correlation coefficients were found to decrease when applying a ROI projection mask to the predicted EPIs, however still yielding strong and moderate correlations, respectively. No statistically significant difference between the correlation coefficients was observed between the two sets ( $p_{PTV} = 0.32$  and  $p_{spCord} = 0.41$ ), however the slope of the regression was found to increase by 93% and 80% for the PTVs and spinal cords, respectively. Taking the weighting mask through another layer of complexity via an intra-angle convolution with the MLC fluence projections also resulted in no statistically significant difference in the correlation coefficients calculated, relative to no weighting mask applied. The slope of the linear regression fit, however, increased by 113% and 196% for the PTVs and spinal cords, respectively; greatly improving the sensitivity of change in transit fluence to a change in key DVH metrics. Future work should consider the specificity of the model, through evaluating some threshold value to trigger the need for plan adaptation, via a receiver operating characteristic (ROC) curve.

This study is consistent with past literature on improving sensitivity via projecting PTVs onto the EPI. For comparison, Piron et al. [6] explored V95% with mean gamma values across the entire EPI as well as by projecting PTV's. Via a meta-analysis of this study, it was found that the correlation between V95% and mean gamma increased from  $\sim 0.55$  to  $\sim 0.70$  when projecting the PTV, as well as the slope of the trend line increasing by  $\sim 270\%$ . Overall, projecting the PTVs onto the EPI was found to be beneficial to both the correlation coefficient and sensitivity, which agrees with the results presented.

In this work, patient data was selected on the basis that plan adaptation occurred due to significant morphological changes within the patient, such as tissue shrinkage, resulting in some regions receiving greater than anticipated dose and others lesser. One of the eight patients used for this research, however, was replanned due to significant changes in neck tilt; resulting in poor patient alignment in the clinic. In this scenario, there was poor agreement in the position of PTV's and Spinal Cord between the pCT and rCT and as a result led to unreliable  $\Delta D98$  and  $\Delta D0.03cc$  values being calculated for the PTV's and spinal cord, respectively. For this reason, the patient data was omitted from this study as the change in datasets reflected an intentional change in patient positioning which would not be encountered when delivering the same plan at different fractions.

When exploring the correlation between change in transit fluence and  $\Delta D0.03cc$  for the spinal cords, it was observed that a much poorer correlation was found. The sensitivity, however, of the spinal cord DVH metric was drastically improved with the implementation of the weighting mask derived, as demonstrated by the 196% slope increase in Fig. 7.f) relative to Fig. 7.b). The y-intercept of the linear regressions, however, pose another issue likely due to the small sample size used. Y-intercepts of up to 3.38% were observed for the spinal cord D0.03cc correlations, suggesting that patients showing a mean (weighted) fluence percentage difference of zero still have some change in dosimetry. Moreover, the 95% confidence interval of the linear regression fit for all three correlations explored do not include the origin of the graph – suggesting some systematic error is present within the data obtained. In the future, more datapoints, particularly for the spinal cord results, should be obtained to yield more reliable results. A forced y-intercept could also be explored, however addressing the systematic error would be the preferential approach to minimising this issue.

317 It is important to note that the DVH metric considered for the spinal cord, D0.03cc, considers the near-  
318 maximum dose received by the spinal cord and is thus derived from very few voxels. The mean percentage  
319 difference, on the other hand, considers the entire volume. D0.03cc is thus much more sensitive to slight changes  
320 in the position of the structure, and as a result is unlikely to be well correlated with mean percentage difference.  
321 The pCT and rCT's utilised are registered as close as possible, however there are still some slight discrepancies  
322 in the anatomy between the two – giving rise to somewhat unreliable D0.03cc values. When considering DVH  
323 metrics that utilise the entire volume of the structure, such as mean dose and D98, it is reasonable to expect a good  
324 correlation. Future work should thus explore the correlation between mean weighted percentage difference and  
325 mean dose received by the parotid glands to explore side effects associated with high parotid gland dose from  
326 H&N radiotherapy such as xerostomia.

327 For the purposes of this study, pCT's were utilised to avoid any uncertainties associated with deformable  
328 image registration of the pCT to CBCT, and dose calculation uncertainty on CBCT. This, however, introduces a  
329 sample size limitation, as one patient plan will only yield one data point per adaptation to be used in the correlation  
330 study. In the future, the use of CBCT's would improve the overall sample size obtained, where the gradual change  
331 in patient anatomy could also be explored. This has the added benefit in that data points early into the treatment  
332 plan would likely include fractions which do not necessarily require adaptation, thus enabling us to explore various  
333 action threshold values for deciding when to replan. The sensitivity and specificity of each threshold value could  
334 be explored through consideration of a receiver operator characteristic (ROC) curve and the area under the curve  
335 (AUC). The simulation toolkit developed would ensure that all changes in transit fluence are a direct result of  
336 change in patient anatomy, rather than incorrect positioning, and thus still be of use in assessing a critical threshold  
337 value. The toolkit can also be applied to multiple regions of interest within a treatment plan, and can be modified  
338 to the clinic's specific tolerance values of, for example, dose to the spinal cord or parotid glands for H&N cancer  
339 plans. The intra-angle convolution mask between the ROI and fluence projections showed to drastically improve  
340 the sensitivity of any regression fits and is thus deemed to be useful in assessing organs at risk.

## 341 **5.0 Conclusion**

342 The simulation toolkit developed provides a useful method to explore the correlation between change in transit  
343 fluence and change in dosimetry for particular regions of interest. The toolkit was capable of predicting change in  
344 transit fluence accurately, where a weighting mask allows the user to consider particular regions on the EPID to  
345 improve sensitivity. Change in D98 was strongly correlated with change in mean weighted percentage fluence  
346 when considering the PTV's, however change in D0.03cc was only moderately correlated for the spinal cord  
347 OARs investigated in this study.

348

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- 379

## Figures



Figure 1

EPID extraction process repeated along every control point for both the pCT and rCT. EPID first positioned 50.0 cm below origin, then rotated to a given control point angle, and translated to 50.0 cm from isocenter

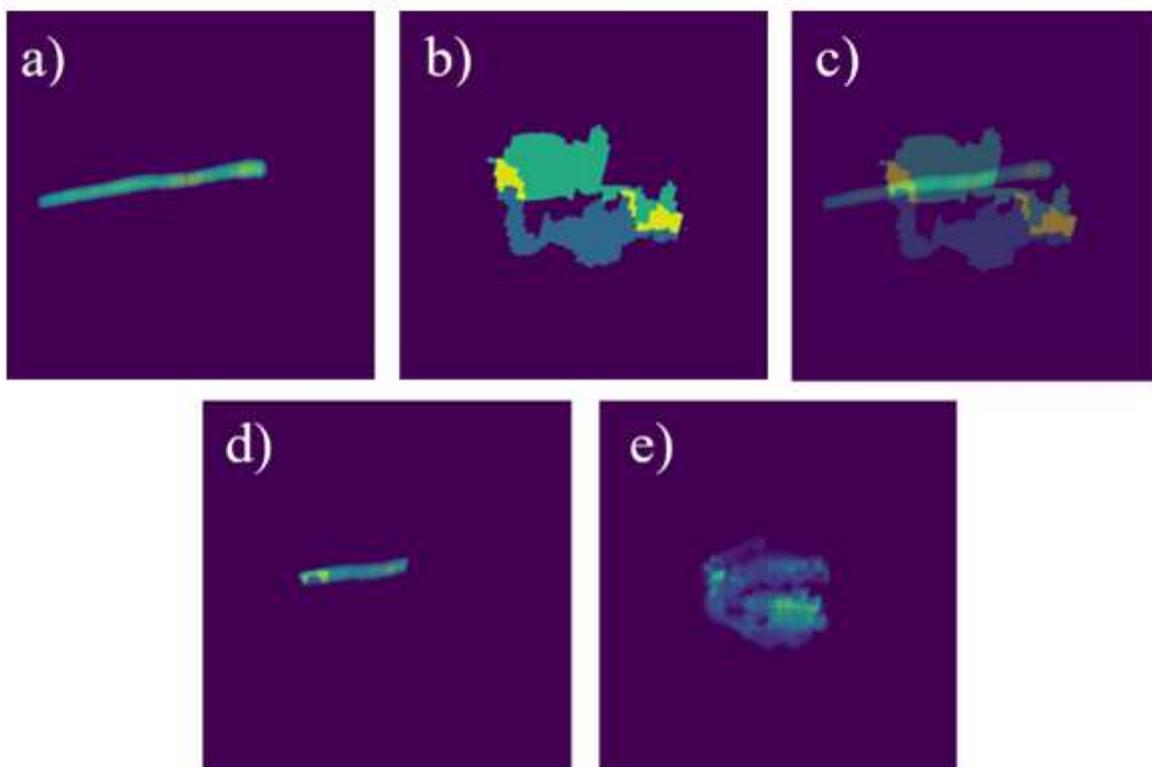
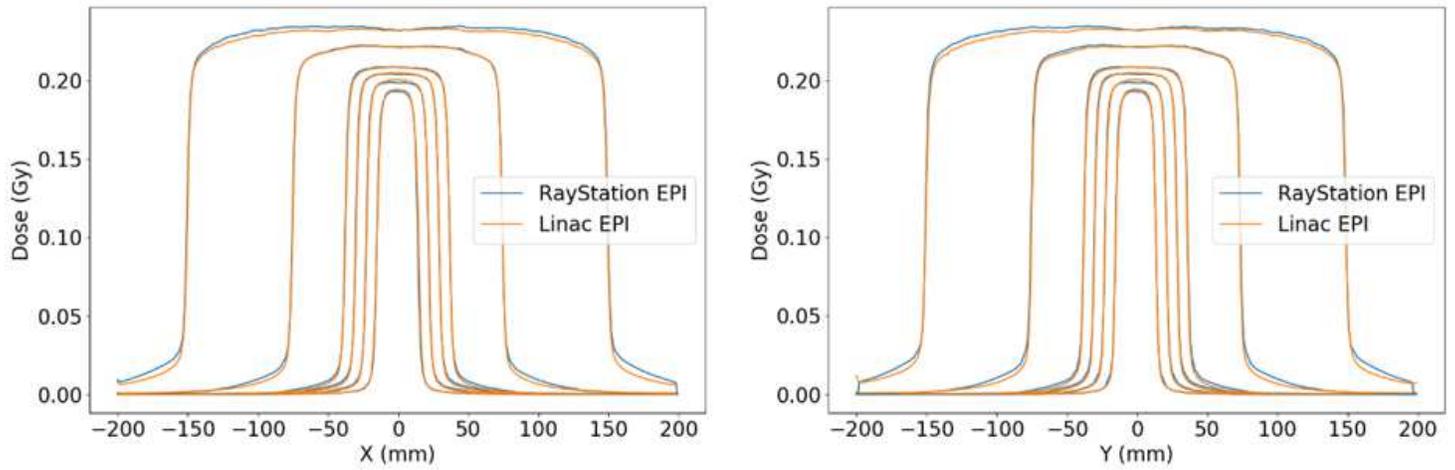


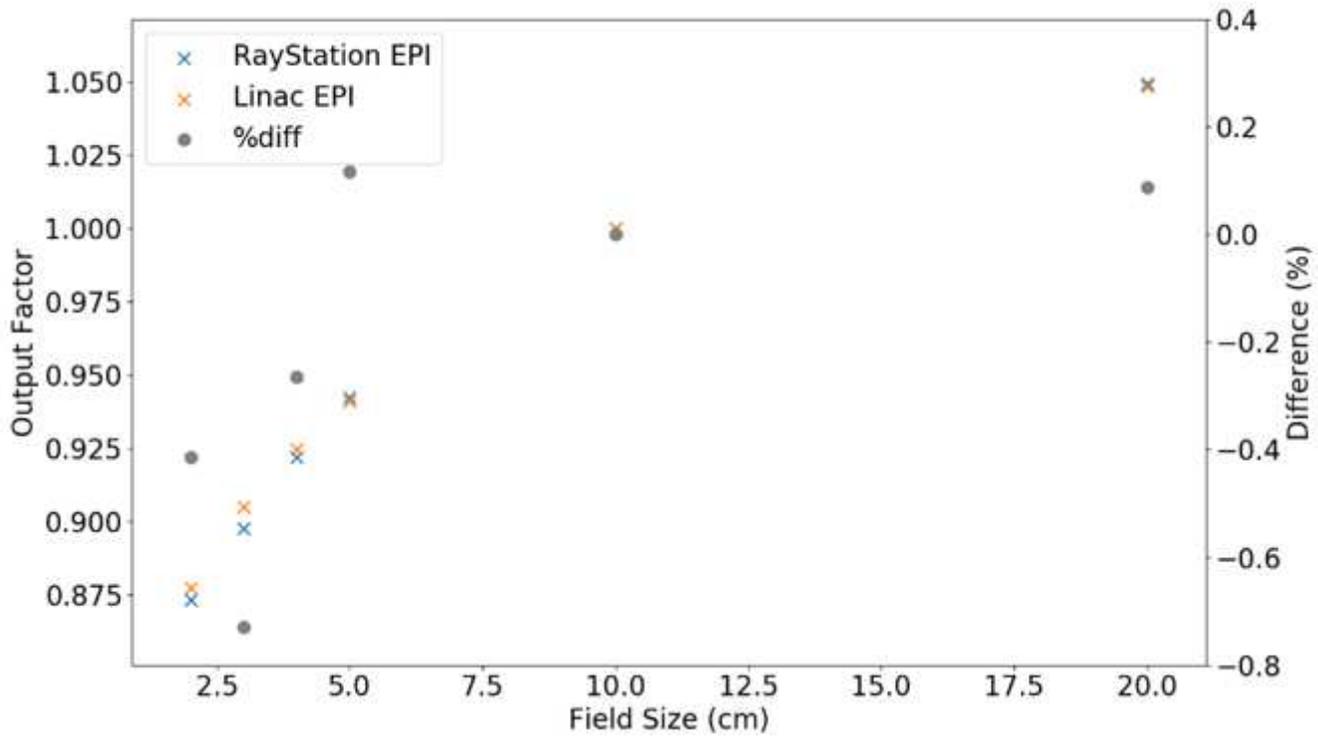
Figure 2

Process used to derive an intra-angle ROI and fluence projection mask. For each control point, a) the structure projection mask and b) fluence projection is used to obtain d) the overlap between the two, as visualised by c). This process is repeated for each control point to achieve e) the final intra-angle ROI and fluence mask



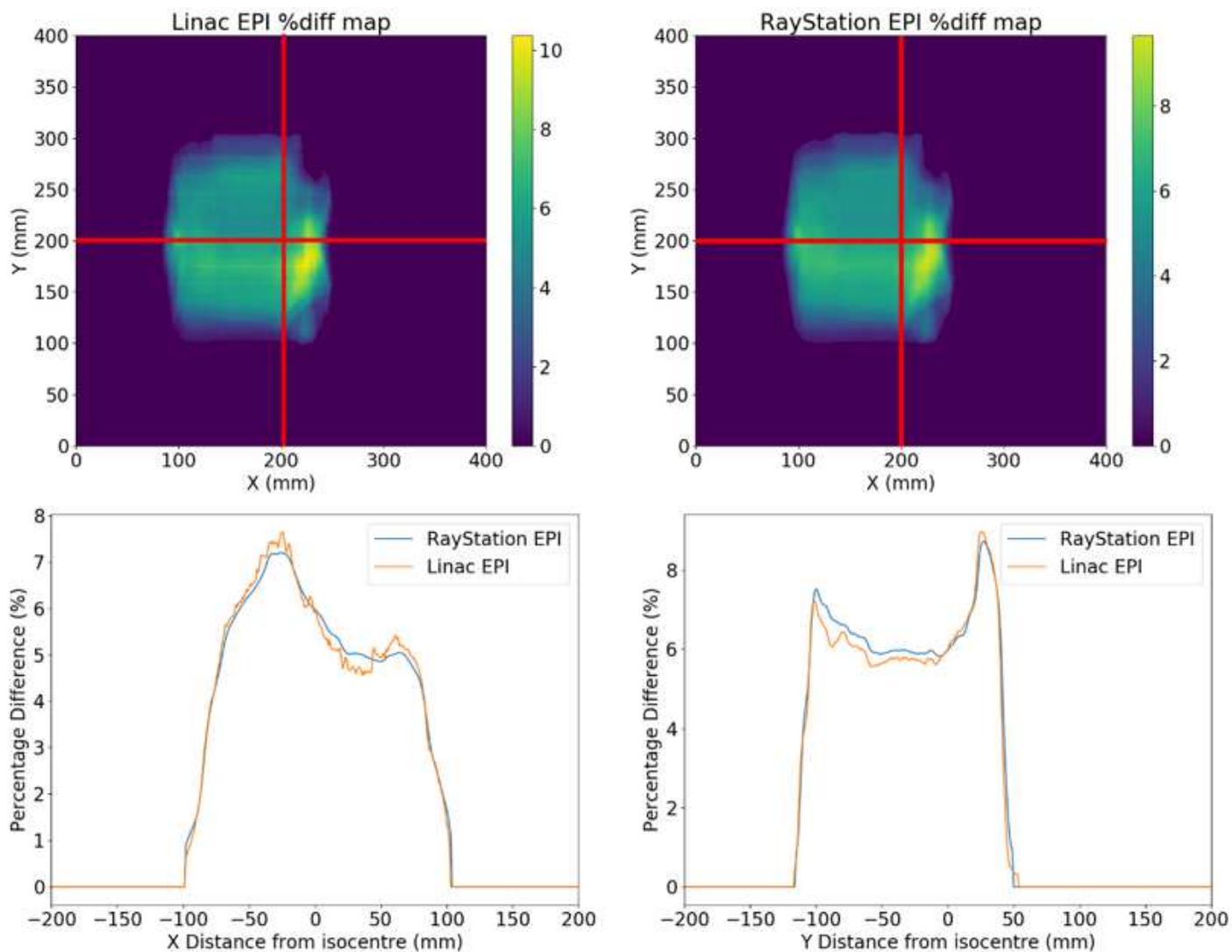
**Figure 3**

True (Linac) and predicted (RayStation) non-transit beam profiles with EPID positioned at 150 cm



**Figure 4**

True (Linac) and calculated (RayStation) output factors from square fields, with percentage difference



**Figure 5**

True (Linac) and calculated (RayStation) 2D percentage difference maps used for model validation, with x and y-profiles

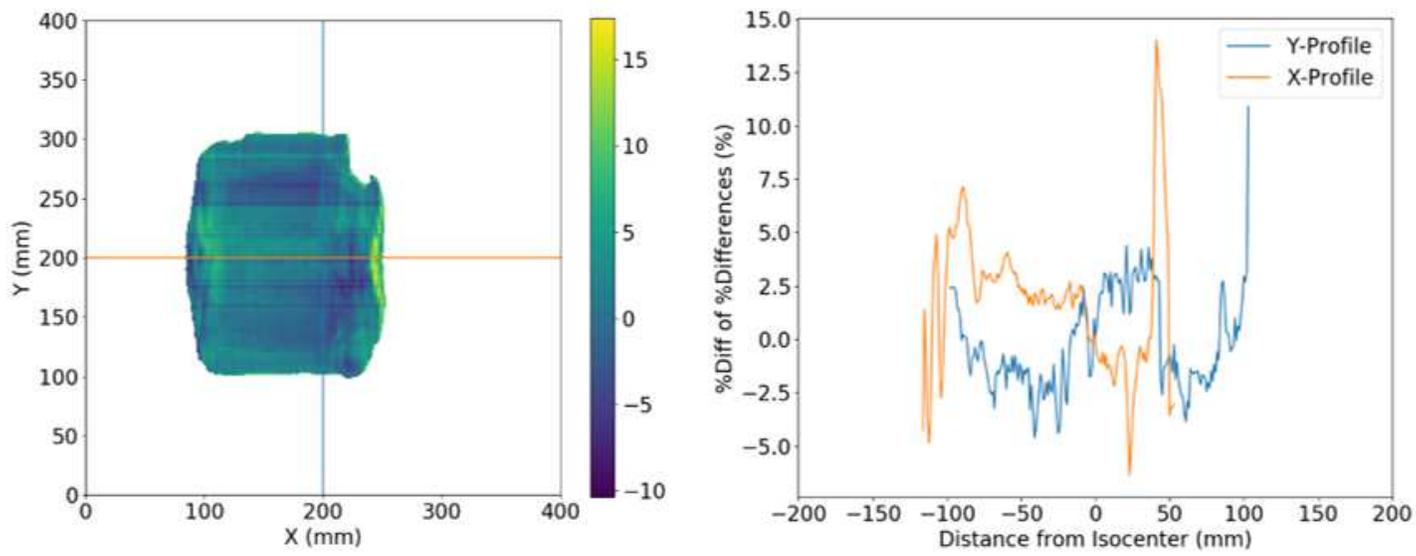


Figure 6

2D percentage error map of the 2D percentage difference maps used for EPID model validation, with X- and Y-profiles

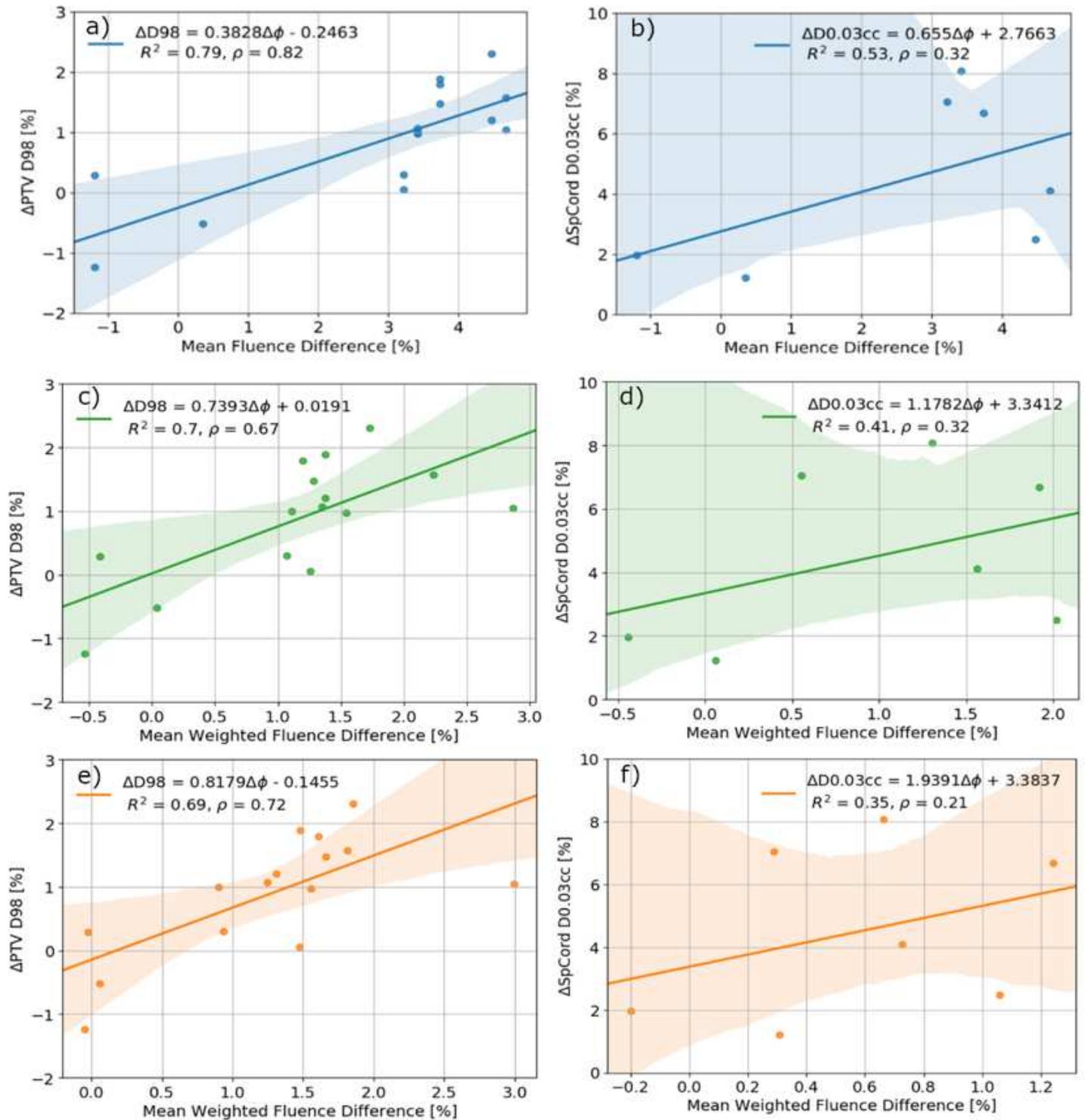


Figure 7

Correlation between change in D98 and D0.03cc with change in mean fluence percentage difference with no mask applied for a) the PTV(s) and b) spinal cord; with the projection mask applied for c) the PTV(s) and d) spinal cord; and with the intra-angle fluence projection mask applied for e) the PTV(s) and f) spinal cord.