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Objectives

Proton therapy of esophageal cancer is beneficial to spare normal tissue in clinical practice. However, intra-fractional and inter-fractional variance of tumor motion during treatment may compromise target coverage. The purpose of this study was to investigate the interplay effect due to intra-fractional motion and the effect of the robust optimization parameters for inter-fractional motion in the intensity modulation proton therapy (IMPT).

Methods

This study retrospectively analyzed 42 patients with esophageal cancer treated at Shandong Cancer Hospital. The patients were divided into two groups. Twenty-one patients had a 4DCT image with 10 respiratory phases reconstructed (Gintra). In addition, twenty-one patients underwent a second 3D CT scan following the initial one (Ginter). The RayStation11B treatment planning system was used to create the IMPT plans for these two groups. 4D dynamic dose (4DDD) was calculated to assess the interplay effect by considering respiratory motion and dynamic beam delivery for Gintra. Seven IMPT plans with different robust optimization parameters were designed for the 21 Ginter patient. The setup uncertainties were set to $\pm 0-6$ mm for Ginter. Plan quality and dose-volume histogram (DVH) parameters were analyzed (Fig.3).

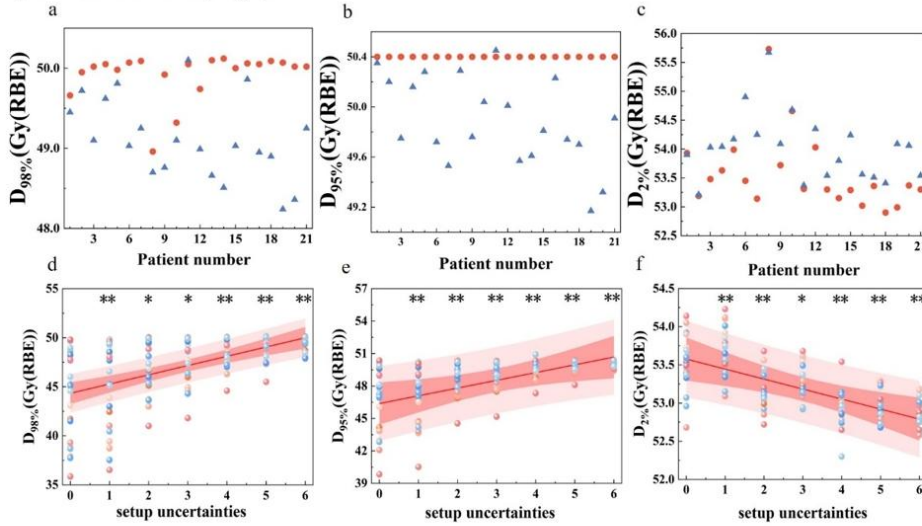
Results

For Gintra, 4DDD was slightly perturbed compared to the nominal plan dose. The mean value of CTV D98% of nominal dose and 4DDD were 49.9 and 49.1 Gy (RBE), respectively, and the CTV D95% were 50.4 and 49.9 Gy (RBE), respectively. For Ginter, the DVH parameters of the target and OARs showed a linear relationship with the corresponding robust optimization parameters in IMPT. When the robust optimization parameters were set with a larger value, the dose coverage of the target was improved. However, the dose of OARs increased at the same time. The D98% of the target for the seven plans (setup6-0 plan) were 49.42 ± 0.75 , 48.95 ± 1.21 , 48.54 ± 1.48 , 47.55 ± 2.31 , 47.07 ± 2.71 , 44.58 ± 4.20 and 44.02 ± 4.44 Gy (RBE), respectively (Fig 1,2).

Conclusions

In this study, the differences in dose distributions between the 4DDD and nominal plans for Gintra can be attributed to the interplay effects. While target coverage remained stable, variations in OAR doses should be evaluated for Gintra. For Ginter, smaller setup uncertainty parameters may not fully mitigate inter-fractional tumor motion, leading to greater variation in target dose and potential inadequate coverage. The linear relationship between setup uncertainty and D98% suggested that improved setup uncertainties can enhance target coverage, while higher setup uncertainties tend to increase OARs doses, particularly to the heart and lungs.

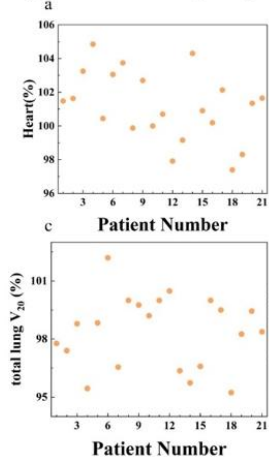
Impact of intra-fraction (target)



Impact of inter-fraction (target)

Fig.1 The DVH parameters of CTV $D_{98\%}$, $D_{95\%}$, and $D_{2\%}$ for the nominal plans and 4DDD of the intra-fraction and inter-fraction groups. For the panel of a-c, the red dots represent the nominal plan dose, and the blue dots represent 4DDD. For the panel of d-f, each dot in the graph represents the patient's dose of the target under the corresponding setup uncertainty parameter. Each point of the same color represents a single patient. The red line in the figure is a linear fit generated from the mean of these data (dark red is the 95% confidence interval estimate and light red is the 95% prediction interval estimate). The symbols above the dots are the results referring to the statistical significance analysis of the differences of the dose metrics (** $p \leq 0.001$; * $p \leq 0.05$; ns, $p > 0.05$).

Impact of intra-fraction (OARs)



Impact of inter-fraction (OARs)

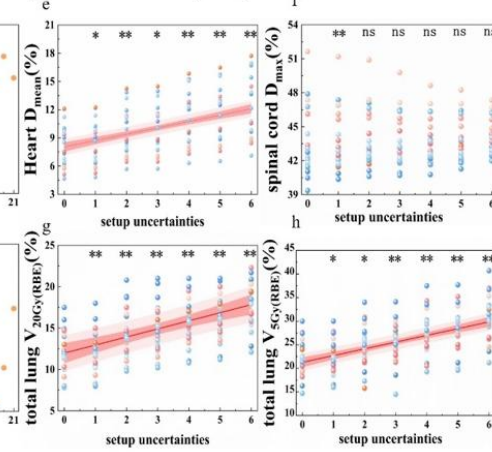
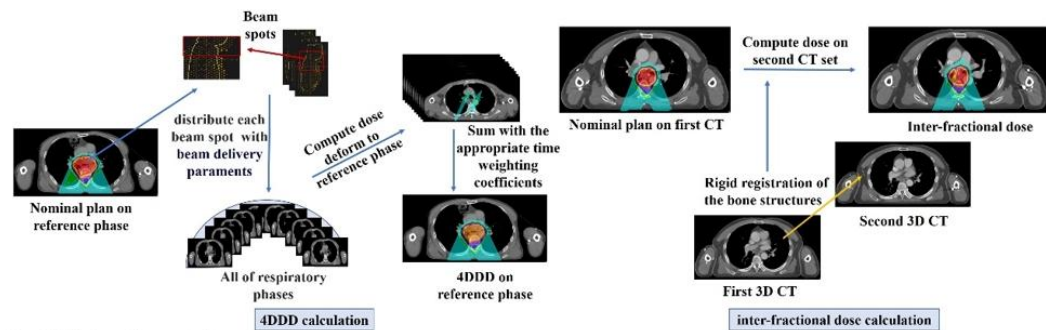


Fig.2 The ratios of 4DDD to the nominal plan for patient's OARs the intra-fraction and inter-fraction groups. For the panel e, f, g and h, each point of the same color represents a single patient. The red line in the figure represents the trend of the organ dose with the changing robust parameter settings (obtained by linear fitting of the average organ dose). The dark red is the 95% confidence interval estimate and light red is the 95% prediction interval estimate in the figure. The symbols above the dots are the results referring to the statistical significance analysis of the differences of the dose metrics (** $p \leq 0.001$; * $p \leq 0.05$; ns, $p > 0.05$).

Flowchart of dose calculation



Dose distributions of representative examples

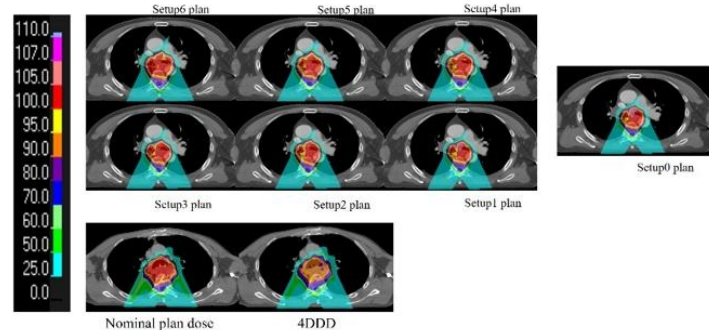


Fig.3 Flowchart of dose calculation and dose distributions of representative examples.