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Abstract Title: Robustness Evaluation with Consideration of Inter-Beam Setup Uncertainty: Head and Neck IMPT Case Study

Ting Chuan Li[1], Bin Yang[1], Hui Geng[1], Wai Wang Lam[1], Chin Chak Ho[1], Ka Keung Tang[1], Yeung Sum Wong[1], Wing Ki Chan[1], Shu Ting Hung[1], Kin Yin Cheung[1], Siu Ki Yu[1]
[1]Medical Physics Department, Hong Kong Sanatorium & Hospital, Hong Kong

Background / Aims:

IMPT with multifield optimization provides superior dose conformity for head and neck (HN) cancers, but setup uncertainties - particularly independent beam positioning errors - may compromise clinical benefits. Current RayStation robustness evaluation method (Universal Robustness Evaluation, U-RE) assumes fully correlated beam errors, potentially underestimating target underdosage risks from realistic misalignments. This study develops a novel evaluation method incorporating inter-beam setup uncertainty to better assess IMPT plan robustness.

Subjects and Methods:

Patient Data & Optimization:

Ten HN IMPT plans (3-beam) were optimized in RayStation 12A using:

1) Universal robust optimization (U-RO): 3 mm setup and 3% density uncertainties applied fully correlated across all beams.
2) Independent-beam robust optimization (IB-RO): 3 mm setup and 3% density uncertainties applied independently per-beam.

Independent-Beam Robustness Evaluation (IB-RE):

An in-house IB-RE Python script simulated inter-beam setup uncertainties. For each beam, there were 30 scenario doses (15 setup directions with ±3% density). Each IB-RE scenario combined randomly selected setup errors from the three beams, maintaining consistent density uncertainty direction (all +3% or all −3%). From 6,720 possible combinations, 60 IB-RE scenarios (30 per density uncertainty direction) were sampled. Statistical adequacy was confirmed by pilot studies.

Result:

Table 1 showed comparable nominal plan quality between IB-RO and U-RO plans. In Table 2, under U-RE, both showed similar robustness. However, under IB-RE, U-RO plans exhibited significantly degraded worst-case CTV $D_{95\%}$ and greater percentage losses in $V_{100\%}$ coverage, especially for high-risk CTVs in anatomically complex regions. Our study shows U-RE method may overestimate robustness by ignoring inter-beam uncertainties. Introducing the IB-RE method revealed that U-RO plans are more susceptible to target underdosage due to beam-specific misalignments. While IB-RO maintained superior coverage robustness, highlighting its potential to improve clinical reliability. These findings support incorporating inter-beam setup uncertainty into both optimization and evaluation protocols to ensure robust IMPT delivery for HN cancer treatments.

Table 1. Comparison of dosimetric metrics between the IB-RO and U-RO planning methods for the nominal plan.

Targets	Metrics	Nominal Plan			
		Mean ± SD		Mean Difference	*p*-value
		IB-RO	U-RO		
CTV_High Risk	$D_{95\%}$ [%**]	102.01 ± 0.82	101.96 ± 0.59	0.06	0.85
CTV_Middle Risk	$D_{95\%}$ [%**]	104.08 ± 3.02	103.82 ± 2.78	0.25	0.06
CTV_Low Risk	$D_{95\%}$ [%**]	101.87 ± 0.54	101.82 ± 0.51	0.05	0.77

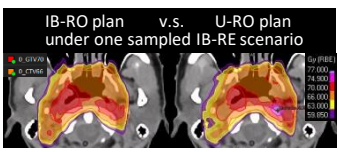

Table 2. Comparison of dosimetric metrics between the IB-RO and U-RO plans for the worst-case scenario in U-RE and IB-RE evaluation methods.

Targets	Metrics	U-RE Worst-Case Scenario				IB-RE Worst-Case Scenario			
		Mean ± SD		Mean Difference	*p*-value	Mean ± SD		Mean Difference	*p*-value
		IB-RO	U-RO			IB-RO	U-RO		
CTV_High Risk	$D_{95\%}$ [%**]	100.78 ± 0.86	100.68 ± 0.61	0.10	0.70	100.09 ± 0.52	97.25 ± 1.93	2.84	0.002*
	RI [%]	2.43 ± 1.51	2.1 ± 1.05	0.33	0.63	4.74 ± 2.37	21.98 ± 12.50	-17.25	0.002*
CTV_Middle Risk	$D_{95\%}$ [%**]	101.6 ± 2.27	101.42 ± 2.03	0.18	0.32	101.11 ± 2.73	98.68 ± 3.61	2.43	0.002*
	RI [%]	3.03 ± 1.39	2.92 ± 1.25	0.11	1.00	4.6 ± 2.86	10.57 ± 8.07	-5.97	0.002*
CTV_Low Risk	$D_{95\%}$ [%**]	100.25 ± 0.56	100.29 ± 0.41	-0.04	0.49	99.97 ± 0.49	98.61 ± 0.99	1.36	0.004*
	RI [%]	4.51 ± 1.90	3.9 ± 1.52	0.61	0.08	5.54 ± 2.20	11.63 ± 5.49	-6.09	0.004*

Notes:
- *p*-values were calculated using the Wilcoxon signed-rank test with exact method (significance level α = 0.05).
- A significant difference ($p < 0.05$) is indicated with an asterisk (*).
- Due to variations in dose prescription to CTVs, $D_{95\%}$ was normalized and presented as percentage of the prescribed dose (%), marked with two asterisks (**).
- Robustness Index (RI) = [$V_{100\%\_nominal}$ – $V_{100\%\_worst\text{-}case}$] / $V_{100\%\_nominal}$)*100%