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Original article

The price of robustness; impact of worst-case optimization on organ-at-risk dose and complication probability in intensity-modulated proton therapy for oropharyngeal cancer patients

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ABSTRACT

Purpose: To quantify the impact of the degree of robustness against setup errors and range errors on organ-at-risk (OAR) dose and normal tissue complication probabilities (NTCPs) in intensity-modulated proton therapy for oropharyngeal cancer patients.

Material and methods: For 20 oropharyngeal cases (10 unilateral and 10 bilateral), robust treatment plans were generated using 'minimax' worst-case optimization. We varied the robustness against setup errors ('setup robustness') from 1 to 7 mm and the robustness against range errors ('range robustness') from 1% to 7% (+1 mm). We evaluated OAR doses and NTCP-values for xerostomia, dysphagia and larynx edema.

Results: Varying the degree of setup robustness was found to have a considerably larger impact than varying the range robustness. Increasing setup robustness from 1 mm to 3, 5, and 7 mm resulted in average NTCP-values to increase by 1.9, 4.4 and 7.5 percentage point, whereas they increased by only 0.4, 0.8 and 1.2 percentage point when increasing range robustness from 1% to 3%, 5% and 7%. The degree of setup robustness was observed to have a clinically significant impact in bilateral cases in particular.

Conclusions: For oropharyngeal cancer patients, minimizing setup errors should be given a higher priority than minimizing range errors.

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Intensity-modulated proton therapy (IMPT) uses proton pencil beams (or 'spots') with individually optimized weights to deliver curative doses to the target with improved sparing of healthy tissues compared with intensity-modulated radiotherapy [1]. However, the dose delivery can easily be perturbed by inaccuracies in the preparation and execution phase of the treatment, such as a misalignment of the target with respect to the proton beams and inaccuracies in the calculated proton range [2,3]. Such inaccuracies may result in underdosing or overdosing the clinical target volume (CTV) and in higher doses delivered to organs-at-risk (OARs), as was also observed in an earlier study by our group [4]. These dose perturbations can be reduced by improving the accuracy of the treatment, for example by image-guided patient positioning, in vivo range verification techniques and adaptive planning strategies. Still, residual variations in patient setup and uncertainties in proton range will always remain and should be accounted for.

In IMPT, residual treatment uncertainties are preferably accounted for by performing 'robust' treatment planning, since the use of traditional safety margins (in combination with uniform field doses) was found to be inadequate or sub-optimal due to additional uncertainties in proton range [5–7]. During robust optimization, errors in patient positioning (setup errors) and proton range (range errors) are explicitly included in the plan optimization, optimizing the expected value or worst-case value of the objective function or individual objectives [5,8–10]. Robust optimization thereby minimizes the impact of residual treatment uncertainties on the dose delivered to the CTV and OARs. However, to achieve adequate CTV coverage in all robustly optimized error scenarios, it is expected that robust treatment planning will result in increased doses to surrounding normal tissues, depending on the size of the uncertainties accounted for [8,9].

Quantifying the impact of the degree of robustness on the dose received by OARs is of clinical importance. It not only quantifies the price to pay for not being accurate, but it also assists in prioritizing and justifying measures to improve treatment accuracy, e.g. image guidance or in vivo range verification. Ultimately, the price of robustness will also influence the number of patients that will

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be selected for proton therapy according to the model-based selection approach [11]. The aim of this study is therefore to quantify the impact of the *degree of robustness* against setup errors and range errors on OAR doses and normal tissue complication probabilities (NTCPs) in oropharyngeal cancer patients.

Methods and materials

Patient data and dose prescription

CT data of 20 oropharyngeal cancer patients (10 unilateral and 10 bilateral) were used in this study. This is a treatment site with large density heterogeneities and many OARs close to the CTV. Dose was prescribed according to a simultaneously-integrated boost scheme: 66 Gy_{RBE} (assuming a constant radiobiological effectiveness (RBE) of 1.1) to the high-dose CTV and 54 Gy_{RBE} to the low-dose CTV, to be delivered in 30 fractions [12]. The median high-dose CTV was 66 ml (unilateral: 43 ml, bilateral: 83 ml) and the median low-dose CTV (including the high-dose CTV) was 215 ml (unilateral: 117 ml, bilateral: 284 ml). The considered OARs were the parotid glands, submandibular glands, spinal cord, brainstem, swallowing muscles, larynx and oral cavity. Table 1 shows the 'wish-list' containing the dose prescriptions for the CTVs and OARs. CTV prescriptions were chosen such that more than 98% of the CTV received more than 95% of the prescribed dose ($V_{95\%} > 98\%$) and less than 2% received more than 107% of the prescribed dose ($V_{107\%} < 2\%$), in all error scenarios included in the robust optimization. We used a 3-beam arrangement with gantry angles of 60, 180 and 300 degrees, as was proposed in literature [12].

Treatment planning system

Robust IMPT treatment plans were generated using 'Erasmus-iCycle', our in-house developed treatment planning system for fully automated plan generation [13–16]. The algorithm uses 'prioritized' or 'lexicographic' multi-criteria optimization. It does not condense the optimization problem into a single weighted-sum objective function, but it optimizes the different objectives one-by-one according to their priorities as defined by the user in the so-called 'wish-list'. The user can also define constraints, which always have to be met during treatment plan generation. For every patient group a single wish-list can be used, which is fine-tuned in close collaboration with radiation oncologists [14,15]. Table 1 shows the wish-list that was used in this study.

Spots were selected and optimized using the resampling method as described by Van de Water et al. [16]. The resampling method iteratively performs: (1) random sampling of candidate spots from a very fine grid, (2) prioritized multi-criteria optimization and (3) exclusion of spots with a low contribution. In the current study, resampling was performed using a sample size of 5000 randomly selected candidate spots per iteration. Plan optimization was terminated after 10 resampling iterations, as solutions were then found to have converged [16].

The dose calculation algorithm implemented in Erasmus-iCycle was developed at the Massachusetts General Hospital - Harvard Medical School where it is implemented in their in-house developed treatment planning system 'ASTROID' [17]. To account for density heterogeneities, the algorithm uses a superposition–convolution method. We used a dose grid resolution of $2 \times 2 \times$ [CT-slice spacing] mm^3. Available proton energies ranged from 70 to 230 MeV and corresponding spot widths ranged from 7 to 3 mm sigma (in-air at the isocenter), respectively. To irradiate superficially located target regions, we assumed that a range shifter of 75 mm water-equivalent thickness could be inserted during the delivery of a field.

Minimax robust optimization

A 'minimax' worst-case approach was used to ensure robustness against setup errors and range errors [5,9]. The method simultaneously included several (error) scenarios and optimized the worst-case value for each constraint and objective in the wish-list [10]. Nine scenarios were included in the robust optimization: one nominal scenario, setup errors in positive and negative directions along three axes (six scenarios) and positive and negative range errors (two scenarios). Setup errors were modeled by laterally shifting the proton pencil beams, while range errors were modeled by adjusting the proton energy.

Study design

We generated treatment plans with varying degrees of robustness against setup errors (denoted as 'setup robustness') and

Table 1
The wish-list used in this study, describing for each constraint and objective the objective function type, dose prescription and robustness setting. The priority numbers indicate the order in which objectives are optimized, a low number corresponds to a high priority. The CTV-intermediate is a transition region between the high-dose and low-dose CTV. The CTV-low' consists of the low-dose CTV excluding the transition region.

Constraints	Structure	Type	Limit	Robust
	CTV-high	Minimum dose	0.98×66 Gy_{RBE}	Yes
	CTV-intermediate	Minimum dose	0.98×54 Gy_{RBE}	Yes
	CTV-low'	Minimum dose	0.98×54 Gy_{RBE}	Yes
Objectives priority	Structure	Type	Goal	Robust
1	CTV-high	Maximum dose	1.06×66 Gy_{RBE}	Yes
1	CTV-intermediate	Maximum dose	1.06×66 Gy_{RBE}	Yes
1	CTV-low'	Maximum dose	1.06×54 Gy_{RBE}	Yes
2	CTV-rings (high-dose conformality)	Maximum dose	$1.06 \times 66/54$ Gy_{RBE}	Yes
3	Parotid glands	Mean dose	0 Gy_{RBE}	Yes
4	Submandibular glands	Mean dose	0 Gy_{RBE}	Yes
5	Spinal cord	Maximum dose	20 Gy_{RBE}	Yes
5	Brainstem	Maximum dose	20 Gy_{RBE}	Yes
6	Swallowing muscles	Mean dose	0 Gy_{RBE}	Yes
7	Larynx	Mean dose	0 Gy_{RBE}	Yes
8	Oral cavity	Mean dose	0 Gy_{RBE}	Yes
9	CTV-rings (low-dose conformality)	Maximum dose	0 Gy_{RBE}	Yes
9	CTV-rings (high-dose conformality)	Mean dose	0 Gy_{RBE}	No
9	CTV-rings (low-dose conformality)	Mean dose	0 Gy_{RBE}	No
10	Total spot weight	Sum	0 Gp	No

Abbreviations: CTV = clinical target volume; Gp = Giga-protons.

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