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Proton arc therapy increases the benefit of proton therapy for oropharyngeal cancer patients in the model based clinic

Bas A. de Jong a,⇑, Erik W. Korevaar a, Anneke Maring a, Chimène I. Werkman a, Daniel Scandurra a, Guillaume Janssens b, Stefan Both a, Johannes A. Langendijk a

a Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, The Netherlands; b Ion Beam Applications SA, Louvain-la-Neuve, Belgium

Abstract

Background and purpose: In the model-based approach, patients qualify for proton therapy when the reduction in risk of toxicity (ΔNTCP) obtained with IMPT relative to VMAT is larger than predefined thresholds as defined by the Dutch National Indication Protocol (NIPP). Proton arc therapy (PAT) is an emerging technology which has the potential to further decrease NTCPs compared to IMPT. The aim of this study was to investigate the potential impact of PAT on the number of oropharyngeal cancer (OPC) patients that qualify for proton therapy.

Materials and methods: A prospective cohort of 223 OPC patients subjected to the model-based selection procedure was investigated. 33 (15%) patients were considered unsuitable for proton treatment before plan comparison. When IMPT was compared to VMAT for the remaining 190 patients, 148 (66%) patients qualified for protons and 42 (19%) patients did not. For these 42 patients treated with VMAT, robust PAT plans were generated.

Results: PAT plans provided better or similar target coverage compared to IMPT plans. In the PAT plans, integral dose was significantly reduced by 18% relative to IMPT plans and by 54% relative to VMAT plans. PAT decreased the mean dose to numerous organs-at-risk (OARs), further reducing NTCPs. The ΔNTCP for PAT relative to VMAT passed the NIPP thresholds for 32 out of the 42 patients treated with VMAT, resulting in 180 patients (81%) of the complete cohort qualifying for protons.

Conclusion: PAT outperforms IMPT and VMAT, leading to a further reduction of NTCP-values and higher ΔNTCP-values, significantly increasing the percentage of OPC patients selected for proton therapy.

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Radiotherapy plays an important role in the treatment of oropharyngeal cancer (OPC) patients. However, radiotherapy is also associated with a wide spectrum of radiation-induced toxicities which reduces quality of life [1]. Technological advances, such as intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), image guided radio therapy (IGRT) and intensity modulated proton therapy (IMPT) combined with more advanced dose optimization strategies, like swallowing and multi-organ sparing [2,3], have been developed to reduce radiation exposure to healthy tissues and organs at risk (OARs) surrounding the target, and subsequent toxicity.

Despite the superior dose distributions and reduced toxicity achievable with proton therapy, in 2018 only 1% of all newly diagnosed cancer cases in the US were treated with proton therapy [4,5]. It is clear that some cancer sites may benefit more than others from the advantages proton treatment can offer [6]. Treatment sites where the benefit of protons was sufficiently shown have become standard indications in many countries [7–9]. However, for some treatment sites the benefit is more heterogeneous and the magnitude of the advantage regarding toxicity reduction is highly dependent on individual patient factors and dose distributions.

Model-based selection is a triage strategy aimed to enrich the proton therapy population with patients who may benefit most [10–12]. The model-based selection procedure compares a photon and a proton treatment plan for the same patient and translates the differences in dose to relevant OARs (Δdose) into differences in normal tissue complication probabilities (ΔNTCP). When ΔNTCP exceeds nationally accepted thresholds, a patient qualifies for proton therapy which will then be fully reimbursed.

Abbreviations: OPC, oropharyngeal cancer; NIPP, national indication protocol for proton therapy; NTCP, normal tissue complication probability; PAT, proton arc therapy; MBA, model based approach; IMPT, Intensity modulated proton therapy; VMAT, volumetric modulated arc therapy; CTV, clinical target volume; PCM, pharyngeal constrictor muscle; PTV, planning target volume.

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In the Netherlands, OPC patients have been selected for proton therapy using the model based approach (MBA) since January 2018. The NTCP-models used to select patients were selected by a group of experts and described in the National Indication Protocol for Proton Therapy (NIPP) [13,14]. The models were updated to obtain the most relevant NTCP-profile estimation [15–17]. Between January 2018 and September 2019, NIPP-models for patient-rated moderate-to-severe (grade ≥ 2) xerostomia and physician-rated dysphagia and tube feeding dependence (grade ≥ 3) were used [12]. From September 2019 onwards, a new version of the NIPP became available, after the NTCP-models were amended [14]. See appendix A (Table 3) for the NTCP model descriptions.

In our centre, a pre-selection tool is used to prevent unnecessary generation of proton plans and subsequent treatment plan comparisons. Initially, a plan comparison was only made when the NTCP-profile of a photon plan exceeded one of the thresholds in the NIPP. Later, a more advanced preselection tool was introduced, which estimates the maximum NTCP-reduction that can be obtained with protons based on the photon dose distribution and the overlap of dose to OARs and target volumes [18]. Only when the maximum reduction in NTCP, determined by the preselection tool, exceeds the thresholds of the NIPP, a proton plan is generated for plan comparison. Patients for which the plan comparison resulted in a NTCP-reduction below the NIPP-thresholds did not qualify for proton therapy and received VMAT.

Proton arc therapy (PAT) is a model undergoing rapid development in recent years [19,20], in which proton radiation is delivered from a large number of gantry angles. The additional gantry angles increase the degrees of freedom in treatment plan optimization compared with IMPT, and potentially allow for the generation of more favorable dose distributions. Recently, treatment planning studies showed the potential of PAT to reduce dose to OARs and NTCP compared to IMPT for head and neck patients [21,22]. The aim of this study was to test the hypothesis that comparison for one of the following reasons: negative result from additional treatment planning objectives used clinically can be found in appendix B (Table 4).

All treatment plans were generated in the treatment planning system (TPS) RayStation (RaySearch Laboratories, Stockholm, Sweden). The photon-based therapy consisted of a dual arc 6 MV energy VMAT technique. Target coverage was ensured by means of PTV-based optimization with a 5 mm or 3 mm CTV-PTV margin. Photon dose was calculated using a 3-mm dose grid resolution and the collapsed cone dose engine.

The proton treatment plans were robustly optimized with 3% range and 5 mm or 3 mm setup uncertainties, employing scenario-based worst-case optimization over 21 scenarios [23]. Proton dose was calculated using a 3-mm dose grid resolution and Monte Carlo dose engine, while a constant RBE of 1.1 was assumed.

The IMPT plans generally employed a total of 4 anterior and posterior oblique gantry angles at approximately 40, 160, 200 and 320 degrees. A range shifter was employed at each gantry angle and two additional fields without range shifter were used at the posterior oblique gantry angles. To conserve department resources, IMPT planning was aborted early for some patients, when it became clear that they could not qualify for proton therapy. These IMPT plans were generally optimized heavily on OAR doses and did not yet reach robust target coverage criteria. As these plans were used for planning comparison purposes only, they were not further optimized.

The PAT plans were produced in a research version 12A-Alpha of the TPS using an energy layer reduction algorithm (ELR) described extensively in a recent publication [22]. The plans employed 360 energy layers distributed over 30 equidistant gantry angles over a full 360 degree arc, the recommended settings to reduce NTCP. The fields at each gantry angle contained multiple energy layers, which makes the plans suitable for static delivery in which the gantry is stationary during irradiation. The plans were optimized to adhere to the clinical treatment planning objectives.

### Materials and methods

#### Patient cohort & model-based selection

A retrospective study on prospectively collected data was performed on a group of 223 OPC patients treated according to the MBA with either IMPT or VMAT. Of the 223 patients, 33 (15%) patients were deemed unsuitable for proton therapy ahead of plan comparison for one of the following reasons: negative result from the pre-selection tool (13 patients), not able to lie on treatment couch (9 patients), post operative treatment (2 patients), reirradiation (2 patients), unacceptable metal artifacts (2 patients), not specified (5 patients).

For the remaining 190 (85%) patients, clinical IMPT and VMAT plans had been generated and plan comparisons were performed. In 148 (66%) patients, one or more NTCP thresholds, as defined in the NIPP shown in Table 1, were met and patients qualified for IMPT treatment. None of the NTCP thresholds were met in 42 (19%) patients, and these patients were treated with VMAT. Of the 42 patients, 27 patients were treated from January 2018 until August 2019 according to NIPP-version 1 and 15 patients were treated from September until November 2021 according to NIPP-version 2 (see appendix A Table 3).

The study population comprised of these 42 patients, and additional PAT-plans were made. NTCP-values were calculated for the VMAT, IMPT and PAT plans using the NTCP-models of the NIPP-version applicable at time of treatment. ANTCP values relative to VMAT plans were calculated for the proton plans and model-based selection was evaluated for the PAT plans. The patients were enrolled in our standardized follow-up program, approved by the medical ethics committee, for which the patients provided written informed consent.

#### Treatment planning

The patients were treated with a simultaneous integrated boost technique, with a prescribed dose of 70 Gy and 54.25 Gy, RBE = 1.1, in 35 fractions to the high-risk and prophylactic lymph node regions, respectively. Treatment planning objectives used clinically can be found in appendix B (Table 4).

All treatment plans were generated in the treatment planning system (TPS) RayStation (RaySearch Laboratories, Stockholm, Sweden). The photon-based therapy consisted of a dual arc 6 MV energy VMAT technique. Target coverage was ensured by means of PTV-based optimization with a 5 mm or 3 mm CTV-PTV margin. Photon dose was calculated using a 3-mm dose grid resolution and the collapsed cone dose engine.

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#### Dose evaluation

Target coverage in both proton and photon plans was assessed using the voxel-wise minimum robustness (multi-scenario) evaluation approach in accordance with the Dutch consensus for proton plan evaluation [24]. We constructed robustness scenarios by performing positive and negative shifts of the CT by the magnitude of the setup uncertainty along the three cartesian axes, as well as 8 unique combinations of 6 previously mentioned shifts. Positive and negative range errors were applied to the 14 shifts, resulting in 28 robustness scenarios.
Integral dose (ID) was defined as:

$$ID = D_{mean} \cdot V$$ (1)

in which $D_{mean}$ and $V$ were the mean dose and volume of the body structure including the target, respectively. Mean dose ($D_{mean}$) was evaluated for all OARs used for NTCP calculation in the NIPP versions 1 and 2.

**Statistical analysis**

Statistical significance of differences in dose and NTCP metrics between PAT and IMPT plans was evaluated using a paired 2-tailed non-parametric Wilcoxon sign-rank test implemented in Python module SciPy (V1.5.0). Significance was determined after accounting for Bonferroni’s correction for multiple testing as having a p-value < 0.025 ($\alpha = 0.05/2$parameters) for target coverage, p-value < 0.005 ($\alpha = 0.05/3$parameters) for OAR dose, p-value < 0.013 ($\alpha = 0.05/4$parameters) for NTCP.

**Results**

The $\Delta$NTCP relative to VMAT in the PAT plans was larger than one of the NIPP selection thresholds in 32 out of 42 OPC patients who had previously been selected for VMAT after plan comparison with IMPT. Fig. 1 shows the number and percentage of OPC patients at each stage in the MBA. The percentage of OPC patients in the complete 223 oropharyngeal cancer patient cohort is shown at each stage.

**Discussion**

This study illustrates the potential of PAT to significantly reduce OAR dose and NTCP relative to IMPT and VMAT in a large cohort of OPC patients selected for photon treatment through the MBA. In an MBA patient selection setting, these improvements could lead to an increased number of OPC patients benefitting from the superior dose characteristics of proton therapy. In our cohort of 223 OPC patients, an additional 32 (14%) patients became eligible for reimbursed proton therapy if PAT instead of IMPT planning was used at the plan comparison stage. NTCPs were lower in the PAT plans for all 42 patients for whom we performed a PAT to VMAT plan comparison, however for 10 patients the NTCP reduction did not meet the selection thresholds defined in the NIPP. These results underline the potential value of PAT for patients, especially when MBA to patient selection is employed.

The observed $\Delta$NTCP in the PAT plans relative to IMPT plans for our subset of 42 OPC patients who were selected for photon treatment, were similar to the reductions reported for a OPC patient cohort in which all patients were treated with IMPT, $4.9 \pm 4.2\%$ VS $4.7 \pm 1.8\%$ on average for xerostomia grade $\geq 2$ and $4.7 \pm 2.9\%$ VS $4.4 \pm 2.9\%$ on average for dysphagia grade $\geq 2$, respectively [22]. The accuracy of the NTCP values for the IMPT plans in this study is limited for the group of patients excluded from PT, because to conserve department resources, treatment planning was sometimes aborted before adhering to all clinical objectives. These plans were generally optimized in favor of lower OAR dose and lack robust target coverage, potentially resulting in lower NTCP values compared with what would be feasible in a clinically acceptable plan.

An increase in the number of patients receiving proton therapy could pose two challenges: initial elevated cost of health care and increased workload for proton therapy centers. Proton therapy is typically associated with higher capital investment and operating costs compared to photon therapy. Due to the higher costs, it is important to perform indication specific cost-effectiveness studies to assess whether the benefits outweigh the costs of treatment [25]. Firstly, our results show that PAT may increase the patient benefit of proton therapy over photon therapy, potentially reducing the costs of secondary healthcare for treatment of side effects and increasing the justification of the higher cost of proton treatment. Secondly, recent studies have discussed the potential of...
PAT to simplify clinical workflows and reduce delivery time compared to current IMPT treatments for head and neck cancer patients [21,22], which may help manage the increased workload proton therapy centers could face. Moreover, the impact of PAT on MBA patient selection could be studied for additional treatment sites, to give a more complete picture of the impact on potential increased referral for proton therapy.

The potential toxicity reduction of PAT becomes meaningful to patients when the plans can be delivered in a clinically feasible time. The potential delivery time for “static” proton arc therapy (PAT) plans with 30 beams and 360 energy layers was estimated and experimentally verified to be 11 minutes, when fully automatic beam sequencing becomes available [22]. A similar amount of time is currently used for IMPT treatment, the estimated potential delivery time can therefore be considered clinically acceptable. In the estimation, automatic beam sequencing eliminates 15 minutes of treatment machine idle time, in which communication between the oncology information system (OIS) and the treatment machine, interactions of the user within the treatment software and security checkouts currently take place. The first steps to move towards an automatic beam sequencing workflow in our institution, could be to eliminate beam loading time between subsequent fields by employing a “device centric” OIS and by eliminating or automating non-safety related user interactions within the treatment software. When these software changes are made, a high dosimetric quality static PAT plan could potentially be delivered within 15 minutes on current hardware.

In this study “static” PAT plans were used, in which the gantry remains stationary during dose delivery. It is expected that “dynamic” PAT, in which the gantry rotates dynamically during dose delivery, will be adopted by most centers, because of its increased delivery efficiency. It is not clear how our results translate to “dynamic” PAT, a comparison between static and dynamic PAT planning could help to clarify this issue.

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**Table 2**

Target coverage defined as the volume receiving at least 94% of the prescribed dose in a voxel-wise minimum distribution \(V_{94\text{, voxmin}}\). NTCP reported separately for patients during the NIPP V1 and NIPP V2 era and average dose in OARs of VMAT, IMPT and PAT plans for 42 OPC patients. P-values for the PAT metrics were marked with an “*” when the difference with respect to IMPT was significant after Bonferroni’s correction for multiple testing.

<table>
<thead>
<tr>
<th>Structure/NIPP version</th>
<th>Metric</th>
<th>VMAT M [SD]</th>
<th>IMPT M [SD]</th>
<th>PAT M [SD]</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV 7000</td>
<td>(V_{94\text{, voxmin}}) [%]</td>
<td>99.7 [0.3]</td>
<td>94.8 [9.6]</td>
<td>98.7 [0.5]</td>
<td>0.089</td>
</tr>
<tr>
<td>CTV 5425</td>
<td>(V_{94\text{, voxmin}}) [%]</td>
<td>99.7 [0.3]</td>
<td>92.8 [9.8]</td>
<td>98.5 [0.4]</td>
<td>0.042</td>
</tr>
<tr>
<td>NIPP Version 1 NTCP</td>
<td>Grade (\geq 2) xer. [%]</td>
<td>40.7 [12.2]</td>
<td>38.0 [13.5]</td>
<td>32.8 [12.5]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Grade (\geq 2) dys. [%]</td>
<td>34.6 [16.2]</td>
<td>30.0 [17.3]</td>
<td>25.7 [16.6]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Tube feeding dep. [%]</td>
<td>5.5 [4.0]</td>
<td>4.7 [4.2]</td>
<td>2.7 [2.1]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NIPP Version 2 NTCP</td>
<td>Grade (\geq 2) xer. [%]</td>
<td>41.5 [10.7]</td>
<td>37.0 [11.5]</td>
<td>32.5 [9.4]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Grade (\geq 2) dys. [%]</td>
<td>14.7 [5.7]</td>
<td>9.2 [4.3]</td>
<td>6.1 [2.9]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Grade (\geq 3) xer. [%]</td>
<td>11.8 [4.2]</td>
<td>10.2 [4.2]</td>
<td>8.6 [3.0]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Grade (\geq 3) dys. [%]</td>
<td>3.4 [1.5]</td>
<td>1.8 [1.0]</td>
<td>0.8 [0.6]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Body</td>
<td>ID [Gy(RBE)*L]</td>
<td>175 [189]</td>
<td>98 [99]</td>
<td>80 [90]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>IL parotid gland</td>
<td>(D_{mean}) [Gy(RBE)]</td>
<td>24.8 [11.3]</td>
<td>21.7 [12.5]</td>
<td>19.7 [12.3]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Submandibular glands</td>
<td>14.7 [9.3]</td>
<td>11.9 [9.7]</td>
<td>8.3 [8.2]</td>
<td>&lt;0.001*</td>
<td></td>
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<tr>
<td>Oral Cavity</td>
<td>51.4 [12.8]</td>
<td>49.3 [13.9]</td>
<td>46.6 [14.9]</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Superior PCM</td>
<td>40.0 [11.3]</td>
<td>30.4 [14.3]</td>
<td>26.6 [14.7]</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Middle PCM</td>
<td>48.3 [12.0]</td>
<td>44.5 [13.8]</td>
<td>39.0 [14.7]</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Inferior PCM</td>
<td>48.2 [11.6]</td>
<td>44.5 [14.5]</td>
<td>36.0 [16.1]</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Cricopharyngeal Inlet</td>
<td>32.6 [14.2]</td>
<td>26.5 [14.5]</td>
<td>16.4 [15.9]</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 2.** Summed \(\Delta\)NTCP relative to VMAT for grade \(\geq 2\) xerostomia and grade \(\geq 2\) dysphagia (\(\Sigma\)NTCP for grade \(\geq 2\) complications) of IMPT and PAT plans for 42 OPC patients. The threshold in the Dutch National Indication Protocol for \(\Sigma\)NTCP for xerostomia and dysphagia grade \(\geq 2\) complications of 15%, is shown. NTCP results for IMPT plans with insufficient target coverage were marked with a red outline.
Furthermore, our IMPT beam setup was designed with the most common anatomical and positioning variations in mind, by for example not treating with lateral or posterior beams in the shoulder region [26]. As future work, target coverage for PAT plans could be assessed on repeated CT images acquired along the treatment, and the necessity of strategies to mitigate the impact of positioning and anatomical variations other than robust optimization could be determined.

Conclusions

Compared to IMPT and VMAT, PAT significantly reduced dose to healthy tissues and subsequent NTCP-values for OPC patients. Compared to IMPT, PAT showed increased $D_{NTCP}$ relative to VMAT, resulting in an increased percentage of OPC patients benefitting from proton therapy in accordance with the MBA.

Table 3

<table>
<thead>
<tr>
<th>NIPP</th>
<th>NTCP endpoint</th>
<th>LP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>grade ≥ 2 xerostomia 6 months after treatment</td>
<td>$-1.507 + 0.052 \cdot D_{mean}[Gy]$ contralateral parotid gland + 0.525 \cdot \text{none-to-little baseline xerostomia score} + 1.482 \cdot \text{moderate to severe baseline xerostomia score}$</td>
</tr>
<tr>
<td></td>
<td>grade ≥ 2 dysphagia 6 months after treatment</td>
<td>$-6.849 + 0.680 \cdot \text{T3-T4 stage} + 0.317 \cdot 1-10% \text{weight loss} + 1.178 \cdot &gt;10% \text{weight loss} + 0.198 \cdot \text{accelerated radiotherapy} + 1.101 \cdot \text{chemoradiation} + 1.716 \cdot \text{radiotherapy + cetuximab} + 0.030 \cdot D_{mean}[Gy] \cdot \text{superior PCM} + 0.013 \cdot D_{mean}[Gy] \cdot \text{inferior PCM} + 0.022 \cdot D_{mean}[Gy] \cdot \text{contralateral parotid} + 0.022 \cdot D_{mean}[Gy] \cdot \text{cricopharyngeal muscle}$</td>
</tr>
<tr>
<td>Tube feeding dependence 6 months after treatment (grade ≥ 3)</td>
<td>$-2.955 + 0.0996 \cdot (\sqrt{D_{mean}[Gy]} \cdot \text{parotid L} + \sqrt{D_{mean}[Gy]} \cdot \text{parotid R}) + 0.0182 \cdot D_{mean}[Gy] \cdot \text{submandibular glands} + 0.495 \cdot \text{little baseline xerostomia score} + 1.207 \cdot \text{moderate-to-severe baseline xerostomia score}$</td>
<td></td>
</tr>
<tr>
<td>Version 2</td>
<td>grade ≥ 2 xerostomia 6 months after treatment</td>
<td>$-3.7286 + 0.0855 \cdot (\sqrt{D_{mean}[Gy]} \cdot \text{parotid L} + \sqrt{D_{mean}[Gy]} \cdot \text{parotid R}) + 0.0156 \cdot D_{mean}[Gy] \cdot \text{submandibular glands} + 0.4249 \cdot \text{little baseline xerostomia score} + 1.0361 \cdot \text{moderate-to-severe baseline xerostomia score}$</td>
</tr>
<tr>
<td>Sept 2019 - Nov 2021</td>
<td>grade ≥ 3 xerostomia 6 months after treatment</td>
<td>$-4.0536 + 0.033 \cdot D_{mean}[Gy] \cdot \text{oral cavity} + 0.0236 \cdot D_{mean}[Gy] \cdot \text{superior PCM} + 0.095 \cdot D_{mean}[Gy] \cdot \text{middle PCM} + 0.0133 \cdot D_{mean}[Gy] \cdot \text{inferior PCM} + 0.9382 \cdot \text{grade 2 baseline dysphagia score} + 1.29 \cdot \text{grade 3–4 baseline dysphagia score} + 0.6281 \cdot \text{primary tumour site in larynx}$</td>
</tr>
<tr>
<td></td>
<td>grade ≥ 2 dysphagia 6 months after treatment</td>
<td>$-7.6174 + 0.0259 \cdot D_{mean}[Gy] \cdot \text{oral cavity} + 0.0203 \cdot D_{mean}[Gy] \cdot \text{superior PCM} + 0.0303 \cdot D_{mean}[Gy] \cdot \text{middle PCM} + 0.0341 \cdot D_{mean}[Gy] \cdot \text{inferior PCM} + 0.5738 \cdot \text{grade 2 baseline dysphagia score} + 1.4718 \cdot \text{grade 3–4 baseline dysphagia score} + 0.5303 \cdot \text{primary tumour site in larynx}$</td>
</tr>
</tbody>
</table>

Conflict of interest statement

This work was co-financed by the Ministry of Economic Affairs and Climate Policy of the Netherlands, by means of the PPP-allowance made available by Top Sector Life Sciences & Health to stimulate public-private partnerships; ION BEAM APPLICATIONS SA (IBA Ltd), Louvain-la-Neuve, Belgium; and University Medical Center Groningen (UMCG), Groningen, The Netherlands. UMCG has a research collaboration with Raysearch Laboratories AB, Stockholm, Sweden.

Appendix A

See Table 3.

Appendix B

See Table 4.

Table 4

<table>
<thead>
<tr>
<th>NIPP</th>
<th>Main clinical objectives and settings used in treatment planning.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PTV coverage VMAT plans</td>
</tr>
<tr>
<td></td>
<td>CTV coverage proton-based plans</td>
</tr>
<tr>
<td></td>
<td>CTV to PTV margin/ setup uncertainty</td>
</tr>
<tr>
<td></td>
<td>Density uncertainty for proton plans</td>
</tr>
<tr>
<td></td>
<td>Maximum point dose</td>
</tr>
<tr>
<td></td>
<td>Maximum dose in 1 cm$^3$</td>
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<tr>
<td></td>
<td>Spinal cord, max dose in 0.1 cm$^3$</td>
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<tr>
<td></td>
<td>High priority OAR, reduce mean dose if marked with *</td>
</tr>
<tr>
<td></td>
<td>IL parotid gland</td>
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<tr>
<td></td>
<td>CL parotid gland</td>
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<td>Submandibular glands</td>
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<td></td>
<td>Oral Cavity</td>
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<tr>
<td></td>
<td>Superior PCM</td>
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<td>Middle PCM</td>
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<td>Inferior PCM</td>
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<td></td>
<td>Cricopharyngeal Inlet</td>
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Appendix C

See Figs. 3-8.

**Fig. 3.** Dose distributions for the VMAT, IMPT and proton arc therapy (PAT) plans for an example oropharyngeal cancer patient. The bottom right panel shows the subtraction of the IMPT from the PAT dose distribution.

**Fig. 4.** $\Delta$NTCP relative to VMAT for grade ≥ 2 dysphagia of IMPT and PAT plans for 42 OPC patients. The threshold in the Dutch National Indication Protocol for $\Delta$NTCP ≥ 10%, is shown.
Fig. 5. ΔNTCP relative to VMAT for grade ≥ 2 xerostomia of IMPT and PAT plans for 42 OPC patients. The threshold in the Dutch National Indication Protocol for ΔNTCP ≥ 10%, is shown.

Fig. 6. ΔNTCP relative to VMAT for grade ≥ 3 dysphagia (NIPPV2) or tube feeding dependence (NIPPV2) of IMPT and PAT plans for 42 OPC patients. The threshold in the Dutch National Indication Protocol for ΔNTCP ≥ 5%, is shown.
Fig. 7. ΔNTCP relative to VMAT for grade $\geq$ 3 xerostomia of IMPT and PAT plans for 42 OPC patients. The threshold in the Dutch National Indication Protocol for ΔNTCP $\geq$ 5%, is shown. No values are shown for patients treated in NIPPV1 era, as no xerostomia grade $\geq$ 3 NTCP model was included.

Fig. 8. Summed ΔNTCP relative to VMAT for grade $\geq$ 3 xerostomia and grade $\geq$ 3 dysphagia (ΣΔNTCP for grade $\geq$ 3 complications) of IMPT and PAT plans for 42 OPC patients. The threshold in the Dutch National Indication Protocol for ΣΔNTCP for xerostomia and dysphagia grade $\geq$ 3 complications $\geq$ 7.5%, is shown. No values are shown for patients treated in NIPPV1 era, as no xerostomia grade $\geq$ 3 NTCP model was included.

References


