Chapter 5

Online adaptive proton therapy of head and neck cancer using dose mimicking

The content is based on a manuscript in preparation that will be submitted soon: Dose mimicking based strategies for online adaptive IMPT in head and neck cancer.

Purpose: This study compares a not adapted (NA) robust planning strategy with three fully automated online adaptive proton therapy (OAPT) workflows based on the same optimization method: dose mimicking (DM). The added clinical value and limitations of the three proposed OAPT methods are investigated for head and neck cancer (HNC) patients.

Material and Methods: The three OAPT strategies use DM applied to different reference dose distributions in order to compensate for inter-fractional anatomical changes by re-optimizing new dose distributions on corrected cone beam CT images (corrCBCTs). Order by complexity the OAPTs were: (1) online adaptation based on dose restoration (OADR) where the approved clinical dose on the planning-CT (pCT) was mimicked, (2) online adaptation using DM of the deformed clinical dose from the pCT to corrCBCTs (OADEF), and (3) online adaptation applying DM to a ML predicted dose on corrCBCTs (OAML). Adaptation was only applied in fractions where the target coverage criteria was not met (D98% $<$ 95% of the prescribed dose). For 10 HNC patients, the accumulated dose distributions over the 35 fractions were calculated for NA, OADR, OADEF and OAML strategies. DVH metrics and the adaptation rate over the treatment were investigated.

Results: Higher target coverage was observed for all OAPT strategies compared to no adaptation. OADEF and OAML outperformed both NA and OADR and were comparable in terms of target coverage to initial clinical plans. All OAPT methods were able to correct for hotspots. However, only OAML provided comparable NTCP values to those from the clinical dose without statistically significant differences. When evaluating the NA initial plan on corrBCTs, 51% of fractiones needed adaptation. The adaption rate was reduced to 25% when selecting the last adapted plan with any of the OAPT strategies as the scheduled plan. The reduction was even more important (down to 12%) when the schedule plan was the best plan over all previously delivered ones.

Conclusion: The implementation of the three OAPT strategies provided superior target coverage compared to no adaptation, higher OAR sparing and reduced the number of needed adaptations.

5.1 Introduction

Intensity-modulated proton therapy (IMPT) offers excellent dose conformity and healthy tissue sparing. Its application is especially interesting in head and neck cancer (HNC) where an important amount of organs at risk (OAR) are in the close vicinity of the tumor. Overdosage to these organs can cause radiation-induced side effects, in particular xerostomia and dysphagia, which negatively impact the quality of life [229, 230]. Unfortunately, IMPT is highly sensitive to uncertainties in patient setup, CT values, and patient anatomy due to displacements of the steep Bragg peak fall-off. Fraction after fraction, changes along the beam path can alter the initially planned Bragg peak causing dose distortions in the approved clinical plan and compromising treatment plan quality [13, 202, 11].

In current clinical practice, robust optimization (RO) for IMPT planning is generally preferred to planning target volume (PTV) optimization. Standard RO usually includes pre-defined setup and range errors during spot weight optimization to generate dose distributions resilient to these specific uncertainties. However, changes in patient anatomy during treatment are harder to address. More sophisticated approaches for RO, such as anatomical RO, explore the incorporation of anatomical scenarios during plan optimization [88, 89, 113]. Nevertheless, it remains difficult to keep the optimality of an IMPT plan while including a wide range of possible anatomical deformations [240].

Although RO can provide a certain level of robustness, it is not the ultimate solution, and treatment plan adaptation is still required in many cases [13, 202, 195, 164]. Usually, offline adaptation triggered by weekly control repeated-CTs (rCTs) or visual inspection of daily CBCTs is used to accommodate for anatomical changes. During offline adaptation recontouring, replanning, treatment plan approval, and additional quality assurance are required in a clinical offline adaptation workflow. As a result, offline adaptation can take several days. In order not to delay treatment delivery and to avoid new anatomical changes during offline replanning, another possibility is to perform online plan adaptation while the patient is on the treatment couch. Since the complete adaptation workflow must be completed in a very short time, online adaptive proton therapy (OAPT) is extremely challenging but it is ideally suited to deal with inter-fractional anatomical changes.

Anatomical changes could be divided into two different types: (1) density changes and (2) non-rigid anatomical changes. A good example of density change in HNC is cavity filling. The anatomy of the patient remains mainly in the same position but it experiences residual rigid translations with an increased density inside the cavity (from air to mucus). On the other hand, non-rigid anatomical changes imply modifications in the relative position between the OAR and the

target volumes. This is the case of complex re-organisations of the anatomy or some tumor shrinkages where the free space left by the reduction in volume is replaced by an OAR that enters the prescription dose region.

Previous studies have shown the potential of dose restoration (DR) strategies to mitigate inter-fractional density changes while maintaining target coverage in lung [204] and prostate cancer [205]. DR is an OAPT strategy that aims at keeping the planned dose distribution stable in every fraction by generating a new (restored) plan with updated proton beam energies and spot weights. Unfortunately, when addressing non-rigid anatomical deformations in HNC, DR is not the most appropriate strategy due to the intrinsic limitations of the method [228].

This study compares a not-adapted (NA) robust planning strategy with three fully automated robust OAPT workflows. The three OAPT methods use dose-mimicking (DM) to generate adapted dose distributions on repeated images. Ordered by complexity the three OAPT strategies are: (1) online adaptation based on dose restoration (OADR) where DM is applied to the reference clinical dose on the planning-CT (pCT), (2) online adaptation using DM on the deformed clinical dose from the pCT to the repeated image (OADEF), and (3) online adaptation using a machine learning (ML) predicted dose on the repeated image followed by DM (OAML). The added clinical value and limitations of the three robust OAPT workflows are compared with respect to no adaptation and between methods in simulated IMPT treatments.

5.2 Material and methods

5.2.1 Patient cohort and treatment planning strategy

Ten bilateral oropharyngeal patients treated with photons were replanned for IMPT delivery to run this study. The prescribed dose (Dp) was 70 GyRBE to the high-dose clinical target volume (CTV) and 54.25 GyRBE to the low-dose CTV in 35 fractions, using a constant relative biological effectiveness (RBE) factor of 1.1. The parotids, submandibular glands (SMGs), the pharyngeal constrictor muscles (PCMs), the oral cavity, the spinal cord, and the brainstem were defined as the main OAR. Target and OAR delineations performed by experienced radiotherapy oncologists were available on all pCTs.

Robustly optimized IMPT treatment plans were semi-automatically planned using the ML model RSL-IMPT-OROPHARYNX-7000-SIB (3.0)*. First, a dose prediction model with UNet architecture [226] provided the predicted IMPT dose distribution. Second, post-processing was applied in order to obtain steep dose volume histograms (DVHs) in the target and spare the OAR (i.e., increase and

homogenize the dose to the target while reducing the dose to OAR). Third, robust DM optimization using voxel-wise and regular objective functions was performed. Until this point, all the described steps were fully automated in RayStation 11B and one single click was required to run the optimization. Plans were created using Monte Carlo dose calculation and classical worst-case robust optimization (setup error (SE) = 4 mm, range error (RE) = 3%). SE scenarios included patient shifts in the three axes of the space x,y,z ($\pm$SE, 0, 0), (0, $\pm$SE, 0), (0, 0, $\pm$SE) and the nominal scenario (0,0,0). Range robustness was also included to account for uncertainties in the conversion from CT numbers to proton-stopping power ratios. RE scenarios were modeled by scaling the mass density by $\pm$3%. The nominal scenario (i.e., 0%) was also included. The combination of seven SE scenarios and three RE scenarios led to an optimization with twenty-one (7x3) error scenarios.

Finally, automatically generated plans were evaluated against the same robustness parameters used during optimization (SE = 4 mm, RE = 3%). Objective weights were manually adjusted and/or extra optimization objectives were added if necessary until target coverage and OAR clinical goals (see Table **??**.) were satisfied, in nominal and worst-case scenarios.

The same beam configuration was used for all patients: two anterior oblique beams at (60º,10º), and (120º,10º) and two posterior oblique beams at (240º, 350º) and (300º, 350º) for gantry and couch angles, respectively. For each patient, the resulting plan from this workflow was considered the reference initial treatment plan.

5.2.2 Anatomy of the day and CBCT correction

CBCT images were acquired with a Halcyon machine (Varian Medical Systems, Palo Alto, CA) during the 35 treatment fractions. Halcyon CBCT images have excellent quality [241] and have been validated for photon dose calculation [242]. Unfortunately, it is well known that artifacts in CBCT images cause unreliable relationships between CBCT intensities and electron densities, especially problematic in IMPT planning. Therefore, correction algorithms are required to enable accurate proton dose calculations [243]. To obtain a more accurate representation of the patient's anatomy of the day, corrected CBCT images (corrCBCTs) were generated in RayStation 11B. The CBCT correction iterative algorithm calculates a correction map and a conversion function for the CBCT based on the pCT. In other words, it removes the low-frequency artefacts and converts CBCT intensities to HU. To compensate for the limited CBCT field of view (FOV), the areas outside the FOV are filled in by deformably mapping intensity values from the pCT. More information about the method of CBCT correction can be found in section 2.8 of the Reference Manual from RayStation 11B [].

Priority	Region of interest (ROI)	Clinical goal
	Target volume clinical goals	
1	Low-risk CTV	D98% >51.54 Gy (95%Dp = 54.25 Gy)
1	High-risk CTV	D98% >66.50 Gy (95% Dp = 70 Gy)
1	High-risk CTV	D0.03 cm3 >74.90 Gy (107% Dp = 70 Gy)
2	Low-risk CTV	D98% >53.17 Gy (98% Dp = 54.25 Gy)
2	High-risk CTV	D98% >68.60 Gy (98% Dp = 70 Gy)
	Organs at risk clinical goals	
1	Body	D0.03 cm3 >74.90 Gy (107% Dp = 70 Gy)
1	Spinal Cord	D0.03 cm3 <45 Gy
1	Brain Stem	D0.03 cm3 <54 Gy
3	PCMSup/PCMMid/PCMInf	Mean dose <40 Gy
3	Parotids (left and right)	Mean dose <26 Gy
3	SMGs (left and right)	Mean dose <40 Gy
3	Oral cavity	Mean dose <35 Gy
3	Mandible	D0.03cm3 <70 Gy
3	Glottic area	Mean dose <40 Gy
3	Esophagus	Mean dose <35 Gy
3	Cochlea (left and right)	Mean dose <30 Gy

Table 5.1: List of clinical goals from the planning protocol used in this study to generate the initial treatment plans .D98% and D2% are the doses received at 98% and 2% of the target volume, respectively. Abbreviations: CTV = Clinical Target Volume, PCM = pharyngeal constrictor muscles, Sup = Superior, Mid = Mid = Middle, Inf = Inferior, SMG: submandibular glands

Two different contours sets were available in all corrCBCTs: rigidly mapped contours and deformably mapped contours from the pCT to the corrCBCT using rigid registration (RIR) and deformable image registration (DIR), respectively. The DIR algorithm was the ANACONDA algorithm available in RayStation 11B [244].

5.2.3 Adaptive strategies

Dose mimicking

The three proposed OAPT strategies used RayStation dose mimicking (RSDM) as the optimization method to generate online adapted plans in the corrCBCTs. The RSDM used in this study corresponds to the mimicking method integrated with the ML model RSL-IMPT-OROPHARYNX-7000-SIB (3.0) [227].

RSDM is formulated as a voxel-wise least squared error (LSE) minimization

problem. The LSE objective function is divided into two one-sided terms, enabling different weights depending on whether the optimized dose is greater or less than the reference dose given as input. For OAR, voxels with smaller dose values than the reference dose are not penalized. In addition to the voxel-wise LSE objective, a weighted sum of conventional radiotherapy objective functions is added to the problem, as implemented in RayStation 11B.

RSDM procedure consists of two separate runs, between which the clinical dose is calculated accurately. These two runs consist of 125 and 80 iterations respectively, which in our study were completed in between 13 to 17 minutes for the 21 robust scenarios. Optimizations were run on a GPU0 Quadro P5000, 15 GB, WDDM.

For the moment, proton dose computation on corrCBCTs is not available clinically, but only in research versions. In collaboration with RaySearch, the RSDM model was adapted to run on corrCBCT instead of pCT and to receive as input not only an ML predicted dose but any other given dose distribution. When using RSDM, the contours of the ROIs to which the optimization objectives are applied also need to be specified.

5.2.4 Online adaptation strategies

Three OAPT workflows were fully automated using the RayStation scripting interface. The ROIs and reference doses given as input to the RSDM to run new plan optimizations on the corrCBCTs are shown in Figure 1.

- **Online Adaptation using Dose Restoration (OADR)**. The initial reference dose and manually delineated contours on the pCT were rigidly mapped to the corrCBCT and given as input to the RSDM.

- **Online Adaptive using Deformable image registration (OADEF)** . The initial reference dose and manually delineated contours on the pCT were mapped to the corrCBCT using DIR and given as input to the RSDM.

- **Online Adaptive using a Machine Learning predicted dose (OAML)**. Manually delineated contours on the pCT were deformably mapped to the corrCBCT. The deformed contours were given as input to the ML model to predict a new dose distribution on the corrCBCT. Later, the RSDM was applied to the predicted dose using the deformed contours.

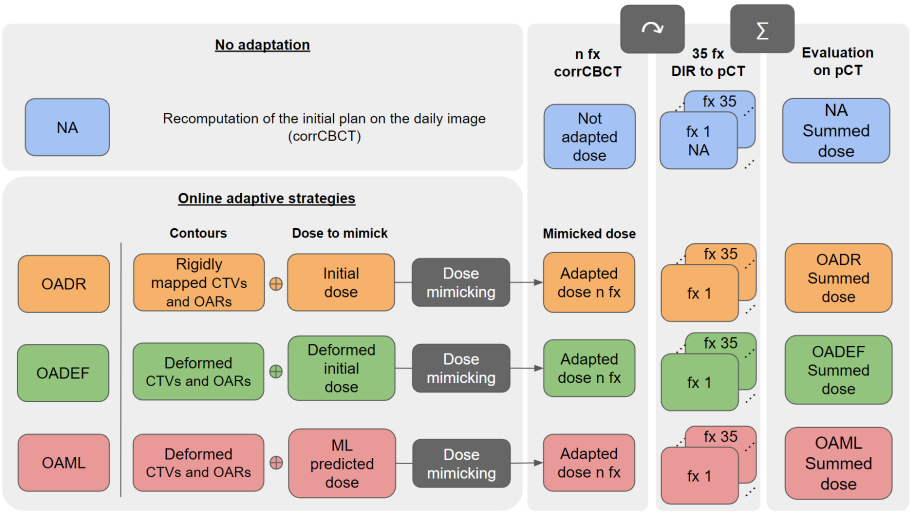

Figure 5.1: Figure 1. Summary of the workflow to compare the not adaptive (NA) strategy with the three proposed online adaptive methods based on dose mimicking: OADR, OADEF and OAML. Abbreviations: corrCBCT = corrected CBCT, DIR = Deformable Image Registration, fx = fraction, ML= Machine Learning, NA = No Adaptation, OADR = Online Adaptive based on Dose Restoration, OADEF = Online Adaptation based on DEFormed dose, OAML = Online Adaptation based on ML predicted dose, pCT = planning-CT.

5.2.5 Adaptation schedule

The objective was to simulate online adaptation only in the fractions where it was needed rather than to explore a daily adaptation schedule for each strategy. To trigger the adaptation, initial plans were recomputed on the corrCBCT and the target coverage was evaluated on the propagated (i.e deformed) contours from the pCT to the corrCBCT. A fraction was flagged as requiring adaptation when the target coverage criteria (i.e D98%CTV ¡ 95% Prescribed dose (Dp)) was not met for high-risk and/or low-risk deformed CTVs. From the 10 patients, 7 needed adaptation in more than 15 fractions (from 33 to 16), while 3 required only adaptation in 1 to 10 fractions.

5.2.6 Evaluation strategies

For not adapted treatments (NA), the dosimetric effects of anatomical and setup uncertainties were calculated by recomputing the initial plans on the corrCBCTs. The adapted doses in each fraction were simulated by optimizing a new adapted plan on the daily image (corrCBCT), using the different OAPT methods (OADR, OADEF and OAML) as described in Figure 1.

With 35 fractions per patient and a total of 10 patients, 350 fractions were available to evaluate target coverage on the deformed CTVs for NA, OADR, OADEF and OAML strategies. Ideally, the evaluation of the OAPT strategies should be performed on manually delineated contours on the corrCBCTs for each fraction. However, the re-delineation of 350 corrCBCTs would imply an unreasonable workload for the clinical staff at our institution. As an alternative, we decided to use dose accumulation on the pCT in order to simulate a complete treatment delivery (see Figure 1.). A verification on a subset of 2 corrCBCT per patient, corresponding to 20 treatment fractions, was performed on re-contoured targets and OAR (see section 2.5.2).

Evaluation on accumulated doses

According to the initial plan treatment schedule (section 2.4) for each patient, NA, OADR, OADEF and OAML plans were computed on the 35 corrCBCTs to simulate the final delivered dose by each method. Using DIR (from the pCT to corrCBCT), each fraction dose was warped back to the pCT. The 35 warped fraction doses were summed up to four different accumulated dose distributions per patient (NA, OADR, OADEF and OAML summed doses), and compared to the initial reference dose. It is important to keep in mind that daily adaptation was not performed. Therefore, OADR, OADEF and OAML summed doses contained NA doses in the fractions where adaptation was not required (i.e target coverage criteria were already met by using the initial clinical plan without adaptation for that specific treatment fraction). Since all the doses were warped back to the pCT, the metric evaluation was performed on the manually delineated contours on the pCT.

For each summed dose, differences with respect to the clinical dose in D98 values (dose received by 98% of the volume) were calculated for low-dose and high-dose CTVs. Differences in Dmean (average dose) were reported for the parotids, SMGs, PCMs and the oral cavity while differences in maximum doses (i.e dose received at 0.03 centimeters cube (D0.03cc)) were calculated for the spinal cord, brainstem and the body. These metrics were evaluated for NA, OADR, OADEF and OAML accumulated doses and compared to the initial dose distribution values. Median, minimum and maximum values of the differences, Median (Min, Max), were reported to illustrate how far the NA and OAPT doses were from the initially planned dose distribution. Normal Tissue Complication Probability (NTCP) values were also calculated from the OAR metrics using the formulation proposed by Langendijk et al.[245].

Evaluation on corrected contours in corrCBCT

The dose accumulation method previously described has limitations since the DIR used to deform the contours from the pCT to the corrCBT was also used (inversely) to map the NA, OADR, OADEF and OAML dose distributions in each corrCBCT to the pCT. It could be that inaccuracies in the DIR used for contour mapping would have been underestimated because of the posterior inverse dose mapping to the pCT. In this case, OADEF and OAML strategies would have biased evaluations giving too optimistic results.

To overcome the DIR limitations we asked experienced radiation oncologists to correct CTV and OAR volumes in two fractions per patient. Fractions with low target coverage in the deformed CTVs were selected: one fraction before the first half of the treatment and another one towards the end of the treatment. CTV and OAR contours were deformably mapped and manually corrected when necessary. With two fractions for each of the 10 patients, 20 fractions with manually corrected contours were available for direct evaluation of each OAPT strategy.

Evaluation of different treatment schedules

The scheduled plan is defined as the plan that should be delivered to a patient at a specific n treatment fraction ($n \leq 35$). In this study, we evaluated for each of the OAPT strategies the number of fractions needing adaptation depending on different scheduled plans for each fraction n:

- **Initial plan (IP):** The IP optimized on the pCT was the scheduled plan for fraction n.
- **Last adapted plan (LAP):** From all the previous fractions, the plan corresponding to the last adapted fraction X is the scheduled plan for fraction n ($X < n$).
- **Best adapted plan (BAP):** The plan with the highest target coverage after the re-computation of all previously adapted plans on the corrCBCT of the fraction n is chosen as the BAP. The BAP corresponding to a previous fraction Y ($Y \leq X < n$) is the scheduled plan for fraction n.

5.2.7 Statistical significance

Grouped data were tested for statistical significance using two-sided Wilcoxon-Mann-Whitney tests using SciPy version 1.5.2. The differences were considered statistically significant for p-values < 0.05.

5.3 Results

5.3.1 Target coverage in corrected CBCTs

Median values of target coverage across the 350 corrCBCT (including adapted and not adapted fractions) are given as a percentage of the prescribed dose in Table 2.a) for low and high-risk CTV. With NA strategy relying on the robustness of the initial plan, 52%(181/350) of the fractions required adaptation since target coverage criteria (D98% $>$ 95%Dp) was not fulfilled for one or both CTVs. When applying OADEF or OAML to these fractions, target coverage was ensured in all corrCBCT. This was not the case with OADR, which could not ensure target coverage in 9% and 5% of the cases for low-risk and high-risk CTV, respectively. For all strategies, NA, OADR, OADEF and OAML coverage of low-risk CTV was lower than high-risk CTV. OADR improved median target coverage in 0.9 Gy compared to NA plans. While OADEF had the highest performance with less than 0.2 Gy difference with respect to OAML.

5.3.2 Target coverage in accumulated doses

Table 2.b) contains the median values of D98 metrics for both CTVs accross the 10 accumulated dose distributions (one per patient). Without any adaptation, low-risk CTV did not receive the prescribed dose in 3 patients (30%). When implementing OADEF and OAML to the selected fractions for adaptation, accumulated dose distributions recovered target coverage in all patients. For OADR, the low-risk CTV of patient 3 received only 93.46% of the prescribed dose, being the only patient for which the method was not able to compensate for the anatomical changes.

Differences in D98% values of NA, OADR, OADEF and OAML strategies with respect to the initial plan are shown in Figure 5.2 Whether the differences with respect to the initial dose and between models are statistically significant ($p < 0.05$) or not statistically significant (n.s, $p > 0.05$) was reported in Table 5.3.

NA plans presented statistically significant degradation in target coverage with respect to the initial plan. In the high-risk CTV the median value of the difference for D98 metrics NA plans was -0.84 (-1.21, 0.11) Gy Gy. On the contrary, when applying OAPT strategies median differences were not statistically significant with respect to the initial plan with 0.01 (-1.17, 0.62) Gy for OADR, 0.29 (-1.22, 0.94) Gy for OADEF and 0.16 (-0.83, 0.61) Gy for OAML.

a) Evaluation on deformed CTVs for the 350 corrCBCTs **Median** (Min - Max) % of prescribed dose				
Planning strategy	Low risk CTV (Dp = 54.25 Gy)	Fail cases Abs (%)	High risk CTV (Dp = 70.00 Gy)	Fail cases Abs (%)
NA initial plan	**95.21** (60.77 - 96.79)	151 (43%)	**96.11** (73.38 - 97.89)	117 (33%)
OADR	**96.13** (74.35 - 97.24)	34 (9%)	**97.04** (84.39 - 98.20)	18 (5%)
OADEF	**96.54** (95.01 - 97.43)	0 (0%)	**97.52** (95.08 - 98.22)	0 (0%)
OAML	**96.43** (95.01 - 97.27	0 (0%)	**97.38** (95.08 - 98.10)	0 (0%)
b) Evaluation of the 10 accumulated dose distributions on the planning contours **Median** (Min - Max) % of prescribed dose				
Planning strategy	Low risk CTV (Dp = 54.25 Gy)	Fail cases Abs (%)	High risk CTV (Dp = 70.00 Gy)	Fail cases Abs (%)
NA initial plan	**96.07** (92.73 - 97.42)	3 (30%)	**96.47** (96.20 - 97.89)	0 (0%)
OADR	**97.30** (93.46 - 98.01)	1 (10%)	**97.61** (96.58 - 98.14)	0 (0%)
OADEF	**97.87** (97.04 - 98.24)	0 (0%)	**98.03** (96.52 - 98.84)	0 (0%)
OAML	**97.82** (97.10 - 98.07)	0 (0%)	**97.90** (97.07 - 98.57)	0 (0%)
c) Evaluation on manually delineated CTVs for 20 selected corrected CBCTs **Median** (Min - Max) % of prescribed dose				
Planning strategy	Low risk CTV (Dp = 54.25 Gy)	Fail cases Abs (%)	High risk CTV (Dp = 70.00 Gy)	Fail cases Abs (%)
NA initial plan	**93.74** (59.76 - 95.99)	16 (80%)	**95.05** (89.13 - 97.52)	9 (45%)
OADR	**95.83** (90.18 - 96.94)	4 (20%)	**97.36** (86.66 - 98.10)	3 (15%)
OADEF	**96.70** (95.96 - 96.91)	0 (0%)	**97.80** (92.54 - 98.19)	1 (5%)
OAML	**96.50** (96.12 - 96.89)	0 (0%)	**97.66** (90.48 - 98.04)	1 (5%)

Table 5.2: Median, minimum and maximum values for low-risk CTV and high-risk CTV target coverage for three different evaluation strategies: (a) evaluation on deformed CTVs over the 350 fractions (10 patients with 35 fractions per patient), (b) evaluation on the manually delineated contours on the planning-CT after dose accumulation of the 35 fractions on the planning-CT (one dose distribution per patient, so 10 accumulated dose by strategy) and (c) evaluation on the corrected CTVs on a subset of 20 selected fractions. The number of cases where the target coverage criteria failed (D98 $<$95%Dprescribed) is also reported in absolute value (Abs) and as a percentage of the number of total evaluated data points: 350 for (a), 10 for (b) and 20 for (c). Abbreviations: Abs = Absolute, CTV = Clinical Target Coverage, NA = Not adapted, Min = Minimum, Max = Maximum.

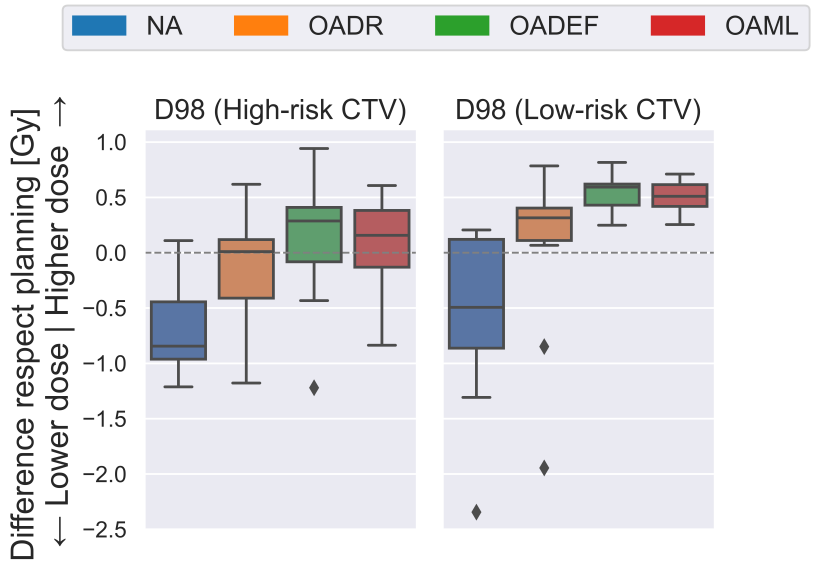

Figure 5.2: Figure 1. Summary of the workflow to compare the not adaptive (NA) strategy with the three proposed online adaptive methods based on dose mimicking: OADR, OADEF and OAML. Abbreviations: corrCBCT = corrected CBCT, DIR = Deformable Image Registration, fx = fraction, ML= Machine Learning, NA = No Adaptation, OADR = Online Adaptive based on Dose Restoration, OADEF = Online Adaptation based on DEFormed dose, OAML = Online Adaptation based on ML predicted dose, pCT = planning-CT.

For the low-risk CTV (i.e union between both left and right nodes) differences in D98 values experience a drop in target coverage of -0.50 (-2.34, 0.20) Gy for NA plans. On the contrary, when applying OAPT strategies, low-risk target coverage was increased even to greater values than the ones from the reference plan, with a median D98 values of 0.32 (-1.95, 0.78) Gy for OADR, 0.59 (0.25, 0.82) for OADEF and 0.51(0.25, 0.71) for OAML. For OAML and OADEL the differences with respect to the clinical dose were statistically significant.

Analysing the performance between methods, OADEF provides the highest target coverage overall but with an outlier for patient 10 for which only one fraction was adapted. OADEF and OAML perform very equally, ensuring target coverage for all accumulated dose distribution. The differences in target coverage with respect to the initial dose for both low-risk and high-risk CTV between OADEF and OAML were not statistically significant.

	D98(Low risk CTV)				D98(High risk CTV)			
	NA	**OADR**	**OADEF**	**OAML**	**NA**	**OADR**	**OADEF**	**OAML**
Clin	0.008	n.s	0.002	0.002	0.004	n.s	n.s	n.s
NA		0.010	0.002	0.002		0.019	0.006	0.002
OADR			0.003	n.s			0.019	0.027
OADEF				n.s				n.s

Table 5.3: Statistical significance of the different strategies (NA, OADR, OADEF and OAML) compared to the reference clinical dose and between them. Statistically significant (s.s) implies p $<$0.05. Pink cells represent the values for which no statistically significant difference (n.s.s) was reported (p $>$0.05).

5.3.3 Target coverage for re-delineated contours

Median values of target coverage across the 20 re-delineated corrCBCT were reported as a percentage of the prescribed dose in Table 2.c) for both CTVs. When the initial plan was delivered without any correction, adaptation was required in 80% and 45% of the 20 fractions to ensure target coverage for low-risk and high-risk CTV, respectively. In some cases, the target coverage was extremely low, not even achieving 60% of the prescribed dose for one outlier. With no adaptation, the median value of D98% metric for the low-risk CTV was below 94% of the prescribed dose. When applying OADR to this subset of fractions, median D98% was recovered above 95% of the prescribed dose for low-risk CTV and increased from 95% to 97% of the prescribed dose for high-risk CTV. However, some of the fractions still did not reach the clinical goal (D98% $>$ 95%Dp). Although OADEF and OAML strategies increased target coverage for both CTVs, none of the methods could ensure coverage of the high-risk CTV for one of the fractions when evaluating the real (i.e corrected) structures.

5.3.4 OAR sparing and toxicity on accumulated doses

The differences with respect to the initial dose in the OAR and NTCP evaluation metrics were displayed in Figure 3. and Figure 4., respectively. Median values of the differences in the OAR metrics were in most of the cases less than 1 Gy. A bigger variability was shown in the PCMs, especially on the superior and medium PCMs. Overdosage to the PCMs was translated into a higher probability of dysphagia in grades 2 and 3, especially for NA plans. When applying OADR and OADEF, NTCP values were reduced close to the initial values. The lowest NTCP values were achieved by OAML doses, with no statistical significance compared to NTCP values from the initial plans.

Two outliers were observed in the spinal cord for NA plans with overdosages of 6.8 Gy and 14.5 Gy. Both were compensated with the implementation of any of the OAPT strategies. Maintaining target coverage came at the cost of a slightly increased dose to the brainstem and the spinal cord for OADR and OADEF strategies, although always within clinical limits. Moreover, an increased dose to the parotids in OADR dose distributions was translated into a median increase of 0.5% probability for xerostomia grade 2. The NTCP values never exceeded more than 1.2% for xerostomia nor 3.9% for dysphagia. Moreover, in the case of dysphagia, NTCP values were always lower when applying any of the OATP strategies than with no adaptation.

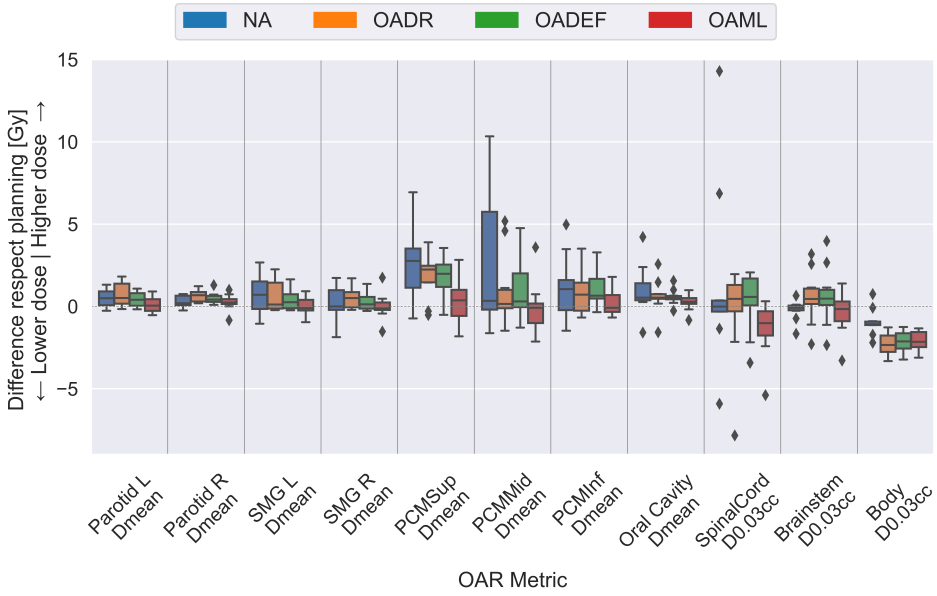

Figure 5.3: The differences in DVH metrics (Dmean and D0.03cc) between accumulated doses of NA, OADR, OADEF and OAML, and the clinical plans. Differences greater than zero indicate an overdosage to the OAR while values below zero indicate OAR sparing. The boxes indicate the median and interquartile range (IQR). The whiskers extend to a minimum of 1.5 times the IQR and diamonds represent the outliers.

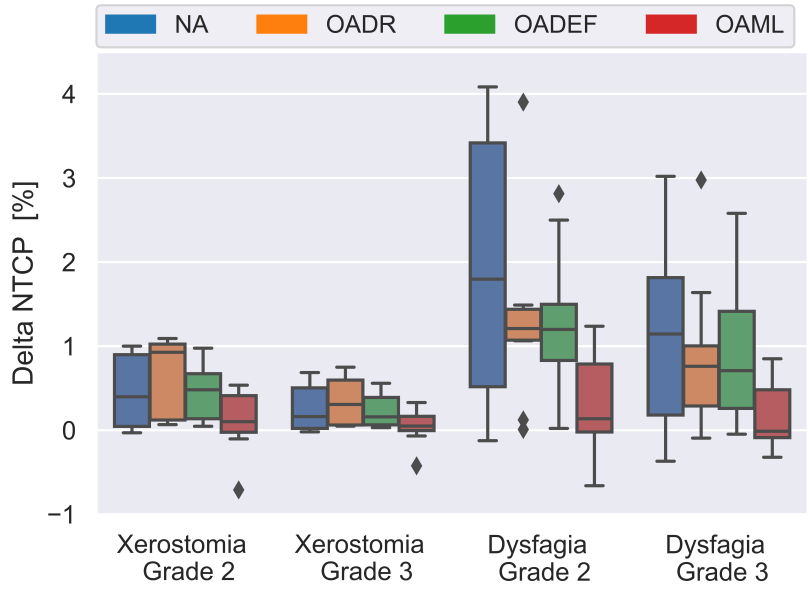

Figure 5.4: Difference in NTCP values respect to the clinical plan NTCP values, ΔNTCP = NTCP(OAPT strategy) - NTCP(clinical plan). The higher the difference in the NTCP values, the bigger the deviation from NTCP from the clinical plan and the higher probability of developing secondary effects associated with toxicity (for values above 0).

5.3.5 Analysis of adaptation rates

In Table 4. the adaptation rates for three different scheduled plans: initial plan (IP), last adapted plan (LAP) and best adapted plan (BAP) were reported. More than half of the fractions (51%) required adaptation to ensure target coverage criteria when the initial plan was chosen to be delivered without any adaptation. On the contrary, when LAP was selected as the scheduled plan, the need for adaptation was reduced by more than half for any of the OATP strategies: 25% of adaptation required for OADR, 16% for OADEF and 21% for OAML. The adaptation rate decreased, even more, using the BAP as the scheduled plan. In this case, when applying 20% of adaptation was achieved for OADR, 14% for OAML and in the best case scenario, only 12% of the 350 fractions (instead of 51%) was required when OADEF was chosen.

5.4 Discussion

Three robust IMPT planning strategies based on dose mimicking were fully automated and integrated into the commercial TPS RayStation 11B. The three methods, OADR, OADEF and OAML, increased target coverage compared to no

	Number of adapted fractions						
	Initial plan	Last adapted plan (LAP)			Best adapted plan (BAP)		
Patient	(IP)	OADR	OADEF	OAML	OADR	OADEF	OAML
1	33	28	14	21	20	11	14
2	32	13	12	14	9	8	10
3	26	20	7	7	19	5	7
4	22	5	5	5	4	4	4
5	20	5	4	5	5	4	4
6	18	4	3	11	3	3	4
7	16	5	5	5	5	2	2
8	10	5	4	5	3	3	4
9	2	2	2	2	2	2	2
10	1	1	1	1	1	1	1
%Total of the 350 fractions	51%	25%	16%	21%	20%	12%	14%

Table 5.4: The number of adapted fractions per patient according to the target coverage criteria (D98% >95% Prescribed dose) evaluated in each fraction. Since manually delineated contours were not available in every fraction, the recomputation of the schedule plans for that fraction (i.e the initial plan (IP), the last adapted plan (LAP) or the best adapted plan (BAP)) was evaluated on the deformed target volumes.

adaptation while reducing the need for offline adaptation. It was shown that the adaptation rate could be reduced from 51% for NA plans, to less than 25% when using LAP as the scheduled plan, and below 12% for BAP. BAP is computationally more expensive than LAP since it requires more than one proton dose recalculation. However, the workflow could be easily parallelized to quickly evaluate all previously adapted plans.

Due to the proximity of small OAR to the CTVs in HNC, maintaining the target coverage during all fractions slightly increased the dose to the parotids and PCMs. This was translated into increased NTCP with respect to the initial plan, especially for OADR and OADEF strategies. However, for dysphagia, the increase in NTCPs was always lower for any OATP strategies than for NA, while for xerostomia it never exceeded more than 2%. This could seem an acceptable tradeoff in exchange for a higher target coverage and tumor control probability (TCP). Overall, OAML dose distributions showed the best performance, maintaining or even improving target coverage and OAR sparing and with no statistical signifi-

cance in NTCP values with respect to the initial plan for all toxicities and grades. Moreover, all three OAPT strategies were also able to correct hot spots.

Previously presented robust dose restoration strategies required an additional manual step in the planning phase for each patient [204, 228, 16]. This approach could make difficult the usability of the method in a clinical setting due to the increased workload [117]. On the contrary, in our proposed OADR, the manual configuration of the mimicking parameters is performed once during the commissioning of the ML model. Once the mimicking settings are chosen for a specific protocol (i.e tumor location, beam configuration, robustness parameters etc.), the mimicking model can be used for all subsequent patients without manual tuning.

Manual contour delineation of the new patient anatomy is the most time-consuming step in the adaptive workflow and probably one of the bottlenecks hampering online adaptive implementation [246]. The advantage of the three proposed OAPT strategies is that they do not require new contour delineation before re-optimization, contours from the pCT are instead (a) rigidly or (b) deformably mapped to the corrCBCT.

When (a) rigid mapping is applied, we gain stability in the dose shape compared to the initial clinical plan, which facilitates plan approval and quality assurance (QA). Only addressing density changes, the offline adaptation rate was not zero but it was reduced by more than 50%. To cover a wider range of anatomical deformations, including non-rigid deformations, other adaptive strategies including deformed contours (b) were required. These results are in agreement with a previous study by Borderias-Villarroel et al. [228] where offline adaptation was necessary to correct the dose distortions that dose restoration could not compensate for. The proposed OADEF and OAML strategies could be alternatives to offline replanning in such cases to avoid increased workload and treatment delays. Ideally, the re-contouring (i.e volume segmentation) could be performed automatically by artificial intelligence models [209, 213]. These tools have been proven very effective on CT image quality data sets but would need to be adapted to be used on low-quality CBCT images [247, 248] or synthetic CTs [239]. Unfortunately, nowadays both DIR and automatic segmentation cannot be relied on blindly, without human verification [203]. Therefore, contour modification and approval by the doctor are still required, as is the case in the Ethos System from Varian or the MRLinacs [157, 83].

Although the benefit of adaptation is already seen with only some of the fractions being adapted, it could be that its main advantages, such as higher OAR sparing, are diluted by the non-adapted fractions. A bigger difference between

NA plans and OAPT plans would have probably arisen from a comparison with a daily adaptation schedule. However, with the current technology daily online adaptation is still a cumbersome task that will increase the workload and the time spent by the patient on the treatment couch. This could be detrimental for the patient due to increased setup error uncertainties in fractions where adaptation is not needed to achieve the clinical goals. On the other hand, higher adaptation rates open the path to decreasing robustness parameters accounting for setup and range errors that could be translated into OAR sparing and reduced toxicities.

The feasibility of fully integrated and automated adapted proton plans using Monte Carlo optimization on corrected CBCT images in less than 20 minutes, brings OAPT one step closer to its clinical implementation. However, some of the limitations of our study still need to be addressed.

First, the CBCT image quality was out of the scope of the study since our main objective was the comparison between adaptive strategies all computed on the same corrCBCT. Nevertheless, it is an important field of research in OAPT since an improved CBCT image quality would enable more accurate evaluation, optimization and proton dose calculation [100, 249, 134].

Second, the DIR algorithm introduces uncertainties during contour mapping, dose warping and accumulation especially when important anatomical changes occur and when reporting small volume dose metrics (i.e parotids or SMGs) in steep dose gradients [250, 251, 121]. In our study, NTCPs were calculated with OAR median doses taken directly from the DIR-based deformed contours. However, differences in NTCPs between DIR-based and manual contouring should be within the range caused by inter-observer variability as reported by Gan et al. [252]. It was also shown the evaluation on deformed contours can be suboptimal to estimate the real delivered dose to the patient leading to an underestimation of the adaptation need. The evaluation of OAPT strategies directly on a subset of fractions with manually corrected contours attempted to mitigate the limitations of the DIR-based dose accumulation. However, this probably came intrinsically with the introduction of inter-observer variabilities. Moreover, with the introduction of DIR-mapped contours in automatic proton treatment re-planning, there is a crucial necessity to develop automatic tools able to identify when propagated contours are likely to be incorrect, acting as a flag for manual review of these contours [253].

Third, depending on the available tools and medical staff OADR, OADEF, OAML or offline adaptation could be chosen as adaptive strategies. A fast-independent Monte Carlo dose calculation could help in the decision-making and

as a pre-treatment patient-specific QA procedure [254]. Parameters such as the degree of weight loss, reduction in lateral neck diameter or Dice Similarity Coefficient (DSC) between rigidly and deformably mapped contours could also be monitored to trigger patients receiving the greatest benefit of adaptation and appropriate candidates for each of the OAPT [228, 210]. In any case, all online adapted plans should be followed by an extensive and fast, patient-specific quality assurance including machine log files after delivery [65].

Finally, it would be interesting to evaluate the three OAPT methods compared to reference clinical plans manually generated instead of fine-tuned automated ML plans.

In conclusion, all adapted plans provided closer DVH metrics to the validated initial plan compared to no adaptation, sometimes reestablishing or even improving the initial plan. OAML had the overall better performance in target coverage, OAR sparing and NTCPs, closely followed by OADEF. The three methods have the potential to be integrated into an online adaptive clinical setting to generate adapted plans which can compensate for inter-fractional anatomical changes and reduce the need for offline adaptation. This is key to deliver the most personalised treatment plan to the patient while avoiding an unaffordable increased workload to the radiation therapy department.