**Online adaption approaches for intensity modulated proton therapy for head and neck patients based on cone beam CT and Monte Carlo simulations**

**Introduction**

Head and neck (H&N) tumors are often very close to organs at risk (OARs) such as the parotids, larynx, submandibular glands or others. Due to this, H&N cases may benefit from steep dose gradients in the planned dose distribution to better spare the OARs while giving therapeutic doses to the target. Intensity modulated proton therapy (IMPT) is capable of producing such steep gradients and is an interesting treatment modality for these cases, offering potential benefits over photon treatments [Lee 2018, waddlw 2018]. However, proton plans, and in particular IMPT plans, can be very sensitive to uncertainties that may distort the planned dose distribution [Ahn, Paganetti ...], impacting the treatment quality. There are several sources of systematic and random uncertainties. The patient setup and anatomy are two examples of uncertainty sources. The setup uncertainty arises from the patient location on the treatment couch being potentially different to the one recorded in the planning CT. The anatomy uncertainty arises from the patient anatomy evolution throughout the course of treatment, not only due to loss of weight modifying subcutaneous tissue and/or structure locations, but also due to posture on the treatment couch. Both uncertainty sources might introduce high/low density materials in the beamlets path, modifying the planned dose distribution and affecting target coverage and OAR sparing.

These uncertainty sources can be taken into account during the planning procedure with the creation of safety margins around the target in an attempt to guarantee treatment quality throughout the treatment fractions. As a consequence, the high dose volume in the patient is enlarged and organs at risk (OARs) receive higher doses. It is therefore desirable to shrink the safety margin to improve IMPT plan quality. An alternative to the target expansion is robust IMPT optimization, which consists of IMPT plan optimization considering different patient scenarios. With this approach, the resultant plan would provide proper target coverage and OAR sparing at delivery, as long as the current patient characteristics were included as a scenario during the optimization. This technique is able to maintain the original plan standards better than the safety margin approach in the general case. However, robust planning usually softens dose gradients, which, again, results in enlarged high dose volumes and higher dose to OARs compared to a plan performed in a single scenario. *Additionally, there are some novel trends under investigation on adjustable robust optimization, which has the potential to provide good plan quality by automatically giving selecting the plan parameters for the current patient geometry. Its success, however, depends on creating an accurate set of scenarios forecasting the patient anatomy changes, which, again, introduces uncertainties and might produce a bigger high dose volume.* The previous techniques can be applied after careful selection of the beam angles to reduce the impact of uncertainties, which may give satisfactory results, but do not offer a general solution to account for setup and anatomy uncertainties and shrink safety margins at the same time. An ideal solution that might fulfill both requirements is to perform online IMPT plan adaptation at every fraction. This is an ambitious interpretation of the role of online adaptation. In a more modest interpretation of the application of online plan adaptation is to avoid treatment replanning in scenarios when the robust IMPT plan does not fulfill treatment standards. In both cases, online plan adaptation would be have a big impact on the treatment quality through better plan quality of avoiding replanning steps that may delay the delivery of the full treatment.

Another uncertainty source comes from the dose calculation algorithm. In the case of H&N and other sites [GRASSBERGER lung and others], analytical dose calculations accuracy of proton beams might be compromised by tissue heterogeneity [JAN?]. If uncertainty margins due to the dose calculation algorithm are intended to be reduced in H&N plans, Monte Carlo-based (MC) adaptation is desirable. However, using MC calculations for online adaptation imposes big time constrains, as they are slower than analytical algorithms. Employing graphics processing units (GPU) for MC simulations and novel adaptation strategies, could allow online IMPT plan adaptation based on GPU-MC calculations on clinically applicable times.

The goal of online plan adaptation is to tailor an original IMPT plan to the setup and anatomy of each patient at each fraction. In other words, an online plan adaptation algorithm would tune a plan to a patient geometry different from where it was originally designed. The algorithm would need a two inputs containing the new information: an imaging system capable of providing the patient anatomy at treatment position and an updated set of contours localizing the target and OARs. The algorithm would then generate an appropriate set of new or modified beamlets for the new geometry. All these steps should occur in a few minutes to fit clinical requirements.

Several studies have been performed on online and offline IMPT adaptation. Automatic offline full plan reoptimization for H&N cases on deformed planning CT and contours was reported by [KURZ 2016], where new spot maps were created and optimized. Jagt et al. [JAGT 2017] published an online dose restoration procedure that is capable of restoring a dose distribution in prostate cases on the original contours, correcting the spot energies and fully reoptimizing the spot weights. Recently, Bernatowicz et al. [BERNATOWICZ 2018] extended the work presented by Jagt et at. to allow other reoptimization strategies, applying them to nasopharynx, H&N and lung (1 case each). All previous approaches rely on full plan reoptimization, which, in turn, requires the costly calculation of full dose-influence matrices. A different approach without plan reoptimization was presented by Moriya et at. [MORIYA] in a different context. They adapted the range shifter thickness of passive scattering plans for lung cancer cases. This methodology could be expected to have limited success if non-uniform energy shifts are needed, but it is an example of possible adaptation approaches that do not require full plan reoptimization. Alternatives to circumvent full plan reoptimization are still to be published to the best knowledge of the authors. As summary, the publications here cited are either not an online algorithm (Kurz et al.) or they were not demonstrated on deformed contours (Jagt et al. and Bernatowicz et al.). Additionally, none of them include Monte Carlo simulations as dose calculation engine.

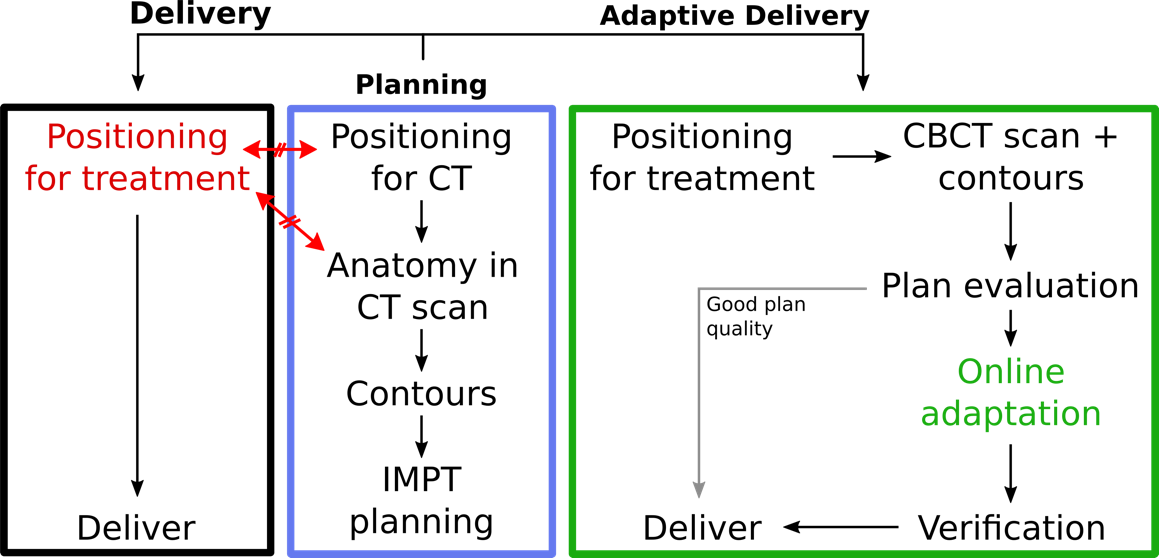
Therefore, it is the main goal of this manuscript to perform online adaptation of IMPT plans on weekly acquired cone beam CT (CBCT) scans of H&N patients, with automatically propagated deformed contours and using a GPU MC code, gPMC [XUN, NAN], as dose calculation engine. Such algorithm would be applied while the patient is on the couch and can potentially allow security margins reduction or reduce the number of replanning steps, increasing workflow efficiency. As a secondary goal, the adaptation using energy and position changes from the delivery systems was compared with the utilization of range shifters and couch shifts.

**Methods**

At the beginning of this section an hypothetical adaptive delivery workflow is introduced and then the adaptation algorithm inputs are explained, setting the scenario in which this tool would be applicable. The adaptation algorithm is then detailed. Afterwards, the patient cohort is included. Finally, the approaches studied with the algorithm operation modes are explained along with the quantities selected to judge the performance.

*Adaptive delivery workflow*

The presented algorithm aims to adapt IMPT plans online, before each fraction delivery, to account for patient setup and geometry uncertainties using GPU MC simulations. The current planning-delivery workflow, shown in figure 1 from the planning stage to the left, contains the uncertainties of the patient positioning and anatomy. This may be solved by employing an adaptive workflow, shown in figure 1 from the planning stage to the right.



The first step of such adaptive workflow would be to acquire information about the patient geometry, including a possible automatic generation of contours. Then the original IMPT would be evaluated on the new patient geometry with a GPU MC simulation. If the clinical requirements were still met, then the plan would be delivered. However, if the clinical requirements were not met, the patient information would be fed as inputs to the presented online adaptation algorithm. If the adaptation was successful, the patient would be treated, else, a replan would be necessary. As stated above and in the introduction, it is an important goal of this manuscript to maintain high dose calculation accuracy at every step by using GPU MC simulations, therefore, gPMC was employed as dose calculation engine at the initial IMPT planning step, at the plan evaluation on the daily patient geometry and at the dose calculations in the online adaptation algorithm.

*Inputs: CBCT, vector field map and contours*

The required adaptation inputs are: the patient geometry contained on a CBCT, a vector field (VF) mapping the original planning CT to the CBCT, and a set of new contours localizing the structures in the CBCT.

CBCTs are known to provide limited accuracy for dose calculation [REFERENCES]. In order to employ the CBCT for dose calculation, an *a priori* planning CT-based scatter-correction algorithm [PARK, KURZ 2015] was applied. Park et al. have reported average accumulated WEPL errors across different locations of 2.3 ± 1.9 %. The CT and CBCTs were aligned at the plan isocenter, which better maintains the original plan quality at every evaluation, as opposed to alignment to a given OAR. This is not necessarily always the optimal clinical practice for every case if extra protection to a given OAR is desired.

The contours defined in the planning CT were propagated onto the weekly CBCT applying a VF. The VF map was calculated between the planning CT and the CBCT with deformable image registration (DIR) using the GPU parallelized B-spline algorithm in Plastimatch, an open source suite for radiotherapy and medical imaging [SHACKLEFORD, PLASTIMATCH]. The correctness of the structures on the weekly geometry was visually verified. To the best knowledge of the authors, there is no automatic and reliable procedure to generate the structure contours for H&N cases [REFERENCE???].

It is important to note that the accuracy of the CBCTs and the VFs employed in this manuscript does not affect the evaluation of the adaptation algorithm. It is understood that the CBCTs and VFs introduce uncertainties. However, even though the CBCTs and VFs may not perfectly represent the current patient geometry and deformation, they represent plausible geometries and deformations of the patient. As long as the geometry contained in the CBCTs is plausible, the algorithm should be able to adapt the initial plan to it. The same argument can be applied to the VF and, therefore to the propagated contours. Improvement of CBCT accuracy and automatic propagation/generation of structure sets is still a research focus in the field [CITATIONS]. There are other practical issues about the usage of CBCTs analyzed in the discussion section.

The scatter correction increases the accuracy of these images, but the limited field of view (FOV) of these scans might limit the usability in some cases. The limited FOV might also pose problems during DIR and those might be contained in the propagated contours. Several approaches have been followed regarding the imaging modality needed to perform online adaptation. An alternative option as the one here utilized is to register and warp the planning CT to the CBCTs. However, this method, for instance employed by Kurz et al [MORE EXAMPLES], has the issue that it has the accuracy of the DIR vector field. Another possibility is to have the availability of in-room CT, which may provide high quality images, but the positioning system might introduce uncertainties. All three options have drawbacks and advantages, but for the scope of this manuscript, the usage of scatter corrected CBCTs provides a challenging scenario to prove the efficacy of the algorithm.

*Adaptation algorithm*

The adaptation algorithm was designed as a two-step process, where, firstly, the beamlets positions and energies were adjusted to form the geometrical adaptation and, secondly, the beamlets weights were tuned, if necessary.

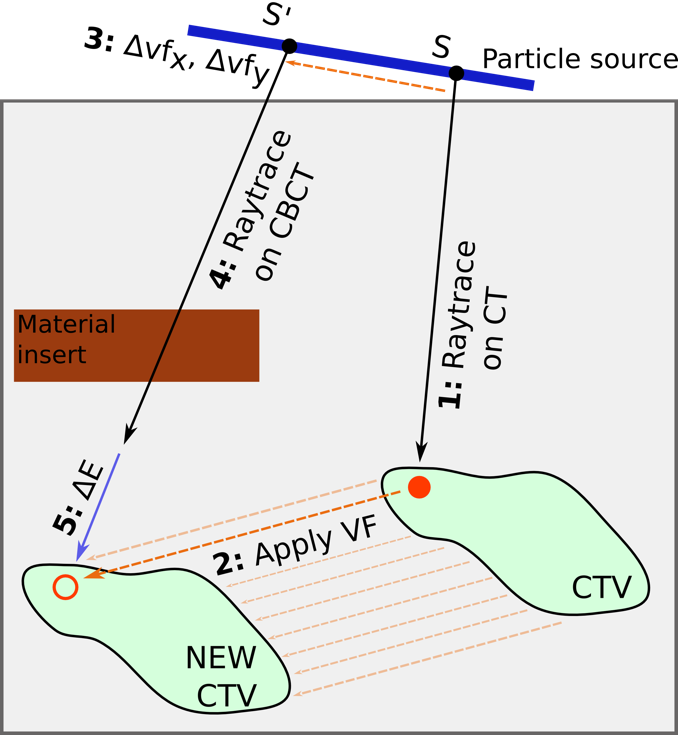
After verifying with gPMC on the CBCT that the original IMPT plan needs adaptation, the algorithm would perform the next steps:

1. Geometrical adaptation
2. Simulation on CBCT
3. If clinical requirements are met: deliver
4. Else: spot weights tuning
5. If clinical requirements are met: deliver
6. Else: replan

*Geometrical adaptation*

The geometrical adaptation adjusted the position and energy of the beamlets to the new geometry.

The adaptation steps are depicted in figure 2. Each spot in the plan was raytraced along its central axis until the end of range in the planning CT (1). The locations resulting from the raytracing were called endpoints. Due to the heterogeneity of the patient’s tissue and the subsequent deformation of the Bragg peak, the density of each voxel along the central axis was averaged with its surroundings. The average was calculated adding a set of 8 probes defined at the orthogonal plane around the central axis. The distance and relative weights between the probes and the central axis were calculated from the expected beamlet profile in water at the equivalent depth. The angular position of the first probe was randomized. Because the patient deformation is captured in the VF, the set of original endpoints defined in the CT was warped applying the VF, yielding the position that should be occupied in the new geometry by each endpoint, and, therefore, by the high dose region of each beamlet (2). This is the same deformation previously applied to the contours propagation. The new position of each warped beamlet in the particle source plane was calculated next (3). Then, the shifted spots were raytraced in the CBCT applying the averaging algorithm (4). Finally, the energy was adjusted to match the end of range in the CBCT with the warped endpoint (5).



After the geometrical adaptation, the adjusted plan was simulated with gPMC on the CBCT. Should the dose distribution fulfill the clinical requirements, the adaptation process would end and the plan would be delivered.

*Weight tuning*

After applying the geometrical adaptation to the original plan, the clinical requirements might not be fulfilled. A possible reason for this is that the shapes of the original spots might be changed by the adaptation and the new geometry. Not only the materials traversed may affect the adapted beamlets, but also the beamlet energy may have changed, which would change the beamlet width and energy spread coming from the delivery system. Additionally, the relative positions between endpoints may be different if the VF contains non-parallel deformations, creating potential cold/hot-spots. All of these effects may have drastic consequences on IMPT plans. Therefore, it might be necessary to tune the number of protons delivered per spot to fulfill clinical requirements.

The usual IMPT problem solves an expression of the form of equation 1, with some objectives and constraints to the final dose distribution . In equation 1, is the full dose-influence matrix containing the dose distribution given at each voxel per beamlet and unit of fluence and is the beamlet weights to be calculated. However, calculating a full matrix with GPU MC to solve such a problem is computationally demanding and not suitable for an online application. In order to comply with the requirements of an online application, a solution to extract enough information to define a matrix from the geometrically adapted plan validation was found. It was observed that a minority of the spots in an IMPT plan carry the majority of the weight and, therefore, deliver the majority of the dose to the patient. This observation has a special meaning in the context of MC simulations, as the simulation uncertainty decreases with the number of simulated protons. As a consequence, this implies that there is a subset of beamlets simulated at the verification step with enough precision to be used for the weight tuning. Additionally, this subset is responsible for the majority of the dose in the patient and, therefore, may have the biggest influence on the plan performance.

To implement the ideas from the previous paragraph, the dose distribution calculated as verification after the geometrical adaptation was stored spot-by-spot, forming a weighted full matrix (, where are the original IMPT weights and *F* stands for full). Accumulating the dose of each spot, the total dose per voxel given by the geometrically adapted plan is retrieved. The smallest set of spots carrying at least 50% of the total weight were extracted from , obtaining the matrix representing the subset . The number of selected spots was enforced to be at least 10% of the total to provide more flexibility to the weight tuning process. These two parameters, the weight and minimum number of spots percentages, could be tailored to each case and more advanced criteria could be developed in the future, however, provisionally, they were chosen empirically. The dose provided by the non-selected spots was accumulated as baseline dose. The prescription dose in the target minus the baseline is the dose that the selected spots should provide. The weights of the selected spots were then tuned to complement the baseline and provide coverage, while limiting hot spots in the target and sparing the OARs. The IMPT problem in equation (1) was therefore changed to equation (2), where are in practice scaling factors of the initial plan weights. The same optimizer, Opt4D, from the original IMPT plan was used (see patient cohort section for details). The same set of OAR objectives and/or constraints can be enforced. If specific dose-volume histogram (DVH) points were utilized, the non-zero baseline should be taken into account, but this was not the case for the plans here included. In the case of the target, the weight tuning can be enforced to keep the same dose levels providing voxel-dependent maps to define the required dose per voxel (the baseline is voxel-dependent). After the weight tuning, another verification with GPU MC would not be required, as the new dose distribution could be computed from and the baseline.

Additionally, matrices can be large files that could cause an overflow in the memory of GPU devices during MC simulations. To facilitate storage and speed up the optimization, matrices are usually post-processed and voxels below a certain threshold are dropped, however, this approach cannot be used online while is being constructed. To solve this issue, gPMC was extended to score dose in arbitrary regions defined by input masks, allowing the significant reduction of the matrices size. Voxelized masks representing the dose-bath were passed to the device, defining sensitive regions.

*Operation modes and implementation*

The geometrical adaptation and geometrical+weights adaptation approaches were individually studied. Four types of geometrical adaptation were implemented: 1) allowing free beamlet position and energy changes from the delivery system; 2) changing the isocenter with a couch shift; 3) changing the energy with range shifters; 4) constraining the position and energy changes with a isocenter and range shift. In total, 8 approaches were included in this manuscript. The isocenter shift was calculated from the average of the VF at the spots endpoints.

The algorithm was written in C++/OpenMP with the raytracing parallelized for NVIDIA GPUs with CUDA. The GPU MC code, gPMC, and the IMPT optimizer, Opt4D, were spawned as subprocesses, automatically providing the required inputs. Automatic dashboard plots with VF, geometrical adaptation and weight tuning analysis are produced using Matplotlib [REFERENCE], a Python plotting library.

*Patient cohort and original plans*

A representative set of 10 H&N patients with 5-7 weekly CBCT each was studied, for a total of 60 cases. The set is summarized in table 1. All patients were treated with photons (IMRT), so new plans were created for IMPT. The plans consisted of 60 Gy(RBE) to the clinical target volume (CTV) with no safety margin delivered in 30 fractions. This is not clinical practice at our institution, but it provides a common and sensitive scenario to test the adaptation algorithm. A single dose level was selected in the CTV, creating a more challenging scenario for the plan adaptation, as allowing higher dose in the innermost part of the CTV potentially reduces the cold spots in the periphery of the structure. The field of view of the weekly CBCT images sets a limit on the tumor extensions that can be included in this study. We believe, however, that the situations present in the cohort are a representative set.

The tumor locations include larynx, oropharynx, mouth, tonsil, tongue and hypopharynx. Tumor volumes ranged from 9.0 to 116.5 cm3, with an average of 53.2 38.4 cm3. The target volume was observed to evolve throughout the CBCT sets. This evolution is a direct consequence of the deformation registered in the VF. In H&N cases, the target volume is often very hard to delineate and, therefore, this CTV volume change was not confirmed at every fraction. For the purpose of this study, the VF and the warped contours were accepted as long as the VF was observed to map the discernible structures well from the planning CT to the CBCTs; and that it was seen to present a smooth behavior around the non-discernible structures in terms of its nominal value and the Jacobian. The dice similarity coefficient, measuring the overlap between the original target contour and the contour propagated to each CBCT, was on average 0.83 0.09. The small dice coefficient value in patient 1 is due to the fact that this oropharynx case has a thin target and a small displacement causes a drop in this coefficient.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Pat. No. | Tumor location | N fields | N CBCTs | Plan CTV volume (cm3) | Average CTV vol. ratio change (min, max) | Average CTV dice (min, max) |
| 1 | Oropharynx | 4 | 6 | 22.3 | 1.00 (0.97, 1.05) | 0.58 (0.50, 0.67) |
| 2 | Tonsil | 2 | 6 | 9.0 | 1.02 (0.94, 1.12) | 0.87 (0.83, 0.90) |
| 3 | Oropharynx | 3 | 7 | 30.7 | 0.93 (0.90, 1.00) | 0.82 (0.77, 0.88) |
| 4 |  | 4 | 6 | 81.3 | 1.03 (0.98, 1.06) | 0.79 (0.75, 0.84) |
| 5 | Hypopharynx | 3 | 5 | 59.6 | 0.97 (0.95, 0.98) | 0.89 (0.87, 0.91) |
| 6 | Mouth | 3 | 7 | 116.5 | 0.78 (0.75, 0.82) | 0.87 (0.83, 0.90) |
| 7 | Larynx | 3 | 6 | 25.0 | 1.21 (1.08, 1.34) | 0.84 (0.77, 0.88) |
| 8 | Tongue | 4 | 5 | 79.9 | 1.06 (1.04, 1.11) | 0.87 (0.82, 0.91) |
| 9 | Tonsil | 2 | 6 | 12.0 | 0.98 (0.95, 1.00) | 0.87 (0.83, 0.93) |
| 10 | Oropharynx | 3 | 7 | 95.9 | 0.96 (0.91, 1.02) | 0.89 (0.85, 0.92) |
| Summary: | - | - | 60 | 53.238.4 | 0.990.11 | 0.830.09 |

As stated at the beginning of the methods section, gPMC was also utilized as dose calculation engine to create the original IMPT plans. This approach increases the accuracy at this step and provides a consistent framework throughout the experiment, avoiding systematic differences between the adapted plan evaluations with gPMC and the treatment planning system (TPS). To create the IMPT plans, all the necessary information was extracted from the TPS, including the spot maps. matrices were created with gPMC and optimized with Opt4D, an in-house optimization tool originally developed for temporo-spatial studies (TROFIMOV, 2005). The beam angles were selected to better spare OARs and avoid artifact regions in the CT and the set of CBCTs.

*Studied strategies and evaluation metrics*

The 9 adaptation strategies are listed in the following lines along their identification keyword:

* None: Original IMPT plan delivered to the fraction geometry.
* Geo: Geometrical only adaptation with the 4 modes described in the operation modes.
* Weights: Weight tuning after the 4 geometrical adaptation modes.

The modes are repeated here for clarity:

1. Free: Free movement and energy correction of spots at the delivery system.
2. CS: Spots movement constrained to a couch shift.
3. RS: Spots energy correction constrained to a range shifter.
4. CS & RS: Spots movement and energy correction constrained to a couch shift and a range shifter.

The DVHs of the None strategy and the original plan provide the baselines to evaluate the performance of the adaptation algorithm.

Dosimetric comparisons in the target were mainly performed based on V95 and V107. Other publications [REFERENCES] have reported their results based on the same metrics. The dose to OARs were analyzed in terms of mean and maximum dose. The performance was analyzed based on the weekly dose accumulation and also on a weekly basis, extrapolating the values per week to full treatment for better comparison. Although the total accumulation is more clinically meaningful, if hypofractionation schemes are intended to be employed, good performance at every fraction would be desired.

**Results and discussion**

In this section, firstly we analyze the performance of the original plans on the weekly geometries and, secondly, the adaptation results. Appendix 1 in the supporting documents shows several examples of the VFs as probed by the adaptation procedure and also how the spot’s energy, positions and weights change with the adaptation procedure.

*Original plans on weekly scans*

The performance of the original plans on the new geometries sets the scenario the adaptation algorithms must solve. This scenario was expected to be worse than most clinical cases because the plans were performed without CTV margins. However, it was the goal of this study to test the possibility of planning with no security margin for the anatomy uncertainty.

Figure XXX(left) shows the accumulated (cum.) and weekly in the CTV per patient. It also shows the weekly variations of the same magnitude. The patient results are also aggregated with a boxplot to better represent the plan evolution trend. A gradual descend on the value of this parameter is observed as treatment progresses, although a given patient does not necessarily follow this trend. All the patients except 2 and 5 present a 5% drop in at least one week. Half the patients show a drop of the accumulated dose of at least 5% in V95, which was 100% in the plan. If V95 = 95 % is employed as replanning criteria for the target coverage, half the cases here presented should be replanned from this criteria only. In figure XXX it can be deduced that few cases has a V100 > 90%. Although not shown explicitly for brevity, only patient 5 presents an accumulated V100 > 90 %, which might trigger replanning for all cases, depending on the institution protocol. The average D98, mean and D2 dose percentage in the target changed from 98.9, 103.3 and 106.9 % at the original plans to 90.2, 101.8 and 108.4 % after being fully delivered to the patients.

Some cases, such as patient 5, do not show big CTV coverage drops (figure XXX(top-right)), but the dose levels to OARs increase due to the geometry changes and the loss of conformality. On the other hand, patients such as 4, 7 and 8 show drastic plan quality drops. The plan and accumulated DVHs for patient 7 are shown in figure XX(right-bottom).

|  |  |
| --- | --- |
| imgs/plan_evolution_week.name_V95_diff.png | imgs/unadapted_cumulative_DVHs.png |
| **Caption:** |

In general, the studied conditions produce a decrease in parameters measuring target coverage \with respect to the original plan, while parameters measuring target overdose increase, smoothing the target DVH. However, at any given point the parameters measuring target overdose should be judge having the target coverage in mind, as a D2 value similar or better than the plan only is relevant if the target is covered at the same time. Dose to OARs is also increased on average.

The evolution of more CTV DVH points were included in figure XXX and are explained in the next subsection.

*Geometrical adaptations*

As a summary of the results here presented, the geometrical adaptation without weight tuning did not provide a general improvement upon the unadapted plan delivered to the weekly patient geometries. In other words, should the patient require replanning, this adaptation method would not avoid it.

Figure XXX shows V95, V98, V100, V107, V110, D2 and D98 (%) for the original plans and the original plans fully delivered to the weekly geometries with and without geometrical adaptation. In practice, this plot allows the comparison of the CTV DVH bands. Each boxplot represents the given parameter corresoinding to the cumulative dose distribution delivered to the weekly anatomies for the 10 patients, except for the plan boxplot, which is the reference baseline. Boxplots are included for the original plans in the planning CTs (Plan), the plans delivered to the weekly geometries with no adaptation (None) and the 4 geometrical adaptation modes described in the methods: free energy and position changes (Free), isocenter shifts (Iso), range shifters (RS) and the last two combined (Iso-RS).

The plot shows the original plan delivered 95 and 98 % of the prescription dose to the whole CTV volume (orange, leftmost boxplots). The volume percentage decreased as the dose increased until it was ~5% for V107 and close to 0% at V110. The average D98, D2 doses were 99.0 and 107.0 %. However, this behavior was not reproduced in when the original plans were delivered to the weekly geometries without adaptation (None, yellow, second boxplot from the left), as explained in the previous subsection.

It is clear in figure XXX that the geometrical adaptation methods also failed to reproduce the original plans’ boxplots. The Free and Iso methods improve in some cases the performance with respect to not adapting the plan, according to V95 and V98, but in others they perform worse. Both methods using a range shifter (RS, Iso-RS) worsed the CTV coverage. In all cases, the smoothing of the DVH caused also an increase of higher dose regions in the CTV.

In general, as stated in the first sentences of this subsection, the geometrical adaptations without weight tuning did not recover good plan quality. There are several reasons that might account for this issue, individually or in combination. Although theses methods reposition the spots’ end-of-range position in the target according to the deformation, the change of shape of the dose distribution of each spot after adaptation produced by the new patient geometry generate cold/hot spots in the target that impact the plan quality. Additionally, because the VFs were probed at the end of range position of the spots, there was an underlying assumption that VFs behaved smoothly. Any non-smooth regions of the VFs might not be captured by the probing procedure, but they would certainly be used to warp the original contours, potentially creating deformations that the algorithm would not take into account. All these issues might be solved by tuning the spots weights.

*Geometrical adaptations with weight tuning*

The weight tuning algorithm described in the methods, section YSYSYYS, was applied after simulating the geometrical adaptations in a per-spot fashion.

As shown in figure XXX, the weight tuning was able to recover good plan quality in terms of the CTV DVH parameters. Again, the boxplots represent the distribution of values for the given parameter evaluated at every patient’s cumulative dose distribution after delivering each method to the available patient’s CBCTs. The plot scale may have hidden the boxplot color, the order is the same as in the legend. The Free and Iso methods were seen to closely represent the distribution of results shown by the initial plan boxplots, significantly improving the performance of the original plan without adaptation. The methods utilizing range shifters necessitated higher dose levels to achieve similar coverage.



The previous figure does not provide information about the patient-by-patient difference with respect to the original plan, but only about the general distribution of DVH values at the tested points. Also, the plotting scale dose not allow easy comparison in all cases.



Figure XXX focuses on the patient specific differences with respect to the original plan (method – plan *Δ%*). Weekly variations of the dose distributions are also included here, not only the cumulative as in the previous plot. The methods utilizing range shifters were not included in this figure for clarity and because the previous one showed they had worse performance than the Free and Iso methods. The results with no adaptation were not included because the force a scale change in the plot, preventing the difference between the cumulative and the weekly to be seen. The data shown in figure XXX was written in table XXX to allow easier comparison, including the data corresponding to the plans without adaptation.



The target coverage was restored by the weight tuning algorithm after geometrical adaptation in Free and Iso modes. Both modes showed very similar results in the CTV, with the Free geometrical adaptation mode showing slightly improved nominal values, but the difference was not statistically significant over all. The average difference between the adaptations and the original plan for V95 was less than 1% (99.4 – 99.9 for the free mode) and less than 2% for V98 (97.4 – 98.9 for the free mode). In order to deliver such coverage, the adaptations increased V107 by ~ 4%, from 2.4 to 6.4 %, however it impacted V110 less than 1%. The minimum and maximum dose were also well maintained with average differences smaller than 2% across patients.

|  |  | Cumulative | | | | Weekly | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| All in % |  | min | mean *sd* | Median (IQR) | max | min | mean *sd* | Median (IQR) | max |
| V95 | Plan | 99.6 | 99.9 *0.1* | 99.9 (0.0) | 100.0 | 99.6 | 99.9 *0.1* | 99.9 (0.0) | 100.0 |
|  | Free | 96.7 | 99.4 *0.9* | 99.7 (0.2) | 99.9 | 96.1 | 99.0 *1.0* | 99.4 (0.6) | 100.0 |
|  | Iso | 96.8 | 99.1 *1.2* | 99.7 (0.4) | 100.0 | 94.9 | 98.9 *1.1* | 99.4 (0.7) | 99.9 |
|  | None | 84.0 | 94.1 *5.2* | 95.6 (7.3) | 99.4 | 79.2 | 93.9 *5.2* | 95.2 (8.0) | 100.0 |
| V98 | Plan | 97.2 | 98.9 *1.0* | 99.4 (1.4) | 100.0 | 97.2 | 98.9 *1.0* | 99.4 (1.4) | 100.0 |
|  | Free | 93.1 | 97.4 *1.7* | 98.2 (0.8) | 98.6 | 92.1 | 96.4 *1.8* | 97.2 (2.6) | 98.5 |
|  | Iso | 93.1 | 97.2 *2.0* | 98.0 (1.8) | 99.0 | 90.6 | 96.5 *1.9* | 97.4 (2.0) | 98.4 |
|  | None | 71.4 | 87.3 *9.4* | 89.2 (14.8) | 97.7 | 63.7 | 86.0 *9.0* | 87.5 (13.4) | 99.5 |
| V107 | Plan | 0.2 | 2.4 *1.9* | 2.4 (3.2) | 5.2 | 0.2 | 2.4 *1.9* | 2.4 (3.2) | 5.2 |
|  | Free | 0.5 | 6.4 *4.7* | 5.1 (3.7) | 14.5 | 5.2 | 12.8 *5.8* | 12.0 (8.4) | 30.6 |
|  | Iso | 0.4 | 6.6 *6.2* | 4.1 (7.5) | 19.2 | 4.6 | 12.3 *6.4* | 9.8 (9.9) | 31.7 |
|  | None | 0.1 | 6.3 *5.9* | 4.9 (6.2) | 19.5 | 0.8 | 9.0 *5.0* | 8.3 (5.3) | 26.1 |
| V110 | Plan | 0.0 | 0.1 *0.1* | 0.0 (0.0) | 0.3 | 0.0 | 0.1 *0.1* | 0.0 (0.0) | 0.3 |
|  | Free | 0.0 | 0.4 *0.7* | 0.1 (0.2) | 2.1 | 0.0 | 2.1 *2.4* | 1.1 (2.5) | 11.8 |
|  | Iso | 0.0 | 0.9 *1.9* | 0.0 (1.1) | 6.0 | 0.1 | 2.1 *3.1* | 0.6 (2.9) | 16.6 |
|  | None | 0.0 | 1.1 *1.3* | 0.6 (1.1) | 3.8 | 0.0 | 2.2 *2.4* | 1.8 (1.6) | 15.2 |
| D98 | Plan | 97.5 | 98.9 *1.0* | 99.1 (1.3) | 100.3 | 97.5 | 98.9 *1.0* | 99.1 (1.3) | 100.3 |
|  | Free | 93.5 | 97.5 *1.5* | 98.2 (0.8) | 98.5 | 91.2 | 96.7 *1.7* | 97.3 (1.3) | 98.3 |
|  | Iso | 92.7 | 97.2 *2.1* | 98.0 (1.3) | 99.0 | 86.5 | 96.6 *2.2* | 97.5 (1.5) | 98.3 |
|  | None | 67.5 | 90.2 *8.9* | 92.8 (6.8) | 97.8 | 40.5 | 89.5 *9.0* | 91.3 (8.8) | 99.0 |
| D2 | Plan | 105.8 | 106.9 *0.7* | 107.1 (1.0) | 108.0 | 105.8 | 106.9 *0.7* | 107.1 (1.0) | 108.0 |
|  | Free | 106.3 | 108.0 *1.1* | 107.9 (0.8) | 110.2 | 107.8 | 109.7 *1.4* | 109.3 (2.0) | 113.7 |
|  | Iso | 106.3 | 108.2 *1.8* | 107.6 (1.9) | 112.3 | 107.7 | 109.8 *2.4* | 108.8 (2.3) | 122.8 |
|  | None | 105.8 | 108.4 *1.7* | 108.8 (2.2) | 110.7 | 106.3 | 109.8 *1.9* | 109.8 (1.5) | 117.5 |

Outlook

Better spot selection for weight adaptation: cold/hot spots

Better selection of number of spots to re-optimize