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PROTON THERAPY SPECIAL FEATURE: REVIEW ARTICLE

Online daily adaptive proton therapy

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ABSTRACT

It is recognized that the use of a single plan calculated on an image acquired some time before the treatment is generally insufficient to accurately represent the daily dose to the target and to the organs at risk. This is particularly true for protons, due to the physical finite range. Although this characteristic enables the generation of steep dose gradients, which is essential for highly conformal radiotherapy, it also tightens the dependency of the delivered dose to the range accuracy. In particular, the use of an outdated patient anatomy is one of the most significant sources of range inaccuracy, thus affecting the quality of the planned dose distribution. A plan should be ideally adapted as soon as anatomical variations occur, ideally online. In this review, we describe in detail the different steps of the adaptive workflow and discuss the challenges and corresponding state-of-the art developments in particular for an *online* adaptive strategy.

INTRODUCTION

The concept of adaptive radiation therapy was introduced more than 20 years ago for photons.[1] However only recently patients can be treated with an online adaptive workflow[2–9] and first clinical results showed a promising increase of tumour control for inoperable pancreatic patients.[10]

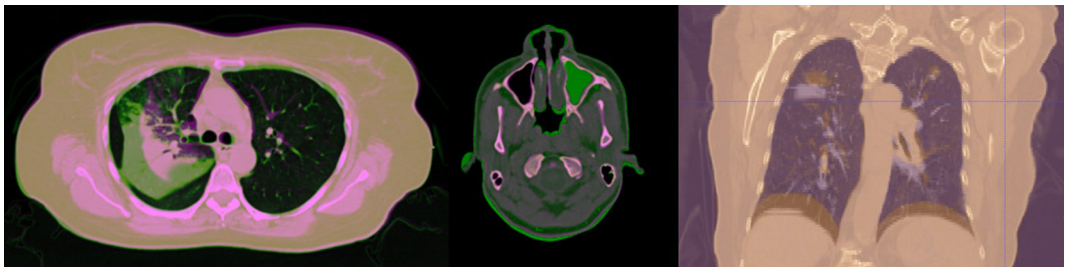
Although most research in adaptive radiation therapy was performed for photon treatments, for proton therapy the necessity for plan adaptation is even more important. Indeed, the precision in proton radiotherapy strongly depends on the accuracy of the position of the Bragg peaks *in vivo*, and any density change along the beam direction can deteriorate the dose distribution. A change in the patient anatomy occurring through the course of radiotherapy is probably *the* most significant source of range uncertainty. It is well recognized that for most indications planning on a patient image acquired some time before the start of the therapy and use the same plan for the whole treatment is suboptimal.[11–16] Therefore, several centres have started to regularly monitor the anatomy of the patient during the course of the treatment to trigger adaptation if necessary.[17–19] However, due to the complexity of the labor and time-intensive workflow, and the lack of automatization, for proton therapy it is not yet possible to adapt the dose online.

The adaptive proton therapy (APT) process is therefore currently performed offline. Typically, it takes a few days from the acquisition of a new three-dimensional (3D) image to the delivery of the clinically approved adapted plan. Such an adaptive approach, although improving the delivered dose especially in case of slow inter fractional changes such as weight gain or loss, is inadequate in presence of faster changes (*e.g.* organs fillings). Indeed, to fully profit from the APT approach, the whole process needs to be established within the time span of the anatomy changes. Therefore, an online daily plan adaptation is necessary to deal with daily interfractional changes, as for example variation of the nasal cavity- or rectal fillings (see examples in Figure 1).

Due to the time- and resource-consuming nature of such adaptive interventions, some authors have recently proposed alternative ways to include, in addition to range and setup uncertainties, also anatomical changes directly in the optimization process, with the aim to reduce the need of adaptation.[20–23] Although these pioneering works report promising improvement in the plan robustness against anatomical changes, the extra advantage of using an adaptive proton therapy approach, in particular to reduce the dose to the normal tissue is acknowledged.[21]

Therefore, there is a growing interest also in the proton therapy community to clinically implement an online daily adaptive proton therapy (DAPT) workflow, to properly cope with interfractional changes.[24–27] For intrafractional changes, an even more frequent imaging acquisition and

Figure 1. Examples of possible anatomical changes are shown by overlaying CTs acquired at different instance during the therapy. (a) Shrinkage of target volume between the planning CT and the end of the treatment (can be dealt with offline adaptive process), (b) Changes in the nasal cavity filling between two consecutive treatment days (can be dealt with online adaptive) (c) difference in the tumor position between two phases of the same 4D-CT (can be dealt with real-time adaptive). 4D, four-dimensional.



a faster plan adaptation procedure (in real time) is needed.[28–30] Since the latter is an interesting research topic but still farther from clinical implementation, in this review we focus on the ongoing research of *online* DAPT.

One possible workflow for the online adaptive approach is depicted in Figure 2. The workflow before the treatment start is the standard workflow typically followed in every radiotherapy unit. A 3D image (typically a CT) of the patient is acquired and used to optimize a plan satisfying the clinical requirements. After the clinical approval of the calculated plan, a physical check, which for most proton centres includes measurements of the plan, is performed. For the daily online process, which lasts as long as a patient appointment, a daily 3D image has to be acquired with the patient in the treatment position. The pre-defined structures have to be transferred to the new image. Optionally, the need of a plan adaptation has to be assessed online. Successively, the adapted plan has to be optimized on the new geometry. Due to the time restriction a pre-delivery measurement based patient specific verification cannot be performed. Thus, the adapted plan has to follow an automated, calculation-based physical and clinical quality assurance check before it can be delivered to the patient. During (or immediately after) the delivery, the verification of the delivered plan can be performed. Finally, after the completion of the patient appointment, the delivered dose can be transformed and accumulated on a reference image (*e.g.* the pre-treatment CT), to record the cumulative dose.

This review is organized following the DAPT process as proposed in Figure 2. For each step, a summary of the problem and of the relevant ongoing research is highlighted.

DAILY 3D IMAGING IN TREATMENT POSITION

Generally, in radiotherapy, there are three modalities currently available to acquire a 3D image of the patient in the treatment position: in-room CT, cone beam CT (CBCT) and integrated MR imaging.

CT-based planning is the current standard in proton therapy, as it allows to best calculate the range of protons in the patient anatomy (see the review of Richter in the same journal). The same imaging methods can be applied for plan adaptation. However, the necessity to acquire frequent or even daily CTs inevitably increases the imaging dose to the patient. Nevertheless, with the rapid development of new acquisition protocols aimed at reducing the imaging dose (*e.g.* low-dose CT protocols for lung cancer screening reach values of only 0.3 mGy[31]), it is foreseen that the extra imaging dose might become insignificant compared to the expected reduction in the integral dose achieved with the DAPT.[24] In order to optimize the DAPT workflow, the CT image has to be acquired with the patient in treatment position such that not only anatomical changes but also daily misalignment can be mitigated, thus reducing the importance of considering set-up uncertainties in the planning process. This, together with the possibility to use innovative, less anatomically

Figure 2. Workflow for an online adaptive process

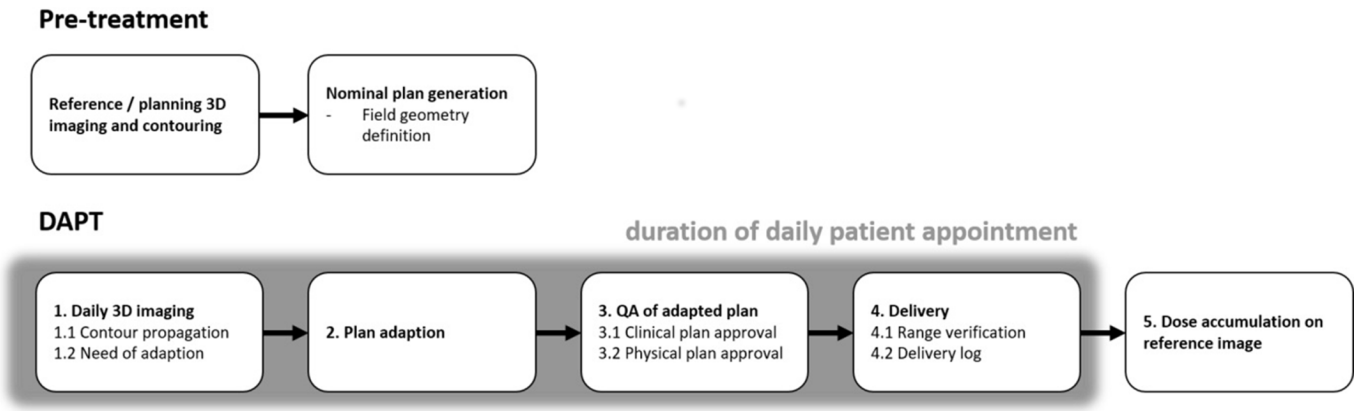
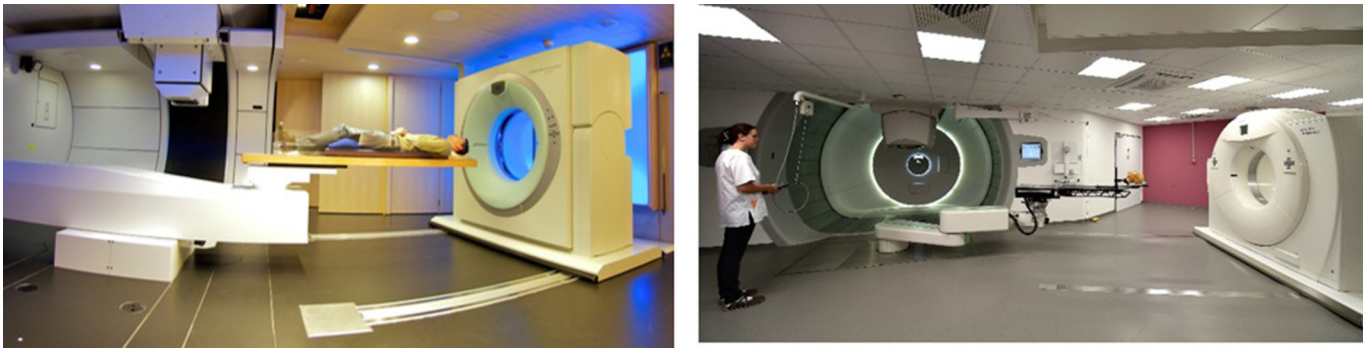


Figure 3. Examples of in-room CTs from: left side, PSI Gantry 2 [32], on the right side Oncoray, Dresden right side (with permission)



robust, beam arrangements result in the delivery of less dose to the normal tissue, at least for some indications.[24]

The acquisition of a CT in treatment position is possible with an in-room CT (Figure 3). Although the acquisition of a daily out-of-room CT is sufficient to mitigate anatomical changes, it might limit the advantage of using a DAPT workflow, as daily misalignments have to be dealt with by the standard positioning procedure or a shuttle-based workflow has to be defined *ad hoc*, as for example the one described by Bolsi et al.[33]

CBCTs are widespread in conventional therapy and recently became available also for proton therapy machines. The availability of 3D images acquired daily with the patient in treatment position, makes the CBCT a desirable modality for a daily adaptive workflow. However, the low image quality of CBCTs and the difficulty to accurately convert grey levels to relative stopping power are nowadays still the major limitations for applying CBCT images for proton dose calculation. Promising methods to correct the intensity of CBCT images and reducing acquisition artefacts, by either deforming the planning CT[34–36] or using alternative, *e.g.* machine learning based algorithms[37,38] have been recently developed. However, although much work is being pursued in this direction, to our knowledge the extraction of accurate stopping power information from CBCT to the same level of accuracy as with diagnostic CT images is still in a research stage. This, together with the limited field of view available for CBCT, limit their benefit for the APT process.[39–41]

Finally, MR images have a high resolution and are dose free. Therefore, an integrated MRI system would be the ideal modality for daily plan adaption. Promising research is ongoing into generating pseudo-CTs based on daily MRI either using atlas-based conversions[42–45] or employing deep learning approaches[46,47] and recently it has been shown that a proton dose can be calculated with a sufficiently high accuracy using these pseudo-CTs, at least for certain indications.[48]

Contour definition

Before generating the newly adapted plan, it is necessary to have new contours available in the 3D image of the day. These could be obtained either by propagating the reference volumes through a rigid or deformable registration or by auto-segmenting the daily image. Unfortunately, with both approaches it is still necessary, for most of the cases, that a clinician correct the contours, thus extending the treatment time. The manual editing of these volumes is currently one of the bottleneck of most common online photon ART workflow[3,6,49,50] and it is the step most prone to error.[51] The development of robust segmentation algorithm is not only important for the ART workflow but also for radiotherapy in general and it is outside the scope of this review to cover all the developments in this field[52,53].. Important developments of advanced segmentation algorithms have been proposed by considering the prior information of the anatomical structure or organ appearances, such as single or multiatlas in combination of deformable registration,[54] or shape modelling based on principle component analysis.[55–57] Additionally, segmentation algorithms based on machine learning[58] and deep learning concepts[59–62] are foreseen to transcend the limitations from both aspects of speed and accuracy, by exploiting large prior knowledge of the correlation of multimodality images and annotated volume segmentation.

In spite of these developments, residual uncertainties on the volume definition will nonetheless be present. Therefore, more research to understand their clinical impact is highly encouraged.

Need of adaptation

As there is currently no online adaptive proton therapy workflow clinically available, most literature describing DAPT strategies include the use of the daily image to trigger adaption. With this approach, time and resources can be saved, when choosing the nominal plan over adaption. Although no consensus regarding the threshold to trigger adaptation exists, for photons, a semi-quantitative traffic light protocol has been described.[63]

Recently, several methods to reduce the need of daily adaptation have been proposed. Some authors suggested to include anatomical changes directly in the optimization algorithm by including multiple CT scenarios during the initial process of plan optimization.[21,64,65] Others proposed to adjust daily patient positioning to reduce the differences between planned and daily dose in the presence of anatomical changes.[66] Another approach suggests to rely on a library of pre-calculated plans and to select daily the plan most resembling the current anatomy.[67]

However, it has been shown that even though using an anatomical robust optimization is a valid strategy to mitigate the effect of

anatomical changes, the use of a DAPT approach has the advantage of reducing integral dose and improving dose conformity.[21] Additionally, the use of an online DAPT approach was shown to be the key for enabling the use of alternative, more conformal field arrangements that would normally be considered unrobust, thus resulting in a further integral dose reduction.[24] It is therefore expected that as soon as an online adaptation workflow is clinically available, this will become the standard treatment modality, at least for selected indications.

GENERATION OF DAILY-ADAPTED PLAN

The generation of the adapted plan and the subsequent physical plan acceptance need to be fast to limit the chance of slow intra fraction motion (*e.g.* bladder filling) and to limit the overall treatment time.

To achieve the speed requirements for DAPT, the process must be highly automated. Once this is fulfilled, time for plan generation is dominated by the computation. Graphical processing units (GPUs) have been widely deployed for speeding up this computationally demanding task. GPUs have been employed for subsecond analytical dose calculations,[68] fast Monte Carlo (MC) dose calculations (down to 1–15 min)[40,69] and pencil beam fluence optimization in only few seconds.[40,69,70] Approaches for complete adaptive plan generation with a MC dose calculation were achieved in 5 min for standard indications[40] and with an analytical dose calculation in below 10 s.[70] It has recently been shown that the uncertainties in the dose distribution due to anatomical changes outweigh differences between analytical and MC dose calculations,[71] legitimizing the use of analytical algorithms for DAPT if no fast MC is available.

Automation of adaptive plan generation with limited user inputs has been a strong focus in recent research. Described methods are based on restoring the position of the Bragg peaks in the daily patient geometry and/or reoptimizing the pencil beam fluences to restore the dose distribution of the nominal plan.[72,73] The benefit of these approaches is that the adapted treatment plan is similar to the nominal plan, facilitating its clinical validation. On the other hand, optimizing the plan on the daily anatomy, without any restriction including the placement of additional Bragg peaks, could also help to exploit daily anatomies that are more favourable for treatment. For example, the relative position of the tumour and organs at risk (OARs) can be different on a daily basis, thus allowing a better sparing of the OAR with the increasing of its distance to the target volume.[24] Examples of re-optimization methods on the daily anatomy, which includes new Bragg peak placement and an optimization following DVH prescription parameters are described.[40,70,74] Clearly, the development of an automated and simplified plan approval process is required. Modern optimization techniques to generate Pareto optimal plans might also facilitate this fast plan approval. A reference point method to reduce the adapted plan generation time for a Pareto optimal plan down to 3 min compared to a full multicriteria optimization, which takes 25 min, is described in a recent publication.[74]

QA OF THE ADAPTED PLAN

Clinical plan approval

The adapted plan can be highly similar to the nominal one, but being a new plan it has to follow some, ideally automatized, quality assurance steps before it can be delivered. Although this is a key point for the successful implementation of a DAPT workflow in the clinic, not much research has been conducted in the direction of fast plan acceptance. Some tools to assess plan quality using machine learning approaches and compare the plan under evaluation to a database are proposed for fast plan acceptance in photon therapy.[75,76] Additionally, the daily plan can be assessed taking into account the dose accumulated on the reference image (see Dose accumulation section). However, due to inaccuracies of the dose summation especially around sliding tissues and in case of mass changes caution is recommended.[77] In photon therapy, conservative approaches such as a *parameter adding* approach, in which the maximum point dose of organs at risk are summed over all the fractions; or a *iso-toxicity* approach, for which the previously delivered dose is neglected and each daily plan is evaluated *de novo*, are commonly used for the daily clinical evaluation.[50]

Physical plan approval

Physical QA of the adapted plan needs to guarantee the deliverability of the new plan. In the DAPT workflow, as the patient is imaged in the treatment position shortly before the start of the delivery, the adapted plan is applied for the first time directly to the patient and there is no time for standard measurement based QA beforehand. This is an obvious challenge of online adaptive therapy. For photon therapy, research has been conducted addressing this challenge[3,78] and many of the issues are translatable for particle therapy. It is recognized that an independent dose calculation is compulsory to double-check the otherwise untested initial dose calculation.[79–81] Preferably, one of the two calculations should be a MC simulation. However, MC simulations, which are fast enough to meet the ambitions time restriction of DAPT, are just recently emerging.[40] Once the dose calculation is double-checked, as much of the pre-delivery data transfer and conversion steps as possible should be examined. One proposed method is to tap into the data stream of the delivery machine and use this data to check delivery integrity by reconstructing the dose based on this data into the patient anatomy.[79] Recently, it has been proven that reconstructing the dose in the patient anatomy based on the delivery machine file is more sensitive in detecting errors in the planning process or the delivery than conventional water phantom verification measurements.[82] Conceptually this approach is similar to the ones proposing to rely on log-files for patient specific verification, rather than water phantom measurements (see Log file reconstructed dose section), with the difference that it can be completed before the delivery, when the log-files are not yet available. The machine file method is therefore limited to checking the delivery machine input data. Such an independent check of data conversion and transfer, together with a comprehensive daily delivery machine QA program, provides a redundant and safe quality assurance procedure for DAPT.

DELIVERY AND PLAN "IN-VIVO" VERIFICATION

As discussed above, the time restrictions imposed by DAPT make a full patient specific verification including water phantom

measurements impossible. Therefore, in addition to the pre-delivery QA described in QA of the adapted plan, it is suggested for a safe DAPT workflow to check the delivered dose distribution extensively.[27,82,83] This could be done either with an in-direct range measurement in the patient or by reconstructing the dose recorded by the log-files on the daily anatomy. These two approaches could potentially complement each other.

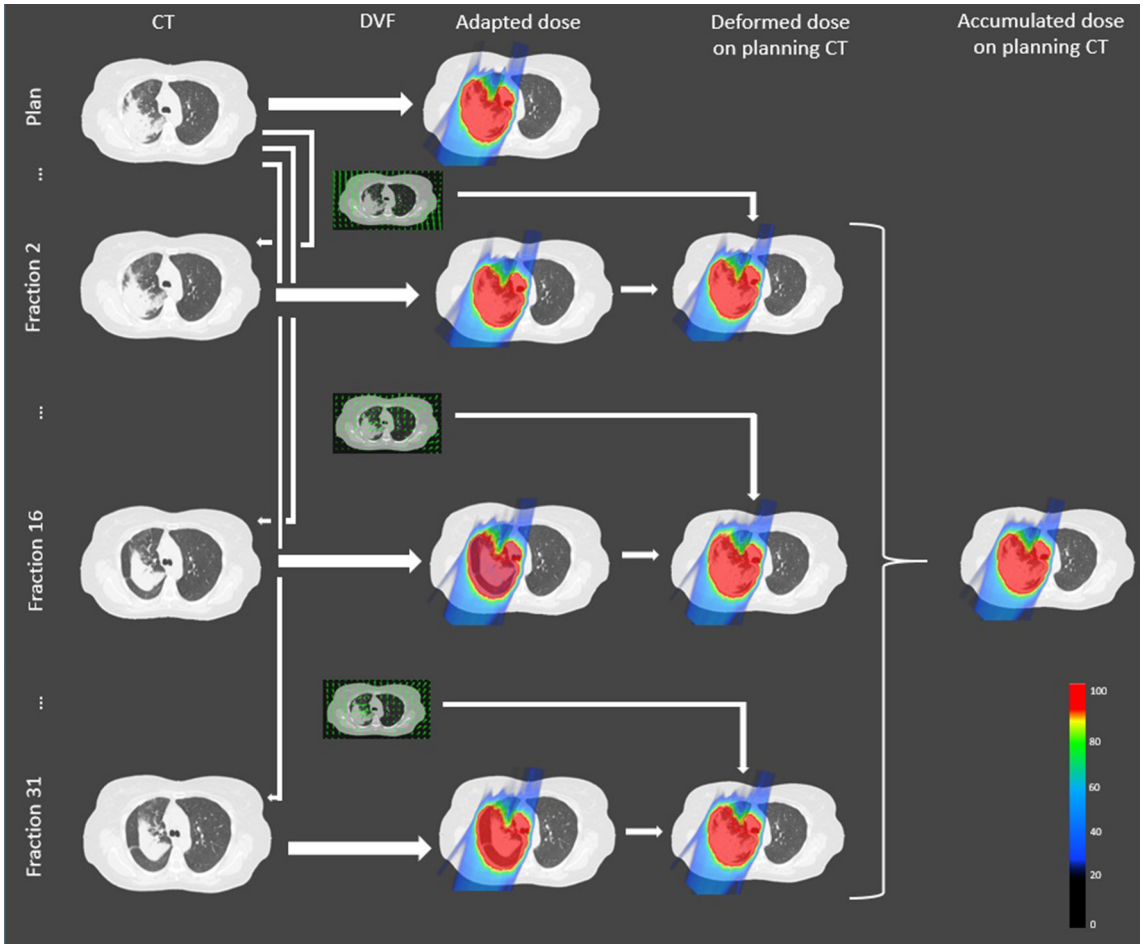
In-vivo range measurements

Direct dose measurements in the patient during therapy are challenging, invasive and limited to certain anatomical regions.[84–86] As such, alternative ways to verify the Bragg peak position in the patient anatomy (*i.e.* the proton range), during (or immediately after) the therapy have been suggested and previously reviewed[87–89] : reported methods include the use of in-beam positron emission tomography (PET) scanner, online prompt γ, proton radiography (and range probe) and ionoacuoustic detectors. Although PET imaging hold the promise to verify additionally the delivered dose distribution, due to several limiting factors, including the low accuracy in the range detection, its clinical usefulness for proton therapy is still unclear.[90–92] On the other hand, the detection of prompt-gamma rays emitted during the proton therapy has a higher range prediction accuracy (in general less than 2 mm)[93,94] and has been recently introduced in the clinic.[95] Moreover, the radiographic (or tomographic) transmission of highly energetic beam through the body enables the possibility to image the patient with the same beam quality as the one used for treatment.[96–100] Along this line and to reduce the imaging dose, it has been suggested to use a (limited number of) single highly energetic Bragg peak shooting through the patient (the so called "range probes"), as alternative to measure the integral range crossed by the beam.[101,102] In spite of the promising results, neither proton radiography nor the range probe have yet reached the stage of clinical application.[87] Finally, in contrast to range verification using nuclear imaging techniques, it is also possible to detect the thermoacoustic signals that are generated due to localized energy loss of ion beams in tissue (ionoacoustics).[103,104] More details on the latest developments for *in-vivo* range measurements are summarized in the *review of Parodi [in same journal]*. None of these *in-vivo* imaging methods could be used as direct input for plan adaptation, but all of them could be used to trigger the necessity of a new 3D image acquisition for plan adaption.

Log file reconstructed dose

During the delivery, beam parameters like Bragg peak position and number of monitor units are usually recorded in a so-called log file. In the last years, there have been several publications

Figure 4. An example of the dose accumulation workflow, using the planning CT as reference image. Deformable vector fields for the three fractions are displayed on the reference CT. DVF, displacement vectorfield.



proposing to use the measured beam parameters to reconstruct the delivered dose in the patient.[27,79,80,82,83,105–108] This approach has been firstly introduced clinically at PSI to retrospectively analyze the delivered dose for all patients treated from 2013 onward.[105,106] It was shown to be a valid approach to detect both delivery errors, as for example an unplanned systematic shift of the Bragg peak position[105,106] and also of artificially introduced errors in the machine files.[82] Additionally, such an approach has been recently implemented, as a proof of principle, in a clinical treatment planning system to allow for the assessment of the conformity between planned and delivered dose distribution for a four-dimensional treatment.[83] Of course, the accuracy of the reconstructed dose is limited by the accuracy of the dose and Bragg peak position monitors.[107] A log-file based dose reconstruction calculated with a MC algorithm[108] allows to access the delivered dose distribution without expected errors due to the analytical algorithm or machine delivery inaccuracies. Such a reconstruction of the delivered dose directly on the daily patient anatomy, allows for an unprecedented accuracy in the delivered dose recording. This can be exploited for dose accumulation, as discussed in Dose accumulation section. However, if used for dose accumulation, the measured parameters and the dose reconstruction need to be carefully validated.

DOSE ACCUMULATION

To accurately record the treatment dose over the course of any fractionated radiotherapy, it is necessary to accumulate the daily delivered dose on a common anatomy.[109] To accomplish this task, the daily image has to be registered to the reference image either by a rigid or deformable registration (DIR) process. The daily dose is then deformed by applying the same displacement vector field (DVF) generated during the image registration (see example in Figure 4). The accuracy of deformable dose accumulation is dependent on the integrity of the DVF vector and any uncertainties in the DVF propagate then to the accumulated dose. Comprehensive reviews on image registration[110–112] and on deformable dose accumulation[113] have been published in the last years. Challenges are independent on the treatment modalities and most of the reported clinical experience is based on photon treatment. Here, only the basic concepts are presented.

As, finding the optimal displacement that maximizes the alignment between two pair of deformed images is a degenerate problem, the application of different DIR methods to the same image pair could result in different DVF.[110–112] The problem is especially important around low contrast regions and in the presence of mass alterations. Deformation vectors in these regions depend directly on the transformation model and regularization of the selected algorithm and it is unavoidable that ambiguity between different algorithms is present.

Although several authors have proposed different approaches to estimate the impact of these uncertainties in the accumulated dose distribution,[114–120] results presented are often patient and indication specific and research on this topic is highly encouraged. Additionally, debates on the appropriateness of deforming dose along with deformable image registration are still ongoing, especially in the case of mass alterations.[113,121,122]

Nonetheless, it is suggested that the use of deformable dose accumulation is a powerful tool to report the cumulative dose and to perform outcome analysis based on correlation of the treatment dose with tumour control, local recurrences and toxicities.[109] On the other hand, for the daily assessment, clinical decisions are mostly taken neglecting the previously accumulated dose and the use of more conservative methods are advisable (see Clinical plan approval section).[50]

OUTLOOK

Thanks to the successful introduction of the MRI-linac into the clinic, it is expected that this will speed-up the clinical implementation of an online adaptive workflow also for protons. Clearly, it would require a strong collaboration between treatment planning system and proton system vendors such that all the steps outlined in Figure 2 can be fully integrated.

However, as we are just entering in a new era, where the patient will be treated with a plan optimized on the daily anatomy, there are several aspects, common to both photon and proton therapy, that need further research.

One key aspect of the new workflow is speeding up and increasing the accuracy of the contouring process on the daily image. The current experience from MRI-Linac users is that this step is one of the bottlenecks of the adaptive workflow[3] as it requires substantial manual intervention. It is foreseen that with the use of artificial intelligence,[58–62] the accuracy and the speed of the segmentation process will improve. However, more research in understanding the clinical impact of residual uncertainties on the volume definition is beneficial.

Moreover, with a better knowledge of the daily delivered—and the cumulative dose a more accurate patient outcome can be modelled.[109] However, substantial developments in terms of understanding the uncertainties in the accumulated dose are still necessary.[113–120]

With the advent of daily adaptive therapy, new planning strategies will also become available. For example, it will become possible to adapt plan according to the target volume evolution along the whole treatment session. However, before changing treatment approaches, the definition of clinical trials are advisable.[77]

Finally, some authors have already envisioned the combination of MRI with proton therapy.[123–125] This holds the promise to be the future for real-time adaptive therapy as it combines the advantage of a better imaging modality with proton therapy, superior in terms of reducing normal tissue integral dose.

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