White paper

Adaptive Proton therapy utilizing an in-room CT

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1. Introduction

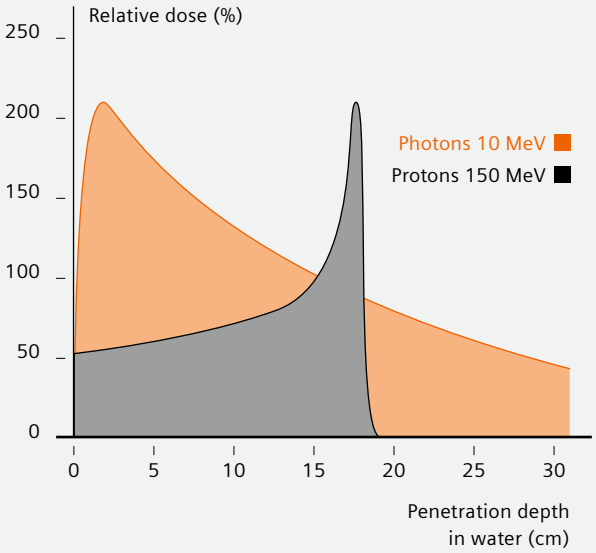
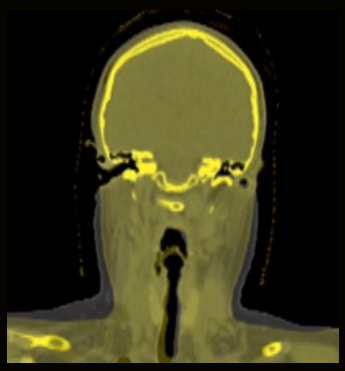


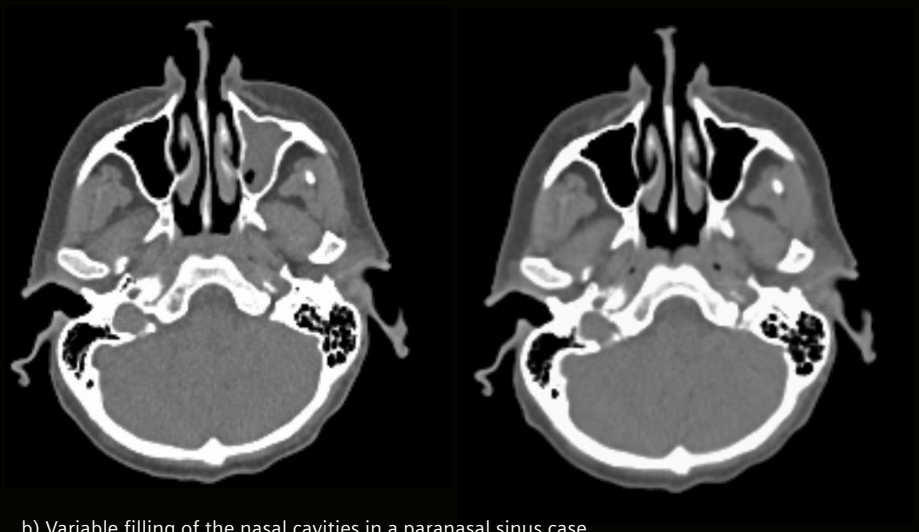
Figure 1. Depth dose curves for photons (orange) and protons (gray). Note the sharp and well-defined Bragg peak at the end of range for the proton curve.

The aim of radiotherapy is to concentrate energy, as deposited by ionizing radiation, in the tumor, whilst minimizing, as much as possible, the irradiation of surrounding normal tissues and organs. The more energy, referred to as dose, that can be concentrated in the tumor, the higher the chances of cure. Alternatively, improved dose sparing of normal tissues will lead to reduced treatment-related toxicities. Thus, the concept of 'dose conformation' to the tumor is of critical importance.

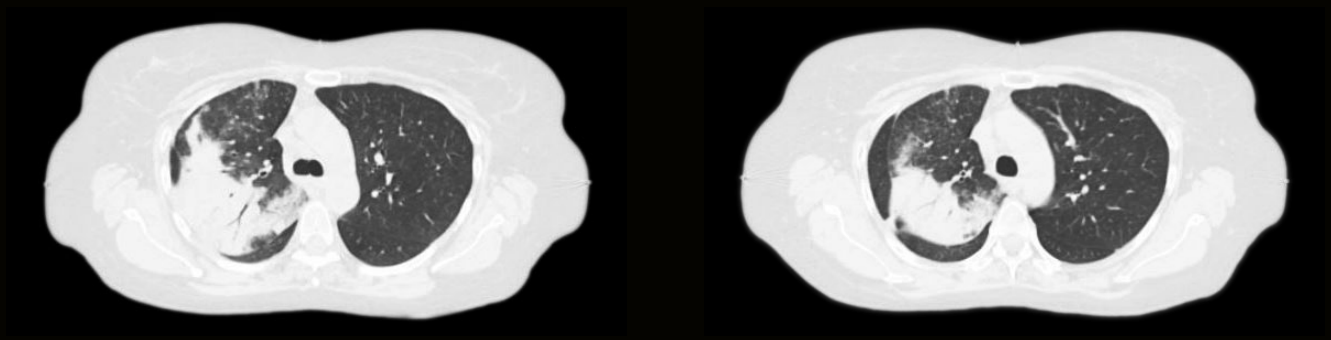
The potential advantages of protons for dose conformation were first pointed out by Robert Wilson in the 1940s [1]. In his seminal paper, the physical characteristics of protons were described, in particular the advantage of the Bragg peak (Figure 1). Due to the fact that protons are charged particles, as they pass through material, they lose energy at a rate proportional to the inverse of the square of their velocity. As such, most of their energy is deposited in material at the end of their range (where their velocity approaches zero), leading to a concentration of high dose in the characteristic Bragg peak. This has obvious advantages when compared to the dose deposition characteristics of high energy-photons, which in contrast are gradually absorbed, leading to a slow, exponentially decreasing deposition of dose as they penetrate material (Figure 1). Since Wilson's paper, the adoption of proton therapy was however relatively slow, with the first patients being treated in the 1950s, followed by a very limited increase in treated patients until the 1970s. Driven by the development of X-ray CT however, through which the internal densities of the patient could be imaged, proton therapy has slowly become more prevalent, with a boom of facilities now in operation, under construction, or being planned. This expansion has also been driven by the development in the 1990s of pencil beam scanning (PBS) [2] and intensity-modulated proton therapy (IMPT) [3], both of which allow for the full exploitation of the potential of the Bragg peak for conforming dose to complex and large tumors.



a) Weight loss in the neck region during a head and neck irradiation



b) Variable filling of the nasal cavities in a paranasal sinus case



c) Tumor shrinkage in the lung during radiotherapy

Figure 2. Examples of anatomical changes during treatment

2. CT-based, image-guided proton therapy

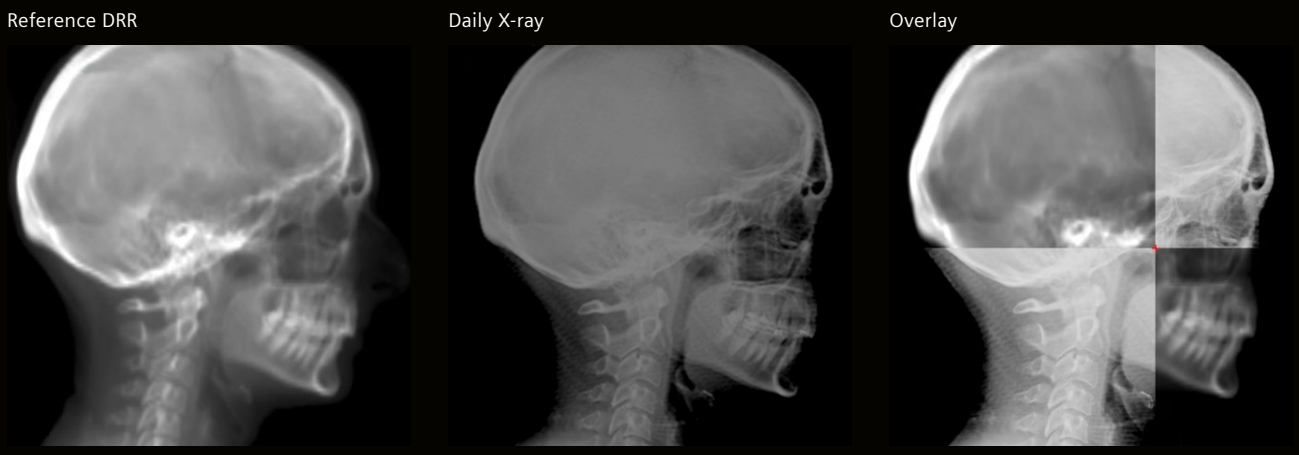
2.1 2D/2D and 3D/3D imaging

Image-guided radiotherapy (IGRT) has become the norm in all forms of radiotherapy over the last 20 years. In short, IGRT refers to the use of regular, often daily, imaging of the patient immediately prior to the delivery of each treatment fraction. Using such images, uncertainties in patient positioning (e.g., caused by shifts and/or rotations) can be monitored and corrected, for instance, by correcting the couch position before therapy delivery. Interestingly, IGRT can be considered to have been pioneered in proton therapy. Given the exceptional advantages of proton therapy in the 1970s and 1980s, it was quickly understood that, whilst not so important for the rather basic technology of X-ray based radiotherapy in that era, daily imaging of the patient directly before proton treatment was essential to ensure accurate irradiation of the tumor. As such, the acquisition of (at least) orthogonal 2D X-rays prior to irradiation, and their comparison to reference DRRs (Digitally Reconstructed Radiographs) generated from the planning CT data quickly became a standard of care in proton therapy (figure 3a). As such, there is not a proton facility in the world that has not performed daily image-guided proton therapy, in most cases using treatment-nozzle-mounted X-ray sources and detectors to image the patient in, or very close to, the treatment position.

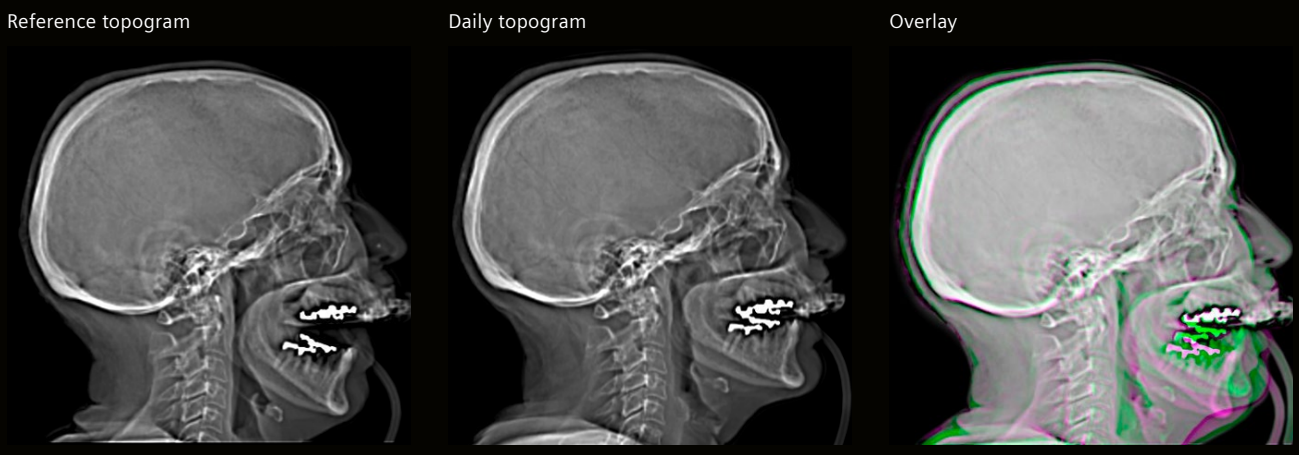
In the 1990s at the Paul Scherrer Institute, the Pencil Beam Scanning (PBS) approach to proton therapy was developed [3]. It revolutionized proton therapy, and all new or planned proton therapy facilities are based on this technique, which provides even better dose conformation to the tumor than the previously used passive scattering approach. Along with this development came the introduction of a dedicated CT scanner as an imaging device for daily imaging and positioning of patients being treated on the world's first PBS proton gantry at PSI. This facility has now been in operation for 22 years with a diagnostic CT scanner being used on a daily basis for evaluating and correcting the position of every patient in the "2D/2D" mode – where both the reference and daily images of the patient are acquired using the CT scanner in topogram (scout) mode [4]. Although an unconventional use of a CT scanner, this has a major advantage in comparison to treatment mounted X-ray imaging, as shown in figure 3b. This shows the reference (left-hand side) and an example daily topogram for a patient treated at our facility. In contrast to the conventional approach of generating the reference image using DRRs calculated from the planning CT (c.f. figure 3a), our reference image is the topogram image taken on the CT scanner, immediately before acquisition of the planning CT. As this and the daily setup image have been acquired on a machine with the same imaging characteristics (i.e., the daily setup images are also acquired on a CT scanner using topogram mode), a comparable image quality and resolution is available in both images, making the comparison and quantification of positioning differences easier and more precise. Using this approach to daily patient imaging and setup correction, Bolsi et al. [4] reported patient positioning accuracies of 0.4/0.6/0.5 mm and precisions of 1.3/2.0/2.5 for cranial, head and neck, and extra-cranial cases respectively in a population of 94 patients.

2D/2D imaging is still the most prevalent method for patient setup in proton therapy for two reasons. First, equipment allowing for 3D imaging of the patient in treatment position has been slow to be introduced in proton therapy. Second, for many indications treated with protons, and due to the excellent patient fixation devices used, 2D/2D imaging is considered sufficient. Nevertheless, there is undoubtedly a need for 3D/3D imaging for positioning patients in more challenging treatment sites, such as head and neck, thoracic, and abdominal tumors, where rotations and deformations can pose significant challenges. Particularly for patient deformations, 3D imaging is essential to estimate the magnitude, not only for positional purposes, but also

to assess and correct for potential range changes resulting from such deformations. For example, in a recent publication from our group, it was found that 33% of cases required one or more repeat CT scans to quantify anatomical changes and adapt the treatment to these [5]. As concluded in that paper, however, it is expected that the rate of replanning as a result of anatomical changes will be much higher than this when workflows and planning tools are improved in order to reduce the time needed to calculate and validate new treatments. As such, and despite the excellent results and clinical outcomes achieved with 2D/2D imaging, there is no doubt that efficient and high-quality 3D imaging on a daily basis will be the future of image guidance in proton therapy.



a) X-ray versus DRR (Digitally Reconstructed Radiographs)



b) Example use of CT topograms for positioning

Figure 3. Examples of 2D/2D positioning

2.2 CT-based 3D/3D image-guided proton therapy

There are three modalities currently in use for 3D/3D image-guided radiotherapy: Cone Beam CT (CBCT), in-room CT, and (much more recently) on-board MR imaging. As for proton therapy, the practicality and usefulness of the latter is unclear, we will concentrate on CBCT and in-room (diagnostic) CT imaging.

CBCT is widespread in conventional radiotherapy, and is now supported on most commercial proton therapy machines. Indeed, CBCT currently has a major advantage as a 3D imaging modality for patient setup imaging, as tomographic data is acquired directly in the treatment position, thus requiring no movement of the patient from the imaging position to the treatment position. On the other hand, it also has a number of limitations for proton therapy.

First and foremost, the image quality of CBCT is inherently worse than that of conventional CT (see, e.g., figure 4). Although this does not mean that CBCT cannot be used, it makes the comparison of the daily and reference 3D images (taken from the planning CT acquired on a diagnostic-quality scanner) more challenging. Second, although much work is being pursued in this direction

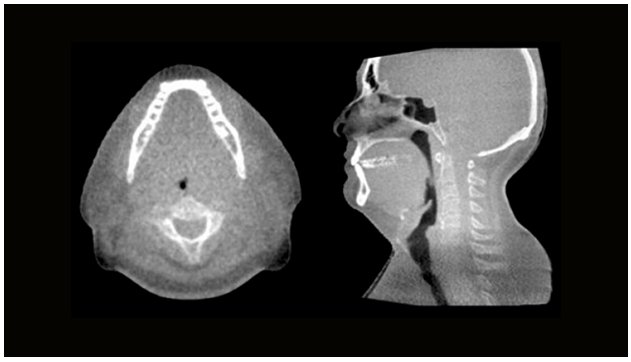


Figure 4. Example of typical image quality for cone beam CT (CBCT)

[6,7], it is still a "work in progress" to extract density information from CBCT to the same level and accuracy as can be achieved with diagnostic-quality CT. This is currently a severe limitation for the usefulness of CBCT for proton plan adaption. However, given the rapid developments aimed at improving CBCT image quality, it will be interesting to see how these two modalities develop in the coming years. Nevertheless, at our institute we have opted for an in-room diagnostic CT scanner in our Gantry 2 (figure 5), as we believe that, currently, this will provide the most accurate and proton-relevant information (i.e., accurate definition of proton stopping power) for adaptive therapy concepts (see below). In addition, it provides daily 3D images of similar quality, geometry, and resolution to those of the reference (planning) CT image. In the coming years, however, we will be able to more directly test the pros and cons of both systems in clinical practice, as we bring the CBCT system installed on our newly operational Varian ProBeam proton gantry into clinical practice.

2.3 In-room positioning

As mentioned above, the main advantage of CBCT is that it images the patient in the treatment position. With a diagnostic-quality CT scanner, this is not currently possible, at least for proton machines. The imaging of the patient has to be done away from the treatment position. Nevertheless, mobile CT units (e.g., CT sliding gantry) have been installed in the treatment room for "near-to-treatment-position" imaging at a number of facilities. The first was on Gantry 2 at PSI, where a

Figure 5. Gantry 2 at PSI showing the treatment machine (left) and the CT sliding gantry (right) used for daily positioning and adaptive therapy

Siemens Healthineers CT sliding gantry has been installed laterally to the treatment position (figure 5). Using the same robotic positioning system, the patient, in the treatment position on the couch, can be positioned a few meters away from the patient nozzle, in such a way that the CT gantry can slide along its rails and over the patient to acquire either topogram or 3D images. This system has now been in clinical use for more than five years, and has proved to be efficient and effective.

A recent study has shown that, topogram-based 2D/2D positioning can achieve accuracies of 0.15/0.28/0.4 mm and precisions of 1.2/1.6/2.3 for cranial, head and neck, and extra cranial cases respectively. One additional worry about an in-room diagnostic CT scanner is the risk of radiation damage to the electronics due to stray neutrons resulting from the proton irradiations. We can report, however, that after eight years of operation (including the intense use of beam during the acceptance and commissioning process of the gantry in the run up to the first patient treatment), we have seen no degradation of image quality or reliability of our in-room CT scanner. This indicates that worries about the effects of neutrons are likely unwarranted, at least for the position of the CT scanner in our setup. Although not quite as convenient as CBCT imaging in the treatment position, we believe that the much-improved image quality of in-room diagnostic CT scanners more than compensates for the potential disadvantages.

2.4 Remote positioning

Although not a widespread technique, daily imaging and positioning of patients on a diagnostic CT scanner has also been performed outside of the treatment room (so-called remote positioning), an approach that was practiced for more than 20 years at our institute. Our experiences with this approach have been reported by Bolsi et al. [4], and the excellent clinical outcomes are presented in numerous clinical publications [8–10]. From the technical point of view, one of the main concerns with remote imaging is whether the patient moves between imaging and treatment. In the work of Bolsi et al., this was assessed through periodic post-treatment imaging on the same CT scanner, typically four to five times during a complete course of treatment. Given that such post-treatment images were typically acquired 20–30 minutes after the pre-treatment images and after two shuttles of the patient from the CT scanner to the treatment machine and back, mean differences of 0.6/1.5/1.8 mm for bite-block, mask, and extra cranial patients respectively show that the approach is surprisingly precise. They also show, however, that good patient fixation devices are required, as indicated by the larger uncertainty for patients with thermo plastic masks (2.0 mm) in comparison to those with vacuum bite-blocks (0.4 mm). This approach also necessitates a precise and reproducible mounting of the same treatment table on the CT scanner and treatment machine, as well as a precise and smooth shuttle for moving the patient between devices. In addition, the coordinate systems of the CT scanner and treatment device were spatially correlated, such that the isocenter of the CT scanner could be directly related to the isocenter of the treatment machine. This has the added advantage that there is no need for laser-based positioning on the gantry, as an accurate transfer of isocenter between imaging and treatment is guaranteed. On the other hand, additional QA measurements, ensuring the validity of this coordinate transfer are necessary, such as the use of couch mounted fiducial markers visible in the CT scanner and at the treatment machine. Finally, and as pointed out by Bolsi et al., and subsequently investigated through simulations by Fava et al. [11], by positioning outside of the room, an improved patient throughput could be achieved, at least for single-room proton facilities.

In summary, remote positioning, using either in-room or remote imaging, can be effective and efficient, and allows to exploit the improved image quality of diagnostic CT scans for daily positioning and adaption of proton therapy treatments. Although the out-of-room approach is rather radical and probably not practical for more mobile tumors such as those in the abdomen and thorax, when combined with a smooth and flexible patient transporter/shuttle system, it could be a useful approach for some indications. Particularly for single-room solutions, it might also bring some advantages in patient throughput. On the other hand, in-room solutions provide a more versatile and flexible approach which can be applied to a wider range of indications, whilst still providing the advantages of diagnostic-quality 2D or 3D images.

3. CT-based, adaptive proton therapy

3.1 The adaption process in proton therapy

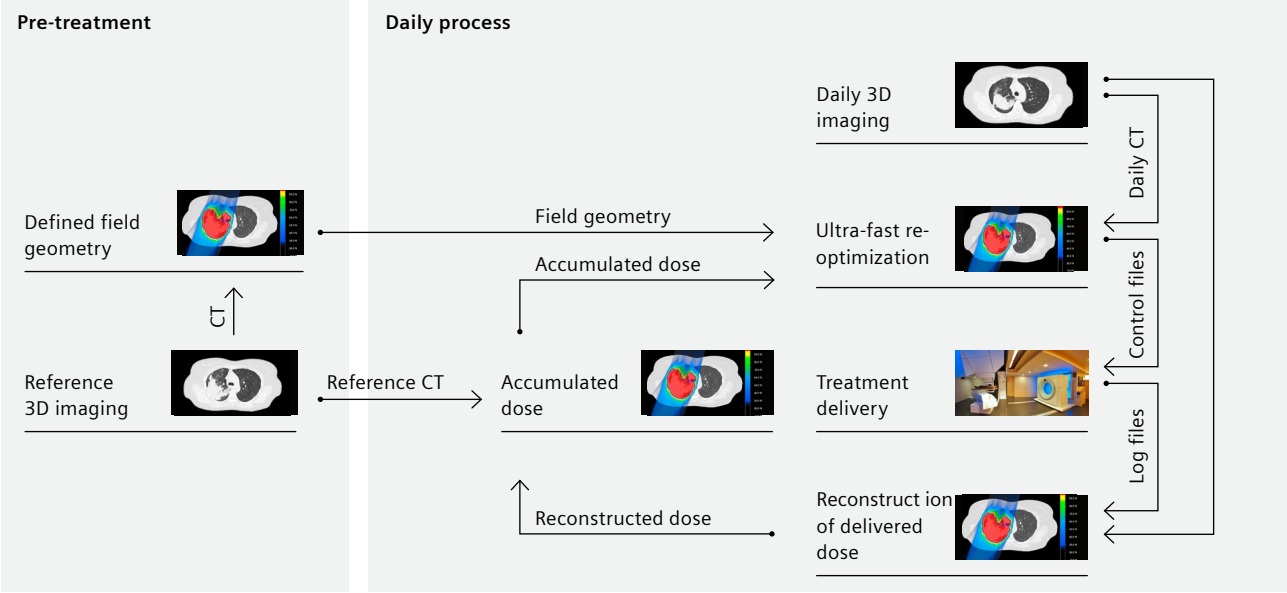


Figure 6. The daily adaptive proton therapy (DAPT) process

Some of the largest uncertainties that can occur in proton therapy are those caused by anatomical changes in the patient during the course of treatment (figure 2). Although such changes do not occur in all patients, they can be of large magnitude and are particularly prevalent in head and neck and lung tumor patients. For the latter, range changes can occur due to shrinkage of the tumor during the treatment course, or due to chest wall thinning [12], whereas for head and neck tumors, substantial weight loss during treatment is common, particularly with concomitant radio- and chemotherapy regimes. Although in vivo range imaging techniques such as PET activation or prompt photon imaging [13] have been proposed to detect such changes during treatment, by far the most intuitive and effective approach is to image and detect such changes before delivering a fraction, and adapt the treatment as necessary. This is the idea behind adaptive proton therapy, the workflow of which is shown in figure 6.

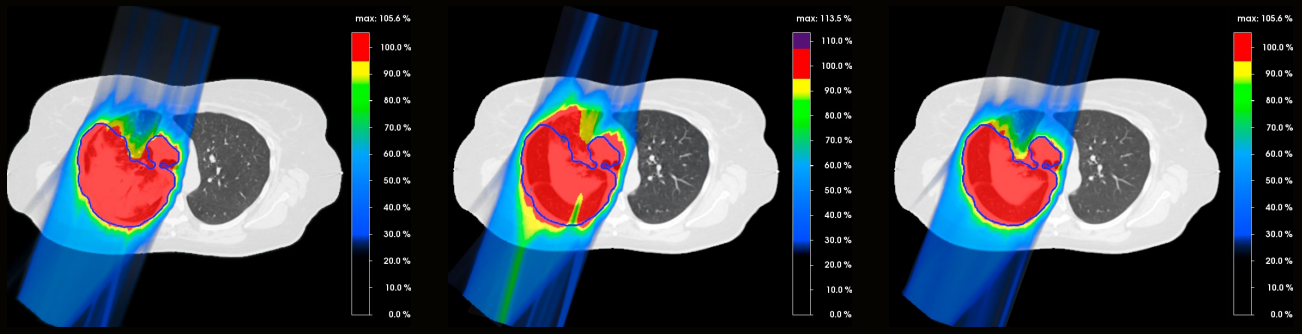
In this process, the treatment plan is redefined (adapted) based on each new 3D image of the patient, therefore taking into account any anatomical or tumor changes that may have occurred during the treatment course.

All contours defining the tumor and critical structures need to be transformed onto this new 3D data set, and the treatment plan completely replanned and recalculated. After an automated quality assurance check of the new plan, including, as necessary, an MD approval, the adapted plan can then be delivered to the patient. However, this process produces multiple 3D representations of the patient (one for each adapted plan), each of which has a new (and different) calculated dose distribution. In order to be able to assess the total dose at any point in the patient, the dose distribution for each plan must be transformed and accumulated on a reference data set of the patient (for instance, the pre-treatment planning CT), so as to record a cumulative dose at each point within the patient. Optionally, this delivered dose can be calculated from log files recording the actual delivery and could also be used to close the adaptive loop by feeding the accumulated dose back into the replanning process for the next plan adaption.

3.2 The role of CT imaging in adaptive therapy

Plan adaption is already widely practiced in proton therapy, but with typical periodicities between re-plans of weeks rather than days. However, given the sensitivity of proton treatments to even small anatomical changes and setup errors, there are good arguments, at least in some tumor entities, to move to a daily adaption regime. Indeed, if the workflow in figure 6 can be applied on a daily basis, daily positioning uncertainties would also be automatically corrected, mitigating the need to apply table corrections before treatments.

In principle, any 3D imaging modality could be used for the imaging step of the adaptive loop shown in figure 10. However, for reasons discussed above, in-room diagnostic CT is the current modality of choice. CT is still by far the most accurate method for predicting proton stopping powers in patients, especially if dual energy CT (DECT) is used [14,15]. To reduce the chance of patient motion between imaging and delivery, an in-room device is also extremely desirable. For the same reason, the time required for replanning and plan validation procedures must be reduced to just a few minutes. On the other hand, with a daily adaption regime, it is also important to reduce imaging dose as much as possible. From this point of view, it is therefore important to use low-dose imaging protocols, as long as these do not compromise image quality and the accuracy with which the CT data can be used to accurately predict proton range in the patient.



a) Original PBS proton plan using the planning CT shown in figure 2c, left

b) Dose recalculated on the CT image after tumor shrinkage (c.f. figure 2c, right)

c) Dose distribution after complete replanning using the CT scan from Figure 2c, right
Note that the dose distribution is almost completely restored to that of the original planning CT

Figure 7. The effectiveness of plan adaption in the lung

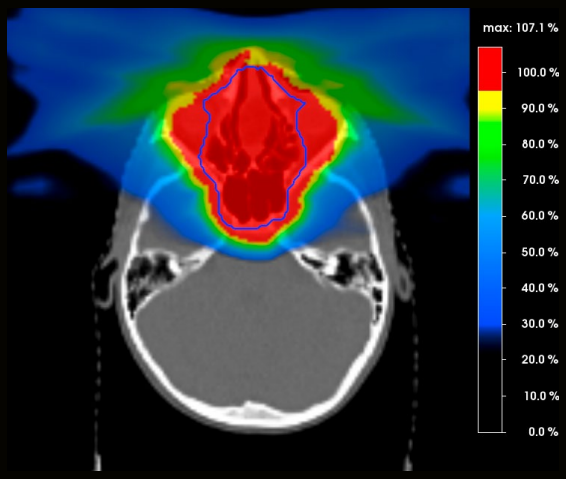
4. Clinical advantages of adaptive proton therapy with in-room CT imaging

To finish off this report, we will discuss some expected clinical advantages of adaptive proton therapy when combined with in-room CT imaging.

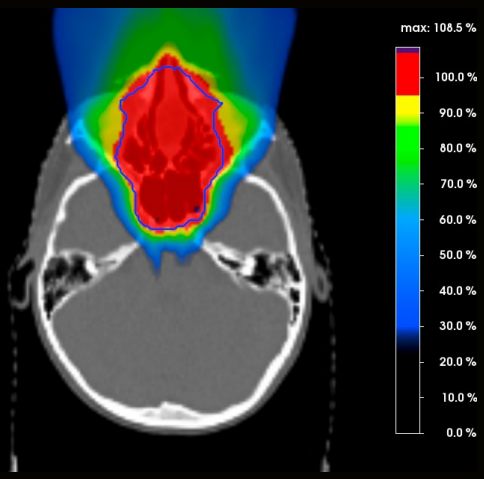
Figure 7 shows the potential and necessity of adapted proton therapy when treating lung cancer. Figures 7a and 7b show the original dose distribution calculated using the planning CT shown on the left figure 2c, and the dose distribution resulting from the same plan (i.e., unadapted) being delivered based on the anatomy in the CT scan performed during treatment (figure 2c, right). Due to the clear loss of tumor mass during therapy, the delivered dose changes substantially, resulting in a significant region of increased dose in the unaffected lung distal to the original tumor volume (figure 7b). However, if the treatment were replanned using the new patient anatomy, then dose coverage and homogeneity could be retrieved to close to that of the original plan (figure 7c).

In this case, CT-guided adaption of the plan would preserve dose coverage of the target, whilst continuing to minimize the dose to the unaffected lung tissue. Indeed, whereas in this example the target volume has been assumed to remain unchanged throughout the treatment course (which may be required in order to treat any residual and invisible microscopic tumor spread), adaption would make it possible to “cone-down” the high-dose treatment volume to the residual visible tumor in figure 2c (right), thereby further reducing the dose to the surrounding lung.

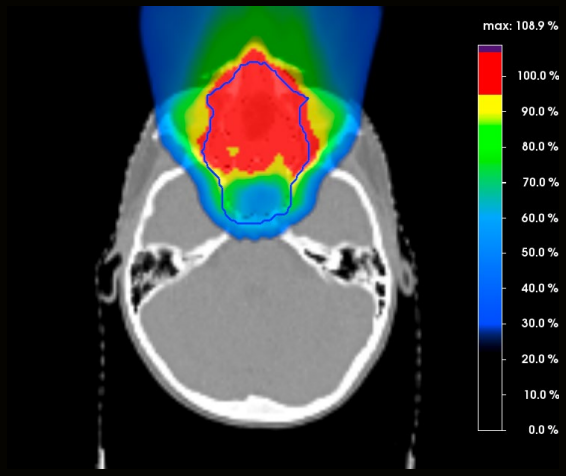
Finally, figure 8 illustrates a more nuanced advantage of adaptive proton therapy. Paranasal tumors of the kind shown in the figure are typically irradiated at our institute using the field arrangement shown in figure 8a. However, a more conformal approach would be to exploit the stopping characteristics of protons even more and treat the tumor using just three field directions, all coming from the anterior direction (figure 8b). Such field arrangements are not used currently, due to the sensitivity of this arrangement to potential changes in the filling of the nasal cavities, the effects of which are shown in figure 8c. Here, fluid has collected in the cavities since the first planning CT, substantially affecting the range of all the fields and drastically reducing dose coverage of the posterior portion of the target volume. By adapting the plan to these changes as shown in figure 8d, target coverage can be preserved, which allows this highly conformal field arrangement to be delivered safely. As demonstrated by this example, CT-guided plan adaption may therefore not just be a technique for mitigating anatomical changes, but could also be the key to improved and more effective field arrangements for proton therapy.



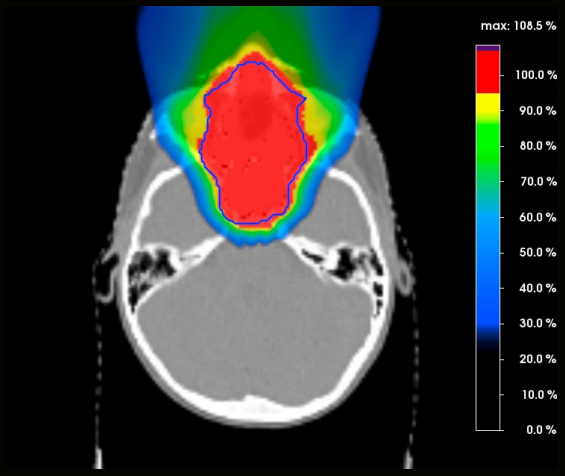
a) The clinical four-field plan



b) A more conformal approach using anterior beams only through empty nasal cavities



c) The detrimental effect of filled nasal cavities



d) The adapted plan, taking into account the different cavity filling – note the fully restored coverage of the tumor.

Figure 8. The effectiveness of plan adaption in paranasal tumors

5. Conclusions

Regular, maybe even daily, adaptive therapy will be an essential process to fully exploit the potential of proton therapy. The use of regular diagnostic 3D imaging with an in-room CT scanner is the current modality of choice for this approach to ensure accurate range predictions and to minimize the time between imaging and delivery.

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