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Time of PTV is ending; robust optimization comes next

Optimisation robuste ; la fin du PTV ?

Titre court: robust optimization / optimisation robuste

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Résumé

Depuis l'utilisation thérapeutique des radiations ionisantes, la manière de prescrire, enregistrer et décrire la radiothérapie n'a cessé de s'améliorer par paliers. L'International Commission of Radiation Units (ICRU) a fourni un langage commun aux médecins et physiciens pour planifier et évaluer leurs traitements. Le concept de PTV utilisé pendant plus de deux décennies devient obsolète car la marge du CTV au PTV crée un nuage de dose statique qui ne décrit pas correctement toutes les incertitudes. Le concept d'optimisation robuste est récemment apparu comme devant remplacer le concept de PTV. La planification inverse avec optimisation robuste minimise les déviations par rapport à la distribution de dose prévue grâce à l'intégration des incertitudes dans les objectifs de planification. Elle pourrait permettre de mieux exploiter le potentiel clinique de la protonthérapie. Elle peut également améliorer la qualité des traitements hypofractionnés des tumeurs mobiles et plus largement de radiothérapie en photons. Toutefois, contrairement au concept de PTV, la métrique d'une méthode d'évaluation de la qualité des plans (a posteriori), appelée évaluation robuste, est encore à développer. Cette métrique est nécessaire pour comparer une planification de radiothérapie par photons basée sur un PTV ou par protons basée sur une optimisation robuste et pour une sélection de traitement basée sur des modèles NTCP. Les ressources informatiques, l'impact d'approximations intégrées dans les algorithmes d'optimisation robustes ainsi qu'une métrique d'évaluation de la qualité des plans sont encore nécessaires, mais un palier a été franchi pour l'amélioration de la précision de la prescription en radiothérapie.

Mots clés : radiothérapie, PTV, CTV, optimisation robuste, incertitudes

Abstract

Continuous improvements have been made in the way to prescribe, record and report dose distributions since the therapeutic use of ionizing radiations. The international commission for radiation units and measurement (ICRU) has provided a common language for physicians and physicists to plan and evaluate their treatments. The PTV concept has been used for more than two decades but is becoming obsolete as the CTV-to-PTV margin creates a static dose cloud that does not properly recapitulate all planning vs delivery uncertainties. The robust optimization concept has recently emerged to overcome the limitations of the PTV concept. This concept is integrated in the inverse planning process and minimizes deviations to planned dose distribution through integration of uncertainties in the planning objectives. It appears critical to account for the uncertainties that are specific to protons and should be accounted for to better exploit the clinical potential of proton therapy. It may also improve treatment quality particularly in hypofractionated photon plans of mobile tumors and more widely to photon radiotherapy. However, in contrast to the PTV concept, a posteriori evaluation of plan quality, called robust evaluation, using error-based scenarios is still warranted. Robust optimization metrics are warranted. These metrics are necessary to compare PTV-based photon and robustly optimized proton plans in general and in model-based NTCP approaches. Assessment of computational demand and approximations of robust optimization algorithms along with metrics to evaluate plan quality are needed but a step further to better prescribe radiotherapy may have been achieved.

Key words: radiotherapy, CTV, PTV, robust optimization, uncertainties

I Introduction

Since the therapeutic use of X-rays, radiotherapy target volumes have been defined to achieve the highest probability of tumor control while minimizing the risk of unacceptable toxicities (1). Improvements have been achieved at different levels from imaging-based definitions of target volumes to radiotherapy delivery accuracy and safety. Moreover, the International Commission on Radiation Units and Measurements (ICRU) has continuously contributed to improve the prescription, recording and reporting of radiotherapy. With respect to photon-based radiotherapy, the Planning Target Volume (PTV) concept has been integrated in routine photon radiotherapy to provide adequate target coverage (of clinical target (CTV) volumes and the gross tumor (GTV)) under the presence of uncertainties. The CTV-PTV margins represent a geometrical security zone around the target to ensure that the desired dose to the CTV is achieved for a majority of treatments of a patient population. This static geometric expansion to the CTV has worked relatively well to ensure megavoltage photon dose distributions although a geometrical miss is still possible. The PTV concept has been an improvement to prior prescription modalities. PTV metrics are well admitted in the photon community and user-friendly for daily routine practice. However, the PTV concept is now considered as an obsolete approximation and is currently challenged by robust optimization, whereby deviations from the nominal (i.e. error-free) dose distribution are integrated in the planning process. Robust optimization for radiotherapy planning has initially been investigated to incorporate organ motion and setup-in intensity modulated radiotherapy (IMRT) planning in the 2000's but has appeared as even more critical in proton therapy planning to account for range uncertainties. Robust optimization is now integrated in most proton therapy treatment planning systems (TPS) and is increasingly integrated in photon TPS. The current article aims to explain the robust optimization concept, to compare and to challenge it against the current PTV concept and to anticipate its wider application in photon radiotherapy.

II Better prescribing and reporting with the PTV concept

ICRU report 29 (1978) (2) introduced the target volume(s) where the target volume was enclosed by a given isodose surface. Prescription of the target absorbed dose(s) preceded the determination of the dose distribution in the patient. ICRU report 50 (1993) further introduced volumes extracted from dose distribution such as the Treated and Irradiated Volume and introduced the current specification of volumes (GTV, CTV and PTV) for radiotherapy (3) (Figure 1). ICRU report 83 introduced the planning target volume (PTV) (3),. While GTV and CTV definitions are based on anatomy and biology, defined prior to treatment planning, PTV is defined during treatment planning and Treated and Irradiated Volumes are a result of treatment planning.

Determination of the CTV-to-PTV margins

According to ICRU (3), the PTV is a static geometrical concept that ensures that the CTV receives the prescribed dose. Nevertheless, large margins increase the irradiation of organs at risk and may result in unnecessary morbidity. Therefore, determination of PTV margins is a compromise between efficacy and toxicity. ICRU Report 62 (4) supplements ICRU report 50 with a list of factors and distinguishes uncertainties related to internal or set-up margins. Internal Margins (IM) around the CTV intend to compensate for physiologic variations (breathing, heartbeats, bladder filling, bowel movements etc.) in size, shape and position of the CTV during therapy. IM is commonly asymmetric. The Internal Target Volume (ITV) includes the CTV and IM. Setup Margins (SM) consider uncertainties (inaccuracies and lack of reproducibility) in patient positioning and alignment of the therapeutic beams during treatment planning and through all treatment sessions. Factors influencing SM vary from one center to another and from one machine to another. They include patient positioning (immobilization devices, patient preparation, IGRT procedure, mechanical and software uncertainties in image-guidance), mechanical uncertainties of the equipment, dosimetric uncertainties, planning image co-registration errors, transfer set-up errors from CT to treatment unit and human factors (skills and experience of the team).

Combining margins

ICRU report 62 (4) proposes different clinical scenarios for margin combination (Figure 1). In scenario A, all margins are added and $PTV = CTV + IM + SM$. However, this approach often leads to a large PTV that will likely result in toxicities. In most clinical situations, a global safety margin is adopted (Scenario C). An intermediate scenario (scenario B) aims at optimizing the width of the global safety margin using a quantitative approach. To this end, ICRU report 71 (5) and van Herk (6) distinguished overall systematic errors (i.e. treatment preparation errors) and overall random errors (i.e. treatment execution errors). Their impact on dose distribution is different: random errors blur the dose distribution, whereas systematic errors cause a shift of the cumulative dose distribution relative to the target. Overall systematic errors (Σ) can be derived by adding separate systematic errors quadratically, as follow:

$$\Sigma = (\Sigma_{set-up}^2 + \Sigma_{organ\ motion}^2 + \Sigma_{delineation}^2)^{1/2} \quad (1)$$

Similarly, overall random errors (σ) can be derived by adding separate random errors quadratically, as follow:

$$\sigma = (\sigma_{set-up}^2 + \sigma_{organ\ motion}^2)^{1/2} \quad (2)$$

Based on the probability distribution of the cumulative dose over a patient population (dose-population histogram), van Herk *et al.* (7) further determined m_{PTV} , the CTV-to-PTV margin as follows:

$$m_{PTV} = \alpha \Sigma + \beta (\sigma - \sigma_p) \quad (3)$$

Where Σ is calculated from eq. 1, α is obtained from a 3D Gaussian probability density function for a specific confidence level of the population (e.g. 90% of patients in the population), β is the distance between a given isodose surface (e.g. 95%) and the 50% isodose surface of the blurred dose distribution arising from random errors, σ_p describes the width of beam penumbra fitted to a Gauss function, σ is calculated from eq. 2 combined with σ_p . Note that m_{PTV} , Σ , σ and σ_p are vectors, thus

allowing eq. 3 to be used for defining non-isotropic margins. A simplified approximation of eq. 3 in which the width of the penumbra has been excluded is proposed as follow:

$$m_{PTV} = \alpha \Sigma + \gamma \sigma \quad (4)$$

van Herk *et al.* (7) provided values of α for various confidence levels between 80% and 99% and β and γ values for dose levels between 80% and 99%. For example, the PTV margin required to cover a CTV with the 95% isodose surface for 90% of the patients is $m_{PTV} = 2.5 \Sigma + 0.7 \sigma$. Note that a confidence level of 100% and/or a CTV dose coverage of 100% cannot be achieved since that would require an infinite margin. The confidence level and isodose coverage can be adjusted for each clinical situation to obtain adequate margins. Although a confidence level of 90% may appear insufficient, the resulting biological impact (tumor control probability (TCP) reduction in the population) was estimated to be very low (less than 1% for conformational 3D prostate treatments) (6). Similarly, Stroom *et al.* (8) proposed a margin recipe based on coverage probabilities. The CTV-to-PTV margin that ensures that, on average, 99% of the CTV is included in the 95% isodose surface is $2 \Sigma + 0.7 \sigma$. Although very close to the equation obtained with the dose-population histogram approach by van Herk, this approach cannot differentiate between situations where 1% of the CTV is missed completely for all patients or where, for instance, 50% of the CTV is missed completely for 2% of the patients. However, the two approaches similarly emphasize that the impact of systematic errors on PTV margins is preponderant compared with random errors.

Evolution of CTV-to-PTV margins with technological developments

A major evolution is the reduction of CTV-to-PTV margins with more accurate treatment preparation and delivery technologies. For example, the volume of PTV for prostate treatments decreased from 500 cm³ in the 1990s to less than 100cm³ today (1). Treatment preparation was improved using 3D computer tomography system (CT), better image quality and spatial resolution, use of 4D-CT and multimodal images (despite co-registration uncertainties). Image-Guided Radiation Therapy (IGRT) has evolved from external markers and 2D (film, electronic portal image system, 2D-kV) to 3D (kV or

MV cone-beam CT, MVCT, MRI-Linac) and even in-room 4D imaging. Overall, the use of immobilization devices, and the enhancement of mechanical treatment performances and imaging devices led to significant SM reduction. Algorithms have also evolved considerably, reducing dosimetric uncertainties.

Evolution of CTV-to-PTV margins with treatment techniques

IGRT led to the development of motion management techniques such as gating, tracking or adaptive radiotherapy. All these techniques contribute to reduce systematic and random setup and organ motion errors, and thus to reduce CTV-to-PTV margins. For IMRT, volume definition and uncertainties remain unchanged but ICRU report 83 (9) excludes the possibility of compromising PTV margins if they encroach in OAR. Moreover, it requires to quantify margin requirements in view of increasing relevance due to the steep absorbed-dose gradients obtained with IMRT (9). These requirements are exacerbated with Stereotactic Body Radiation Therapy (SBRT) delivering a few high-dose fractions. In intracranial radiosurgery, using dedicated devices, the total geometric uncertainties can be less than 1 mm ($k=1$). In these cases, it is not uncommon to treat without a PTV (10). In contrast, it seems impossible to completely eliminate all geometrical errors in extracranial cases (6)[8][10].

Requirements for CTV-to-PTV margins determination

The PTV is a relatively practical tool and it uses well accepted metrics, such as 95% of the prescription dose in 90% of the patients, but the methods used to quantify CTV-to-PTV margins combining systematic and random errors are based on simplifications [8]: patient populations are assumed to be homogeneous, tumors distortions are ignored, and random error are ignored if radiotherapy includes many fractions. Moreover, PTV is a static geometrical tool and all the non-geometric uncertainties (dosimetric, densities and tissues assignment) are translated in distances based on simplifications. One important limitation lies in PTV's inability to identify all the causes of errors and

to quantify the corresponding uncertainties (11)(12) . Consequently, margins are generally derived from published experiences, from clinical trials and applied without local adaptation. Technological developments may add new sources of uncertainty (such as MRI distortion) and the sources of uncertainties listed in the first publications [4-9] are no longer comprehensive. Tridimensional images allow accounting for rotations and organ deformations in addition to translations. However, deformations are generally not carried out. End-to-end tests on phantoms should be performed to quantify the total system accuracy and its uncertainties as recommended in ICRU report 91 (10).

III The PTV concept is over

Limits of PTV definition and ICRU formalism.

In ICRU report 50 [3], where the PTV was defined, it was already shown that the PTV concept is not always adequate for dose specification: for a simple breast treatment with two tangential fields, the PTV cannot be used for dose reporting (Fig.2). Because of the necessity of using “flash margins” to account for chest movements during irradiation, the PTV concept is inadequate because minimum dose is in the air. This situation occurs in cases where there is no electronic equilibrium in the PTV, i.e. when the CTV or GTV is superficial (13) or surrounded by low density regions (14). Robust optimization gives a solution for this issue, without PTV dose reporting.

Other issues are related to PTV margin. No consensus has yet been reached to determine the value of the PTV margin. Two different formulas were cited before, and their authors have published many modifications since. Many other propositions from different teams can be found in the literature and in ICRU report 83 [9]. Even in the recent IAEA publication about uncertainties in radiotherapy, there is no clear explanation on how PTV margin calculation should be handled (11). To our knowledge, a model that considers all the uncertainties does not exist.

One of the largest uncertainties, i.e. GTV and CTV delineation (15) should be taken into account in the PTV according to ICRU reports 83 [9] and 91 [10]. However, this results in a large increase of the PTV, making this recommendation difficult to follow in practice. CTV delineation uncertainties are

currently an active area of investigations with standardization (several consensus have been written in head and neck, prostate and lung cancers for example).

ICRU 83 report [9] insists that one should not compromise with PTV margin, for example towards rectum for prostate treatment. One should create PTV sub-volumes for optimization and keep a “real PTV” for reporting. Every radiation therapy oncology group (RTOG) and European oncology radiation therapy committee (EORTC) protocol uses a restricted margin posteriorly toward the rectum. This exception to the PTV rule is given as an illustrated example in ICRU report 83, suggesting that the clinical precautionary principle may prevail over the PTV rule.

The PTV margin depends on the dose gradient around the CTV (3): the steeper the gradient, the larger the margin for a same CTV coverage probability. It means that when an organ at risk close to the CTV is optimized specifically, one should increase the PTV in its direction, which is contrary to the practice described above. The only way to solve this contradiction is to use robust optimization instead of PTV margin.

Furthermore, the importance of covering the CTV with the full prescription dose depends on the slope of the tumor control probability (TCP) curve. While considerable uncertainties are associated to TCP data (16), this is rarely taken into account for PTV definitions. A simple example is tangential breast radiotherapy after surgery, where the priority is given to organs at risk whereas PTV calculation would conduct to a large margin with poor outcomes (17).

Finally, the contours for GTV, CTV and PTV are represented as concentric volumes, suggesting a linear addition of the errors in early ICRU reports. ICRU reports 62 and 83 proposed a quadratic approach for the ITV and set-up margin only, but oddly not for the whole combination. At least, and according to Stroom *et al.* (18) in contrast to his proposals in 1999 (8), CTV uncertainty and PTV margin should be combined with a quadratic approach too. CTV is of course a major source of uncertainty that was not significantly reduced in the last years (19), unlike many others such as patient positioning, dose calculation algorithm, multimodality imaging for GTV, etc. Why increase the coverage probability of a very uncertain volume? In fact, CTV and PTV may be considered as arbitrary boundaries: “there

are probably tumor cells outside the CTV and even outside the PTV, but these do not require the same dose to be killed “.

So the future of dose distribution optimization cannot stand in new recipes for PTV, but rather in new approaches, such as robust dose optimization, or other experimental ways to take into account uncertainties (19,20).

For SBRT, the PTV does neither predict the dose to the CTV nor the outcomes. When SBRT treatments are delivered with the same machine and immobilization devices as for conventionally fractionated treatments, classical uncertainties add to those that are specific to the technique: fewer sessions, high doses, steep gradients that produce heterogeneity in PTV. Using few sessions (with online IGRT), there are no more random errors but only systematic errors, which should lead to a larger PTV margin, steep gradients, as reported above (3), too. So, there is an intrinsic contradiction between PTV definition and SBRT.

ICRU report 91 [10] suggested maintaining the historical prescription of a dose onto the PTV envelop. ICRU report 91 lists the effects of high doses to target volumes: DNA damage, vascular damage to tumors, enhanced anti-tumor immunity, and bystander effect. Is the peripheral dose to the PTV likely to be reliably correlated with these effects? F. Lucia *et al.* recently demonstrated that “Inhomogeneous tumour dose distribution provides better local control than homogeneous distribution in SBRT for brain metastases”(21). T.B Brunner *et al.* showed that the maximum dose is a better predictor of local control than peripheral dose (22). Klement *et al.* showed that mean dose to the GTV is the best predictor of local control after SBRT for early stage non-small cell lung cancer (23). So, if the outcomes are not determined by the minimum dose, how should we calculate the PTV margin?

Although volume definitions given by ICRU reports are essential, there are unmet needs and reporting should not only describe one dose level but also D98%, D50%, D2% for every target volume(24). The PTV may be used only in a pragmatic way: the PTV does not represent the dose delivered to the tumor cells but does not account for all the uncertainties of the complex preparation

and delivery processes of radiotherapy. It may be considered as an arbitrary uncertainty-handling compromise between expected toxicities and tumor control.

IV Definition of *robust optimization to achieve robust radiotherapy plans*

The concept of robust planning through robust optimization is based on three main assumptions: the CTV should receive the entire prescribed dose notwithstanding all uncertainty; the constraints to the OARs should be satisfied notwithstanding planning or delivery errors; the constraints to serial OARs should be respected to the detriment of the CTV coverage. The overall “robust planning” may also integrate other aspects of treatment preparation, such as choice of beam ballistics, but is not the scope of the current paper.

Robust optimization relies on the concept of inverse optimization, which is widely used for IMRT and intensity modulated proton therapy (IMPT) treatment planning. The optimization algorithms consist of two elements: the objective function f_{obj} which defines the treatment plan quality and collects together the clinical objectives to be achieved during the planning process, and the optimization algorithm that is going to find the pencil beam or beamlet intensities that will minimize the objective function f_{obj} . A good treatment plan corresponds to a low objective function value. Hence, the best treatment plan is found by minimizing the objective function with respect to the beamlet intensities using mathematical optimization algorithms.

The objective function generally includes the clinical constraints proposed by the physician. The most commonly used is a quadratic function representing the difference between the calculated and the prescribed dose (25). In its simplest form, it is written as:

$$f_{obj} = \alpha \sum_{i \in \text{target volumes}} (D_i - D_p)^2 + \beta \sum_{i \in \text{organs at risk}} (D_i - D_t)^2$$

$$\text{And } D_i = \sum_j D_{ij} x_j$$

$$x_j \geq 0$$

Where $D_i(x)$ is the dose in voxel i , x_j the fluence of pencil beam, and D_{ij} is the dose contribution of pencil beam j to voxel i ; D_p is the prescribed dose and D_t is the tolerance dose. The first and the second terms of the equation represent respectively the dose distributions to the target volume and

to the organs at risk, respectively. The terms α and β represent the respective penalties imposed on target volumes and organs at risk when the constraints are not respected.

What changes with robust optimization is that uncertainties are also incorporated in the optimization process. Deviations from the nominal dose distribution are calculated explicitly for each “error scenario” and minimized using planning objectives.

In the formulation of the IMPT or IMRT problem, geometric uncertainty is modeled as uncertainty in delivering the dose, as specified by pencil beams or beamlet intensities. Whereas it is assumed that the treatment machine can accurately deliver the treatment plan as specified by the beam intensities, there is an uncertainty on what the dose distribution yields in the patient, due to above mentioned problems. As described by Unkelbach *and Paganetti*, the easiest way to understand this approach is to assume that different dose-influence matrices D_{ij}^S may apply (26). Here, S is an index of possible error scenario.

There are two prevailing approaches in robust optimization:

- The stochastic programming or probabilistic approach, which optimizes the expected plan quality
- The minimax or worst-case approach, which optimizes plan quality for the worst error considered

Stochastic programming or probabilistic approach

The probabilistic approach consists in minimizing a weighted sum of objective functions evaluated for all scenarios. This means that the operator knows the probability of occurrence of a given scenario. Formally, this can be written as:

$$\text{Minimize } \sum_S p_S f_{obj}(d^S)$$

$$\text{Subject to } d_i^S = \sum_j D_{ij}^S x_j$$

$$x_j \geq 0$$

Where P_S represents importance weights for the error scenarios ($\sum p_S = 1$). In practice, a high weight will be given to a scenario which is more likely to occur, whereas, a low weight is given to a scenario that may happen but with low probability. The probabilistic approach aims to find a solution that yields a good treatment plan for all scenarios, i.e. for all possible dose distributions d^S . An illustration of the approach is given in Figure 3.

Minimax optimization or worst-case approach

The worst-case approach consists in minimizing the maximum of objective functions, taken over all scenarios (27). Formally, this can be written as:

$$\text{Minimize } x \max_s f_{obj}(d^s)$$

$$\text{Subject to } d_i^s = \sum_j D_{ij}^s x_j$$

$$x_j \geq 0$$

This means that the worst-case approach gives the best possible plan for the worst scenario.

There exist several variations of the worst-case approach:

- The voxel-wise worst-case approach, i.e. at each iteration, the algorithm selects the worst dose in each voxel from the different scenarios.
- The composite worst-case approach, i.e. at each iteration, the algorithm selects the scenario, which gives the worst score of the objective function on all the organs.
- The objective-wise worst-case approach, i.e. at each iteration, the algorithm calculates the objectives function based on the worst value of the objective functions on each structure.

An illustration of each approach is given in Figure 4.

Why using CTV-based robust planning instead of PTV-based planning?

Treatments with photon beams

As mentioned above, uncertainties related to radiotherapy planning are commonly managed using CTV-to-PTV margins. For a treatment with a photon beam, modest changes in the anatomy, or clinically relevant geometrical uncertainties, are likely to have little effect on dose distribution. This theory, inherent in the PTV concept, while not perfect, works well, even in the presence of heterogeneities. For example, Karlsson K *et al.* (28) investigated the accuracy of the dose calculated to the CTV with the static dose cloud approximation, i.e. the PTV, in SBRT of lung tumors considering setup errors and breathing motion. The dose-shift approximation was determined to be accurate to approximately 2% (root mean square (RMS)) within the CTV, for clinically relevant geometrical uncertainties (up to 10mm) for SBRT of lung tumors. Similarly, in IMRT, the interplay effect is

negligible provided that an appropriate ballistic is used, which is not the case for proton beams, in particular, using IMPT technique (29) (Figure 5). However, one main limitation of the PTV approach using photon beams is for tumors displaying large intra-fraction motions. Indeed, performing PTV or ITV-based planning means that the delivered dose will be the same whatever the location probability of the tumor in a given region. Robust optimization could help in delivering higher doses to the regions mostly occupied by the tumor, providing better target coverage, and reducing the dose to the healthy tissues. Such dose distributions, leading to hot spots inside or at the edge of the targets, has been referred to as edge enhanced or horns (30).

Thus, several studies have shown that, in particular for moving targets, performing robust optimization instead of PTV-based planning led to better target coverage and better OARs sparing. Instead of generating a PTV by adding margins around the ITV, robust optimization deal with uncertainties such as tumor motion and variation in shape more effectively. Zhang *et al.* investigated the use of RayStation photon minimax robust optimization method for lung cancer patients (31). ITV-static IMRT and ITV-VMAT were compared to PTV margin-based plans. Patient setup errors of 5-10 mm were used for robust optimization, and 17 error scenarios were generated. Plan robustness was thereafter examined by shifting isocenters by 3-5mm. Robust optimization plans yielded better ITV-dose coverage, better conformity index, worse homogeneity index, and better OARs sparing compared to corresponding PTV margin-based plans for both static IMRT and VMAT techniques. PTV margin-based plans also yielded greater variations in mean dose compared to robust optimized plans. Finally, PTV margin-based plans had higher number of monitor units (MUs) than robust optimization plans.

Another way to use robust planning for photon beam radiotherapy is for breast IMRT optimization. Breast cancer treatment planning is interesting from several perspectives: 1/ the PTV is close to the surface of the skin, 2/ breast shape changes during treatment, and breast edema can extend the target into the surrounding air, 3/ because of respiratory motion. In a recent study (32). three different skin-flashing methods for IMRT breast planning were compared: 1/ manual opening of the multileaf collimator (MLC) and jaw to obtain flash, after optimization on the nominal PTV, 2/ optimization on an expanded PTV beyond the skin, 3/ robust optimization that simultaneously optimizes on the nominal CT data set and on a second simulated geometry error CT data set. To simulate geometry error on the second data set, an expansion of 15 mm of the body towards the external direction was done on the breast tissue region only. Plan robustness against target position variations was studied by simulating 0, 5, 10 and 15mm geometry errors. The robust optimization was the only one able to meet acceptable criteria in terms of PTV coverage with the 95% isodose or maximum dose to the PTV, in both the nominal and simulated geometry error scenarios.

Other studies have also reported benefits for head and neck cancer, which might be subject to important anatomic change over the treatment course. Miura *et al.* compared robust versus PTV-based optimization for larynx cancer (33). The robust plan exhibited superior CTV coverage and reduced dose to the OARs compared to the PTV-based optimization. Again, robust optimization provided less MUs than PTV-based optimization. Wagenaar *et al.* compared bilateral head and neck cases and included a plan adaptation during the third week of treatment (34). The dose was calculated on daily acquired CBCTs, mapped onto the planning CT and cumulated. Robust optimization significantly increased the CTV D98% and decreased the mean dose of the ipsilateral parotid (-2.8 Gy), inferior pharynx constrictor muscle (-0.7 Gy) and the oral cavity (-0.8 Gy). This translated into significantly reduced NTCP of tube-feeding dependence (0.9%) and xerostomia (2.8%).

Hence, PTV-based planning is a standard of modern photon radiotherapy and has proven its reliability for several years. However, robust optimization for radiotherapy planning is an interesting alternative, in particular, for targets subject to large inter or intra -fraction motions, or anatomic changes.

Treatments with proton beams

The fundamental assumption of static dose cloud approximation is not valid when considering proton beams. Unlike photons, proton range is much more sensitive to treatment and dose calculation uncertainties.

First, dose calculation for proton beams is less robust than for photon beams because of uncertainty in the conversion of Hounsfield numbers to proton stopping power. For example, Schaffner *et al* estimated that the range of protons in the human body can be controlled over $\pm 1.1\%$ of the water equivalent range in soft tissue and $\pm 1.8\%$ in bone, which translates into a range precision of about 1-3 mm in typical treatment situations (35). However, more important range uncertainty is expected in presence of lung tissue (5%) (36), or metallic implants (37). For example, Jäkel *et al.* showed that the range error of lateral beam passing through tungsten and steel in a pelvic phantom were of -5% and -18%, respectively (37). Recent studies suggest that the accuracy could be increased by using dual-energy CT (DECT) instead of single-energy CT (SECT). Zhu *et al.*, in a phantom study, showed that DECT enabled reducing maximum dose errors observed (12.8% and 2.2% for SECT and DECT, respectively), and improving accuracy in dose calculation in high dose regions (RMS being 2.1% and 0.4% for SECT and DECT, respectively) (38). Finally new paths are being explored with the use of

proton CT imaging, which provides the potential for a the more accurate estimation of stopping-power ratio inside a patient (39). However, this remains a big challenge because of the limitations on image quality arising from the multiple scattering of protons.

Besides this uncertainty, there is the performance of the dose calculation algorithm. For example, pencil beam algorithms have been mainly used until now for proton beams, because of their computational efficiency, whereas for photon beams, the Monte Carlo algorithm is used in routine for several years. The use of pencil beam algorithm brings more uncertainty in the location of the distal dose fall-off, at interfaces from low to high density tissues parallel to the beam (underestimation of scattering). Schuemann *et al.* compared passively scattered treatment field dose distributions predicted by an analytical pencil beam algorithm with those obtained using Monte Carlo simulations (40). Based on the results, they were able to deduce site-specific range margins using pencil-beam algorithm. In homogeneous sites such as prostate or whole brain treatment, range margins of $2.8\text{--}2.1\% + 1.2\text{mm}$ were considered sufficient for considering the total range of uncertainties and uncertainties from dose calculation alone. However, in presence of heterogeneities (i.e. breast, lung or head and neck), range margin of $6.3\% + 1.2\text{ mm}$ would be required.

In addition to range uncertainties, setup errors, organs' internal motions, or patient anatomy may seriously impact dose distribution. This is mainly due to two issues effects (41):

- the misalignment of dose contributions from different beam directions
- the misalignment of density heterogeneities e.g., metal implants

As IMPT optimization tends to produce highly inhomogeneous dose contributions of individual fields, a shift of the patient may lead to a shift of the dose contributions of individual beams relative to each other. As a consequence, contrarily to photon beams, where setup errors will affect the shape of the dose distribution in the vicinity of density gradients (i.e. edge of PTV...), positioning and path errors will not only affect the edges of the proton PTV but lead to heterogeneities over the entire volume of the tumor. In addition, highly perturbed dose distribution is expected if a high-density structure like a metal implant moves into the path of the pencil beam. Another aspect which is not on the scope of this paper is uncertainty on the relative biological effectiveness (RBE).

To try to minimize uncertainties, the physicist uses different planning methods. Among those is the choice of the beam directions. A treatment plan should have beam directions which should not go through regions subject to large anatomic changes, or cross material or tissue with important density variations. Another way to limit uncertainties is to use a more important number of beams in presence of heterogeneities.

Hence, IMPT based on PTV margins alone does not guarantee us to obtain a robust plan against treatment uncertainties. A potentially more appropriate method to manage these uncertainties is robust planning. In practice, robust planning technique is:

- Avoids dose gradients in beam direction in the dose contribution of individual beams. Hence a shift of the dose distribution along the incident beam direction will have a moderate impact on the dose distribution.

- Automatically extends the irradiated region distal to the target volume, i.e. automatically generates the appropriate margin necessary to achieve target coverage for the assumed range error without the need to manually define PTV margins.

- Avoid placing the distal edge of a pencil beam in front of OARs. Instead the lateral fall-off is used to shape the dose distribution in the region where OAR and target abut (26).

Robust IMPT optimization has been investigated exclusively for range and setup uncertainty. While setup errors are calculated by shifting the dose distribution in the 3 directions, range error scenarios are commonly calculated by downscaling or over-scaling the HUs in the planning CT. For example a downscaling of the HUs will simulate an overshoot scenario.

Is a method superior to the other?

Today, robust optimization methods are implemented in most of TPS. Raystation (RaySearch, Sweden) was the first to provide a commercial solution, using the composite worst-case method, whereas Pinnacle (Philips, The Netherlands) uses the probabilistic approach and Eclipse (Varian, USA) follows the voxel-wise worst case method. In theory, the probabilistic approach optimizes the average plan quality and may not achieve the desired dose quality for the worst scenario. On the contrary, the minimax approach optimizes the plan for the worst scenario only and does not expect to provide the best quality plans for scenarios that are more likely to occur. *Fredriksson and Bokrantz* (27) aimed to identify circumstances where methods may behave differently for a prostate cancer treatment plan using IMPT. Methods yielded equally robust plans when the conflict between target coverage and normal tissue sparing was small. Composite worst case led to low plan quality in boundary scenarios that were less difficult than the worst-case ones. Objective-wise, worst case generally led to non-robust plans. Voxel-wise worst case led to overly conservative plans with respect to dose volume-histogram (DVH constraints), which resulted in excessive dose to normal tissues, and less sharp dose fall-off than the other two methods. *Unkelbach et al.* tested different setup scenarios

in prostate cancer treatments (41). Stochastic programming against minimax optimization (30) showed no conflict between target and OARs results. However, when the dose to the adjacent OAR was more penalized, the minimax method neglected easy scenarios where target coverage need not to be compromised. Hence the worst-case approach is more sensitive to the definition of the uncertainty set than the probabilistic approach.

Robustness evaluation

It is important to evaluate plan robustness even after robust optimization because there are no clear metrics yet, to evaluate for plans done without a PTV. Indeed, two plans with similar CTV coverage in the nominal scenario can behave differently in the presence of different simulated error scenarios. Evaluation methods consist in applying positive and negative shifts of the isocenter of the treatment plan in the antero-posterior, superior-inferior, and lateral directions of values typically corresponding to CTV-to-PTV margins. Whereas this option of “perturbed dose calculation” is available in some TPS, it is time consuming, and does not offer the possibility to simultaneously evaluate the impact of several combinations of setup and range uncertainties scenarios of IMPT. Note that to allow evaluating robustness evaluation in terms of range uncertainty, common methods are to perturb the density by downscaling or over-scaling the HUs in the planning CT.

In its latter version, Raystation (V8.2) TPS proposes a “robust evaluation” option, which enables calculating dose distributions for errors scenarios combining different setup and range uncertainties (42). While not perfect, because the range uncertainty is likely to vary along the path of the pencil beam, this option enables visualizing in a single DVH the dose distributions to the OARs and targets for all the scenarios. Among other options is the possibility to visualize the voxel-wise minimum and the voxel-wise maximum dose distributions, which are composite of lowest and maximum dose per voxel in all scenarios respectively.

Dose reporting and robust plan evaluation

Because of the current lack of metrics associated with robust optimization, intercomparisons between photon and proton plans usually rely on PTV metrics from photon plans. As such, the weighed anisotropically voxel-based plans achieved with robust proton therapy optimization may, paradoxically, be evaluated as deviating plans in their dummy runs or true cases. This is especially the case in clinical trial protocols (such as in pediatric oncology) designed for photons but that also allow

proton plans too. This can happen so even if robust evaluation has further confirmed robustness to uncertainty scenarios of proton therapy plans achieved with robust optimization. Physicians and physicists may also have to deal with deviations between IMRT or SBRT plans designed with a PTV or a robust optimization approach. The model-based approach is based on plan intercomparisons to predict normal tissue complication probability (NTCP) and select the best radiotherapy modality for a given patient. The prerequisite for a selection on NTCP is that CTV coverage is at least as good as with the reference plan. The model-based is therefore particularly affected by the lack of common metrics between the two approaches. While to date there are no definitive answers to that question to date and a robust optimization vs PTV ICRU report has not been written yet, some solutions have been proposed by teams expert in model-based approaches to select patients for proton therapy rather than IMRT (42). The definition of common metrics will be a critical step if robust optimization is to be generalized in not only proton but also photon radiotherapy. Korevaar *et al.* (42) showed that the CTV D98 from classical PTV-based plans correlated very well with voxel-wise minimum dose distributions using worst case scenario dose evaluation to assess CTV coverage. Similarly, CTV D2 from classical PTV-based plans correlated well with voxel-wise maximum dose distributions to assess plan quality in terms of hot spots. These common metrics are however not as straightforward as they may seem in routine practice because of computation times, which may not be consistent in a busy patient TPS workload. Approximations made in robust optimization algorithms will probably require external assessment of plan quality and correlation with classical plan metrics.

Conclusion

Limitations of the PTV concept have led to the definition of new optimization algorithms that are currently called robust optimization, an eloquent word that will also certainly also suffer criticisms in the future but emerges as a step further in prescribing radiotherapy. This is particularly the case for proton therapy due to its sensitivity to uncertainties, but a little less in the case for photon radiotherapy, except maybe for hypofractionated photon radiotherapy of mobile tumors. Yet, reporting of robustly optimized plans suffers from the lack of metrics for evaluation and comparisons with plans designed with reference method, i.e. PTV based optimization. Computational demand, algorithms approximations and learning curve to adopt the robust optimization concept might be the limitations and should also be assessed.

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Figure legends

Fig.1: Schematic illustration of the different volumes defined in the report 50 of ICRU (from [2]).

Fig.2: Schematic representations of the relations between the different volumes (GTV, CTV, IM, SM and PTV) in different clinical scenarios. From Report 62 ICRU (from [4]).

Scenario (A) A margin is added around GTV to consider potential “subclinical” invasion. This margin defines the Clinical Target Volume (CTV). To ensure that all parts of the CTV receive the prescribed dose, additional margins for geometric variations and uncertainties must be considered. An Internal Margin (IM) is added for the variations in position and/or shape and size of the CTV. A Set-up Margin (SM) is added to consider all of the variations/uncertainties in patient---beam positioning.

Scenario(B) The simple (linear) addition of all factors of geometric uncertainty, as indicated in scenario A, often leads to an excessively large PTV, which would be incompatible with the tolerance of the surrounding normal tissues. In such instances, instead of adding linearly the Internal Margin and the Set-up Margin, compromise combinations are used errors than to group them by origin, i.e., physiological or set-up.

Scenario (C) in most clinical situations, a “global” safety margin is adopted. In some cases, the presence of an Organ at Risk dramatically reduces the width of the acceptable safety margin (e.g., presence of the spinal cord, optic nerve, etc.). In other situations, larger safety margins may be accepted. Since the incidence of subclinical invasion may decrease with distance from the GTV.

Fig.3: from ICRU report n°50
PTV represented as dotted area

Fig.4: Probabilistic approach

Three set up errors scenarios (Sc) in left-right direction are simulated, each scenario having a probability (Ps) to occur. In grey, is represented one organ at risk (i.e. brainstem), in which is represented a dose distribution in each voxel (1-2.5 Gy), for each scenario. In red is represented the CTV, and the dose distribution in each voxel (1-3Gy). $(f)_{oj}^{sc}$ is the objective function calculated for one scenario. D_{organ}^{sc} is the calculated dose in one organ and D_{organ}^{obj} is the objective dose defined by the physicist. At each iteration, the algorithm selects a weighted sum of the doses collected in each voxel from the different scenarios.

Fig. 5: Worst-case approach

Three set up errors scenarios (Sc) in left-right direction are simulated. In grey, is represented one organ at risk (i.e. brainstem), in which is represented a dose distribution in each voxel (1-2.5 Gy), for each scenario. In red is represented the CTV, and the dose distribution in each voxel (1-3 Gy). Panel A: *voxel wise worst-case scenario*. At each iteration, the algorithm selects the worst dose (i.e. lowest dose for the CTV, highest dose for the OAR) in each voxel from the different scenarios. In this example, the worst dose for each voxel is framed in red. Panel B: *composite worst-case scenario*. $(f)_{oj}^{sc}$ is the objective function calculated for one scenario. D_{organ}^{sc} is the calculated dose in one organ and D_{organ}^{obj} is the objective dose defined by the physicist. At each iteration, the algorithm selects the scenario which gives the worst score of the objective function on all the organs. In this

example, the worst score of the objective function is found for a set up error of “-3mm” (framed in red). Panel C: objective wise worst-case scenario. $(f)_{oj}^{sc}$ is the objective function calculated for one scenario, and for one organ. D_{PTV}^{sc} and D_{OAR}^{sc} are the calculated dose in PTV and OAR, and D_{PTV}^{obj} and D_{OAR}^{obj} the objective doses defined by the physicist. At each iteration, the algorithm calculates the objective functions based on the worst value of the objective functions on each structure. In this example, the worst score of the objective function is found for a set up error of -3mm and +3mm, for the CTV and the OAR, respectively.

Fig. 6: Dose distributions calculated on phases 0 (panels a&c) and 50 % (panels b&d) of a 4D simulation CT scan, for a lung case, for a photon-VMAT plan (Panel a&b), and for an IMPT plan (Panel c&d).

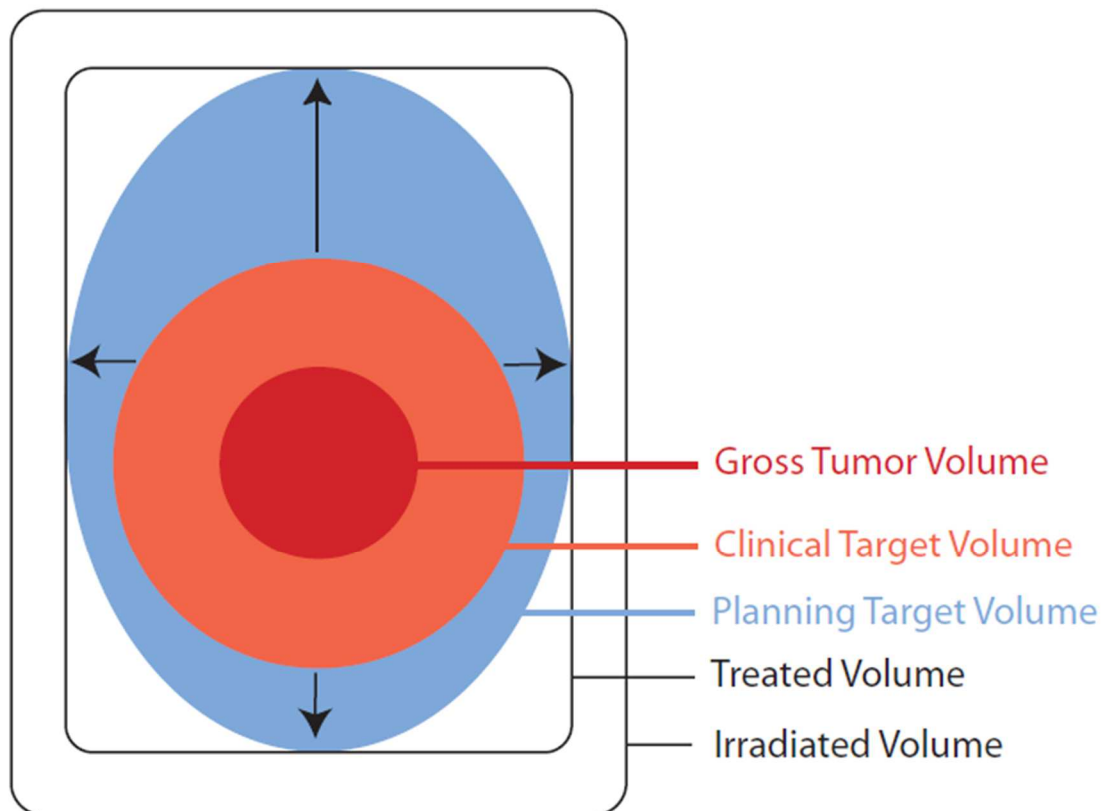


Fig.1: Schematic illustration of the different volumes defined in the report 50 of ICRU (from [2]).

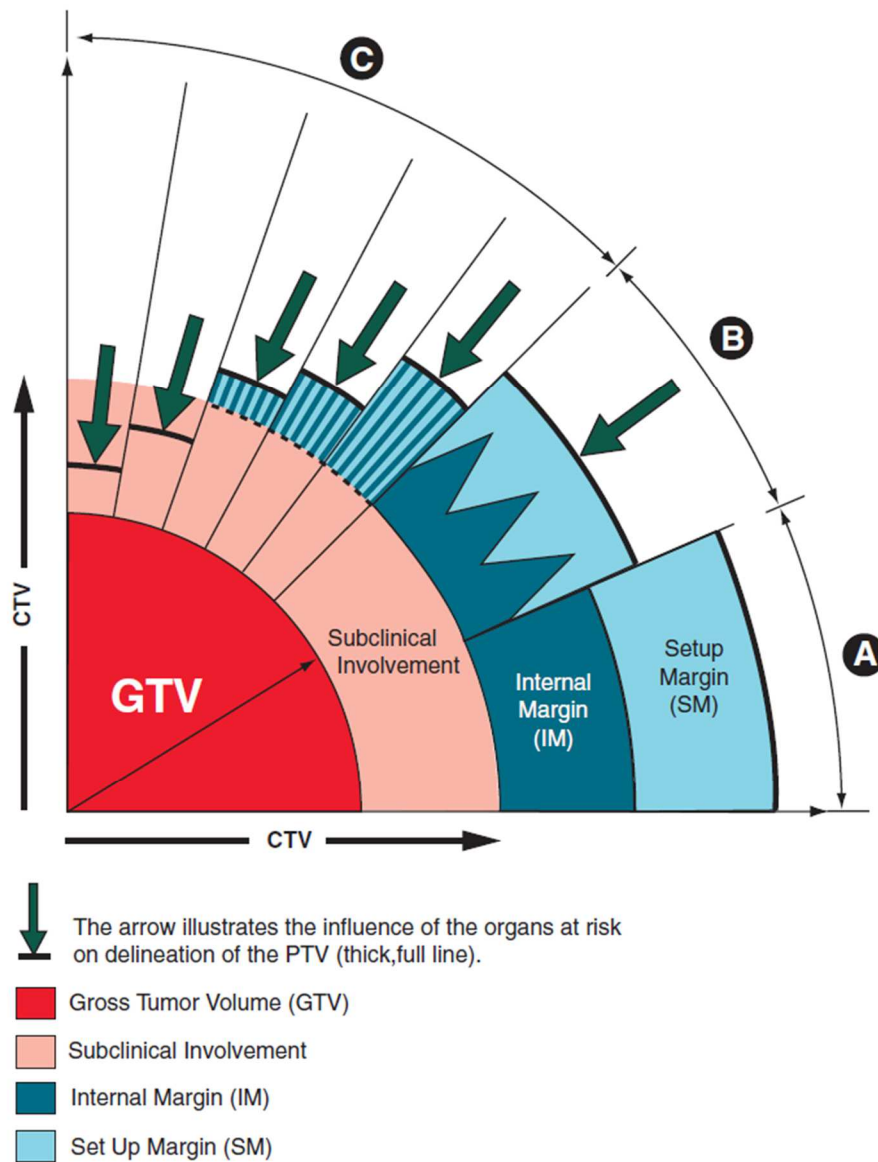


Fig.2: Schematic representations of the relations between the different volumes (GTV, CTV, IM, SM and PTV) in different clinical scenarios. From Report 62 ICRU (from [4]).

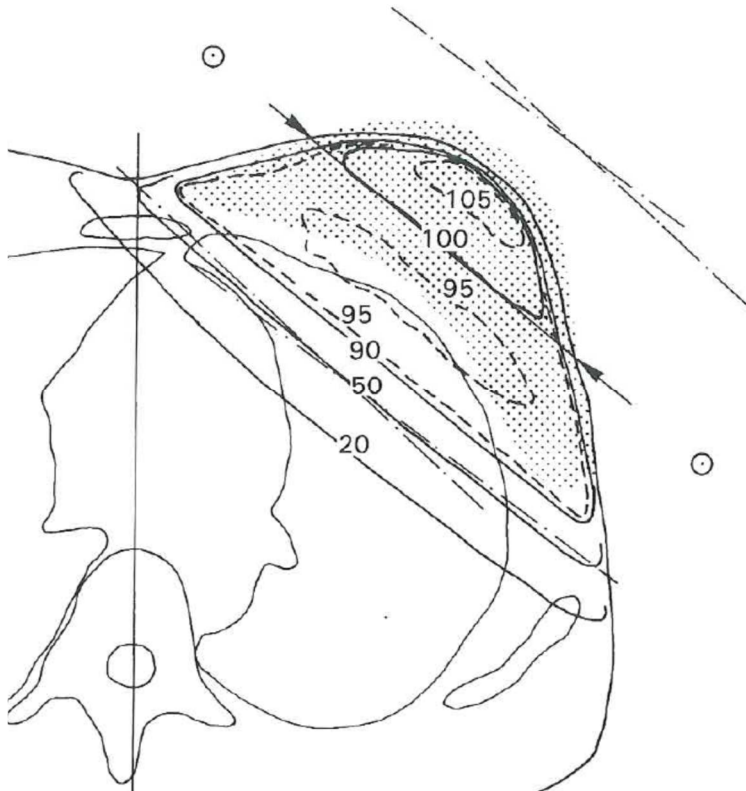


Fig.3: from ICRU report n°50

Probabilistic approach

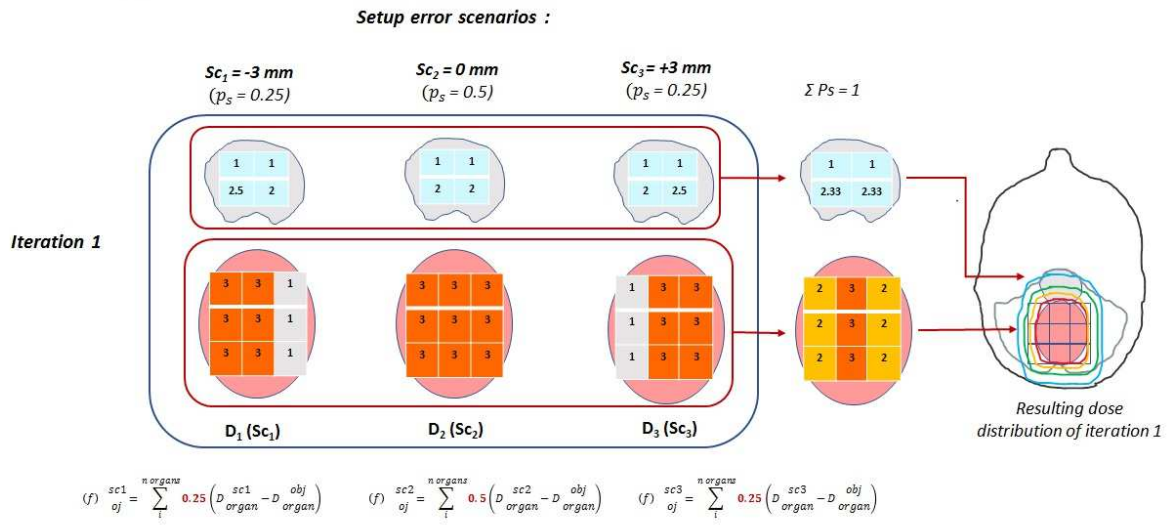
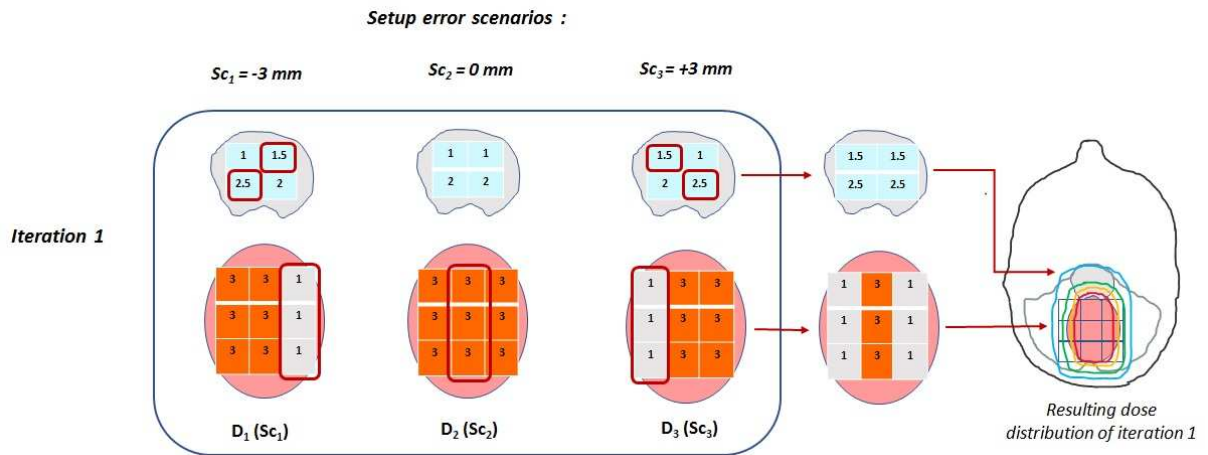


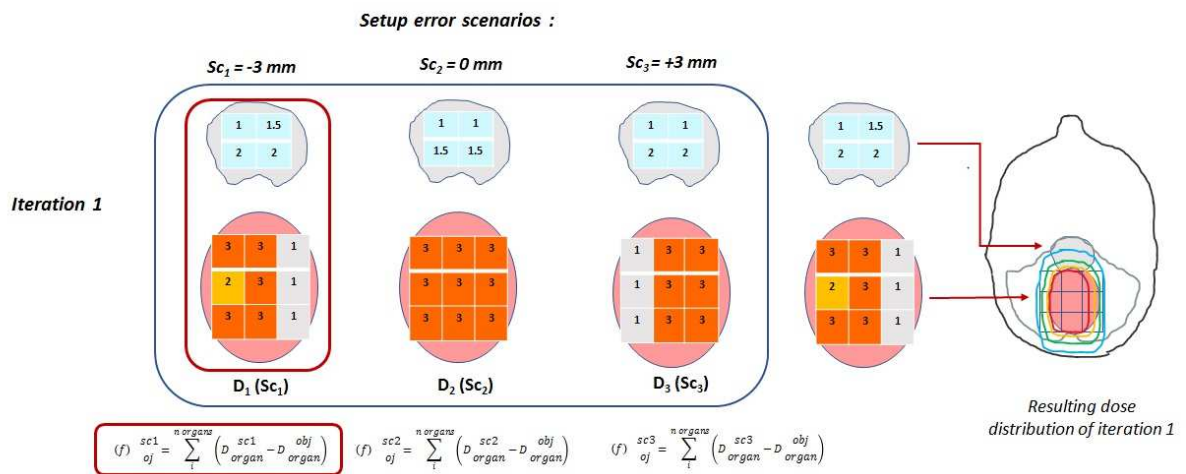
Fig.4: Probabilistic approach

A:



B:

Composite worst case scenario



C:

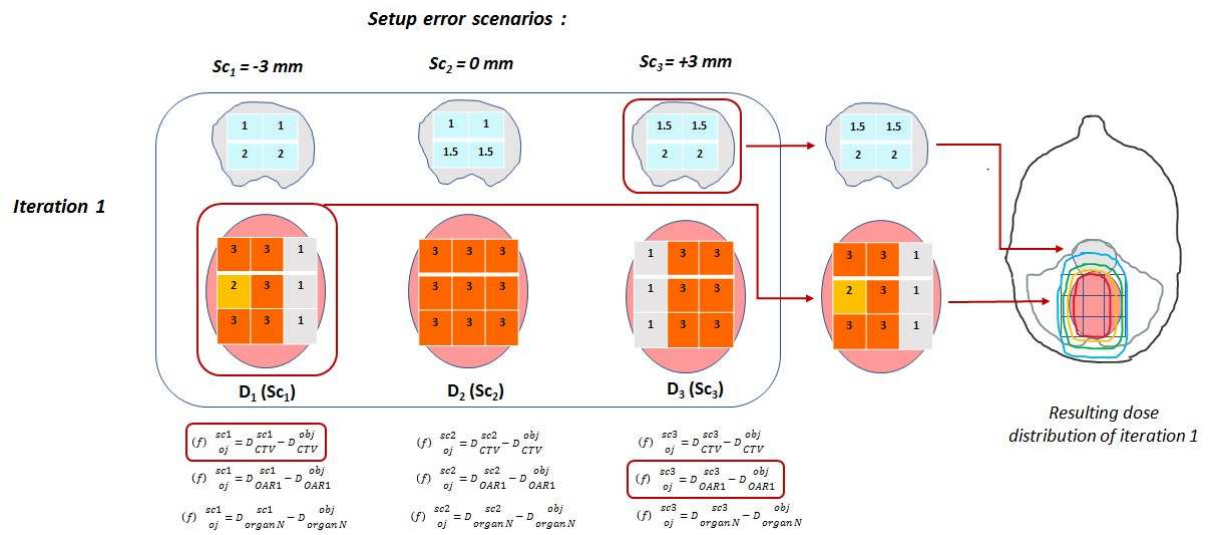


Fig. 5: Worst-case approach

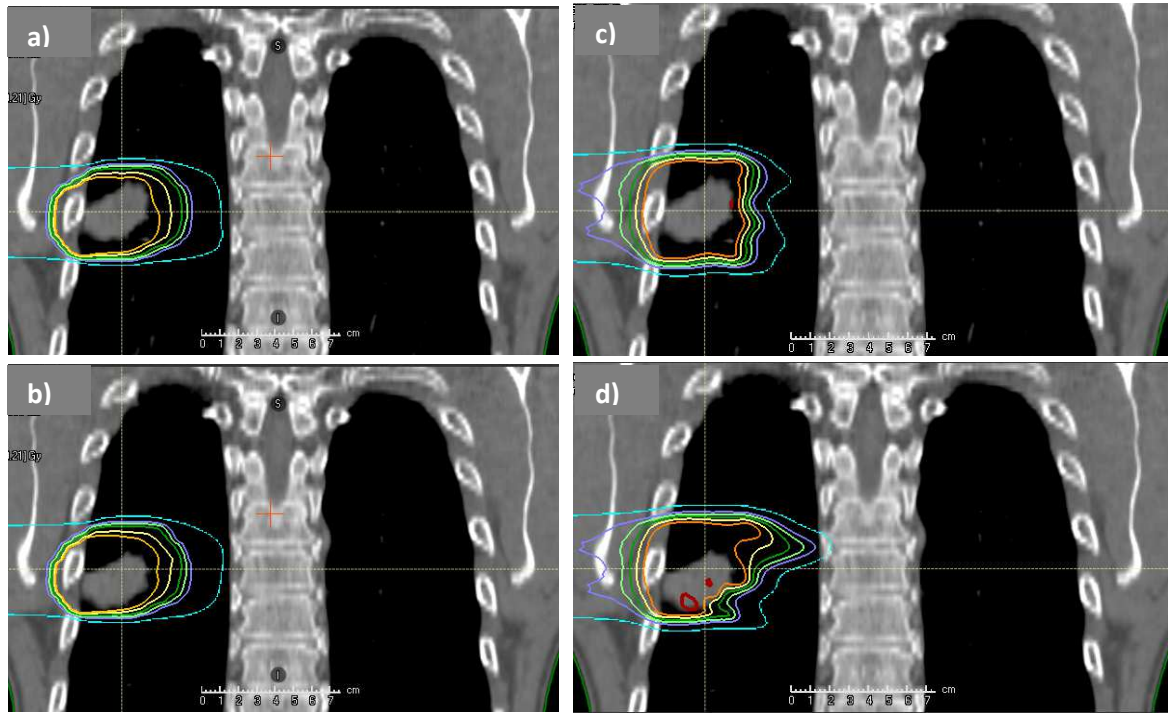


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