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Original Research Article

Considerations for radiotherapy planning with MV photons using dose-to-medium

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ABSTRACT

Background and purpose: Radiotherapy planning considerations were developed for the previous calculation algorithms yielding dose to water-in-water ($D_{w,w}$). Advanced algorithms improve accuracy, but their dose values in terms of dose to medium-in-medium ($D_{m,m}$) depend on the medium considered. This work aimed to show how mimicking $D_{w,w}$ planning with $D_{m,m}$ can introduce new issues.

Materials and methods: A head and neck case involving bone and metal heterogeneities outside the CTV was considered. Two different commercial algorithms were used to obtain $D_{m,m}$ and $D_{w,w}$ distributions. First, a plan was optimised to irradiate the PTV uniformly and get a homogeneous $D_{w,w}$ distribution. Second, another plan was optimised to achieve homogeneous $D_{m,m}$. Both plans were calculated with $D_{w,w}$ and $D_{m,m}$, and the differences between their dose distributions, clinical impact, and robustness were evaluated.

Results: Uniform irradiation produced $D_{m,m}$ cold spots in bone (-4%) and implants (-10%). Uniform $D_{m,m}$ compensated them by increasing fluence but, when recalculated in $D_{w,w}$, the fluence compensations produced higher doses that affected homogeneity. Additionally, doses were 1% higher for the target, and + 4% for the mandible, thus increasing toxicity risk. Robustness was impaired when increased fluence regions and heterogeneities mismatched.

Conclusion: Planning with $D_{m,m}$ as with $D_{w,w}$ can impact clinical outcome and impair robustness. In optimisation, uniform irradiation instead of homogeneous $D_{m,m}$ distributions should be pursued when media with different $D_{m,m}$ responses are involved. However, this requires adapting evaluation criteria or avoiding medium effects. Regardless of the approach, there can be systematic differences in dose prescription and constraints.

1. Introduction

According to ICRU recommendations, one of the goals in MV photon treatment planning is to deliver a uniform dose to the PTV [1,2]. This objective was established to ultimately deliver a uniform dose to the CTV. As CTV composition is usually homogeneous, this is achieved by irradiating it with a uniform photon energy fluence, but this fluence must be extended within the PTV to cover all CTV contouring uncertainties and positions throughout the treatment. Consequently, the resulting goal is to irradiate the PTV uniformly, which translated into achieving a homogeneous dose in the PTV.

This approach was developed for the previous-generation dose calculation algorithms that considered all tissues and materials to be water of different densities. However, more accurate algorithms must distinguish between media. Consequently, apart from their inherent accuracies, some of the discrepancies among algorithms are due to how they handle the different media. This results in three distinct dose quantities that can be described as $D_{dm,tm}$, where dm is the medium of the deposition voxel, tm is the medium of radiation transport, and both can be either w for water or m for medium.

Treatment planning system (TPS) algorithms can be roughly classified according to their associated dose quantity [3]. Dose to water-in-water ($D_{w,w}$) is reported by convolution/superposition (C/S) algorithms using pencil beam kernels and some using point kernels. Dose to medium-in-medium ($D_{m,m}$) is reported by Monte Carlo (MC), grid-based Boltzmann solvers (GBBS), and some implementations of the Collapsed Cone point kernel C/S algorithm. Actually, the doses of point kernel C/S algorithms are a mix of $D_{m,m}$ and $D_{w,w}$, being closer to one or the other depending on the implementation. Lastly, dose to water-in-medium ($D_{w,m}$) can also be reported by MC and GBBS advanced algorithms. These

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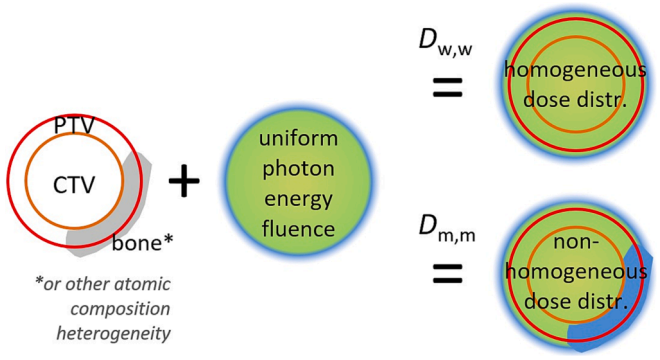

Fig. 1. $D_{w,w}$ and $D_{m,m}$ distributions when a PTV encompassing a homogeneous CTV and bone (or other atomic composition heterogeneity) is irradiated uniformly.

advanced algorithms can generally be configured to report $D_{m,m}$ or $D_{w,m}$, although some MC implementations define all materials as water and yield $D_{w,w}$. Each quantity has its advocates [3–6], but the consensus seems to move towards $D_{m,m}$ to maximise consistency [7]; therefore, we focused on $D_{m,m}$ in this study.

The approaches followed to calculate $D_{w,w}$ and $D_{m,m}$ yield different doses in different media because photon and electron interactions depend on atomic composition [8]. This affects radiation transport and energy deposition, introducing discrepancies within materials and at material interfaces. For soft tissues, $D_{w,w}$ and $D_{m,m}$ values are around 1% similar for a range of beam energies and depths [3], but discrepancies can be higher for other materials [8]. For cortical bone, $D_{m,m}$ doses are 4%-5% below $D_{w,w}$ [8,9], and the differences increase for other materials containing metal [10]. If several materials are involved, build-up and build-down regions exist at material interfaces that can only be correctly modelled by advanced algorithms [8,9,11,12].

Most TPSs use simple $D_{w,w}$ algorithms in plan optimisation for speed purposes. Still, computation improvements allow the introduction of more accurate algorithms, being feasible to optimise plans for $D_{m,m}$ in some systems. This is advantageous if the final plan is also calculated in $D_{m,m}$ because the whole process is consistent, and the results are more likely to fulfil the objectives [13,14]. However, the differential behaviour of $D_{w,w}$ and $D_{m,m}$ can affect the goal of delivering a uniform dose to the PTV to assure a homogeneous CTV dose in all circumstances. This is illustrated in Fig. 1, where a uniform photon energy fluence irradiates a PTV encompassing a homogeneous CTV and part of a bone heterogeneity. Assuming charged particle equilibrium exists, the resulting dose distribution is also uniform if a $D_{w,w}$ algorithm is considered since atomic composition is constant and dose is locally independent of density according to Fano's theorem [15]. However, if a $D_{m,m}$ algorithm is used, the dose response in the heterogeneity differs and the dose distribution is inhomogeneous. In a case like this, achieving a uniform $D_{m,m}$ distribution during optimisation would require introducing local fluence compensations in the heterogeneity, thus deviating from uniform fluence.

How to proceed in this situation when using $D_{m,m}$ needs to be clarified. There are two options: irradiate uniformly, or request homogeneous $D_{m,m}$ distributions to mimic previous planning based on $D_{w,w}$. The first option keeps clinical practice but implies accepting inhomogeneous $D_{m,m}$ distributions that are difficult to evaluate. The second option modifies patient irradiation and deviates from previous clinical practice, which can have clinical consequences in all treatment scenarios.

This work aimed to demonstrate that mimicking $D_{w,w}$ planning with $D_{m,m}$ to achieve homogeneous $D_{m,m}$ distributions can introduce new clinical and robustness issues to consider if atomic composition heterogeneities are involved.

2. Materials and methods

A head and neck case involving air, bone, teeth, and implants outside the CTV and partially inside the PTV was considered for illustration. No approval was required by our institutional ethics committee. Simultaneous integrated boost was delivered to three PTVs (54, 60, and 70 Gy) in 33 fractions. For clarity, we focused on the CTV_{70Gy}, the PTV_{70Gy} (5 mm margin), and the mandible (metal implants excluded) as organ-at-risk (OAR).

The planning process was performed in the Eclipse v15.6 TPS (Varian Medical Systems, Palo Alto, CA, USA). The AAA v15.6.05C/S algorithm and the Acuros XB (AXB) v15.6.05 GBBS algorithm were used to obtain the $D_{w,w}$ and the $D_{m,m}$ distributions, respectively, with 1 mm voxel size.

Depending on the algorithm, the medium characterisation of each CT image voxel is performed differently. AAA retrieves its electron density using a CT number-to-electron density table. AXB requires its mass density and atomic composition. The mass density is derived analogously, and is then linked to a material with a well-known composition specified in the AcurosXB-13.5 material library [16]. The library comprises several tissues for automatic assignment, each associated with a density range. Adjacent tissues present regions of overlapping densities which are modelled to change linearly from one tissue to another, thus providing a mixture that enables smooth transitions. The library also includes materials that users can assign manually.

Fig. 2 presents the case and the composition of each volume considered by AXB, provided by in-house software that emulated the AXB medium characterisation process.

2.1. Plan with uniform $D_{w,w}$ and plan with uniform $D_{m,m}$ in the PTV_{70Gy}

We optimised two plans with volumetric modulated arc therapy (VMAT) for a 6 MV photon beam from a Varian TrueBeam accelerator (Varian Medical Systems).

The first plan was optimised to irradiate the PTV uniformly. This could be done directly in Eclipse because it used a dedicated simple algorithm (MRDC) yielding $D_{w,w}$ to speed up the optimisation [16] and, consequently, the resulting plan used a uniform photon energy fluence to obtain homogeneous MRDC $D_{w,w}$.

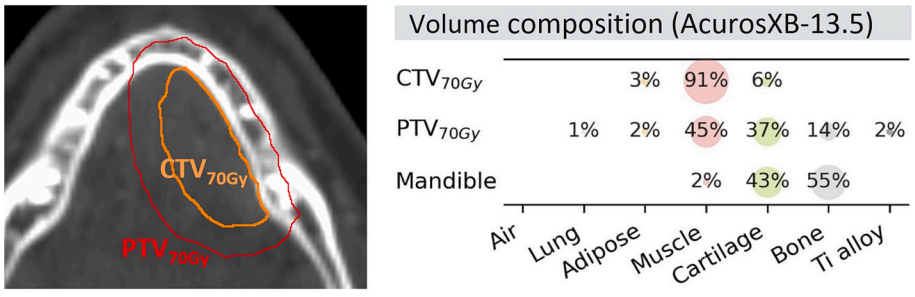

Fig. 2. Head and neck case used in this work. For each structure, percentages of each pure medium as considered in the Acuros XB v13.5 material table (densities in the overlapping regions decomposed into their pure components).

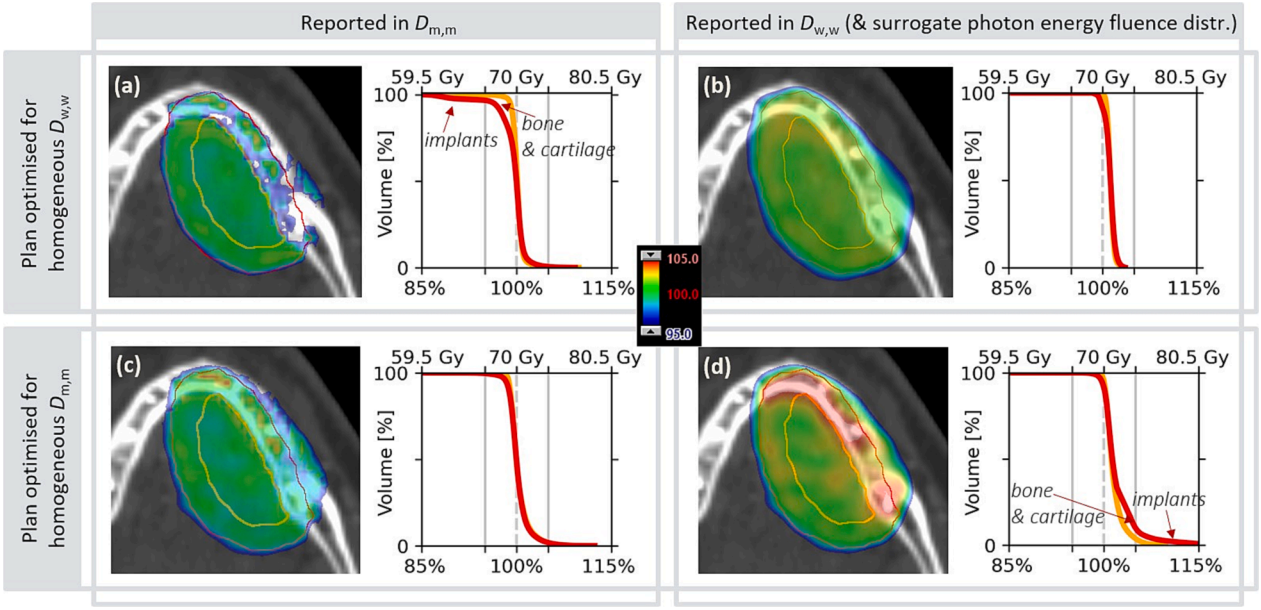

Fig. 3. $D_{m,m}$ and $D_{w,w}$ distributions, and DVHs for the target volumes (CTV_{70Gy} orange, PTV_{70Gy} red) for the plans with homogeneous $D_{w,w}$ (a)(b) and homogeneous $D_{m,m}$ (c)(d) in the PTV_{70Gy}. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The second plan was optimised to mimic previous $D_{w,w}$ distributions and achieve uniform $D_{m,m}$ in the PTV. This was done using Eclipse's "intermediate dose" option during optimisation [16]. This option allowed performing a more accurate calculation in one of the optimisation steps, computed the discrepancies with the distribution calculated by the internal $D_{w,w}$ algorithm at this step, and incorporated the voxel-by-voxel differences as penalties into the optimiser's cost function. Thus, if the intermediate dose calculation was performed with AXB $D_{m,m}$ and PTV dose homogeneity was requested in the objectives, the resulting optimised plan presented a homogeneous AXB $D_{m,m}$ in the PTV.

Both plans were calculated with AXB $D_{m,m}$ and normalised to the PTV_{70Gy} median dose. They were also calculated with AAA to analyse the differences with $D_{w,w}$-based clinical practice.

2.2. Plan analysis

The dose distributions were quantitatively evaluated in the nominal scenario for the target volumes using dose-volume-histograms (DVH) and the ICRU 83 reporting parameters [2]: near-minimum dose $D_{98\%}$, median dose $D_{50\%}$, near-maximum dose $D_{2\%}$, and homogeneity index $HI=(D_{2\%}-D_{98\%})/D_{50\%}$. A slice-by-slice visual inspection was also performed to investigate spatial correlations between dose and medium heterogeneities. These evaluations were done with reference to the detailed composition information provided in Fig. 2.

For the second plan with uniform $D_{m,m}$, we evaluated the clinical impact associated with its $D_{m,m}$ and $D_{w,w}$ distributions in the nominal scenario, and plan robustness [17]. Plan complexity was not considered as it is particularly useful when comparing plans, but there is only one in this case.

The clinical impact was evaluated in the nominal scenario by comparing target response and mandible toxicity predictions made by $D_{m,m}$ with those made by $D_{w,w}$ -for which most clinical experience was established-. For the target, we compared the DVHs for the CTV_{70Gy}. For the mandible, we compared the normal tissue complication probabilities (NTCP) estimated using the van Dijk et al. model for osteoradionecrosis [18] and several DVH-based parameters [19–22]: near-maximum dose $D_{2\%}$, dose to 30% of volume $D_{30\%}$, mean dose D_{mean}, and volume receiving at least 50 Gy V_{50Gy}.

Plan robustness was studied against setup errors [23]. The additional treatment scenarios consisted of rigid translational setup errors in both directions of the three Cartesian axes, and towards the nearest main heterogeneity (worst-case scenario). They were simulated by shifting 5 mm (CTV-PTV margin) the plan's isocenter, and the dose distributions were calculated in $D_{m,m}$. Plan robustness was quantified by the variations across scenarios of the dosimetric parameters mentioned above for the CTV_{70Gy}.

Additionally, we analysed the photon energy fluence distributions to facilitate the interpretation of the results. Their accurate computation requires MC calculations, but this is complex and involves external tools. In this study, we were more interested in unveiling fluence variations and their spatial correlation with medium heterogeneities than in accuracy. For this reason, we used the $D_{w,w}$ distributions as surrogates since, as their dose values are not sensitive to atomic composition heterogeneities, any $D_{w,w}$ inhomogeneity would correspond to actual fluence changes.

Table 1
Dosimetric parameters for the PTV_{70Gy}. Bold highlights values beyond acceptability criteria.

	Plan optimised for homogeneous $D_{w,w}$		Plan optimised for homogeneous $D_{m,m}$	
	$D_{m,m}$	$D_{w,w}$	$D_{m,m}$	$D_{w,w}$
$D_{98\%}$	**89.4%**	99.7%	97.5%	99.1%
$D_{50\%}$	100%	101.4%	100%	101.2%
$D_{2\%}$	106.5%	103.4%	104.9%	**111.4%**
HI	0.171	0.036	0.074	0.122

3. Results

Fig. 3 and Table 1 show the dose distributions, the DVHs, and the dosimetric parameters for the plans optimised to achieve homogeneous $D_{w,w}$ and homogenous $D_{m,m}$ in the PTV, both reported in $D_{w,w}$ and $D_{m,m}$.

3.1. Plan with uniform $D_{w,w}$ in the PTV

The optimisation resulted in a homogeneous $D_{w,w}$ distribution in the PTV_{70Gy} (Fig. 3(b)). If calculated in $D_{m,m}$ (Fig. 3(a)), the dose in the CTV_{70Gy} -consisting almost exclusively of muscle (Fig. 2)- was also

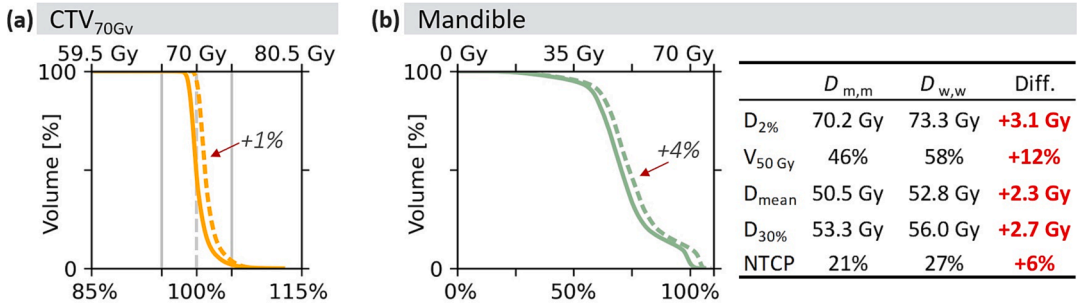

Fig. 4. Clinical impact for the CTV_{70Gy} (a) and the mandible (b) in the nominal scenario. Solid and dashed lines in the DVHs correspond to $D_{m,m}$ and $D_{w,w}$ distributions, respectively. For the mandible, the parameters associated with toxicity are presented and compared for each dose quantity.

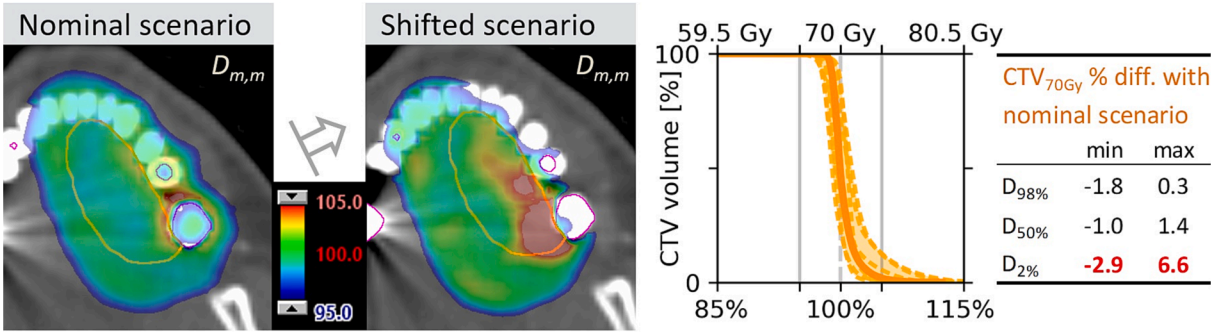

Fig. 5. CTV_{70Gy} robustness against setup errors. Metal implants contoured in pink. The DVH combines the DVHs of the nominal (solid) and shifted (dashed) scenarios. For each dosimetric parameter, the percentage differences between the nominal scenario and the scenarios where presented its minimum/maximum values are shown. Red highlights differences higher than 2%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

homogeneous. However, the PTV_{70Gy} presented cold regions of around −4% and −10% matching bone and metal implants, respectively. Due to the proportion of these materials in the volume, the DVH was distorted and some dosimetric parameters were affected, with $D_{98\%}$ well below 95% -and beyond classical acceptability criteria- and a low *HI* value.

3.2. Plan with uniform $D_{m,m}$ in the PTV

In terms of $D_{m,m}$ (Fig. 3(c)), the dose inhomogeneities of the previous plan were corrected and all dosimetric parameters were within planning objectives. Nevertheless, hot regions appeared if the dose distribution was calculated in $D_{w,w}$ (Fig. 3(d)), increasing $D_{2\%}$ and inhomogeneity above acceptability criteria. Visual inspection showed that these higher $D_{w,w}$ doses matched the location and value (although in the opposite direction) of the previous plan's lower $D_{m,m}$ regions. Interpreting the $D_{w,w}$ distribution as a surrogate of actual photon fluence energy distribution, this means that fluence increases locally in bone and metal to compensate for the lower $D_{m,m}$ values and achieve $D_{m,m}$ homogeneity.

The clinical impact in the nominal scenario is shown in Fig. 4. The CTV_{70Gy} received the prescribed dose homogeneously for $D_{m,m}$, but the corresponding $D_{w,w}$ values were around 1% higher systematically. For the mandible (metal implants excluded), $D_{m,m}$ values were about 4% lower than those of $D_{w,w}$ and all the dosimetric parameters associated with toxicity appeared to be lower. Taking as reference the values calculated with $D_{w,w}$, the toxicity risk was significantly higher than that predicted with $D_{m,m}$, and the NTCP was underestimated by up to 6%.

Lastly, CTV_{70Gy} robustness against setup errors is presented in Fig. 5. $D_{2\%}$ variations from the nominal scenario generally exceeded 2% and were as high as 6.6%. Assessing the scenarios slice by slice, we found that this lack of robustness was due to positional mismatches between the atomic composition heterogeneities and the corresponding fluence increases introduced during optimisation.

4. Discussion

Trying to mimic with $D_{m,m}$ the homogeneity of previous $D_{w,w}$ distributions seems natural. However, this should be done cautiously if the PTV composition is heterogeneous. The study was performed in Eclipse, but the conclusions should also apply to any TPS capable of optimising $D_{m,m}$ distributions obtained with MC, GBBS, or, to a lesser extent, Collapsed Cone $D_{m,m}$ implementations. To our knowledge, only Eclipse TPS currently allows this, but the increasing adoption of advanced algorithms and computational improvements will make it feasible in more TPSs in the future, as exemplified in Feygelman et al. [13].

The underlying cause behind the new issues is the dependence of $D_{m,m}$ values on medium atomic composition. If the PTV contains materials with different dose responses and homogeneity is requested, local fluence variations must be introduced to compensate for the different dose values in these media. The influence of material interface effects can be ignored as a first approximation since their extent is limited to a few mm and are smoothed out for typical voxel sizes [11]. Furthermore, the percentage of voxels affected in clinical practice is generally low, and abrupt transitions between materials are rare due to partial volume effects in the CT images (and in this study also because of the gradual mixture for nearby densities).

In any case, and as discussed in the literature, these compensations should be avoided [24–26]. On the one hand, they deviate from previous practice where fluence was homogeneous. Patients are irradiated differently, usually with higher doses as fluence needs to be increased in most media involved in radiotherapy planning. The clinical impact of these higher doses depends on whether they are located in the CTV or an OAR partially included in the PTV, thus increasing tumour control probability or toxicity risk, respectively. On the other hand, robustness is impaired if the fluence variations and their corresponding heterogeneities mismatch (Fig. 5). The impact of these issues depends on the type

and relative proportion of atomic composition heterogeneities. In this work, we used an illustrative case with a relatively high volume of non-water-like media in the PTV, but in clinical routine there is a wide variability in the proportions and their influence [10,24]. Nevertheless, all the problems described can occur, and their effects can be significant depending on the case. It is worth noting that they can be overlooked if plan analysis is performed solely based on the $D_{m,m}$ distribution, as is the case for the two works that study plans specifically optimised for $D_{m,m}$ algorithms [13,14]. More aspects should be analysed if this planning strategy is adopted.

As has been argued, plans with uniform irradiation are preferable for clinical and robustness reasons. However, they are neither straightforward to obtain nor to evaluate with $D_{m,m}$. Plan evaluation can be affected as $D_{m,m}$ inhomogeneities can alter the values of some dosimetric parameters beyond acceptability criteria. This way, it is hard to distinguish if a plan does not fulfil the objectives because of these effects or because it is not optimal. This problem also disturbs plan optimisation since it is driven by the evaluation of the dose distribution within each iteration using dosimetric instead of fluence-related parameters. As a result, the optimiser inevitably introduces the fluence compensations we try to avoid.

There are several approaches to solve this, although neither is optimal. Theoretically, robust optimisation would be the preferred option. Dispenses with PTV and should produce a more homogeneous fluence when necessary to reach a compromise between robustness and dose objectives. However, it is not available for photons in most TPSs, it increases optimisation time, and it is not well-established how robust evaluation should be performed.

Another possibility could be adapting ICRU criteria (minimum target dose, homogeneity, etc.) and optimisation objectives. Nevertheless, it is unclear how this could be done depending on the media involved and their relative amounts within volumes.

The most practical solution is to avoid $D_{m,m}$ sensitivity to medium composition. Various approaches can be used [11,12,25]: override the material, optimise and/or recalculate in $D_{w,w}$, or use the dose to reference-like medium ($D_{ref,m*}$). The first two options can compromise radiation transport accuracy. $D_{ref,m*}$ is a new quantity based on advanced algorithms that keeps radiation transport accuracy and whose values are not sensitive to medium atomic composition [14]. Its rationale is similar to that proposed by Reynaert [11] and, although it is not yet available in TPSs, $D_{ref,m*}$ is simple to implement.

Regardless of the planning strategy adopted, dose prescription and clinical response prediction are affected if the reference data is based on $D_{w,w}$. Targets usually present a water-like composition, and $D_{m,m}$ values are 1% lower. This difference is addressed in the AAPM TG-329 document [3] by decreasing the doses of $D_{w,w}$ algorithms (tuning the TPS configuration) to report dose-to-muscle values. If prescription doses are not rescaled accordingly, the doses received by patients are systematically 1% higher than before. For bony organs, the dose discrepancies increase up to 4% for cortical bone, and the risk of toxicity may be underestimated. Specific $D_{m,m}$ constraints should be used, or $D_{w,w}$ should be calculated for evaluation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] ICRU. ICRU Report 62, Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU 50). vol. os32. Bethesda, MD: 1999. 10.1093/jicru/os32.1.Report62.

[2] ICRU. ICRU Report 83: Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy (IMRT). Bethesda, MD: 2010. 10.1093/jicru/10.1.Report83.

[3] Kry SF, Feygelman V, Balter P, Knöös T, Ma C -M. C, Snyder M, et al. AAPM Task Group 329: Reference dose specification for dose calculations: dose-to-water or dose-to-muscle? Med Phys 2019:mp.13995. 10.1002/mp.13995.

[4] ICRU. ICRU Report 91, Prescribing, Recording, and Reporting of Stereotactic Treatments with Small Photon Beams. Bethesda, MD: 2017. 10.1007/s00066-018-1416-x.

[5] Gladstone DJ, Kry SF, Xiao Y, Chetty IJ. Dose Specification for NRG Radiation Therapy Trials. Int J Radiat Oncol Biol Phys 2016;95:1344–5. https://doi.org/10.1016/j.ijrobp.2016.03.044.

[6] Al-Hallaq HA, Chmura SJ, Salama JK, Lowenstein JR, McNulty S, Galvin JM, et al. Benchmark Credentialing Results for NRG-BR001: The First National Cancer Institute-Sponsored Trial of Stereotactic Body Radiation Therapy for Multiple Metastases. Int J Radiat Oncol Biol Phys 2017;97:155–63. https://doi.org/10.1016/j.ijrobp.2016.09.030.

[7] Kry SF, Lye J, Clark CH, Andratschke N, Dimitriadis A, Followill D, et al. Report dose-to-medium in clinical trials where available; a consensus from the global Harmonisation group to maximize consistency. Radiother Oncol 2021;159:106–11. https://doi.org/10.1016/j.radonc.2021.03.006.

[8] Andreo P. Dose to 'water-like' media or dose to tissue in MV photons radiotherapy treatment planning: still a matter of debate. Phys Med Biol 2015;60:309–37. https://doi.org/10.1088/0031-9155/60/1/309.

[9] Ma C-M, Li J. Dose specification for radiation therapy: dose to water or dose to medium? Phys Med Biol 2011;56:3073–89. https://doi.org/10.1088/0031-9155/56/10/012.

[10] Muñoz-Montplet C, Marruecos J, Buxó M, Jurado-Bruggeman D, Romera-Martínez I, Bueno M, et al. Dosimetric impact of Acuros XB dose-to-water and dose-to-medium reporting modes on VMAT planning for head and neck cancer. Phys Med 2018;55:107–15. https://doi.org/10.1016/j.ejmp.2018.10.024.

[11] Reynaert N, Crop F, Sterpin E, Kawrakow I, Palmans H. On the conversion of dose to bone to dose to water in radiotherapy treatment planning systems. Phys Imaging Radiat Oncol 2018;5:26–30. https://doi.org/10.1016/j.phro.2018.01.004.

[12] Jurado-Bruggeman D, Munoz-Montplet C, Vilanova JC. A new dose quantity for evaluation and optimisation of MV photon dose distributions when using advanced algorithms: proof of concept and potential applications. Phys Med Biol 2020;65:235020. https://doi.org/10.1088/1361-6560/abb6bc.

[13] Feygelman V, Latifi K, Bowers M, Greco K, Moros EG, Isacson M, et al. Maintaining dosimetric quality when switching to a Monte Carlo dose engine for head and neck volumetric-modulated arc therapy planning. J Appl Clin Med Phys 2022;23:e13572.

[14] Kamaleldin M, Elsherbini NA, Elshemey WM. AAA and AXB algorithms for the treatment of nasopharyngeal carcinoma using IMRT and RapidArc techniques. Med Dosim 2018;43:224–9. https://doi.org/10.1016/J.MEDDOS.2017.08.009.

[15] Andreo P, Burns DT, Nahum AE, Seuntjens JP, Attix FH. Fundamentals of ionizing radiation dosimetry. WILEY-VCH; 2017.

[16] Varian Medical Systems. Eclipse photon and electron algorithms reference guide. CA: Palo Alto; 2017.

[17] Hernandez V, Hansen CR, Widesott L, Bäck A, Canters R, Fusella M, et al. What is plan quality in radiotherapy? The importance of evaluating dose metrics, complexity, and robustness of treatment plans. Radiother Oncol 2020;153:26–33. https://doi.org/10.1016/j.radonc.2020.09.038.

[18] van Dijk LV, Abusaif AA, Rigert J, Naser MA, Hutcheson KA, Lai SY, et al. Normal Tissue Complication Probability (NTCP) Prediction Model for Osteoradionecrosis of the Mandible in Patients With Head and Neck Cancer After Radiation Therapy: Large-Scale Observational Cohort. Int J Radiat Oncol Biol Phys 2021;111:549–58. https://doi.org/10.1016/j.ijrobp.2021.04.042.

[19] Owosho AA, Tsai CJ, Lee RS, Freymiller H, Kadempour A, Varthis S, et al. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): The Memorial Sloan Kettering Cancer Center experience. Oral Oncol 2017;64:44–51. https://doi.org/10.1016/J.ORALONCOLOGY.2016.11.015.

[20] Aarup-Kristensen S, Hansen CR, Forner L, Brink C, Eriksen JG, Johansen J. Osteoradionecrosis of the mandible after radiotherapy for head and neck cancer: risk factors and dose-volume correlations. Acta Oncol 2019;58:1373–7. https://doi.org/10.1080/0284186X.2019.1643037.

[21] Kubota H, Miyawaki D, Mukumoto N, Ishihara T, Matsumura M, Hasegawa T, et al. Risk factors for osteoradionecrosis of the jaw in patients with head and neck squamous cell carcinoma. Radiat Oncol 2021;16. https://doi.org/10.1186/S13014-020-01701-5.

[22] Möring MM, Mast H, Wolvius EB, Verduijn GM, Petit SF, Sijtsema ND, et al. Osteoradionecrosis after postoperative radiotherapy for oral cavity cancer: A retrospective cohort study. Oral Oncol 2022:133. https://doi.org/10.1016/J.ORALONCOLOGY.2022.106056.

[23] Unkelbach J, Alber M, Bangert M, Bokrantz R, Chan TCY, Deasy JO, et al. Robust radiotherapy planning. Phys Med Biol 2018:63. https://doi.org/10.1088/1361-6560/aae659.

[24] Hardcastle N, Montaseri A, Lydon J, Kron T, Osbourne G, Casswell G, et al. Dose to medium in head and neck radiotherapy: Clinical implications for target volume metrics. Phys Imaging Radiat Oncol 2019;11:92–7. https://doi.org/10.1016/j.phro.2019.08.005.

[25] Sterpin E. Potential pitfalls of the PTV concept in dose-to-medium planning optimization. Phys Med 2016;32:1103–10. https://doi.org/10.1016/j.ejmp.2016.08.009.

[26] Jurado-Bruggeman D, Muñoz-Montplet C, Hernandez V, Saez J, Fuentes-Raspall R. Impact of the dose quantity used in MV photon optimization on dose distribution, robustness, and complexity. Med Phys 2022;49:648–65. https://doi.org/10.1002/MP.15389.