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Review Article

Report dose-to-medium in clinical trials where available; a consensus from the Global Harmonisation Group to maximize consistency

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ABSTRACT

Purpose: To promote consistency in clinical trials by recommending a uniform framework as it relates to radiation transport and dose calculation in water versus in medium.
Methods: The Global Quality Assurance of Radiation Therapy Clinical Trials Harmonisation Group (GHG; www.rtqaharmonization.org) compared the differences between dose to water in water ($D_{w,w}$), dose to water in medium ($D_{w,m}$), and dose to medium in medium ($D_{m,m}$). This was done based on a review of historical frameworks, existing literature and standards, clinical issues in the context of clinical trials, and the trajectory of radiation dose calculations. Based on these factors, recommendations were developed.
Results: No framework was found to be ideal or perfect given the history, complexity, and current status of radiation therapy. Nevertheless, based on the evidence available, the GHG established a recommendation preferring dose to medium in medium ($D_{m,m}$).
Conclusions: Dose to medium in medium ($D_{m,m}$) is the preferred dose calculation and reporting framework. If an institution's planning system can only calculate dose to water in water ($D_{w,w}$), this is acceptable.

To maximize the power of clinical trials, and to ensure results are broadly interpretable, it is essential that dose be calculated consistently across all participating institutions [1]. Clinical practice must also be consistent with the framework of clinical trials to ensure that patients maximally benefit from the results of trials. As current trials are often international, these issues need global consideration and endorsement. Therefore, the Global Quality Assurance of Radiation Therapy Clinical Trials Harmonisation Group (GHG; https://rtqaharmonization.org/) promotes uniform standards for clinical trials involving radiation therapy [2].

One inconsistency in radiation oncology is the medium in which radiation transport and dose deposition are calculated. While radiotherapy equipment is calibrated in terms of dose-to-water according to protocols such as TRS-398 [3], TG-51 [4,5], or the UK protocol [6,7], the corresponding dose calculation in the treatment planning system (TPS) is not consistent in terms of which medium is used and can be described either as dose to water or dose to medium.

The medium of radiation transport and dose deposition is only one difference between different algorithms that affects dose calculation accuracy. Different algorithms have different inherent accuracies [8–13], particularly at interfaces [14–17]. Nevertheless, the medium of transport and calculation remains substantially

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inconsistent across radiation oncology practice [18]. This topic is an issue of ongoing debate [19], and represents an opportunity for a more uniform solution. This report therefore focuses on this single issue of how to achieve the most consistency in terms of the medium of radiation transport and dose calculation.

This issue is most studied for megavoltage external photon beams and this report therefore focuses on this application. However, identical questions exist in relation to brachytherapy, particle beam therapy, or kV applications. Particularly as external beam therapy is often coupled with, or directly compared to, brachytherapy or particle beam therapies, the need for consistency in dose reporting between treatment modalities is clear.

Dose specification in radiotherapy

The medium for radiation transport and dose calculation is handled differently in different treatment planning systems. There are actually three separate quantities used to specify the dose:

1. Dose to medium, as implemented in some Superposition/Convolution (S/C) algorithms (including Monaco, Oncentra, and Pinnacle), the Grid Based Boltzmann Solver (GBBS; Acuros AXB), and most Monte Carlo (MC) algorithms (including Cyberknife, iPlan, Monaco, and Raysearch): dose to medium-in-medium, $D_{m,m}$.
2. Dose to water with variable electron density, as implemented in some S/C (including Xio, Raysearch, and Tomotherapy), as well as in the Anisotropic Analytical Algorithm (AAA), Pencil Beam (PB) algorithms, and one Monte Carlo implementation (ViewRay): dose to water-in-water, $D_{w,w}$.
3. Dose to water converted from dose to medium using post processing. This is implemented commonly with stopping power ratios (as in some MC) as the dose to a small Bragg-Gray cavity of water surrounded by the medium: dose to water-in-medium, $D_{w,m}$ [20].

These three different approaches are shown in Fig. 1. A review of how major commercial algorithms handle radiation transport and dose deposition is available in the AAPM TG-329 report [18].

Dosimetric differences

These three different approaches to dose calculation yield different doses in different media. It is worth noting that these differences do not arise because of differences in density: dose is energy deposited per unit mass and when density increases, both deposited energy and mass increase proportionally. Rather, this issue is about chemical composition and its impact on photon and electron interaction cross sections. Biological tissues are chemically different from water, and as such, dose deposition is different in these as compared to water.

Dose differences are illustrated in Fig. 2, which shows a percentage depth dose for a 6 MV photon beam with different slabs of material calculated with dose to medium ($D_{m,m}$) and dose to water ($D_{w,m}$ and $D_{w,w}$). Some things are immediately apparent: (1) None of the three options agree with each other, (2) the difference in dose is most pronounced for bone, (3) the $D_{w,w}$ algorithms show smooth behaviour at interfaces instead of the build-up and build-down regions that really exist, and (4) as is particularly evident in bone, $D_{w.m}$ can be further away from conventional dose to water ($D_{w,w}$) than the dose to medium ($D_{m,m}$) results. This last point is particularly interesting as $D_{w,m}$ was introduced mainly to reproduce historical $D_{w,w}$ results [20], which, in fact, it does not do [19,21,22].

1) Soft tissue

In soft tissue, the difference between $D_{m,m}$ and $D_{w,w}$ is systematic and relatively uniform in slab geometries: $D_{m,m}$ is lower than $D_{w,w}$ by 0.7% to 1.4% in megavoltage beams across a range of beam energies, depths, and different compositions of soft tissue and muscle [18]. Evaluations of clinical treatment plans found similar results, with an average difference in mean dose of 1.0–1.4% between $D_{m,m}$ and either $D_{w,w}$ or $D_{w,m}$ [23,24]. $D_{w,m}$ and $D_{w,w}$ were found to agree within 0.1% [24].

2) Lung

In lung, differences between $D_{m,m}$, $D_{w,m}$, and $D_{w,w}$ have been noted. In clinical lung plans, the D100 (i.e., the minimum target

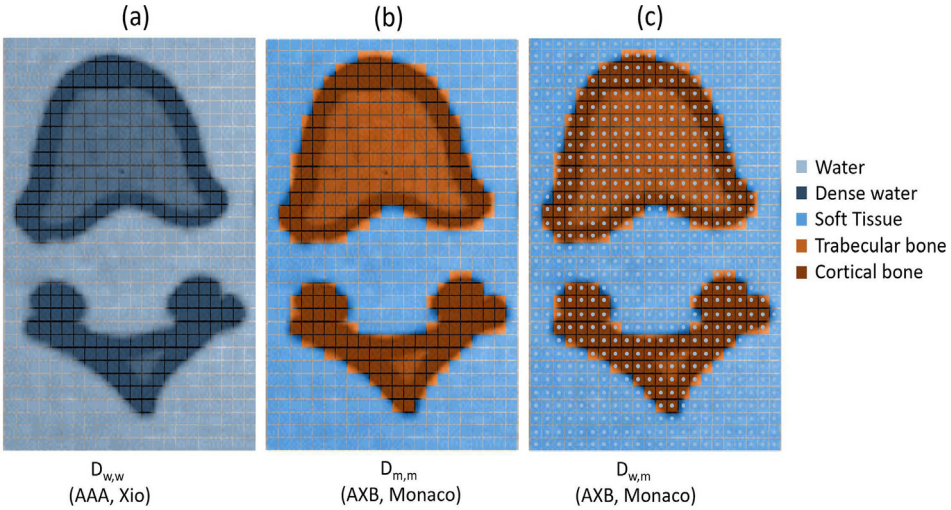

Fig. 1. Illustration of the different conceptual approaches used to calculate dose in a voxelized geometry for (a) a TPS calculating dose to variable density water ($D_{w,w}$), (b) a TPS calculating dose to the medium of each voxel ($D_{m,m}$), and (c) the conversion back to dose to water from the dose to medium using stopping power ratios ($D_{w,m}$).

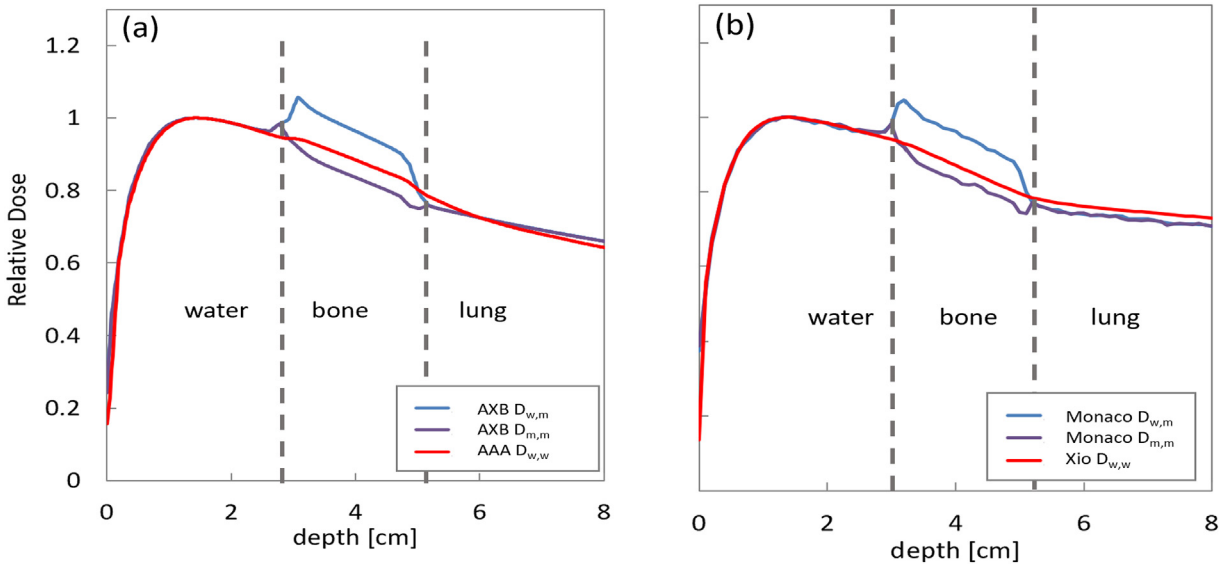

Fig. 2. The depth dose curves through slabs of different media with a 6 MV beam calculated with (a) Eclipse AcurosXB dose to water ($D_{w,m}$) and dose to medium ($D_{m,m}$) and AAA ($D_{w,w}$), (b) Monaco MC dose to medium ($D_{m,m}$) and dose to water ($D_{w,m}$) and Xio ($D_{w,w}$).

dose) was lower by 5% on average and target coverage was incomplete when plans originally calculated with AAA ($D_{w,w}$) were re-calculated with Acuros dose to medium ($D_{m,m}$); Acuros dose to water ($D_{w,m}$) and AAA ($D_{w,w}$) were statistically equivalent [25]. However, smaller effects were reported when less sensitive metrics were evaluated, such as D_{98} [26].

3) Bone

The most pronounced differences are seen in bone (as seen in Fig. 2), which can be relevant as a site of treatment or an organ at risk. In slab geometries involving dense bone, $D_{m,m}$ can be more than 10% less than $D_{w,m}$, with $D_{w,w}$ falling in between [21,22,27].

In clinical situations the effect is smaller. In head and neck plans, the $D_{m,m}$ (Acuros) average dose to bone was 2.4% lower than with $D_{w,w}$ (AAA), and 4.2% lower than with $D_{w,m}$ (Acuros) [24]. Clinical spine plans showed a difference in mean dose of only 2.9% on average (range: 1.7–4.2%) between $D_{m,m}$ and $D_{w,m}$ (Monte Carlo iPlan) [28]. Clinical prostate plans showed a difference in mean femoral head dose of 5.1% on average (range: 4.3–6.2%) between $D_{m,m}$ and $D_{w,m}$ [23]. As a relatively extreme clinical example, the cranium is part of the PTV for dermal sarcomas and the authors of this report found differences of approximately 8% in volumetric parameters depending on the dose specification. In general, the reduced impact of medium specification in clinical situations (2–8%) versus slab geometries (>10%) makes sense. Slab geometries tend to be based on dense cortical bone, whereas actual bone is typically less dense. This is accentuated in the clinic because many bone diseases, including plasmacytomas and several common metastases, are lytic (bone dissolving) [29], further reducing the density of bone and its difference with soft tissue. However, there are situations when the effect in a clinical situation may be more pronounced. For example, bisphosphonates may be given to patients to strengthen the bone [30] (which they do by increasing the density of the bone at the site of metastases). These mechanically strengthen the bone, but by doing so they may act to increase the dose ($D_{m,m}$) and act as a local radiation booster.

Using dose to bone in the TPS will predict a lower dose than dose to water (either $D_{w,m}$ or $D_{w,w}$) (as well as changing the fluence/dose optimization in intensity modulated radiotherapy [31]). Therefore, for the same calculated dose, the highest dose is actually delivered to the bone when $D_{m,m}$ is used, and the lowest dose is delivered to the bone when $D_{w,m}$ is used. A higher dose is likely to improve control of bone disease receiving curative intent [32] but could also increase the risk of side effects when bone is an organ at risk.

In addition to being the largest effect, bone is also a conceptually interesting case because it has a complex physical structure with varying densities of bone as well as marrow. A recent detailed Monte Carlo investigation found similar results between $D_{w,m}$ and $D_{m,m}$ for thoracic spine. For the cranium, $D_{w,m}$ was closest calculation of the actual bone marrow dose, suggesting a preference for $D_{w,m}$ [33]. However, other studies have reasoned that, based on current CT and TPS voxel resolution, the average voxel dose is best described by $D_{m,m}$ [22].

Considerations for clinical trials

While not a dramatically large issue, the choice of medium is an important question because it is a systematic issue that affects the dose calculation and reporting for all patients. The recent IAEA report on accuracy requirements emphasized that systematic dosimetric issues should be controlled at the 1–2% level [34]. This highlights that even the 1% difference between soft tissue and water is an important distinction that should be made uniform. There are reasons to prefer each of $D_{m,m}$ and $D_{w,w}$, and even $D_{w,m}$. In this section we review the merits and rationale for considering each.

1) Clinical and clinical trial experience

Clinical experience and the history of clinical trials is varied. In some regions (e.g., Europe, Australia) doses were intended as "to water", and dose response data and clinical experience are primarily based on dose to water. However, this is complicated because the S/C algorithms of Pinnacle, Oncentra, and Monaco inherently report $D_{m,m}$ (or at least are best described by $D_{m,m}$, [18]), so many of the dose-to-water data are, in fact, based on dose-to-medium. In contrast, North American clinical trials have always been defined as "dose-to-muscle" and dose response and clinical experience are based primarily on this framework. For algorithms that inherently calculated dose to water, the linac calibration was typically modified by 0.99 to produce a dose-to-muscle calculation

[18]. However, this was never applied consistently, or necessarily appropriately, as different algorithms inherently calculate dose differently [18]. In summary, it is hard to say that the global experience shows a preference for selection of $D_{m,m}$ versus $D_{w,w}$, although it does highlight the need for standardization. No trials or clinical experience has been intentionally based on a $D_{w,m}$ framework, although almost certainly some small subsets of $D_{w,m}$ data have been present.

2) Clinical significance

The dose difference between $D_{m,m}$ and $D_{w,w}$ is ~1% in soft-tissue. While this would not show an obvious clinical impact over a small number of patients, it may be relevant for a large number of patients, such as in a clinical trial [34] or indeed the broad clinical practice of radiation oncology. The dose difference in soft tissue is particularly relevant because the vast majority of clinical trials involve tumours and organs at risk that have a soft tissue nature. Therefore, there is considerable benefit to select a consistent, and most accurate, calculation of dose in soft tissue.

Dose to bone typically differs by 2 to 5% between $D_{m,m}$ and $D_{m,w}$, with $D_{w,w}$ falling inbetween. The magnitude of this difference is larger than the 1% in tissue, and in a clinical trial setting with a large number of patients it certainly represents a sizeable dose difference with the potential to perturb the outcome and add additional noise for bone-dependent outcomes. As discussed previously, the complexity of bone raises questions about what dose reporting framework makes most sense conceptually, and arguments have been made for $D_{m,m}$ [22] and $D_{w,m}$ [33]. While a $D_{w,m}$ approach may be conceptually appealing for bone marrow effects, other bone effects (e.g., fractures) may not be accurately captured by this framework. Also problematic is that soft-tissue would not be modelled as soft-tissue in such a framework, and additionally there is an absence of clinical experience or outcome data using $D_{w,m}$.

3) Coordination with established guidelines

Historically, recommendations have been varied. In 2007 the AAPM TG-105 report recommended that TPSs, when possible, should be able to calculate both $D_{m,m}$ and $D_{w,m}$ [20]. In 2010 the ICRU recommended a $D_{w,m}$ framework [35]. However, as the substantial differences between $D_{w,m}$ and $D_{w,w}$ became more apparent, more recent recommendations have shown a preference for the use of dose to medium. Both the NRG and TROG have endorsed reporting dose-to-medium for clinical trials ($D_{m,m}$) [36], which is also consistent with the AAPM TG-329 framework on this topic [18]. Given the increasingly international nature of clinical trials, there is a clear advantage in having a broadly unified framework.

4) Radiation transport

Most of the latest algorithms (Monte Carlo and GBBS) inherently transport radiation through the actual medium. This makes sense as it is conceptually the most coherent approach and is inherently the most accurate way to manage radiation transport. It also means that $D_{m,m}$ is directly calculated and available in the most advanced and accurate algorithms available. In contrast, converting this value to dose to water ($D_{w,m}$) is not an accurate representation of dose to water, nor is it consistent with historical "dose-to-water" values [21,22]. The dose-to-water frameworks ($D_{w,m}$ or $D_{w,w}$) do not take advantage of the most accurate dose calculation frameworks available.

5) kV conditions

While the dose differences between $D_{m,m}$ and $D_{w,w}$ are relatively small for megavoltage beams, this is not the case for energies in the kV range. Here differences greater than 5% are usual in soft tissue, and differences can exceed 100% in bone [37]. While kV is rarely used for treatment in clinical trials, it remains a clinically utilized modality, and it is a common energy for pre-clinical studies that can define trial design. Additionally, kV imaging beams are regularly used in image guidance procedures for megavoltage treatments and can, in some situations, contribute nontrivial doses to the treated volumes, including organs at risk [38]. Displaying the sum of the doses from imaging and treatment beams is desirable in the latter case and necessitates a consistent dose reference. When kV energies are employed, a $D_{w,w}$ approach should be expected to produce a substantially different dose than a $D_{m,m}$ framework. This application further emphasizes the need to standardize on the most accurate solution.

6) Measurement based validation of calculated doses

Measurements in water are the norm and standards are well established through calibration protocols and inter-compared regularly (Key Comparison Database, https://www.bipm.org/kcdb/). When water is the medium of interest, there is a direct link between measurement and calculation based on $D_{w,w}$. However, when the medium is not water (e.g., soft tissue or bone), direct measurement and validation are not well defined. For soft tissue, detectors have sometimes been calibrated in terms of dose-to-muscle by scaling the dose delivered to water by 0.99 [18]. While this provides a reasonable estimate of dose to muscle, there is clear room to improve this approach. There is less precedent for measurement of dose in bone, and effort is needed to improve the capacity and standardization for direct measurement in bone.

One solution could be for the TPS to calculate $D_{m,m}$ for patient calculations, but also calculate $D_{w,w}$ for validation measurements in a water phantom. Ideally, and particularly for credentialing for clinical trials, a more rigorous solution would employ quality assurance using an anthropomorphic phantom with measurements in non-water materials such as soft tissue, bone and lung. Such measurements are more complex but provide a closer approximation to true patient dosimetry. These measurements will require correction factors as detector calibrations currently relate to dose to water. Conducting such measurements and determining these factors first requires that a consistent approach to dose definition be established, which is the goal of this work.

Recommendations

Based on the above considerations, the following recommendations are made with the goal of improving the consistency of dose in clinical trial data and minimising uncertainty in the future. These recommendations are made with the understanding that no approach is 100% preferred over the others, but also that only one framework should be endorsed overall.

1. The Global Harmonization Group recommends calculating and reporting dose in a $D_{m,m}$ framework where possible.
2. Many algorithms do not allow the user to select the medium of dose calculation. In such a case, the user should report whatever is determined by the TPS, and $D_{w,w}$ is acceptable.
3. The GHG does not recommend conversion from $D_{m,m}$ to $D_{w,m}$.
4. For consistency, recommendations 1–3 should be broadly applied across modalities and treatments, including external beam therapy, but also in particle therapy, brachytherapy, and pre-clinical studies.

5. For the future, as vendors develop and refine their radiation transport and dose calculation frameworks, a $D_{m,m}$ framework should be implemented to maximize consistency.
6. The dose calculation framework, particularly if changes are made in clinical practice, should be documented and understood by all involved parties.

Implications and conclusion

These recommendations have implications for clinical trials as well as for clinical practice. Due to the inconsistent management of this issue at present, transitioning to a common $D_{m,m}$ framework will necessitate changes in the specifications for many future clinical trials, as well as clinical practice for many institutions.

For clinical trials, the proposed framework will provide standardization of dose reporting for future trials, and consequently will allow for clear interpretation of outcome data moving forward. Historical trial data for soft tissues will be substantially equivalent, and while historical trial data for bone may show differences, the historical data is not cleanly defined in terms of $D_{w,w}$ or $D_{m,m}$ (as described earlier) and therefore does not, at present, represent any form of standard on this issue.

In terms of clinical practice, the oncologist's clinical experience should substantially translate smoothly as the changes discussed here are small for the majority of clinical scenarios. The uncertainties from dose reporting, although not unimportant, are small compared to the biological uncertainties. The use of $D_{m,m}$ versus $D_{w,m}$ for clinical nasopharyngeal or lung patients results in minimal DVH differences in the target or organs at risk [39]. There is potential for clinically important differences for bony structures with doses already close to the tolerance limit. Such cases may require additional care. However, it should be noted that for most of the advanced algorithms (Monte Carlo or Acuros), there is no available calculation of $D_{w,w}$. A move away from an older $D_{w,w}$ algorithm will therefore produce a different result regardless of how the new algorithm is implemented, and so clinical re-evaluation would always be necessary. An interesting additional advantage of the $D_{m,m}$ framework presented here is that $D_{m,m}$ is actually numerically closer to $D_{w,w}$, and therefore represents a smaller change than to $D_{w,m}$.

The inconsistency in the medium in which dose deposition is calculated in radiation oncology can cause several percent of difference, particularly in tissues such as bone. Currently different TPSs have taken different approaches and calculate in differing ways. The Global Harmonization Group for QA in clinical trials proposes a consensus that, where available, dose-to-medium should be reported to maximize consistency.

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.

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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