Biological weighting of absorbed doses in proton and heavier ion-beam therapy: ICRU-IAEA recommendations on the isoeffect-dose concept.

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Abstract

Absorbed dose is an essential quantity in radiation therapy, and should be specified for all relevant points and/or volumes. In addition, treatment conditions should be reported as completely and accurately as possible in order to allow full understanding, interpretation and reconstruction (if needed) of the treatment. Besides absorbed dose, the clinical outcome depends on a number of other factors such as dose per fraction, overall treatment time, dose rate, instantaneous dose rate, dose homogeneity, radiation quality (RBE) and other technical or biological (e.g., degree of oxygenation) conditions. Therefore, when absorbed doses delivered under different conditions are compared or combined, weighting factors (functions) have to be applied to the quantity absorbed dose. This leads to the concept of "isoeffect absorbed dose".

The isoeffect dose $D_{IsoE}$ is the dose that delivered under reference conditions would produce the same clinical effects as the actual treatment, all other conditions being identical. One set of conditions have to be selected as the "reference". To facilitate exchange of information, in photons delivered in 2 Gy per fraction, in 5 daily fractions per week are recommended as the Standard Reference Conditions. The isoeffect dose $D_{IsoE}$ is thus the product of the absorbed dose (in Gy) and a weighting factor $W_{IsoE}$ which includes the effects of all parameters that could affect the clinical outcome:

$$D_{IsoE} = D \times W_{IsoE}.$$ 

As the isoeffect dose and the absorbed dose are both expressed in Gy, it is important to clearly specify to which quantity a given numerical value corresponds.

In fractionated external photon beam therapy, the dose per fraction and the overall time are the two main parameters that the radiation oncologist can adjust (they are included in $W_{IsoE}$). If the dose per fraction is altered the weighting factor for this parameter is evaluated using the linear-quadratic ($\alpha/\beta$) model, usually assuming that $\alpha/\beta$ is 3 Gy for late effects and 10 Gy for early effects. There is little information or agreement on how to account for changes in overall treatment time.

When reporting the $D_{IsoE}$ it is important to specify if the weighting is applied for differences in doses per fraction, overall times or both.
In proton-beam therapy, in addition to the parameters involved in photon-beam therapy, the $D_{isoE}$ depends on radiation quality (RBE). For protons, a generic RBE of 1.1 is assumed for current clinical conditions and thus $D_{isoE} = D_{RBE} = D \times 1.1$, all irradiation conditions (dose per fraction, overall time, etc.) being identical for protons and photons. $D$ and $D_{RBE}$ (the RBE-weighted absorbed dose) are both expressed in Gy. To avoid confusion Gy, followed by a space and the parenthetetical descriptor "(RBE)" should be used when specifying $D_{RBE}$. In proton-beam therapy, the term "equivalent dose" has been used in the past as the product of absorbed dose and a weighting factor accounting for differences in radiation quality ($W_{RBE}$), all other conditions (including fractionation and overall time) being the same for protons and photons. The unit has been designated the gray equivalent, GyE [or Gy(E)], or cobalt-gray equivalent (CGE). However, the concept of "equivalent dose" as defined by the ICRP applies to radiation protection only. "Equivalent dose" may be misleading as it is only relative to photons delivered under the same conditions as the protons. Furthermore, in the International System (SI) of units, no subscript or letter/symbol can be added to a unit. The symbol "GyE" is thus not permitted. The use of "equivalent dose", "GyE" and "CGE" and similar nomenclatures is discouraged. For heavier ions (e.g., C+) the situation is more complex than with protons as the RBE varies markedly with particle type, energy, method of production, depth in tissue, biological effect (e.g. early vs late effects), etc. However, the isoeffect dose concept can be applied as indicated above for other irradiation modalities: $D_{isoE} = D \times W_{isoE}$. The weighting factor $W_{isoE}$ includes all parameters that could affect the clinical outcome. It is important to stress that the effects of some parameters (e.g., dose per fraction) are significantly different for photons and ions. The actual and the reference irradiation conditions should thus both be specified completely. When photons are selected as the reference, fractionation may often be very different from the ion-beam irradiation. Similar to protons, the use of "equivalent dose" and "GyE" and "CGE" is discouraged.
Proton and carbon-ion beam therapy is a rapidly expanding field (see the two figures, courtesy Dan Jones). One can reduce the risk of toxicities (especially late toxicities) by allowing centres to take benefit from the experience gained in other centres mainly from the pioneers in the field. The benefit is particularly appreciable for the new centres entering the field, but it implies that the information is exchanged based on an agreement and consistent use of the involved quantities and units, and harmonization in concepts and terminology. This has always been one of the main goals of the ICRU (International Commission on Radiation Units and Measurements) since its creation in 1925.

For exchanging information and reporting, biological weighting of absorbed dose is necessary. The "Isoeffect-dose" concept is presented and discussed first for radiation therapy in general, and then applied to the specific issues in the field of proton and ion (C+) therapy.
**ABSORBED DOSE: A FUNDAMENTAL QUANTITY IN RADIATION THERAPY**

Absorbed dose is a fundamental and rigorously defined quantity [BIPM, 2006; ICRU, 1998]. Regardless of the type of radiation and biological system, the radiobiological and clinical effects are always related to the absorbed dose. For radiation oncology applications, the ICRU has always recommended that the absorbed ("physical") dose be reported at reference points and in relevant volumes, together with a complete description of the treatment conditions in order to allow full understanding, interpretation and reconstruction (if needed) of the treatment.

**OUTCOME, STAGING**

Scoring systems have been developed by international organizations (e.g., ESTRO, RTOG, EORTC, UICC) for evaluation of therapeutic success and side effects of the treatments. Recommendations have also been made for evaluating initial cancer extent ("staging") in order to avoid recruitment bias when interpreting the outcomes.
NEED FOR BIOLOGICAL WEIGHTING OF ABSORBED DOSE IN RADIATION THERAPY

Absorbed dose alone is in general not sufficient to predict the biological effect(s). The relation between absorbed dose and biological effect is not unique but depends on several factors including absorbed dose rate (and instantaneous dose rate), dose per fraction, overall treatment time (and other time/dose factors), radiation quality (LET), dose homogeneity (e.g., DVH), physiological conditions of the irradiated system and technical irradiation conditions (e.g., degree of oxygenation, temperature, etc.). Therefore, when comparing or combining treatments performed under different technical conditions, or when altering the treatment protocols or designing new protocols, weighting of the absorbed dose is necessary to ensure or compare ultimate biological effect. The weighting factors have to take into account ALL factors that could influence the clinical outcome, which in turn depends on the treatment protocols that are used.

The numerical values of these weighting factors (or functions) may vary significantly with the biological systems or effects considered (e.g., early or late effects, cancer induction, etc.). They may also be influenced by physiological conditions such as oxygenation, temperature, patient anemia, previous and/or concomitant chemotherapy, etc. that are known to affect the clinical outcome. This leads to the concept of "Isoeffect absorbed dose".
The isoeffect absorbed dose, $D_{\text{isoE}}$, is the absorbed dose that, delivered under the reference conditions would produce the same biological effect in a given system as the actual treatment, all other conditions being identical.

It is the product of the absorbed dose and a weighting factor $W_{\text{isoE}}$ which includes all factors that influence the biological effects. These factors could be related to the irradiation conditions and/or the biological system; they are in general not independent of each other (e.g., $\alpha/\beta$ depends on LET, and on early/late effects) $W_{\text{isoE}}$ is dimensionless, $D_{\text{isoE}}$ is thus expressed in Gy:

$$D_{\text{isoE}} = W_{\text{isoE}} \times D$$

The reference conditions are selected so that the isoeffect dose are related as closely as possible to the biological effects of clinical interest.
THE REFERENCE CONDITIONS

Each time two or more different treatment modalities are compared, one of them has to be selected as the reference modality and weighting factors have to be applied to the other ones.

However, in a general attempt to bring all radiotherapy reporting to a common treatment baseline when possible, Standard Reference Conditions are recommended: photons, 2 Gy per fraction, 5 fractions per week.

To avoid confusion, the reference conditions should always to be specified, especially when different from the Standard Reference conditions.

Differences or alteration in treatment modalities could be limited or important including:
● only an alteration in dose per fraction (e.g., in conformal photon-beam therapy).
● a change of several parameters: fractionation, radiation quality (RBE) (e.g., when comparing C+ beams and photons).
Justification/arguments for photons, 2 Gy per fraction, 5 fr per week:

- today and in the past widely this schedule is used for the majority of treatments.
- it is largely accepted by the radiation oncology community.
- relationships between dose and clinical outcomes are well established
- radiation oncologists are familiar with the numerical values associated with the clinical outcomes.

Limits of applicability of the Standard Reference Conditions

- IN THE FUTURE, and depending on the evolution of the radiation therapy technology, other Standard Reference Conditions may become more appropriate.

- FOR SPECIAL TECHNIQUES (such as treatment of uveal melanomas, stereotactic techniques, radiosurgery, permanent seed implants, administration of un-sealed sources), other reference conditions may be more appropriate. Of course, an agreement has to be reached between all centres applying these special techniques.
In external photon-beam therapy, the radiation oncologist can only adjust two main parameters: the dose per fraction and the overall treatment time (yellow). In proton and C+ beam therapy, the effects of variation of radiation quality (RBE) must also be taken into account (red). More important, the effects of these three factors (dose per fraction, overall time, LET) are not independent of each other ($\alpha/\beta$ depends on LET!). The situation is rather simple ion proton-beam therapy where the RBE does not vary by more than ~10%. In contrast for C+, large RBE variations (by a factor >5) have to be taken into account.
The ICRU and IAEA have recently jointly produced 3 reports on reporting proton and carbon-ion beam therapy:

IAEA-ICRU (International Atomic Energy Agency and International Commission on Radiation Units and Measurements), Dose reporting in ion-beam therapy, IAEA-TECDOC-1560, IAEA, Vienna, Austria, 2007


PREScribing, RECORDing, AND REPORTing PROTON-BEAM THERAPY

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Proton-beam therapy

In ICRU Report 78 it is recommended that a proton RBE $= 1.1$ be adopted for all clinically relevant applications ( "generic RBE"). However this generic value of 1.1 is not accepted universally: RBE $= 1.0$ is used in some centres.

Figure 2.5. (a) All RBE versus dose values for acute- and late-reacting experimental animal-tissue systems. The tissues studied include jejunal crypt cells, lung, skin (acute reaction and late contraction), vertebral growth, bone marrow, testis, lens, and tumor (Paganetti et al., 2002; reproduced with permission). (b, c) RBE versus absorbed dose for acute (b) and late (c) reactions in experimental animal-tissue systems. Data derived from (a) (Paganetti et al., 2002), supplemented with data from Kagawa et al. (2002).
A small RBE increase (~5-10 %) has been reported at the end of the spread-out Bragg peak. This small increase results in a range increase of 1-2 mm in the isoeffect absorbed dose. Its clinical relevance is still a matter of debate.
The proton RBE and its variation as a function of depth can be related to the microdosimetric spectra. The shift of the proton spectra relative to the gamma spectrum can explain the 10% increase in RBE. The small shift of the "\( y \)" spectra at the end of the spread out Bragg peak towards the high "\( y \)" value can explain the modest RBE variation.
Reporting proton-beam therapy

Situation # 1
If the proton absorbed dose \( (D) \) is delivered in the same conditions as the photon Standard Reference Conditions (2 Gy, 5 fr week), the proton iso-effect dose \( (D_{\text{isoE}}) \) or the RBE weighted dose \( (D_{\text{RBE}}) \) is simply:

\[
D_{\text{isoE}} = D_{\text{RBE}} = D \times 1.1
\]

As both the absorbed dose \( D \) and the isoeffect dose are expressed using the same unit gray (Gy) and to avoid confusion, the weighting is indicated by appending "RBE" clearly separated from the unit Gy i.e., "Gy\(_{(RBE)}\)".

Example, "for a given clinical situation, the prescribed absorbed dose is: \( D = 63 \text{ Gy} \) and \( D_{\text{isoE}} = D_{\text{RBE}} = 70 \text{ Gy\(_{(RBE)}\)} \) or more explicitly (RBE=1.1)

*The SI (International System of Units, see figure), does not accept any subscript, letter or sign added to a unit symbol. The units and symbols GyE [or Gy(E)] (gray equivalent) or CGE (cobalt-gray equivalent) can thus not be recommended by the ICRU or IAEA.*
Situation # 2

If the protons are NOT delivered in the same conditions as the photon Standard Reference Conditions (2 Gy, 5 fr week), a weighting factor has to be applied for the differences in dose per fraction and overall time in addition to 1.1 for RBE.

Example: \[ D_{\text{IsoE}} = D \times W_{(1.1; \alpha/\beta=3; d=0.5)} = 70 \text{ Gy}_{\text{(IsoE)}} \] or \( (\text{IsoE}_{1.1, \alpha/\beta = 3, d=0.5}) \) assuming \( \alpha/\beta = 3 \text{ Gy} \) for a difference in dose per fraction, 0.5 Gy per day for a difference in overall time, relative to the Standard Reference Conditions for photons:
Heavier ions (C+) beams

For heavier ions (e.g., C+), the situation is more complex than with protons as the RBE varies markedly with particle type, energy, method of beam production, depth in tissues, biological effects (e.g. early vs late), etc.

RBE variation as a function of depth in the C+ beam at Chiba, $^{60}$Co is the reference radiation. The experiments were performed by John Gueulette using intestinal crypt cell regeneration as the biological system.
Isoeffect dose for C+ beams

The isoeffect dose concept is similarly applied for C+ as for protons: $D_{\text{isoE}} = D \times W_{\text{isoE}}$

The weighting factor $W_{\text{isoE}}$ includes all parameters that could affect the clinical outcome. A source of confusion when reporting C+ therapy is often the reference conditions:

- in some reports, $D_{\text{isoE}}$ is expressed relative to the photons delivered in the Standard Reference Conditions.
- in other reports, $D_{\text{isoE}}$ is expressed as a function of depth in tissues.

Fractionation for C+ beams is often very different to that of photons but the influence of the dose per fraction is smaller for high LET (as shown by radiobiological experiments and reported at several occasions by Tsujii based on his clinical experience). Few information is available about the effect of overall treatment time.

An RBE of 3, relative to gamma, at the ~centre of the SOBP is based on the neutron clinical experience in Chiba (same LET → same RBE). Strictly speaking the RBE of 3 is at the end of the SOBP. The RBE variation as a function of depth (relative to 3.0 at the centre of the SOBP) is based on a series of radiobiological experiences performed at Chiba.
Other terminologies, quantities and units

The reference conditions
Other reference conditions have been proposed to those of photons delivered in 2 Gy per fraction and 5 fractions per week.

Biologically Effective Dose, BED
The concept of Biologically Effective Dose (BED) has been proposed for comparison and normalization of therapeutic protocols. It is the “hypothetical” total dose that, delivered with an infinitely large number of infinitesimally small dose fractions in a short time, would produce the same effect, in a given system, as the actual fractionation.
In the present report, BED is not recommended as an alternative to the Standard Reference Conditions (2 Gy/5 fractions a week): it is indeed important (and safer) that the majority of radiation oncologists be familiar with outcomes resulting from various dose levels (numerical values) using Standard Reference Conditions which is not the case with BED [Joiner & van der Kogel, Basic clinical radiobiology, ESTRO, 4th edition, 2009].

Equivalent Dose in 2 Gy Fractions, EQD2
The EQD2 (Equivalent Dose in 2 Gy fractions) [Joiner and Bentzen, 2009] is the weighted absorbed dose for an alteration of the dose per fraction, relative to a dose per fraction of 2 Gy. All other conditions, including overall time, are unchanged.

Numerically, EQD2 and the isoeffect dose weighted for an alteration of the dose per fraction are identical i.e., EQD2 and \( D_{\alpha\beta=3} \) or \( D_{\alpha\beta=10} \) (with \( d=2 \text{ Gy} \)) are thus equal depending whether late effects or early effects on normal tissues are considered (\( d \) is the absorbed dose per fraction).
In the SI system, EQD2 cannot be used as a unit symbol. There is a problem with the term “equivalent” (see below).
**Equivalent and effective dose in proton and C+ therapy**

The concepts of equivalent dose and effective dose have been introduced by the ICRP for radiation protection purposes. They were included in several national and international regulations.

**Equivalent dose in radiation protection**

The "equivalent dose", \( H \), has been introduced to take into account the differences in "effectiveness" (at equal dose) of different radiation qualities for occupational exposure in radiation protection [ICRP 1991, 2008; ICRU 1993].

The equivalent dose (in sievert, Sv) is the product of absorbed dose and a radiation weighting factor \( w_R \) defined by the ICRP.

\[
H = D \times w_R
\]

**Effective dose in radiation protection**

The "effective dose", \( E \), has been introduced to take into account the differences is susceptibility of different tissues or organs to cancer induction at low dose.

The effective dose (in sievert, Sv) is the sum of the products of the mean equivalent organ dose and a tissue weighting factor \( w_T \) defined by the ICRP.

\[
E = \sum ( H \times w_T )
\]

The factors \( w_R \) and \( w_T \) have been selected based on a scientific consensus taking into account mainly cancer induction at low dose in the context of occupational exposure.

To avoid confusion, the term "equivalent" and "effective" dose cannot be used in *therapy* for the weighted absorbed dose (Isoeffect). In addition, the term equivalent could suggest a kind of "general equivalence" while, in therapy applications, the equivalence stands only for well-defined conditions. Adding "therapy" to the term equivalent or effective is not practical and does not avoid the risk of confusion.

**Finally**, the symbols GyE, Gy(E) and CGE are not permitted in the SI system.
CONCLUSIONS

Absorbed dose

For reporting radiation therapy and exchanging information in a relevant and useful way, the ICRU and the IAEA recommend that the (physical) absorbed dose, \( D \), always be reported at reference points and in relevant volumes, together with a complete technical description needed for understanding and interpreting the prescription and if needed for reproducing the applied technical and dosimetric procedures.

"Isoeffect absorbed dose" \( D_{\text{isoE}} \): Biological weighting of absorbed dose

When comparing or combining treatments performed under different conditions, weighting of the absorbed dose is necessary. The weighting factor \( W_{\text{isoE}} \) should include ALL factors that could influence the clinical outcome, in particular, dose per fraction, overall time and radiation quality. The isoeffect dose is the product \( D_{\text{isoE}} = D \times W_{\text{isoE}} \); it is expressed in gray (Gy).

The numerical values of these weighting factors (or functions) may vary significantly with the biological systems or effects (e.g., early or late effects, cancer induction, etc.) and the physiological conditions.

*The isoeffect doses can be compared and combined; they are additive.*

The reference conditions and the Standard Reference Conditions

When treatments performed under different conditions are compared, one of them has always to be selected as the reference. Biological weighting factors have to be applied to the other ones. In a general attempt to bring all radiotherapy reporting to a common treatment baseline when possible: it is recommended to select as

*Standard Reference Treatment Conditions: photons, 2 Gy per fraction and 5 fractions per week.*
Proton and C+ beam therapy: RBE, quantities, units and symbols

In current photon-beam therapy two parameters (dose per fraction and overall time) are adjusted by the radiation oncologist. In proton and C+ therapy, the radiation quality (RBE) has also to be taken into account and it can alter the influence the two other parameters.

**For protons,**
a generic RBE of 1.1 is assumed for current clinical applications. If irradiation conditions (dose per fraction, overall time, etc.) are identical for protons and photons, the Isoeffect absorbed dose $D_{\text{isoE}}$ is the same as the RBE-weighted absorbed dose $D_{\text{RBE}}$.

$$D_{\text{isoE}} = D_{\text{RBE}} = D \times 1.1.$$  

**For C+,**
the isoeffect dose concept can be applied similarly as for protons, the weighting factor $W_{\text{isoE}}$ including ALL parameters that could affect the clinical outcome.

$$D_{\text{isoE}} = D \times W_{\text{isoE}}$$

**For protons and C+,**
$D$ and $D_{\text{isoE}}$ are both expressed using the same unit: the gray. To avoid confusion, each time "Gy" relates to an isoeffect dose, the symbol Gy is followed, after a space, by (IsoE) in parentheses.

For example:

$$D_{\text{isoE}} = 70 \text{ Gy_(IsoE)}$$

*The SI (International System of Units), does not accept any subscript, letter or sign added to a unit symbol. The units and symbols GyE [or Gy(E)] (gray equivalent) or CGE (cobalt-gray equivalent) can thus not be recommended by the ICRU or IAEA.*

Finally, for new techniques such as proton and C+ therapy, exchanging the clinical experience and reporting the treatments in a harmonized way may contribute to reduce the complication risk.