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*INVITED PAPER*

# THE RBE ISSUES IN ION-BEAM THERAPY: CONCLUSIONS OF A JOINT IAEA/ICRU WORKING GROUP REGARDING QUANTITIES AND UNITS

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**This paper summarises the conclusions of a working group established jointly by the International Atomic Energy Agency (IAEA) and the International Commission on Radiation Units and Measurements (ICRU) to address some of the relative biological effectiveness (RBE) issues encountered in ion-beam therapy. Special emphasis is put on the selection and definition of the involved quantities and units. The isoeffective dose, as introduced here for radiation therapy applications, is the dose that delivered under reference conditions would produce the same clinical effects as the actual treatment in a given system, all other conditions being identical. It is expressed in Gy. The reference treatment conditions are: photon irradiation, 2 Gy per fraction, 5 daily fractions a week. The isoeffective dose $D_{IsoE}$ is the product of the physical quantity absorbed dose $D$ and a weighting factor $W_{IsoE}$. $W_{IsoE}$ is an inclusive weighting factor that takes into account all factors that could influence the clinical effects like dose per fraction, overall time, radiation quality (RQ), biological system and effects. The numerical value of $W_{IsoE}$ is selected by the radiation-oncology team for a given patient (or treatment protocol). It is part of the treatment prescription. Evaluation of the influence of RQ on $W_{IsoE}$ raises complex problems because of the clinically significant RBE variations with biological effect (late vs. early) and position in depth in the tissues which is a problem specific to ion-beam therapy. Comparison of the isoeffective dose with the equivalent dose frequently used in proton- and ion-beam therapy is discussed.**

## INTRODUCTION

The relative biological effectiveness (RBE) of ion-beams, relative to photons, is significantly different from unity and, in addition, is not a fixed value but varies, to a large extent, with factors such as dose per fraction, biological system and effect, particle type and energy and depth in the tissues [changes in radiation quality (RQ)]. These factors are not independent of each other: for example, as RBE increases with increasing ion linear energy transfer (LET) the effects of fractionation decrease. Therefore, in ion-beam therapy, when selecting an absorbed dose weighting factor to account for the RBE, it is important to specify and report for which conditions this weighting factor has been selected.

It is also important, when reporting ion-beam therapy, to use the same approach and concepts and, whenever possible, the same definitions and terminology as that used for conventional photon-beam therapy to minimise confusion.

This paper summarises the conclusions of a working group established jointly by the International Atomic Energy Agency (IAEA) and the International Commission on Radiation Units and Measurements (ICRU) to address some of the RBE issues encountered in ion-beam therapy. Special emphasis is put on the selection and definition of the involved quantities and units.

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## ABSORBED DOSE, $D$ AND ISOEFFECTIVE DOSE, $D_{IsoE}$

### Absorbed dose

Absorbed dose is a rigorously defined quantity used to quantify the exposure of humans, biological systems and any type of material to ionising radiation[1,2]. It is a fundamental quantity for radiation therapy, protection and radiobiology. It is expressed in joule per kilogram. The special name of the unit is gray: $1\ Gy = 1\ J\ kg^{-1}$.

Regardless of the type of radiation and the nature of the biological system and effect, the radiobiological and clinical effects are directly related to the quantity absorbed dose.

However, absorbed dose alone is not sufficient to estimate the complete biological effect.

### Weighting of absorbed dose

Even when observing a single biological system and effect, the relation between absorbed dose and radiobiological effect is often not unique but may depend on several factors including: absorbed dose rate, absorbed dose per fraction, overall time (and other time per dose relations), RQ and irradiation conditions (e.g. degree of oxygenation, temperature, etc.).

Therefore, in radiation therapy, when exchanging clinical information and when comparing or combining treatments performed under different technical conditions, weighting of the absorbed dose is necessary to describe the ultimate biological effect. Hence, it is necessary to introduce weighting factors (or functions)[3].

### Reference treatment conditions

This weighting implies the selection of reference treatment conditions. The suggested reference treatment conditions are: photon irradiation (energy between 1 and 30 MV), 2 Gy per fraction, 5 daily fractions per week. The overall time is then ~6–7 weeks for radical treatment.

The selection of these reference conditions is widely accepted by the radiation-therapy community. It is justified by the fact that these treatment conditions have been and are largely used, as the standard for the majority of the patients. Moreover, the relationship between absorbed dose and the observed clinical effects is well established for fractionated photon-beam therapy.

The fraction dose of 2 Gy typically refers to the dose at the ICRU reference point at the centre of the planning target volume (PTV). With the 'classical' irradiation techniques, the dose at that point is, in general and to a large extent, representative of the dose to the PTV. However, with modern techniques (and in particular intensity modulated radiation therapy, IMRT), the dose distribution in the PTV is frequently not homogeneous. Moreover, outside the PTV, the dose to the normal tissues is largely non-homogeneous often with steep dose gradients. Therefore, it is important to be able to correlate the 'clinical equivalence' of the actual non-homogeneous doses with homogeneous doses. For that purpose, a concept like EUD (equivalent uniform dose) may be useful.

For special techniques (such as treatment of uveal melanoma or radiosurgery), other reference conditions may be more appropriate. They should be clearly defined and an agreement has to be reached between all centres participating in a given collaborative study.

Having selected the reference conditions, one can define the concept of isoeffective dose (Figure 1).

### Isoeffective dose, $D_{IsoE}$

The isoeffective dose is the dose that, delivered under the reference conditions (photons, 2 Gy $fr^{-1}$, 5 fr $w^{-1}$, see section 'Reference treatment conditions'), would produce the same effects as the actual treatment in a given system, all other conditions being identical. It is expressed in Gy.

### Isoeffective dose weighting factor, $W_{IsoE}$

The isoeffective dose weighting factor $W_{IsoE}$ is the ratio between the isoeffective dose and the absorbed

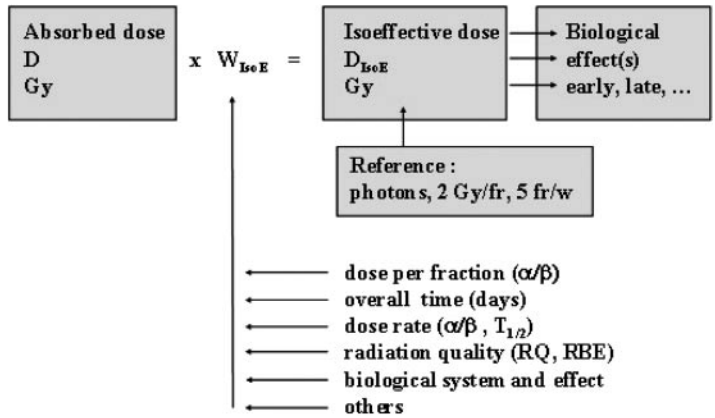


Figure 1. The figure illustrates the relation between absorbed dose and isoeffective dose in radiation therapy. The isoeffective dose $D_{IsoE}$ is obtained by multiplying the absorbed dose $D$ by a weighting factor $W_{IsoE}$ which takes into account all factors, listed in the figure, that may influence the clinical effects. The isoeffective dose is defined relative to the reference conditions: photon irradiation, 2 Gy per fraction, 5 daily fractions per week. The relations between clinical effects and dose are best established for these reference conditions.

dose. It is dimensionless and given by:

$$W_{\mathrm{IsoE}} = D_{\mathrm{IsoE}}/D$$

$W_{\mathrm{IsoE}}$ is an inclusive weighting factor that depends on the biological system and endpoint; it includes the effects of multiple variables such as absorbed dose, dose rate, dose per fraction, RQ and other irradiation conditions known to affect the clinical outcome (as illustrated in Figure 1). "IsoE" is written as a subscript or, eventually, can be written in parentheses: $W_{\mathrm{IsoE}}$ or $W$(IsoE) and $D_{\mathrm{IsoE}}$ or $D$(IsoE).

## WEIGHTING OF ABSORBED DOSE AS CURRENTLY PRACTICED IN RADIATION THERAPY

Weighting of absorbed dose is currently performed in fractionated external photon-beam therapy and in photon brachytherapy.

### Fractionated external photon therapy

The influence of changing dose per fraction on the effects on tumour and normal tissues is well documented and, when a non-conventional fractionation is used, a weighting factor has to be applied to the absorbed dose to allow for the related difference in biological effect.

In the present case, this weighting factor is based on the linear-quadratic ($\alpha/\beta$) model of cell survival [see review by Hall[4]]. When a non-conventional fractionation is used, in order to obtain the same clinical effect as with 2 Gy per fraction, the weighting factor, $W_{\alpha/\beta} = D'/D$, can be derived from the equation:

$$D[1 + d/(\alpha/\beta)] = D'[1 + d'/(\alpha/\beta)]$$

where $D$ and $D'$ are the total doses, and $d$ and $d'$ are the doses per fraction for the 'reference' fractionation and the actual fractionation, respectively. In the absence of more specific information the ratio $\alpha/\beta$ is currently taken to be equal to 3 Gy for late responding tissues, and 10 Gy for early responding tissues[4]. It is often assumed that for many tumours, the ratio $\alpha/\beta$ is the same as for early responding tissues.

The product, $D_{\alpha/\beta} = D' W_{\alpha/\beta}$, expressed in Gy, is the isoeffective dose for the modified fractionation scheme (all other conditions being equal). Subscripts (e.g. $D_{\alpha/\beta\,=\,3}$ or $D_{\alpha/\beta\,=\,10}$) may be useful to indicate whether the dose weighting is done for late or early effects, and to avoid confusion between the (physical) absorbed dose and the isoeffective dose, both being expressed in Gy[5]. $D_{\alpha/\beta}$ is the isoeffective dose, $D_{\mathrm{IsoE}}$, if all other factors, except dose per fraction, are equal.

### Modern brachytherapy: high dose rate (HDR) and pulsed dose rate (PDR) photon irradiation

In brachytherapy, there is a dramatic increase in the use of high dose-rate (HDR) and pulsed dose-rate (PDR) techniques.

While brachytherapy is outside the scope of this paper, a brief mention of the use of weighting factors in brachytherapy is included to stress two points:

- There is an increasingly broad agreement to select the same reference conditions to define the isoeffective dose as in external beam therapy: photon irradiation, with 2 Gy per fraction, 5 fractions a week.
- The selection of the weighting factors is based on the linear-quadratic model as in external photon beam therapy and the same numerical values for the $\alpha/\beta$ ratios are selected for early and late effects.

In practice, in brachytherapy, weighting factors have to be established for the various dose rates, fraction sizes and duration, fraction numbers and separation between fractions. An issue, specific to brachytherapy, is related to cell repair processes during the fractions or incomplete repair between the fractions, depending on the technique used. Therefore, the half-time $T_{1/2}$ for repair kinetics has to be taken into account. The assumption $T_{1/2} = 1.5$ h is widely accepted for most clinical conditions (but with larger uncertainty than the $\alpha/\beta$ values)[6,7].

For HDR applications, the treatment is delivered using a few large fractions. When the duration of these fractions is significant compared to $T_{1/2}$, repair during the fractions needs to be taken into account. For PDR applications, incomplete repair may occur between the numerous small fractions when the interval is as short as 1–4 h. When interpreting the clinical outcomes, the similarities listed above should not diminish consideration of the huge differences in dose distribution between external beam therapy and brachytherapy.

### Influence of overall time

In some specific external photon beam protocols and in many particle-beam therapy protocols, there is a reduction in the overall treatment time, i.e. the time interval between the first and the last fraction. For the same dose, a reduction in the overall time increases the effects of the irradiation in both tumours and normal tissues. A reduction in the overall time prevents tumour cell proliferation during the course of the treatment. On the other hand, it does also prevent cell proliferation in early responding normal tissues and thus reduces their tolerance for acute effects. Selecting the overall time is thus a compromise between improving or decreasing tumour

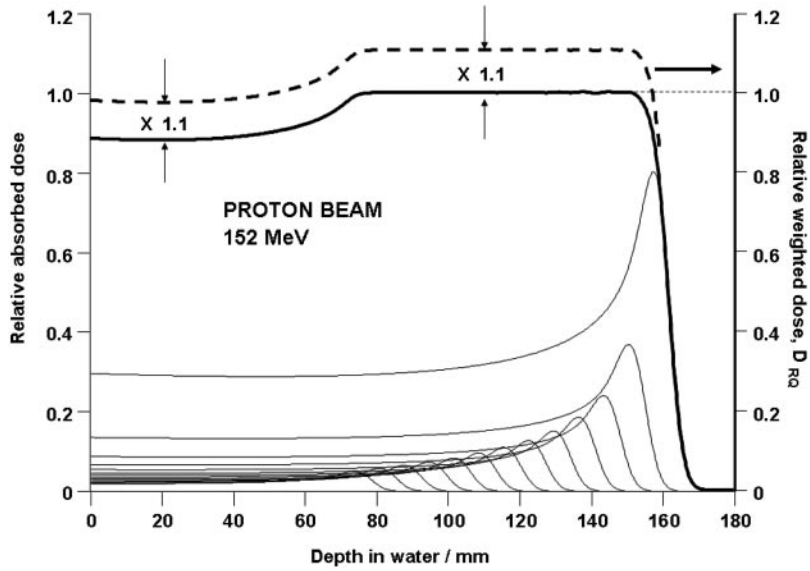


Figure 2. Variation in depth of absorbed dose, $D$ (full line, left ordinate) and dose weighted for radiation quality, $D_{RQ}$ (dotted line, right ordinate) for a 152 MeV proton beam. The dose weighted for radiation quality is obtained assuming a weighting factor $W_{RQ} = 1.1$ at all depths, protons being delivered with the same fractionation conditions and overall time as photons. The figure illustrates how a flat SOBP is obtained by an adequate combination of different proportions of protons of different energies. (Courtesy J.Gueulette and IBA.)

control and increasing or reducing the acute effects in early responding normal tissues. The influence of overall time is complex and a thorough discussion of this issue is outside the scope of this paper. Useful information can be found in Refs. (4,8,9).

## WEIGHTING OF ABSORBED DOSE IN PARTICLE-BEAM THERAPY: THE RBE ISSUES

In photon radiation therapy, the isoeffective dose weighting factor ($W_{IsoE}$) accounts mainly for the effects due to differences in dose per fraction, overall treatment time and interval between fractions. In particle beam therapy, in addition, differences in RQ have to be taken into account.

### Proton-beam therapy

Most radiobiological data agree that RBE = 1.1 for proton beams compared to photon beams in typical irradiation conditions for the biological systems relevant in therapy[10–12]. Clinical observations are in general compatible with these radiobiological data. Therefore, there is a strong tendency in the proton-beam therapy community to adopt a 'generic' RBE value of 1.1 for the proton-beam applications when comparison is made to photon irradiation given in equal numbers of fractions. Figure 2 compares the variation in depth of absorbed dose and weighted dose for RQ assuming $W_{RQ} = 1.1$ at all depths.

However, two issues require consideration. Their clinical relevance is a matter of debate. Firstly, most of the radiobiological data show an RBE increase of 5–10% (>1.1) in the distal part of the spread-out Bragg peak (SOBP). Secondly, because of the significant increase in LET at the extreme end of the proton tracks, the 'biological effective range' of the proton beam is increased in depth compared to the physical range. This increase reaches ~1–2 mm for ~100–200 MeV beams, respectively. The microdosimetric spectra measured at four depths in a proton beam are compared in Figure 3: there is a progressive shift of the spectra towards the high $y$ values in depth[13–15]. It could explain the increase in RBE observed at the distal part of the SOBP.

### Ion-beam therapy

In ion-beam therapy, selection of the RQ weighting factor $W_{RQ}$ is a more complex issue for two reasons. First, there are clinically significant variations of RBE as a function of dose and biological effect (e.g. late vs. early) as observed for all high-LET radiations (e.g. fast neutrons). A second issue, that is specific to ion-beam therapy, is the large RBE variation as a function of particle type and particle energy spectrum and as a function of depth in the tissues.

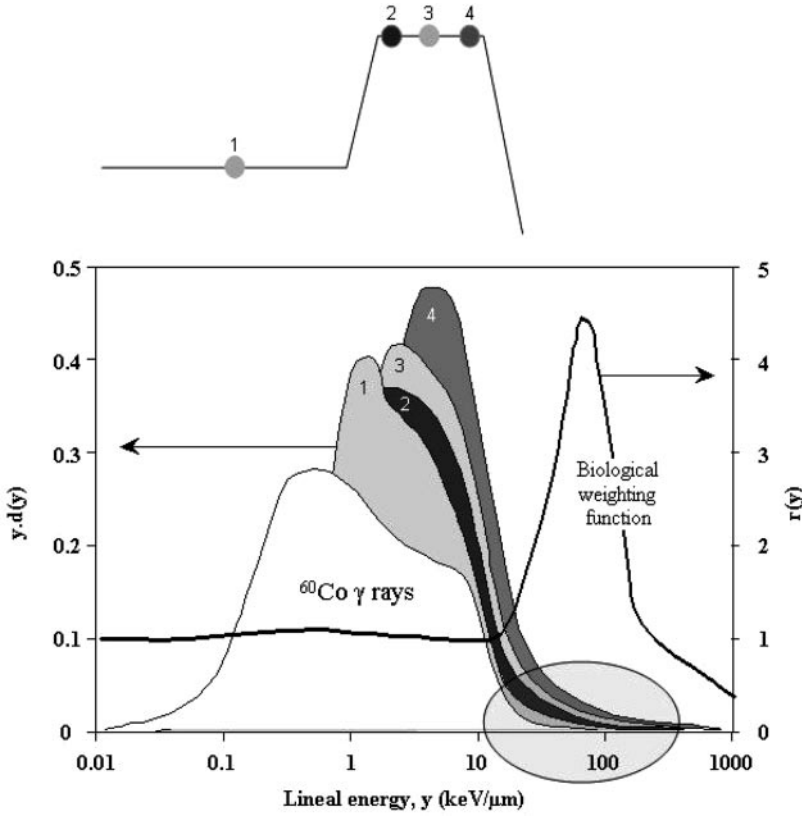


Figure 3. Microdosimetric $y$ spectra measured in a 90 MeV proton beam at the UCL cyclotron of Louvain-la-Neuve. Measurements are performed at the level of the initial plateau (1), and at the proximal (2), middle (3) and distal (4) part of the SOPB as indicated on the schema at the top of the figure. The $y$ spectrum for $^{60}$Co is given for comparison. Compared to $^{60}$Co, the four proton spectra are slightly shifted towards the high $y$ values, which might explain the 10% difference in RBE. In addition, there is a progressive shift, with depth, of the proton spectra towards higher $y$ values that could be responsible for the slight additional RBE increase of 5–10% at the end of the SOBP compared to the initial plateau and other depths in the proton beam. The right ordinate is the 'biological weighting function' which expresses the RBE variation as a function of $y$ for the case of intestinal crypt regeneration. Only a small proportion of the proton spectra overlaps with the ascending part (RBE > 1) of the 'biological weighting function' (as indicated by the grey circle). [Redrawn from Loncol *et al.*[13], Gueulette *et al.*[14], Menzel *et al.*[15]].

The variation of RBE in depth in the carbon-ion beam of HIMAC-Chiba obtained using the intestinal crypt cell system is illustrated in Figure 4[14]. Table 1 gives the RBE values reported by Tsujii[16] for cells *in vitro* and skin reactions in patients. Figure 5 compares the variations in depth of absorbed dose and weighted dose for RQ. It illustrates the differences due to the significant RBE variations in depth[14,16].

## DISCUSSION AND CONCLUSIONS

### The isoeffective dose

The isoeffective dose, as introduced here for radiation therapy applications, is the dose that, delivered under reference conditions (see section 'Reference treatment conditions' and below), would produce the same clinical effects as the actual treatment, in a given system, all other conditions being identical. It is expressed in Gy.

The isoeffective dose is essential for comparing and/or combining treatments performed under different conditions and facilitates relevant exchange of clinical information.

The reference treatment conditions are: photon irradiation, 2 Gy per fraction, 5 daily fractions a week (see section 'Reference treatment conditions'). The isoeffective dose $D_{\mathrm{IsoE}}$ is the product of the physical quantity absorbed dose $D$ and a weighting factor $W_{\mathrm{IsoE}}$.

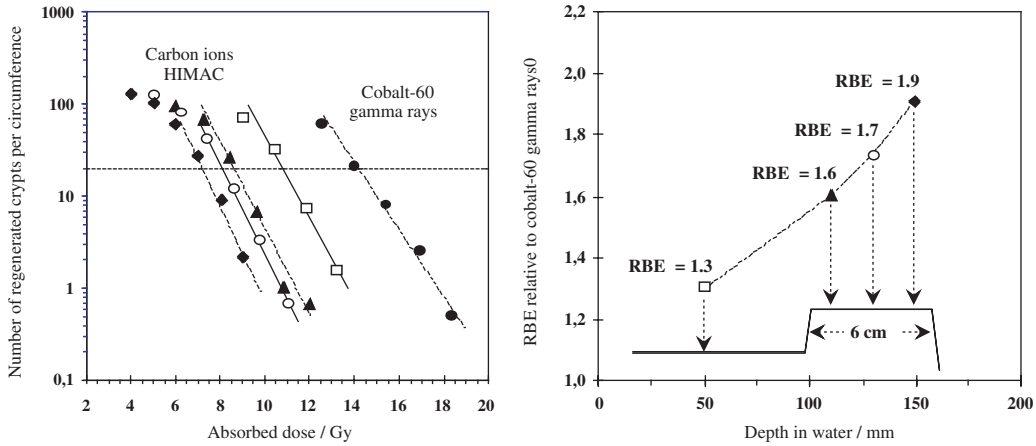


Figure 4. Variation of RBE as a function of depth in the 290 MeV carbon-ion beam at HIMAC-Chiba (Japan). On the right-hand side, the RBE is given at the four depths in water that are indicated. The SOBP is 6 cm thick. The left-hand side presents the full radiobiological dose–effect curves obtained for the ions at the four depths and for $^{60}$Co. The biological system is crypt regeneration in mice; the level of effect chosen for RBE determination is 20 regenerated crypts per circumference after single fraction irradiation. It is obtained for photons after ~14 Gy [Gueulette *et al.*[14]].

**Table 1. Relative Biological Effectiveness (RBE) Values of Modulated 290 MeV/amu Carbon-Ion Beams of the Heavy-Ion Medical Accelerator, Chiba.**

| Position | LET (keV/μm) | RBE values | | |
|---|---|---|---|---|
| | | Single fraction | | Four fractions |
| | | Cell culture | Skin reaction | Skin reaction |
| Entrance | 22 | 1.8 | 2.0 | – |
| SOBP (6 cm) | | | | |
| Proximal | 42 | 2.1 | 2.1 | 2.3 |
| | 45 | 2.2 | 2.2 | – |
| Middle | 48 | 2.2 | 2.3 | – |
| | 55 | 2.4 | 2.3 | – |
| Distal | 65 | 2.6 | 2.3 | 2.9 |
| | 80* | 2.8 | 2.4 | 3.1 |
| Distal fall-off | 100 | – | – | 3.5 |

*The linear energy transfer (LET) value of fast neutrons used in cancer treatment at the National Institute of Radiological Sciences is also 80 keV/μm.

$W_{IsoE}$ is an inclusive weighting factor that takes into account all factors that could influence the clinical effects (dose per fraction, overall time, RQ, biological system and effects, etc.).

The numerical value of $W_{IsoE}$ is selected by the radiation-oncology team for a given patient (or treatment protocol). It is part of the treatment prescription.

The concept of isoeffective dose is currently used in external beam therapy and, more and more, in modern brachytherapy HDR and PDR techniques.

This concept is also applicable in particle-beam therapy. However, evaluation of the influence of the RQ weighting factor on $W_{IsoE}$ raises specific issues because of the large RBE variations with different factors as seen in section 'Ion-beam therapy'. Little agreement on numerical values for $W_{IsoE}$ has been achieved so far.

### Comparison of different approaches and concepts: isoeffective dose and equivalent dose

The term 'equivalent dose' is currently used in the proton-beam community as the product of the absorbed dose by the generic proton RBE of 1.1 (see section 'Proton-beam therapy'). The unit

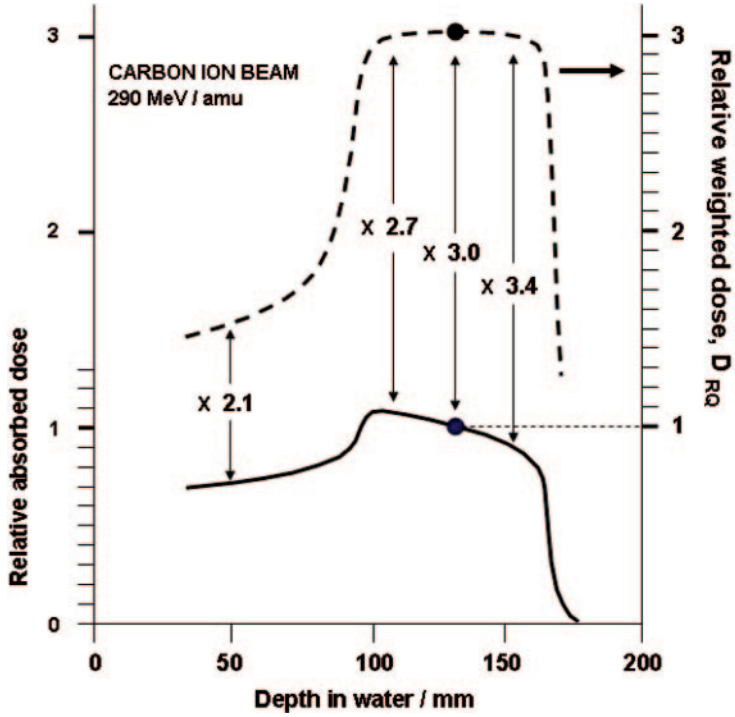


Figure 5. Variation in depth of absorbed dose, $D$ (full line, left ordinate) and dose weighted for radiation quality, $D_{RQ}$ (dotted line, right ordinate) as a function of depth in a 290 MeV carbon-ion beam (HIMAC). The RBE increases with depth and this increase is significant at the level of the SOBP (see Figure 4). Therefore to obtain a homogeneous RQ weighted dose across the SOBP, the absorbed dose should decrease progressively in depth. The RBE of 3, selected at the middle of the SOBP, is a clinical decision of the HIMAC radiation-oncology team based on past clinical experience with neutrons. The variation of the radiation quality weighted dose $D_{RQ}$ used in the figure is derived from the RBE data given in figure 4 (the numerical values of RBE are indicated). [Redrawn based on the data of Gueulette *et al.*[14] and of Tsujii *et al.*[16]].

frequently used is the gray-equivalent (GyE) or the cobalt-gray-equivalent (CGE) when proton doses are compared to photons delivered using the same fractionation as protons, i.e. often different from the reference fractionation (2 Gy per fraction, 5 fractions a week, see section 'Reference treatment conditions').

The difference between equivalent dose and isoeffective dose concept is thus the selection of the fractionation conditions for photons taken for comparison. The CGE is equal numerically to the isoeffective dose only when the protons (and thus the photons taken for comparison) are delivered with the reference fractionation schedule (as defined in section 'Reference treatment conditions'). If this is not the case a factor which takes into account the effects of differences in fractionation has to be applied when comparing the CGE to the isoeffective dose.

The term 'equivalent dose' currently used in ion-beam therapy is the product of the absorbed dose $D$ and a weighting factor for differences in RQ ($W_{RQ}$). This factor ($W_{RQ}$) is the best estimate of the RBE of the ion beam at the point of interest, for a given dose and the relevant clinical effect (e.g. late or early). As mentioned, the unit commonly used is the GyE, but this practice has to be discouraged (see below).

Like for protons, comparison is made with photons delivered with the same fractionation as the ions, which is often significantly different from the reference fractionation selected for the definition for the isoeffective dose.

If the ions are delivered using a fractionation different from the reference fractionation (as defined in section 'Reference treatment conditions') a factor which takes into account the effects of differences in fractionation has to be applied when comparing the ion equivalent dose and the isoeffective dose. However, the radiobiological and clinical observations with carbon ions have shown a reduced effect of fractionation. Therefore, in some centres, the influence of fractionation has been assumed to be negligible within reasonable limits for ion beams[16].

Two remarks need to be made here. First, the term "equivalent dose" is used by the International Commission on Radiological Protection (ICRP), for radiation protection applications, with a totally different meaning than in the present context of therapy. The special unit for the ICRP equivalent dose is the sievert, Sv[17]. Second, according to the International System of Units (SI), no subscript nor letter/symbol may be added to the recommended symbols of units, such as GyE[18].

### General IAEA/ICRU recommendation

As a general recommendation for all treatment modalities[19,20], absorbed dose, in Gy, at all relevant points and/or volumes should always be reported. In addition, treatment conditions should be reported as completely and accurately as possible: they should allow reconstruction of the treatment when useful.

In addition, the best estimate of the isoeffective dose, in Gy, should be reported. The numerical values of the applied weighting factors $W_{\mathrm{IsoE}}$ should also be given together with the rationale used in the determination.

As in the case of absorbed dose, the isoeffective dose and the equivalent dose are expressed in Gy, the names of the quantities should always be given to avoid confusion or ambiguity.

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