A simple approximation for the evaluation of the photon isoeffective dose in Boron Neutron Capture Therapy based on dose-independent weighting factors

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Abstract

The current methodology for determining the biological effect of Boron Neutron Capture Therapy (BNCT) has recently been questioned, and a more accurate framework based in the photon isoeffective dose has been proposed. In this work we derive a first order approximation to this quantity than can be easily evaluated even from limited data, as is the current situation in the radiobiology of BNCT. This procedure removes the main drawbacks of the current method and it is based on new weighting factors that, as a difference with the previously used, are true constants (dose independent). In addition to this, we apply the formalism to allow the comparison to a fractionated conventional radiotherapy treatment, for which there is a lot of knowledge from clinical practice. As an application, the photon isoeffective dose of a BNCT treatment for a brain tumor is estimated. An excel sheet used for these calculations is also provided as supplementary material and can be used also with user-provided input data for the estimation of the photon isoeffective dose for comparison with conventional radiotherapy, both to single and fractionated treatments.

Keywords: Neutron Capture Therapy, photon iso-effective dose, treatment planning

1. Introduction

Boron Neutron Capture Therapy (BNCT), which has recently shown very promising results (Barth et al. 2012), is now facing a renaissance with the introduction of a new generation of accelerator based BNCT centers expected soon (Kreiner et al. 2016). Since the neutron beam spectrum from an accelerator can change substantially from a reactor-based system, a revision of the dose planning procedures is appropriate.

In current BNCT clinical studies the physical dose is calculated as the sum of three contributions: the neutron dose, D_n, the boron dose, D_B, and the gamma dose, D_γ. The neutron dose is usually separated as: the fast dose, D_f, from the secondary particles (mainly hydrogen recoils) produced by neutrons with energy above 0.5 eV and the thermal dose, D_t, for neutrons with energy below 0.5 eV (IAEA 2001, Goorley et al. 2002). The latter is dominated by the ^{14}N(n,p) reaction and sometimes it is also called the nitrogen dose (Joensuu et al. 2003), although the energy is mainly delivered by the ejected proton. The dose contribution from the 2.224 MeV photons from the hydrogen capture of thermal neutrons is excluded from D_t and included in D_γ.

The reason for this separation is to account for the different relative biological effectiveness of these contributions, as the total dose is a mix of high and low LET products in tissue.Therefore, the "biological" or "weighted" dose (D_W) is defined as the sum of the dose components weighted with different factors w_i (IAEA 2001. Joensuu et al. 2003), previously called relative biological effectiveness (RBE) factors (Coderre and Morris 1999):

$$D_w = w_f D_f + w_t D_t + w_\gamma D_\gamma + w_B D_B \quad (1)$$

The quantity D_w is interpreted as the equivalent photon dose which produces the same effect than the BNCT procedure and is expressed in Gy-Eq or Gy(W). The weighting factors w_i are defined as the ratio of the reference photon irradiation dose, D_p, and the value of the physical dose component D_i needed to produce the same effect:

$$w_i = \frac{D_p}{D_i}, \qquad i = t, f, \gamma, B. \quad (2)$$

The current w_i factors were determined in radiobiology experiments, and they are assumed as constants, although they depend on the survival fraction (i.e. the doses delivered) of those experiments. For example, the common value for w_f and w_t of 3.2 for tumors was obtained for an *in-vivo* clonogenic gliosarcoma cell survival of 1%, but for other survival fractions the values vary from 2.8 to 3.5 (Coderre et al. 1993). The photon weighting factor has been taken systematically as one, although there is evidence against this value because of the smaller photon dose rate in BNCT (Kiger et al. 2008, Hopewell et al. 2011, 2012). The boron weighting factor is a compound-dependent factor, also called CBE (compound biological effectiveness), which was obtained by subtraction from the total beam effect and incorporating the biological effect of the rest of components with the assumed values of w_f and w_t (Coderre and Morris 1999). In this way, any deficiency of the other coefficients could be compensated. These factors can be applied reliably to other beams for which the different dose terms are similar to the conditions in which this w_B factor was obtained. However, this may not be the case for different neutron beams for the newly-proposed accelerator-based neutron sources. In particular, for the first accelerator-based neutron source which is performing clinical trials, the C-BENS at Kyoto (Tanaka et al. 2011, Ono 2018), it has been reported important differences with respect to the epithermal beam from a reactor (Tanaka et al. 2009, Ono 2018). This source, based on the ^{9}Be(p,n) reaction, shows aspectrum with a maximum at higher epithermal energies than that for a typical reactor source, which may lead to a different relative contributions of D_f and D_t at different depths. Also, for the reaction ^{7}Li(p,n) near the threshold, which is used in some other facilities such as SOREQ (Halfon et al 2009), it has been measured an spectrum for which the high energy tail of the spectrum ends sharply below the MeV range (Bedogni et al. 2018). This is constrained from the kinematics of the reaction which precludes neutron energies in the MeV range, quite different than the tail of neutrons from reactors. Therefore, the relative contribution of D_f can differ.

In spite of its usefulness in the many clinical trials performed using research reactors, there are some drawbacks in the current procedure that can be improved. First, as mentioned, the weighting factors are not constant as they are dose-dependent. The reason is that while the biological effect, defined as $E \equiv -\ln S$ where S is the survival fraction of cells after irradiation, can be assumed to depend linearly on the dose for high

LET radiation, for photons the dependence is known to have a linear-quadratic (LQ) dependence (Kellerer and Rossi 1974, Chadwick and Leenhouts 1981), as:

$$E \equiv -\ln S = \alpha_p D_p + \beta_p D_p^2 \quad (3)$$

Therefore, for weighting a high LET radiation dose component D_i it has to be used the factor $w_i = D_p/D_i$, where D_p is the reference photon dose required to produce the same effect than this particular D_i value. If this value is used for doses lower than the D_i value chosen to compute D_p, the resulting weighted dose is underestimated, and for higher values of D_i, it is overestimated.

Also, the additivity of the different terms may increase the error in the estimation of the equivalent photon dose by the addition of the weighted dose terms as illustrated graphically by Gonzalez and Santa Cruz (2012). In order to fix these drawbacks, and including other improvements, such as the synergies between different dose components, these authors defined the photon isoeffective dose, D_R, which represents more accurately the photon dose which produce the same biological effect than the BNCT treatment (González and Santa Cruz 2012). It can be calculated from a comparison between the biological effects of both the reference photon radiation and a BNCT treatment of components D_i ($i = f, t, \gamma, B$), via the equation:

$$\sum_{i=1}^{4} \alpha_i D_i + \sum_{i=1}^{4}\sum_{j=1}^{4} G_{ij}(\theta)\sqrt{\beta_i \beta_j}\, D_i D_j = \alpha_R D_R + G(\theta')\beta_R D_R^2 \,. \quad (4)$$

This method takes into account the LQ model for all the dose components, the possible synergies between them and the repair mechanisms as a function of time by including the Lea-Catcheside time factor, $G(\theta)$. This formalism was applied to evaluate previous data for BNCT head and neck patients, finding that this isoeffective dose predicts the clinical responses better than the current weighted dose formalism (Gonzalez et al. 2017).

In this work, we propose a first order approach for the estimation of the photon isoeffective dose that can be applied with the common knowledge of the RBE data, but introducing the most important corrections required by the use of the radiobiological LQ method, which are the quadratic terms of the effect of both the gamma dose component in BNCT and the reference photon dose (the own isoeffective dose). For the incorporation of the radiobiology data to this method we propose the use of newly defined weighting factors which are true constants (i.e. dose-independent).

2. Methods

2.1. Formalism for the estimation of the photon iso-effective dose in BNCT

Our model consists of a first order approximation to the photon iso-effective dose described by Eq. (4) with some simplifying assumptions:

(i) The quadratic parameters are neglected for the high LET radiation components (i.e., $\beta_i \cong 0$ for $i = f, t, B$), a common aproximation in high LET radiobiology (Bloomer and Adelstein 1982). Previous data from in-vitro irradiation in BNCT beams shows survival that follows a quadratic curve, but this includes the effect

of the gamma component of the beam (normally the main component in those beams). Usually, once this component is extracted correctly and only the effect of high LET radiation is represented, it well fit with a linear aproximation that not requires the quadratic parameter β_i.With this assumption, synergic effects between different dose components are also neglected, an effect that has been estimated to be of a 7% of the photon isoeffective dose (González and Santa Cruz 2012). However, the role of the β_i coefficients for the gamma component and especially for the reference photon radiation, accounts for the most part of the much higher discrepance between the photon isoeffective dose and the current formalism of RBE-weighted dose, and they are included in the present formalism This approximation is aimed to use available experimental data, that is still not conclusive for the synergies (Phoenix et al. 2013).

(ii) We assume that the radiobiology coefficients for the gamma dose and the reference radiation, as being those of photons, are the same, which will be called α_p, β_p and can be taken from the extensive literature on the radiobiology of conventional radiation therapy. Although this assumption will continue through the formalism description, the possibility to include specific parameters for the BNCT gamma component, when data is available, is included later on.

(iii) For consistency with the use of conventional photon radiobiology data, the Lea-Catcheside factor $G(\theta')$ for the reference radiation is assumed to be 1 for a single-session treatment and $1/n$ for a fractionated treatment in n sessions where the time between sessions is large (Brenner 2008). Additionally, the G factor for the gamma component of the BNCT treatment is approximated by 1, but if a different value is adopted in the future, it can be introduced in our formalism as will be discussed below, where it will be also shown how a dose reduction factor for this component, as it has been suggested by some authors (Kiger et al. 2008, Hopewell et al. 2011, 2012), can be also incorporated. These options allow to consider the different dose rate effect of the two photon irradiations under comparison.

With these assumptions, Eq.(4) is reduced to:

$$\alpha_t D_t + \alpha_f D_f + \alpha_p D_\gamma + \beta_p D_\gamma^2 + \alpha_B D_B = \alpha_p D_p + \beta_p D_p^2 \,, \tag{5}$$

where we have denoted as D_p our approximation to D_R in order to avoid confusion, but it represents an approximation to the photon iso-effective dose, in units of Gy (IsoE). The left hand side of the equation represents the biological effect E of the BNCT treatment, which is defined as the log of the survival fraction S of cells:

$$E = -\ln S = \alpha_t D_t + \alpha_f D_f + \alpha_p D_\gamma + \beta_p D_\gamma^2 + \alpha_B D_B \tag{6}$$

and the right hand side that of the photon reference irradiation, assumed applied in a single session:

$$E = -\ln S = \alpha_p D_p + \beta_p D_p^2 \tag{7}$$

But we can also relate this effect to that produced by a fractionated conventional radiation treatment, which is known, taking into account repair mechanisms between sessions, described by (Fowler 1990):

$$E = -\ln S = \alpha_p n d_p + \beta_p n d_p^2 \,, \tag{8}$$

Where n denotes the number of sessions, and d_p the dose delivered per fraction. This is

equivalent to approximate the Lea-Catcheside factor for the fractionated treatment by $1/n$, as mentioned above. Therefore, either using equation (5) or Eq. (6) combined with Eq. (8), and dividing by α_p, we obtain:

$$\frac{\alpha_t}{\alpha_p}D_t + \frac{\alpha_f}{\alpha_p}D_f + \left(D_\gamma + \frac{D_\gamma^2}{\alpha_p/\beta_p}\right) + \frac{\alpha_B}{\alpha_p}D_B = \begin{cases} D_p + \dfrac{D_p^2}{\alpha_p/\beta_p} & (9a) \\ n\left(d_p + \dfrac{d_p^2}{\alpha_p/\beta_p}\right) & (9b) \end{cases}$$

We define new weighting factors as:

$$W_i = \frac{\alpha_i}{\alpha_p}\ ,\ i = t, f, B\ . \qquad (10)$$

These are the key factors for the present formalism. Assuming that the dose-survival curve is well described by the LQ model (only linear for the high LET components), the α coefficients do not depend on the survival fraction and therefore the w_i^* factors are true constants. They are only specific to the tissue and the biological end-point.

Then, Eq.(5) reads:

$$W_f D_f + W_t D_t + \left(D_\gamma + \frac{D_\gamma^2}{\alpha_p/\beta_p}\right) + W_B D_B = \begin{cases} D_p + \dfrac{D_p^2}{\alpha_p/\beta_p} & (11a) \\ n\left(d_p + \dfrac{d_p^2}{\alpha_p/\beta_p}\right) & (11b) \end{cases}$$

Just for convenience we will denote the left-hand-side of the equation as:

$$D_W^* = W_f D_f + W_t D_t + \left(D_\gamma + \frac{D_\gamma^2}{\alpha_p/\beta_p}\right) + W_B D_B \qquad (12)$$

So, for finding the photon iso-effective dose of a single session treatment we only have to solve the quadratic equation (11a), which gives:

$$D_p = \frac{\alpha_p/\beta_p}{2}\left\{-1 + \sqrt{1 + \frac{4}{\alpha_p/\beta_p}D_W^*}\right\}, \qquad (13)$$

and, from Eq.(11b), for obtaining the photon isoeffective dose for a fractionated treatment, assuming d_p is known (2 Gy typically), the number of doses of the fractionated iso-effective treatment is given by

$$n = \frac{D_W^*}{d_p\left(1 + \frac{d_p}{\alpha_p/\beta_p}\right)} \qquad (14)$$

from which the fractionated photon iso-effective dose is just $D_p = nd_p$. In both cases, D_W^* is given by Eq. (8).

These formulas (13) and (14) allow to estimate the photon iso-effective dose in a direct way provided we have information on the new weighting factors, which will be discussed below, and the ratio α_p/β_p, which is tabulated for a number of cell lines, tissues (tumor and normal) and specific effects in organs from the large amount of

radiobiology data of conventional radiation. These ratios are commonly used in conventional radiotherapy for adjusting the fractioning of treatments when the planned schedule is altered. This ratio takes large values for tumors and small for normal tissues, except in acute response effects.

Although the photon isoeffective dose formalism of Eq. (2) was originally developed for tumor response, the present approximation given in Eqs. (13) and (14) can give also estimations of normal tissue complications provided that the α_p/β_p values entered correspond to the biological end-point of interest. The reason is that the right hand side of Eq.(11b) represents the well-known biological effective dose (BED) of standard radiotherapy, which is used for estimating also normal tissue effects and α_p/β_p are determined for them. The reliability of the predictions depends on the accuracy of the input data. An implicit assumption in the use of Eq. (11b) is that the ratio α_p/β_p is the same for the gamma component of the BNCT and a fractionated radiotherapy treatment. This could be improved if we know the dose-response of the gamma dose in BNCT dose for the effect of interest and we can estimate their coefficients $\alpha_\gamma, \beta_\gamma$. If this is the case, Eq. (11a),(11b) should be replaced by:

$$W_f D_f + W_t D_t + W_\gamma \left(D_\gamma + G(\theta) \frac{D_\gamma^2}{\alpha_\gamma/\beta_\gamma} \right) + W_B D_B = \begin{cases} D_p + \dfrac{D_p^2}{\alpha_p/\beta_p} & (15a) \\ n\left(d_p + \dfrac{d_p^2}{\alpha_p/\beta_p} \right) & (15b) \end{cases}$$

Where $W_\gamma = \alpha_\gamma/\alpha_p$, which represents a dose reduction factor (DRF) for the gamma dose in BNCT, and $G(\theta)$ is the Lea-Catcheside factor for this component. Therefore, if future knowledge on these parameters is available from experimentation, this formula should be applied.

2.2. Relation between new weighting factors, W_i and previous ones, w_i.

Ideally, the new weighting factors W_i should be determined from radiobiological measurements, obtaining the α_i coefficient for each dose component by a fitting of the function $S_i = e^{-\alpha_i D_i}$ to the survival empirical data of S_i due to this particular dose component i. But it is not common to deal with this data as the irradiation always contains more than one term, and one has to proceed carefully as how to separate the effects of different components, for which data from different type of beams is required. An example of this situation will be mentioned in the next section.

However, and this is the major advantage of this approximation, when we do not have the required data on the survival curve, but limited data such as a particular value of the previous RBE values obtained for a particular dose component, the current method can be applied to estimate the photon isoeffective dose. For this purpose, we will obtain now a relationship between the current weighting factors and the newly defined ones.

If D_{pi} is the photon dose producing the same effect as a particular dose component D_i, then by equating the common effect that corresponds to both doses we can express:

$$\alpha_i D_i = \alpha_p D_{pi} + \beta_p D_{pi}^2, \qquad (16)$$

which can be written as:

$$\frac{\alpha_i}{\alpha_p} D_i = D_{pi} + \frac{D_{pi}^2}{\alpha_p/\beta_p}. \quad (17)$$

Identifying $w_i = D_{pi}/D_i$ and $W_i = \alpha_i/\alpha_p$, the following relation is found:

$$W_i = w_i \left(1 + \frac{D_{pi}}{\alpha_p/\beta_p}\right), \quad (18a)$$

or equivalently, in terms of D_i we find:

$$W_i = w_i \left(1 + \frac{w_i D_i}{\alpha_p/\beta_p}\right). \quad (18b)$$

According to Eq.(18a), w_i is a decreasing function of the dose and coincides with W_i in the limit $D_{pi} \to 0$, therefore W_i can be considered as the maximum RBE value defined previously (Carabe-Fernández et al. 2010).

3. Results and discussion

3.1. Estimation of the new weighting factors for brain tumor treatments from existing data of w_i.

3.1.1. Tumor values of W_f and W_t

Currently it is assumed that the factors w_f and w_t take the same values, that we will denote by w_n and called "pure neutron weighting factor". With this assumption, we will obtain an estimation of the new neutron weighting factor $W_f = W_t \equiv W_n$. However, one should keep in mind that this is not a requirement of the model that can be also applied if from new experiments a different value of W_f than W_t is obtained.

The commonly accepted value of 3.2 for tumor was obtained by Coderre et al. (1993) studying the biological effectiveness factors from a rat 9L gliosarcoma model. The irradiations were performed at a mixed field of neutrons and photons at BMRR. However, they also performed X-ray irradiations that allowed them to remove the effect of the photon component of the mixed beam (assumed, as in this work, that both produce the same dose-response). From the data of the fit of the photon survival that these authors performed, which gave the results $\alpha_p = 0.26 \pm 0.03$ Gy^{-1} and $\beta_p = 0.003 \pm 0.001$ Gy^{-2}, and assuming that the survival fraction from the photon components is function $S_\gamma = e^{-\alpha_p D_\gamma - \beta_p D_\gamma^2}$, we can extract the pure neutron survival data as $S_n = S/S_\gamma$, this is illustrated in Table 1.

D (Gy)	S	D_γ(Gy)	S_γ	D_n(Gy)	S_n
3	0.2±0.05	0.986	0.771±0.024	2.013	0.259±0.073
4.1	0.08±0.04	1.349	0.700±0.030	2.751	0.114±0.062
8.5	0.0014±0.002	2.796	0.472±0.043	5.704	0.003±0.004

Table 1. Factorization of the survival fraction S of the in-vivo results of Coderre et al (1993) in the S_γ and S_n factors corresponding respectively to the effect of the gamma and neutron dose components D_γ and D_n.

Then, fitting the data of S_n as a function of D_n by the expression $S_n = e^{-\alpha_n D_n}$, illustrated if Figure 1, we obtain the result: $\alpha_n = 0.876 \pm 0.083$ Gy^{-1}. Therefore, using Eq.(10), we find that $W_n = 3.37 \pm 0.71$.

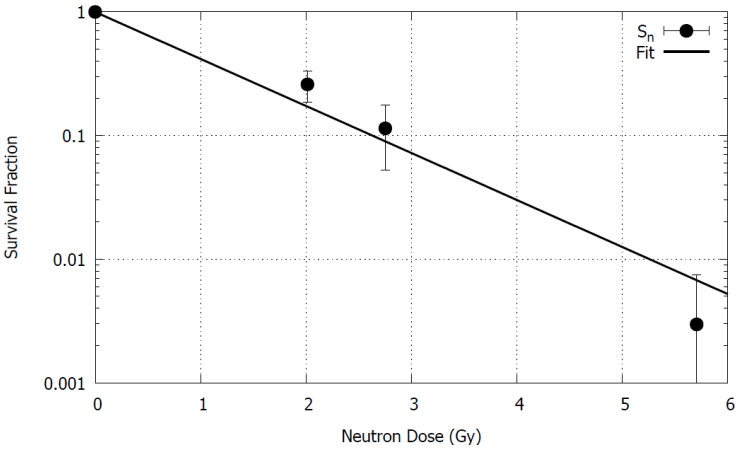

Figure 1. Plot of the pure neutron survival from the measurements of Coderre et al. (1993) as a function of the neutron dose and the fit of the function $e^{-\alpha_n D_n}$ to these data.

Obviously, a linear-quadratic term as used in the original paper of Coderre et al (1993) would provide a better fit, but as they said, they did it for a mathematical (an additional fit parameter) rather than for a physical reason. However, for consistency in our model, where the quadratic terms are neglected for the high LET components, we have restricted to the abovementioned one-paramter fit, which avoids dealing with a parameter with high uncertainty that can have a great impact on the survival for greater doses than dose for which data are available.

3.1.2. Normal tissue values of W_f and W_t

The present formalism is not only useful in these cases where we have information of the survival curve, but also when there is limited data as the RBE calculated at one point. This is the case of the $w_t = w_t \equiv w_n$ factor reported for healthy tissue by Morris et al. (1994). In this work, the myelopathy effects on the spinal cord of rats (end point 50% incidence) under irradiation with a mixed neutron and photon beam was studied. In the absence of ^{10}B, they obtained that the same biological effect was achieved by 13.58 ± 0.38 Gy of their beam than with D_p =19.0 ± 0.2 Gy of X-rays, taken from Wong et al. (1993). From this observation, a mixed RBE equal to 1.4 was derived. As the dose delivered to the blood in the vasculature of the spinal cord verified that $D_t + D_f \approx D_\gamma(22)$, it can be calculated that $D_n = D_t + D_f = 6.79 \pm 0.19$ Gy. We apply our formalism for evaluating the W_n from Eq. (10), which in this particular case can be written as:

$$W_n D_n + \left(D_\gamma + \frac{D_\gamma^2}{\alpha_p/\beta_p} \right) = D_p + \frac{D_p^2}{\alpha_p/\beta_p}$$

from which we find $W_n = 17.3 \pm 1.0$. For this calculation we have used the value of $\alpha_p/\beta_p = 3$ Gy, used in the same paper, from Wong et al. (1993).

The resulting neutron weighting factor for neutrons and normal tissue is larger than for tumor. However, the photon iso-effective dose in normal tissue will remain much lower, as it will be seen in Section 3.5.

In this section we have made the implicit assumption that the concept of photon isoeffective dose, originally conceived for describing tumor cell killing, can be also applied to the estimation, for normal tissue complications, of the photon dose that produce the same effect than the BNCT treatment. This is only valid if all the parameters used in Eqs. (12-15) (i.e. the dose-independent weighting factors or those parameters used to derive them and the alpha/beta ratio for the reference radiation) corresponds to the same biological end-point. The linear quadratic model has been extensively used for the description of the radiation effects at organs at risk different than cell killing (Emami 2013), and alpha/beta ratios are reported for various effects in different tissues and organs (Thames et al. 1990). The rationale beyond our assumption lies on the fact that the normal tissue complication probability (NTCP) of critical organs is considered as a function of the relative effectiveness of the treatment, defined as

$$D\Gamma = D\left(1 + \frac{d}{\alpha/\beta}\right) = \frac{1}{\alpha}(\alpha n d + \beta n d^2),$$

The exponential of $-\alpha D\Gamma$, which appears in the exptression for the NTCP, is the reminiscent of the LQ model for cellular survival (Kehwar 2005). So the hypothesis underlining our approach for normal tissues is that a similar dependence can be assumed for the BNCT treatment, which is fact was assumed by Morris et al. (1994) but with the fixed RBE classical approach.

3.1.3.Tumor value of W_B for BPA

The value commonly used in clinical trials (Joensuu et al. 2003) of $w_B = 3.8$ for tumor and the BPA compound was obtained by Coderre et al. (1993), where the value of $\alpha_B = 2.32 \pm 0.09$ Gy^{-1} was found, after removing from the survival curve the effect of the neutron beam alone. Using the value of $\alpha_p = 0.26 \pm 0.03$ Gy^{-1} from Table 1 (for the same model) and Eq.(6) we find $W_B = 4.35 \pm 0.67$.

3.1.4. Normal tissue value of W_B for BPA

The commonly accepted value for normal tissue of w_B for the compound BPA is 1.3 (Coderre and Morris 1999), which was measured in the experiment of Morris et al. (1994). In this work, the same biological end point mentioned in section 3.2 was found for a total dose of 13.81 ± 0.49 Gy, of which the boron component was $D_B = 4.93 \pm 0.65$ Gy. The partial components for the pure neutron and gamma dose were in this case $D_n = D_\gamma = 4.44 \pm 0.22$ Gy. With the present formalism, using Eq.(11a) and assuming $W_f = W_t = 17.3 \pm 1.0$, $\alpha_p/\beta_p = 3$ Gy, we find that $W_B = 10.45 \pm 3.46$.

3.1.5. Summary and discussion

The estimation of the new weighting factors performed with some existing data are displayed in Table 2. It is important to remark the high uncertainty, due to the own uncertainties of the input data. Therefore, any conclusion from their application should be taken with caution, and new measurements with smaller uncertainties are desirable. These new measurements can be analysed with the present formalism in order to avoid errors from the subtraction of the gamma dose that is always present in neutron irradiation. With this aim we have started a campaign of radiobiology measurements for different cell lines at a pure cold neutron beam at ILL, with the aim of obtaining W_t and W_B values accurately and studying their tissue dependence. These values are key as they

are universal (due to thermal neutrons), while W_f could depend on the particular spectrum and should be measured at each BNCT facility.

Factor	Tissue	Value
W_t	Brain tumor	3.37 ± 0.71
	Normal brain	17.3 ± 1.0
W_f	Brain tumor	3.37 ± 0.71
	Normal brain	17.3 ± 1.0
W_B	Brain tumor	4.35 ± 0.67
	Normal brain	10.45 ± 3.46

Table 2. Estimation of the new weighting factors from current data, as described in the text.

3.2. Application for a brain tumor clinical trial.

In order to illustrate the application of the present formalism, we will consider the average dose components applied in a BNCT clinical trial of brain tumours and we will compare with a conventional radiotherapy treatment by means of the photon isoeffective dose. A typical fractionated conventional treatment with photons delivers a total dose of 60 Gy in 30 sessions of 2 Gy. We will assume for the normal brain, α_p/β_p = 3 Gy (Wong et al. 1993). As an example, we consider a BNCT brain tumor clinical trial of 18 patients (Joensuu et al. 2003), where the different dose components are reported. The average values from all cases of the normal brain maximum (peak) physical doses (in Gy) are: $D_B = 4.46$,$D_\gamma = 3.86$, $D_t = 0.61$, and $D_f = 0.17$ (Joensuu et al. 2003). With the classical procedure, the use of Eq. (1) and the weighting factors: $w_n = w_f = w_t = 3.2$ and $w_B = 3.8$ tumor/1.3 normal tissue, an equivalent photon dose of $D_w = 12.15$ Gy-Eq is obtained. This value does not exceed the maximal tolerated dose for targets 31–40 mm in diameter of 15 Gy in single-session radiosurgery (Lawrence et al. 2010).

We will now apply the new weighting factors, calculated in the previous sections, for this tissue: $W_f = W_t = 17.3$ and $W_B = 10.45$ (see Table 3). With these data we estimate the single-fraction photon iso-effective dose using Eqs. (9,11) as $D_p = 12.95$ Gy (IsoE). So, we found that, even with our larger values of the weighting factors for normal tissue, the dose delivered in BNCT to normal brain would remain below the limit, being not far from the weighted dose obtained with the previous formalism, $D_w = 12.2$ Gy-Eq,

To illustrate another goal of this work, we can also evaluate the iso-effective dose of a fractionated conventional radiation treatment using Eq.(14). This gives a value of $D_p = 41.36$ Gy (IsoE), which corresponds to a photon treatment of about 21 sessions of 2 Gy, a value well below the usual protocols.

Although the physical dose components at the tumor are not reported in this reference (Joensuu et al. 2003), we can also perform an approximate estimation of the photon iso-effective dose delivered to the tumor. With the assumption that the difference with respect to the maximum dose in normal tissue is due to the boron component, we can grossly estimate the physical doses at the tumor as $D_B = 10.6$,

$D_\gamma = 3.86$, $D_t = 0.61$, and $D_f = 0.17$, which gives a total tumor physical dose of 15.2 Gy. Then, the prediction of the current formalism (in this case using $w_B = 3.8$) gives a weighted dose of $D_w = 46.6$ Gy-Eq. With the present approach, using $W_f = W_t = 3.37$, $W_B = 4.35$ and the values $\alpha_p = 0.26\ \text{Gy}^{-1}, \beta_p = 0.003\ \text{Gy}^{-2}$ (Coderre et al. 1993), we estimate a photon iso-effective dose of $D_p = 36.98$ Gy (IsoE), for a single irradiation and of $D_p = 51.65$ (IsoE) for a fractionated treatment, which corresponds to roughly 26 sessions. The photon iso-effective dose estimated with the present formalism is substantially lower than the RBE-weighted dose. This is in agreement with previous results of González and Santa Cruz (2012) for brain and melanoma tumors, González et al. (2017) and Sato et al. (2018) for head and neck cancers.

The comparison to fractionated photon radiotherapy shows the higher selectivity of BNCT with respect to conventional radiotherapy: while the tumor receives a treatment equivalent to 26 sessions of radiotherapy, the effect on normal brain is similar to the one produced by about only 21 sessions. These results are summarized in Table 3. However, it must be taken into account that the inhomogeneities in the BNCT procedure, mainly due to the boron distribution, are much larger then the dose distribution of conventional radiotherapy. Here, as an example for illustrating the procedure, only the mean tumor dose has been considered for the comparison, while the range of values should be considered also when comparing to a conventional procedure.

This example of application is illustrated in an excel file associated to this paper as supplementary material. Although the W_γ factor is assumed to be one in this example, the excel file has the possibility of inserting a different value (a dose reduction factor, if applicable).

Tissue		Dose prescribed with photons (Gy)	Conventional weighted dose for the BNCT treatment (D_W) (Gy-Eq)	New method: Iso-effective dose for the BNCT treatment (D_p) (Gy-IsoE)
Normal brain ($\alpha_p/\beta_p = 3$)	Fractionated:	60 (30 sessions of 2 Gy)		41.36 (21 sessions of 2 Gy)
	Single-fraction:		12.2	12.96
Brain tumor ($\alpha_p/\beta_p = 86.6$)	Fractionated:	60 (30 sessions of 2 Gy)		51.58 (26 sessions of 2 Gy)
	Single-fraction:		46.6	36.98

Table 3: Results of the described example of a BNCT treatment using data from Joensuu et al. (2003) with both the current and the new formalism. The photon isoeffective dose D_p has been obtained from Eq. (13), for the single photon equivalent irradiation and from Eq. (14) for the equivalent fractionated treatment, in both cases with D_W^* given by Eq. (11). They are compared to the previously used weighted dose D_W obtained from Eq. (1).

4. Conclusions

The radiobiology of BNCT is currently facing a renaissance, in which the concept of weighted dose is being replaced by the photon isoeffective dose. In order to calculate this quantity from radiobiology data, a formalism based on the LQ model and dose-independent weighting factors has been proposed. This also allows comparing a BNCT

treatment to conventional fractionated photon therapy. The newly-defined factors can be estimated from the current weighting factors, provided that the biological effect of the gamma dose was subtracted using the LQ model. As this is not the case for most of the data analysed, we propose that new radiobiology experiments should be carried out, and we suggest tabulating the new W_i factors which are independent of the dose or survival fraction.

In spite of the drawbacks of the currently used formalism, the discrepancies between the two methods for the clinical trials performed with reactor-based neutron sources are small and the quality of the previous treatments has been confirmed by the present calculation. However, this might not be the case for treatments in new neutron facilities (e.g. accelerator-based sources for BNCT), where the relative dose contributions may change. In any case, improvements in the determination of the photon isoeffective dose may lead to a better therapeutic outcome. It is important to keep in mind that there are other sources of uncertainty in BNCT treatments which are not the scope of this work, especially the boron distribution both in tumor and in the different healthy tissues under the neutron field, which are difficult to quantify and for which important research efforts are made for reducing them.

The main effects that could play a role and have been neglected in this formalism are the repair mechanism and the synergies between different components, that are not described. They are included in the formalism of the photon isoeffective dose of González and Santa Cruz (2012), summarized in Eq. (4). For obtaining the parameters involved in this equation, we suggest that experimentation at different set ups where the relative dose contribution differ significantly should be performed, in order to avoid quasilinear dependence uncertainties. For example, for studying synergetic effects irradiation with pure neutrons (or with the higher LET particles produced by them), with photons and with both radiations simultaneuosly are required, as done in the experiments of Phoenix et al. (2013). However the data available is still not conclusive (Phoenix et al. 2013) and more experimentation would be useful for quantifying this effect. Therefore we believe that our formalism represents an intermediate step towards the formalism of Gonzalez and Santa Cruz (2012), although the application of the latter that should be the future goal of BNCT radiobiology and that precise experimentation for obtaining the required data with accuracy should be performed. For example, a pure neutron beam as the cold neutron line PF1b at Institute Laue-Langevin previously mentioned where the gamma contamination is negligible could be combined with different gamma-generating media (hydrogen containing) for irradiating different cell lines.

Summarizing, in this model a simple approach to the photon isoeffective dose of a BNCT treatment is proposed. This can be considered as a first order approximation to the more accurate formalism of González and Santa Cruz (2012), keeping the simplicity of former approaches, but incorporating the LQ model just for the photon dose component in BNCT and for the reference photon irradiation, when using Eqs. (9,11) for comparison with a single photon irradiation and Eq. (14) for a fractionated treatment. The model proposed in the present study utilizes more accurately the available radiobiological knowledge, however its predictions should be taken with caution until enough data is known to reduce the uncertainties in the response for different tissues.

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Supplementary Material: An excel file, used for the calculations of the photon isoeffective dose in Section 3.2 is available as Supplementary Material for this paper. In this file the user may introduce his/her own data (dose components, weighting factors and α/β ratios), and both the single-fraction and 2 Gy-fraction photon iso-effective dose are calculated. There are two sheets for different tissues: the first one for the normal tissue of the example and the second one for the tumor.

References

Barth RF, Vicente MG, Harling OK, Kiger III WS, Riley KJ, Binns PJ, et al. 2012. Current status of boron neutron capture therapy of high grade gliomas and recurrent head and neck cancer. *Radiat Oncol* 7, 146-166.

Bedogni R, Costa M, Gómez-Ros JM, Monti V, Pola A, Kreisel A, et al. 2018. Neutron spectrometry of a liquid Lithium based (p, n) beam at SARAF facility using the broad-energy range directional spectrometer CYSP. *Nucl Inst Meth Phys Res A* 902, 144–148.

Brenner DJ, 2008. Point: The linear-quadratic model is an appropriate methodology for determining iso-effective doses at large doses per fraction. *Semin Radiat Oncol* 18, 234–239.

Bloomer WD, Adelstein SJ 1982. The Mammalian Radiation Survival Curve. *J Nucl Med* 23, 259-265.

Carabe-Fernández A, Dale RG, Hopewell JW, Jones B, Paganetti H, 2010 Fractionation effects in particle radiotherapy: implications for hypo-fractionation regimes. *Phys Med Biol* 55, 5685-5700.

Chadwick KH, Leenhouts HP, 1981. A molecular theory of radiation biology. Berlin: Springer-Verlag.

Coderre JA, Makar MS, Micca PL, Nawrocky MM, Liu HB, Joel DD, et al. 1993. Derivations of relative biological effectiveness for the high-LET radiations produced during boron neutron capture irradiations of the 9L rat gliosarcoma in vitro and in vivo. *Int J Radiat Oncol* 27, 1121-1129.

Coderre JA, Morris GE, 1999. The radiation biology of Boron Neutron Capture Therapy. *Radiat Res* 151, 1-18.

Emami B, 2013. Tolerance of Normal Tissue to Therapeutic Radiation. *Rep Radiother Oncol* 1, 35-48.

Fowler JF, 1990. How worthwhile are short schedules in radiotherapy?: a series of exploratory calculations. *Radiother Oncol* 18, 165-181.

Gonzalez SJ, Santa Cruz GA, 2012 The photon-iso-effective dose in boron neutron capture therapy. *Radiat Res* 178, 609-621.

González SJ, Pozzi ECC, Hughes AM, Provenzano L, Koivunoro H et al. 2017. Photon iso-effective dose for cancer treatment with mixed field radiation based on dose–

response assessment from human and an animal model: clinical application to boron neutron capture therapy for head and neck cancer. *Phys Med Biol* 62, 7938.

Goorley JT, Kiger III WS, Zamenhof RG, 2002. Reference dosimetry calculations for neutron capture therapy with comparison of analytical and voxel models. *Med Phys* 29, 145-156.

Halfon S, Paul M, Steinberg D, Nagler A, Arenshtam A, Kijel D, et al. 2009. High power accelerator-based boron neutron capture with a liquid lithium target and new applications to treatment of infectious diseases. *Appl Radiat Isot* 67, S278-S281.

Hopewell JW, Morris GM, Schwint A, Coderre JA, 2011. The radiobiological principles of boron neutron capture therapy: A critical review. *Appl Radiat Isot* 69, 2756-2759.

Hopewell JW, Morris GM, Schwint A, Coderre JA 2012. Boron Neutron Capture Therapy: Application of Radiobiological Principles. In: Sauerwein WAG, Wittig A, Moss R, Nakagawa Y, editors. Neutron Capture Therapy: Principles and Applications. Berlin: Springer.

IAEA 2001. Current status of neutron capture therapy. IAEA-TECDOC-1223. International Atomic Energy Agency, Vienna.

Joensuu H, Kankaanranta L, Seppala T, Auterinen I, Kallio M, Kulvik M, et al. 2003. Boron neutron capture therapy of brain tumors: Clinical trials at the Finnish facility using boronophenylalanine. *J Neurooncol* 62, 123–134.

Kellerer AM, Rossi HH, 1974. The theory of dual radiation action. *Curr Top Radiat Res* 8, 85-158.

Kehwar TS, 2005. Analytical approach to estimate normal tissue complication probability using best fit of normal tissue tolerance doses into the NTCP equation of the linear quadratic model. *J Cancer Res Ther* 1, 168-179.

Kiger JL, Kiger III WS, Riley KJ, Binns PJ, Patel H, Hopewell JW, et al. 2008. Functional and Histological Changes in Rat Lung after Boron Neutron Capture Therapy. *Radiat Res* 170, 60-69.

Kreiner AJ, Bergueiro J, Cartelli D, Baldo M, Castell W, Gomez-Asoia J, et al. 2016. Present status of accelerator-based BNCT. *Rep Pract Oncol Radiother* 21, 95-101.

Lawrence YR, Li A, el Naqa I, Hahn CA, Marks LB et al. 2010. Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys* 76, S20–S27.

Morris G M, Coderre JA, Hopewell JW, Micca PL, Nawrocky MM, Liu HB, et al. 1994. Response of the central nervous system to boron neutron capture irradiation: evaluation using rat spinal cord model. *Radiother Oncol* 32, 249-255.

Ono K, 2018. Prospects for the new era of boron neutron capture therapy and subjects for the future. *Ther Radiol Oncol* 2, 40.

Phoenix B, Green S, Hill MA, Jones B, Mill A, Stevens DL, 2009. Do the various radiations present in BNCT act synergistically? Cell survival experiments in mixed alpha-particle and gamma-ray fields. *Appl Radiat Isot* 67, S318-320.

Sato T, Masunaga S-I, Kumada H, Hamada N 2018. Microdosimetric Modeling of Biological Effectiveness for Boron Neutron Capture Therapy Considering Intra- and Intercellular Heterogeneity in ^{10}B Distribution. Sci Rep 8, 988.

Tanaka H, Sakurai Y, Suzuki M, Takata T, Masunaga S, Kinashi Y, et al. 2009. Improvement of dose distribution in phantom by using epithermal neutron source based on the Be(p,n) reaction using a 30 MeV proton cyclotron accelerator. *Appl. Radiat. Isot.* 67, S258-S261.

Tanaka H, Sakurai Y, Suzuki M, Masunaga S, Mitsumoto T, Fujita K, et al. 2011. Experimental verification of beam characteristics for cyclotron-based epithermal neutron source (C-BENS). *Appl Radiat Isot* 2011; 69, 1642-1645.

Thames HD, Bentzen SM, Turesson I, Overgaard M, Van den Bogaert W 1990. *Radiother Onc*ol 19, 219-235

Wong CS, Poon JK, Hill RP 1993. Re-irradiation tolerance in the rat spinal cord: influence of level of initial damage. *Radiother Oncol* 26, 132-138.