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The Photon-Isoeffective Dose in Boron Neutron Capture Therapy

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With the aim to relate the effects observed in a clinical boron neutron capture therapy protocol to the corresponding outcomes in a standard photon radiation therapy, "RBE-weighted" doses are customarily calculated by adding the contributions of the different radiations, each one weighted by a fixed (dose and dose rate independent) relative biological effectiveness factor. In this study, the use of fixed factors is shown to have a formal inconsistency, which in practice leads to unrealistically high tumor doses. We then introduce a more realistic approach that essentially exploits all the experimental information available from survival experiments. The proposed formalism also includes first-order repair of sublethal lesions by means of the generalized Lea-Catcheside factor in the modified linear-quadratic model, and considers synergistic interactions between different radiations. This formalism is of sufficient simplicity therefore to be directly included in all BNCT treatment planning systems. In light of this formalism, the photon-isoeffective doses for two BNCT clinical targets were computed and compared with the standard dose calculation procedure. For the case of brain tumors and clinically relevant absorbed doses, the proposed approach derives isoeffective doses that are much lower than the fixed RBE method, regardless of considering synergism. Thus, for a tumor that receives a mean total absorbed dose of 15 Gy (value achievable with 50 ppm of boron concentration and typical beams used in the clinic), the photon-isoeffective doses are 28 Gy (IsoE) and 30 Gy (IsoE) (without and with synergism, respectively), in contrast to 51 Gy (RBE) for the fixed RBE method. When the clinical outcome of the Argentine cutaneous melanoma treatments is assessed with regard to the doses derived from the standard procedure, it follows that the fixed RBE approach is not suitable to understand the observed clinical results in terms of the photon radiotherapy data. Moreover, even though the assumed ^{10}B concentration in tumors is lowered to reduce the obtained doses with the standard procedure, the fixed RBE approach is still unsuitable to explain the observed outcomes (the model is always rejected with *P* values of virtually zero). Additionally, the numbers of controlled tumors predicted by the proposed approach are statistically consistent with observed outcomes. As a by-product of this work, a dose-response clinical reference for single-fraction melanoma treatments is developed. © 2012 by Radiation Research Society

INTRODUCTION

Since 1936, neutron capture therapy (NCT) had been proposed conceptually by Gordon Locher (*1*) as a realizable option for cancer treatment. In his work, a comprehensive review of neutron reactions was presented with special reference to those reactions that produce ions after neutron capture.

Currently, the nuclide of preference for NCT is the stable isotope ^{10}B, which occurs naturally with an abundance of 19%. The technique is therefore called boron neutron capture therapy (BNCT). Since a conceptually simple idea is not always straightforward to implement, BNCT is still a work in progress in many countries in regard to basic and applied multidisciplinary research as well as active clinical protocols. A historical perspective of the early approaches and initial applications of BNCT can be found in W. H. Sweet's article (*2*), and the most recent works are presented in the proceedings of the last two BNCT symposia (*3, 4*).

BNCT is strategically based on the high killing efficiency and short track length in tissue of the light ions produced after ^{10}B thermal neutron capture, an α particle and a ^{7}Li recoil nucleus. These particles are ejected, 93.7% of the time, with initial kinetic energies of 1,470 keV and 840 keV, respectively, together with a 478 keV γ photon produced by the decay of the excited ^{7}Li. In the remaining 6.3% of cases, α and ^{7}Li particles are emitted with energies of 1,770 keV and 1,016 keV, respectively, and no γ ray is produced. These light ions deposit their energy in tissue along a path comparable to the size of a mammalian cell, thereby producing high-energy transfer and eventually complex DNA damage, provided that chromatin is intersected by their trajectories.

There are still many open questions in this field of research that are critical to answer to understand the efficacy of BNCT, and to provide common ground for a successful comparison with other treatment options. Although most of these questions are intrinsically related to the biology and physiology of the tissues involved, some intrinsic charac-

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teristics of dose delivery in BNCT are essential to analyze and better correlate tumor and normal tissue dose-effect relationships with conventional radiation therapy.

The Complex Nature of a BNCT Radiation Field

A reactor- or accelerator-based BNCT facility, although tailored to provide the appropriate thermal neutron flux penetration and intensity, always result in an unavoidable mixture of neutrons and γ rays. Several secondary reactions are produced in tissue by neutrons, involving the generation of prompt γ emission from neutron capture in hydrogen, protons and ^{14}C recoils from ^{14}N neutron capture, fast proton recoils from hydrogen elastic interactions with fast neutrons and, of course, ^{10}B neutron capture reactions. From the biological point of view, however, the different contributions have substantially dissimilar effectiveness in cell killing. Despite the stochastic aspects of energy deposition by ionizing radiation which, depending on the particle type, can lead to large uncertainties in the microscopic dose (*5*), ions are typically more effective in producing unrepairable DNA damage per unit dose than are electrons, and thus their relative biological effectiveness (RBE) factors are usually greater than 1. Far from being considered just single numbers, light and heavy ion RBEs are functions of the dose, dose rate and survival level, these dependences being mainly inherited from the reference radiation rather than being characteristic properties of their action on living cells (*6–8*). Moreover, the microdistribution of ^{10}B in tissues, together with the differences in the tumor vasculature and structure compared to normal tissues (*9*), led to a ^{10}B compound-dependent RBE, or compound biological effectiveness factor (CBE) (*10, 11*).

Photon-Isoeffective Dose Calculation

In the current BNCT paradigm, seeking to relate the effects observed in a clinical BNCT protocol to the corresponding outcomes in photon therapy, ''RBE-weighted'' doses [expressed alternatively in Gy-Eq, Gy (RBE), or Gy (W), among others] are customarily calculated by the addition of the different contributions, each one multiplied by a fixed (dose and dose rate independent) RBE factor. These fixed RBE factors are accepted single numbers derived from different studies, biological systems and end points. Despite this diversity, they are assumed to be ''representative'' of the relative effectiveness of each radiation component. The most important objection that can be made to the standard procedure is that these factors are taken as fixed numbers, although they depend not only on the dose (or survival level) but also on the dose rate. However, it is important to remark that fixed RBE values as multipliers are indeed used in reporting isoeffective doses in ion beam therapy, although they change with depth (*8*). The existence of synergistic effects precludes the usually assumed independent action of the different radiations. Therefore, the unrestricted application of fixed RBE factors derived from each radiation considered independently will always lead to incorrect results.

In this work, a general approach for calculating photon-isoeffective doses in BNCT is presented. The formalism includes first-order repair of sublethal lesions by means of the generalized Lea-Catcheside factor in the modified linear-quadratic model and also considers synergistic interactions between different radiations.

Throughout this work, different examples of interest in BNCT are illustrated. First, the impact of applying fixed RBE factors for calculating RBE-weighted doses is analyzed, stressing the fact that the unrestricted use of fixed weighting factors (i.e., single numbers) will always lead to erroneous results. Then, the formalism and procedures presented herein are applied to estimate the photon-isoeffective dose for two BNCT clinical targets, namely, brain tumors and cutaneous melanoma. The first example compares RBE-weighted doses obtained with usual parameters and methodologies used clinically for BNCT with photon-isoeffective doses computed by means of the proposed general approach, and shows the impact of considering synergism between radiations. In the second example, the dosimetry of the cutaneous melanoma BNCT treatments carried out in Argentina is re-evaluated (*12*). To compare the BNCT melanoma clinical outcome with the tumor control rate achieved with standard radiotherapy, a suitable dose-response clinical reference for single-dose treatments is derived using the clinical data of recurrent or metastatic malignant melanomas presented by Bentzen *et al*. (*13*), together with a proposed tumor control probability model for any fractionated regime.

MATHEMATICAL APPROACH

Dose Calculations in Current BNCT Clinical Practice

Before presenting the proposed general approach to compute photon-isoeffective doses in BNCT, two graphical schematic examples that represent the standard procedures followed in clinical practice are discussed. For simplicity and without losing generality, the following examples will comprise only two radiation components.

The first example deals with the calculation of the RBE-weighted dose for a given combination of two radiations that produces a survival level s', applying RBE values for each individual radiation computed for a different level of effect, s.

Assume that 3 Gy of radiation A, 6 Gy of radiation B and 12 Gy of reference radiation R produce the same level of effect, s (Fig. 1). Then, the corresponding RBEs for radiation A and B and level s are $r_A^s = 4$ and $r_B^s = 2$, respectively.

Suppose the RBE-weighted dose for the combination of 1 Gy of radiation A and 1 Gy of radiation B is to be computed. Since the depicted dose-effect curve for the combination of radiation A and B (denoted AB, see Fig. 1) corresponds to that obtained using equal proportions of each radiation, then the

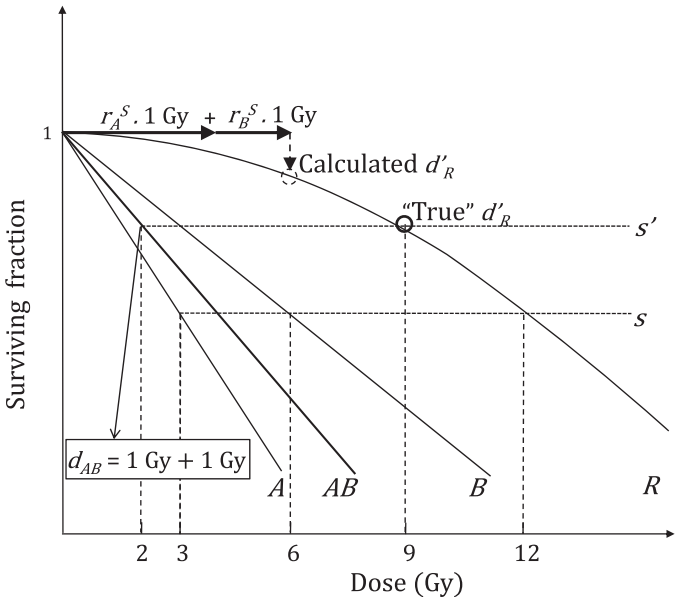

FIG. 1. ''True'' vs. ''Calculated'' RBE-weighted doses for a mixed irradiation with 1 Gy of radiation *A* and 1 Gy of radiation *B*. In this example, fixed RBE factors obtained for each individual radiation at the level *s* were used to calculate the photon-isoeffective dose for the combined 2 Gy of total dose.

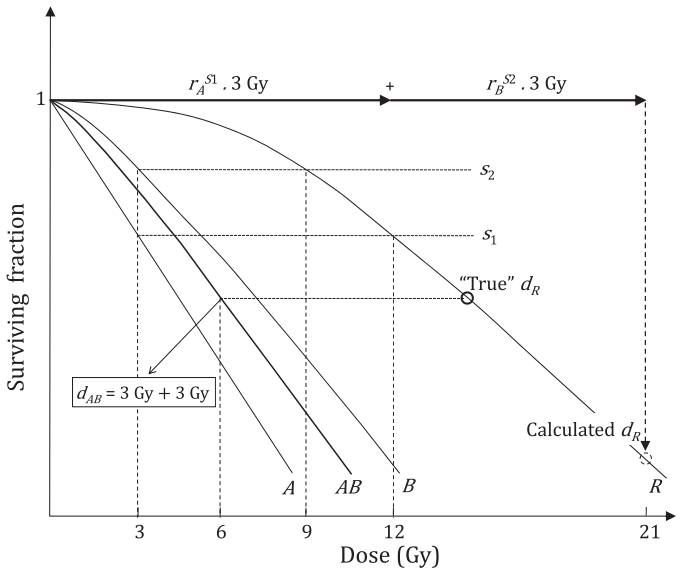

FIG. 2. ''True'' vs. ''Calculated'' RBE-weighted doses for a mixed irradiation with 3 Gy of radiation *A* and 3 Gy of radiation *B*. In this example, fixed RBE factors obtained for radiations *A* and *B* at levels s_1 and s_2, respectively, were used to calculate the photon-isoeffective dose for the combined 6 Gy of total dose.

desired RBE-weighted dose is the one that produces the same level of effect as the combination of 2 Gy of radiation *A* and *B*, i.e., s'. It can be seen in the example that the photon dose for level s', denoted as ''True'' value or d'_R, is 9 Gy.

Figure 1 illustrates one of the procedures used in BNCT for calculating the RBE-weighted dose for a given dose d_{AB} let us assume a total absorbed dose $d_{AB} = 2$ Gy, with radiation *A* and *B* contributing with equal proportions to the dose. Then, fixed RBE factors obtained for the level of effect *s*, i.e., r_A^s and r_B^s, are used to calculate the RBE-weighted dose for the level s' as follows:

$$d'_R = r_A^s \cdot 1\text{Gy} + r_B^s \cdot 1\text{Gy}. \quad (1)$$

The contribution of radiations *A* and *B* to d'_R, first and second terms in Eq. (1), is represented by the two horizontal arrows in Fig. 1. Replacing $r_A^s = 4$ and $r_B^s = 2$ in Eq. (1), the calculated RBE-weighted dose is $d'_R = 6$ Gy (RBE), clearly smaller than the depicted ''True'' value. Conversely, if RBE factors for radiations *A* and *B* and survival level s' were used to compute the RBE-weighted dose for a total absorbed dose producing the surviving fraction $s < s'$, the obtained RBE-weighted dose would be overestimated in this case.

The second example shown in Fig. 2 presents another approach used in BNCT to calculate the RBE-weighted dose for a given combination of radiations *A* and *B*.

Assume that 3 Gy of radiation *A* and 12 Gy of reference radiation *R* produce the same level of effect s_1, and that 3 Gy of radiation *B* and 9 Gy of reference radiation *R* produce the same level of effect s_2 (Fig. 2). Then, RBE values for radiation *A* at level s_1, and radiation *B* at level s_2 are $r_A^{s_1} = 4$ and $r_B^{s_2} = 3$, respectively.

Suppose the RBE-weighted dose for the combination of 3 Gy of radiation *A* and 3 Gy of radiation *B* is to be computed. In this case, fixed RBE factors obtained for levels of effect s_1 and s_2, i.e., $r_A^{s_1}$ and $r_B^{s_2}$, are used to calculate the RBE-weighted dose as follows:

$$d_R = r_A^{s_1} \cdot 3\text{Gy} + r_B^{s_2} \cdot 3\text{Gy}. \quad (2)$$

Replacing $r_A^{s_1} = 4$ and $r_A^{s_2} = 3$ in Eq. (2), the calculated RBE-weighted dose is $d_R = 21$ Gy (RBE), clearly larger than the ''True'' value (lower than 15 Gy) shown in Fig. 2 for the combination $d_{AB} = 6$ Gy. Again, horizontal arrows in Fig. 2 represent the contribution of radiations *A* and *B* to the calculated d_R using Eq. (2).

Background

The primary tenet of the theory of dual radiation action (TDRA), in its initial and more advanced versions (*14–16*), is that lethal lesions arise either from the direct action of single events or by the incoherent action of two independent events that produce damage entities that combine together to produce a lethal lesion. The former occurs with an average yield proportional to the absorbed dose, while the latter takes place at a rate proportional to the square of the dose. To link the average yield per cell of lethal lesions with survival, it is customary to assume that one lesion is enough to inactivate a cell and that the number of lethal lesions is Poisson distributed.[2] These assumptions led to survival

[2] It can be demonstrated by microdosimetric arguments that the yield of lethal lesions is not Poisson distributed, and that at large doses the LQ expression leads to logical inconsistencies (*14, 15*).

expressions formally equivalent to the linear-quadratic (LQ) formalism (*19, 20*).

In TDRA, damage entities that alone do not produce a lethal lesion are referred to as sublesions. These sublesions have the chance to interact together to produce a lethal lesion, providing they coexist in space and time. First-order lesion repair was originally considered in the pioneering works of Lea and Catcheside (*19, 20*), and was later generalized to consider any dose delivery scheme (*14, 21*). The latter led to the generalized Lea-Catcheside time factor, $G(\theta)$, with θ as the irradiation time. This factor takes into account dose protraction or fractionation by reducing the probability of sublesion interaction when repair mechanisms are present. In the context of the linear-quadratic formalism, $G(\theta)$ modifies the quadratic term. Note that although restricted spatial colocalization is a requisite for sublesion interaction (legitimate restitution or not), $G(\theta)$ only considers temporal coexistence without regard to the spatial distribution of the initial sublesions.

Sublesions produced by different radiations that coexist in space and time within the cell's gross sensitive volume have a finite probability of interacting and producing an additional effect that cannot be accounted for by the simple addition of both radiations. This effect is known as radiation synergism (*22*). Considering the LQ formalism, additional mixed terms arise as a consequence of the interactions produced by the different radiations. The number of additional terms is given by the possible combinations between different radiations and these terms are therefore modulated by appropriate Lea-Catcheside factors.

Several experiments have demonstrated the synergistic action of high- and low-LET radiations (*23–29*), when mammalian cells are exposed to sequential doses of different radiations. Zaider *et al*. (*22, 30*) have derived G factors for low- and high-LET radiations considering sequential exposures in biological systems. Suzuki (*31*) has derived the corresponding expressions but for a simultaneous irradiation with multiple types of radiations, which is the situation in BNCT. In this context, several authors (*30, 32*) have suggested that synergistic effects between the different radiations of the mixed field can be instrumental in producing an increased effect.

Therefore, considering the framework presented above, we will develop our formalism to compute BNCT photon-isoeffective doses based on the following assumptions:

1. the survival dose-response relationship is adequately described by the LQ model that accounts for dose-rate dependent sublesion repair [hence forth referred to as ''the modified LQ model'' (MLQ)], and
2. if synergism is taken into account, the survival dose-response is adequately described including the additional mixed terms from TDRA, modulated by the G factor derived by Suzuki (*31*) for a simultaneous mixed irradiation.

Later in this article we will present that for a constant dose-rate survival experiment, the modified LQ model exponentially decreases with the dose at the higher dose levels, approaching a constant slope in the semilogarithmic representation. A model that adequately represents this high-dose region is especially important in BNCT since the doses that are to be translated into single-fraction photon doses are beyond the survival experimental data.

MLQ Formalism

Let $D_1,\ldots D_4$ be the boron, thermal neutron, fast neutron and γ absorbed dose components of the BNCT mixed field. Let D_R be the dose of the reference radiation R. The goal is to find $D_R = D_R(D_1,\ldots D_4)$ (hence forth referred to as ''the isoeffective dose'') that produces the same survival level as a given combination of $D_1,\ldots,D_4$.

Independent Action

Let $S_i = S_i(D_i)$ denote the survival probability for the absorbed dose component i, $i = 1,\ldots,4$. Let $S = S(D_1,\ldots D_4)$ denote the survival probability for the combination of the four radiations. If no synergistic effects are considered, this survival can be written as

$$S(D_1,\ldots,D_4) = \prod_{i=4}^{4} S_i(D_i). \tag{3}$$

Let $S_R(D_R)$ be the survival probability for the reference radiation. Then, the desired value of $D_R = D_R(D_1,\ldots,D_4)$ must satisfy

$$S_R(D_R) = S(D_1,\ldots,D_4). \tag{4}$$

Let us suppose that

$$S_i(D_i) = \begin{cases} e^{-\alpha_i D_i} & i = 1,\ldots,3 \\ e^{-(\alpha_i D_i + G_i(\theta)\beta_i D_i^2)} & i = 4 \end{cases}, \tag{5}$$

where α_i and β_i are the coefficients of the single-fraction linear-quadratic survival model for the corresponding radiations, and $G_{i=4}(\theta)$ is the generalized Lea-Catcheside time factor for the γ component of the BNCT beam. Then, Eq. (4) becomes

$$-\ln(S_R(D_R)) = \sum\nolimits_{i=1}^{4} \alpha_i D_i + G_4(\theta)\beta_4 D_4^2. \tag{6}$$

Note that only the low-LET component is allowed to have quadratic dependence (i.e., permitting combination of sublethal damage only for this component exclusively).

Equation (6) can also be written as

$$D_R(D_1,\ldots,D_4) = \sum_{i=1}^{4} r_i(D_r) D_i, \tag{7}$$

where

$$r_i(D_R) = \begin{cases} \alpha_i \dfrac{D_R}{(-\ln(S_r(D_R)))} & i = 1,\ldots,3 \\ (\alpha_i + G_i(\theta)\beta_i D_i)\dfrac{D_R}{(-\ln(S_R(D_R)))} & i = 4 \end{cases}, \tag{8}$$

are the RBE factors as a function of the reference dose D_R. Note that the RBE factor for the γ component ($i = 4$) accounts for sublethal damage repair and the temporal pattern of dose delivery through the time factor G_4. The RBE factors can also be expressed as a function of survival probability $S = S(D_1,\ldots,D_4)$

$$r_i(S) = \begin{cases} \alpha_i \dfrac{S_R^{-1}(S)}{(-\ln(S))} & i = 1,\ldots,3 \\ (\alpha_i + G_i(\theta)\beta_i D_i)\dfrac{S_R^{-1}(S)}{-\ln(S)} & i = 4 \end{cases}, \tag{9}$$

where $S_R^{-1}(S)$ is the inverse function of the survival probability for the reference radiation.

It is important to stress that the RBE factors given by expressions (8) and (9):

(a) *depend on the reference dose*, and
(b) must be computed using the reference dose that produces the *same survival level S* as the combination of D_i, *i.e.*, $D_R = D_R(D_1,\ldots,D_4)$.

Let us assume that the survival of the reference dose is given by the single-fraction linear-quadratic dose expression:

$$-\ln(S_r(D_r)) = \alpha_R D_R + G_R(\theta')\beta_R D_R^2, \tag{10}$$

With α_R and β_R as the LQ model parameters, and $G_R(\theta')$ as the generalized Lea-Catcheside time factor for the reference radiation. Considering Eq. (10), expression (7) can be rewritten as

$$D_R(D_1,\ldots,D_4) = \sum_{i=1}^{3}\left(\frac{\alpha_i}{\alpha_R + G_R(\theta')\beta_R D_R}\right)D_i + \left(\frac{\alpha_4 + G_4(\theta)\beta_4 D_4}{\alpha_R + G_R(\theta')\beta_R D_R}\right)D_4 \tag{11}$$

Equation (11) is thus the appropriate expression for calculating the photon-isoeffective dose in the mixed-LET BNCT radiation field considering the assumptions stated above. If the reference survival data is obtained at a constant dose rate, the time θ' to deliver the dose D_R for each measured point is different. In this case, Eq. (11) must be numerically solved.

If the survival experiment is performed for a constant irradiation time (i.e., changing the dose rate for each point), $G_R(\theta') = G_R$ is constant. Additionally, if variations of $G_R(\theta')$ during irradiation can be neglected, G_R is approximately constant (e.g., if the irradiation time is much shorter than the characteristic time for repair, $G_R \cong 1$. Therefore, for these cases, Eq. (11) can be solved for D_R,

$$D_R(D_1,\ldots,D_4) = \frac{1}{2}\frac{\left(\frac{\alpha}{\beta}\right)}{G_R} \times \left(\sqrt{1 + \frac{4G_R}{\alpha_R\left(\frac{\alpha}{\beta}\right)_R}\left(\sum_{i-1}^{3}\alpha_i D_i + G_4(\theta)\beta_4 D_4^2\right)} - 1\right). \tag{12}$$

Finally, note that this expression does not explicitly use the RBE factors given by either Eq. (8) or (9), but rather depends on the MLQ model parameters for the BNCT components and reference radiation.

Synergistic Action

Let us now suppose that the different components i cause the effect synergistically, i.e., sublesions produced by one radiation can combine with the sublesions produced by any other radiation to form lethal lesions. The yield of sublesions per unit dose for each radiation component i is accounted for by $\sqrt{\beta_i}$. For each radiation alone, the survival probability is

$$-\ln(S_i(D_i)) = \alpha_i D_i + G_i(\theta)\beta_i D_i^2, \quad i = 1,\ldots,4 \tag{13}$$

where $G_i(\theta)$ is the time factor for radiation i.

The appropriate expression derived from TDRA that describes the synergism between components i and j is

$$-\ln(S_{ij}(D_i, D_j)) = G_{ij}(\theta)\sqrt{\beta_i\beta_j}D_i D_j, \quad i \neq j = 1,\ldots,4 \tag{14}$$

where $G_{ij}(\theta)$ is the time factor that accounts for first-order repair of sublesions produced by radiation i (radiation j) that reduces the probability of interaction with sublesions produced by radiation j (radiation i) during irradiation. Then, the survival probability for the combination of the four radiations is

$$-\ln(S(D_1,\ldots,D_4)) = \sum_{i=1}^{4}\alpha_i D_i + \sum_{i=1}^{4}\sum_{j=1}^{4}G_{ij}(\theta)\sqrt{\beta_i\beta_j}D_i D_j. \tag{15}$$

which includes the quadratic term in Eq. (13) if $i = j$. Assuming that the survival of the reference dose is given by expression (10)

$$\alpha_R D_R + G_R(\theta')\beta_R D_R^2 = \sum_{i-1}^{4} \alpha_i D_i + \sum_{i=1}^{4}\sum_{j=1}^{4} G_{ij}(\theta)\sqrt{\beta_i\beta_j} D_i D_j. \quad (16)$$

Equation (16) is the general expression for calculating the photon-isoeffective dose in the mixed-LET BNCT radiation field.

If variations of $G_R(\theta')$ for the reference data can be neglected ($G_R(\theta') = G_R = \text{const.}$), we finally obtain for the photon-isoeffective dose:

$$D_R(D_1, \ldots, D_4) = \frac{1}{2}\frac{\left(\frac{\alpha}{\beta}\right)_R}{G_R} \times \left(\sqrt{1 + \frac{4G_R}{\alpha_R\left(\frac{\alpha}{\beta}\right)_R}\left(\sum_{i=1}^{4}\alpha_i D_i + \sum_{i=1}^{4}\sum_{j=1}^{4} G_{ij}(\theta)\sqrt{\beta_i\beta_j D_i D_j}\right)} - 1 \right). \quad (A1)$$

This expression reduces to (12) if the high-LET components have only a linear dependence with dose, thus precluding synergistic interactions.

THE PARAMETERS OF THE MODEL

As mentioned above, Eq. (16) depends on the different parameters of the BNCT components and reference radiation that are included in the independent and synergistic MLQ models. In this section, we propose a methodology to obtain a suitable set of parameters for a given cell type from typical cell survival experiments carried out in BNCT.

Several groups have performed cell survival measurements in different experimental conditions with the aim of evaluating fixed RBE factors in diverse cell lines. These experiments consist generally in determining the dose response to: (1) a photon reference radiation; (2) the neutron beam only; and (3) the neutron beam in the presence of the boron compound (*33*).

Based on the three sets of dose-surviving fraction data obtained from these experiments, our approach to derive the model parameters is as follows. Equation (15) can be expressed as a function of the total physical dose $D_T = \sum_{i=1}^{4} D_i$ and the relative contribution of each dose component $f_i = D_i/D_T$:

$$-\ln(S(D_1, \ldots, D_4)) = \left(\sum_{i=1}^{4} f_i\alpha_i\right) D_T + G(\theta)\left(\sum_{i=1}^{4} f_i\sqrt{\beta_i}\right)^2 D_t^2, \quad (18)$$

where G_{ij} are replaced by a single expression G for all i and j, which is based on the considerations presented in Appendix I.

In the following, the characteristic repair time t_0 of the function G [Eq. (A1)] is considered a known datum obtainable from the literature.

Determination of the reference radiation parameters. Expression (10) is used to fit the photon data to obtain the reference radiation parameters α_R and β_R. Note that since survival experiments are usually performed at a constant dose rate, each measured point is obtained by changing the irradiation time. The dependence of G_R with the irradiation time θ' for constant dose rate experiments is then explicitly included in the fitting using Eq. (A1).

Determination of the BNCT radiation parameters. The BNCT radiation parameters of Eq. (18) are a total of eight, four corresponding to the neutron field, two to the boron component, and the remaining to the total γ field. To reduce the number of the free model parameters, it could be assumed that:

(a) For neutrons, $\alpha_2 = \alpha_3 = \alpha_n$ and $\beta_2 = \beta_3 = \beta_n$, based on the similar responses of biological systems when exposed to radiations with comparable lineal energy spectra (*34*).[3]

(b) For photons, $\alpha_4 = \alpha_R$ and $\beta_4 = \beta_R$, based again on the similarities in the lineal energy spectra of the reference photons (^{60}Co, about 1 MeV) and those from the beam (mostly around 2 MeV).

Taking into account these considerations, Eq. (18) is reduced to a four-parameter survival model, i.e., α_n and β_n, for the neutron components and α_B and β_B, for the boron contribution. Based on this model and survival data for the neutron beam only and neutron + ^{10}B-BPA experiments, the four parameters are simultaneously obtained, explicitly include the dependence of the Lea-Catcheside factor with the irradiation time θ for each measured data.

It is important to remark that while in BNCT it is customary to calculate radiobiological parameters ''sequentially'', (i.e., first analyzing the beam-only data and then using the obtained values to derive the boron parameters), the neutron + ^{10}B-BPA experiment contains information regarding the radiation action of neutrons with tissues apart from the ^{10}B neutron capture reactions. Then, a fitting procedure involving a simultaneous minimization of both beam-only and neutron + ^{10}B-BPA survival data is suggested to fully exploit all the available experimental information.

APPLICATION EXAMPLES

In the following, the formalism and procedures presented in sections Mathematical Approach and The Parameters of

[3] Fast neutrons in BNCT beams have energies that are mostly less than about 1 MeV. For this neutron energy group, elastic recoils with hydrogen is the most important contribution to the charged particle slowing down spectrum, with energies comparable to those of protons produced by nitrogen thermal neutron capture.

TABLE I
RBE Values for a Cell Survival Fraction $S = 0.01$ Based on the *In Vivo/In Vitro* Experiment Carried Out at the Brookhaven Medical Research Reactor (BMMR)

Component	r_i^S
X rays/beam γ photons	1
Neutrons (BMRR minus photons)	3.2
Boron (BPA)	3.8

Note. Coderre *et al*. (*35*).

the Model are applied to estimate the photon-isoeffective dose for two BNCT clinical targets, namely, brain tumors and cutaneous melanoma. The first example involves a hypothetical tumor case, and it is introduced with the aim of comparing the dose calculations carried out in the current BNCT clinical practice with those computed by means of the proposed general approach. Additionally, the impact of considering synergism is also presented. The second example is aimed to re-evaluate the clinical dosimetry of the cutaneous melanoma BNCT treatments carried out in Argentina (*12*).

Brain Tumors

Coderre *et al*. (*35*) have used the 9L rat gliosarcoma model to derive the radiobiological parameters from the *in vitro* and *in vivo*/*in vitro* clonogenic cell survival assays, and to obtain brain tumor RBEs for different surviving fractions. Based on this model, they reported 1% survival RBE values for the in *vivo*/*in vitro* experiment, as shown in Table I.

We have used the same experimental data [extracted from Fig. 2 in ref. (*35*)] to fit expression (18) by means of a weighted least-square minimization procedure. For the fitting, we have considered assumptions stated in The Parameters of the Model section, and weights were taken as the inverse of one standard deviation of the surviving fraction. Absorbed dose fractions f_i for each component were calculated based on the dose rate reported values for *in vivo* irradiations at 1.25 MW BMRR reactor power [see table 1 in ref. (*35*)].

For the G factor in Eq. (18), a single repair time of 1 h was assumed in our calculations (see Appendix I) (*36–39*). Table II lists the obtained radiobiological parameters α_R, α_B, α_n, β_R, β_B and β_n of Eq. (18), with and without considering synergism, together with corresponding RBE values.

Compared to those reported in Coderre *et al*. (*35*) (Table I), the RBE values derived with the proposed fitting procedure are smaller, the cause of these differences being the simultaneous fitting of survival data for the neutron beam only and neutron + ^{10}B-BPA experiments, the inclusion of repair of sublethal damage during the irradiation, and synergism between radiations of different quality. The impact of considering repair of sublethal damage becomes evident for the beam γ photons, since the computed RBE is lower than 1 due to the lower dose rate compared to that of the reference X-ray radiation. Note that if the fixed RBE method is applied for computing doses, the immediate consequence of using the RBE values of Table II is that the RBE-weighted doses would decrease compared to those derived with Coderre's reported values.

In the following, we compare the RBE-weighted and photon-isoeffective doses for a hypothetical tumor using correspondingly:

(a) Equation (7) and the fixed RBE values shown in Table I (used to compute tumor RBE-weighted doses in most of the clinical BNCT trials of glioblastoma), and
(b) the general expression (16) with both sets of radiobiological parameters alpha and beta listed in Table II.

Figure 3 shows the RBE-weighted dose (dashed line) and the photon-isoeffective doses assuming independent action (solid gray line) and synergistic action (solid black line) as a function of the total absorbed dose.

For a tumor that receives a mean total absorbed dose of 15 Gy (value achievable with 50 ppm of boron concentration and typical beams used in the clinic), the photon-isoeffective doses are 28 Gy (IsoE) and 30 Gy (IsoE) without and with synergism, respectively, in contrast to 51 Gy (RBE) for the fixed RBE method. It can be seen by comparing the photon-isoeffective doses (considering synergism or not) that allowing interaction between sublesions from different radiations produces a higher

TABLE II
Obtained Radiobiological Parameters for the 9L Rat Gliosarcoma *In Vivo/In Vitro* Assay, with and without Considering Synergism, and Corresponding RBE Values for a Cell Surviving Fraction S = 0.01

	α (Gy^{-1})	β (Gy^{-2})				
Reference X rays	0.2008	0.0078				
	Model with synergism			Model without synergism		
	α (Gy^{-1})	β (Gy^{-2})	r_i^S	α (Gy^{-1})	β (Gy^{-2})	r_i^S
Beam γ photons	0.2008	0.0078	0.953	0.2008	0.0078	0.947
Neutrons	0.4972	0.088	2.786	0.844	0	2.689
Boron (BPA)	0.9091	0.0019	2.936	0.8896	0	2.835

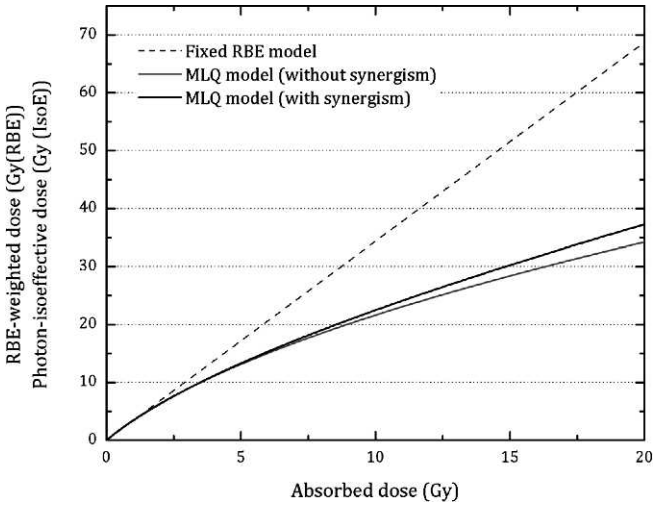

FIG. 3. RBE-weighted and photon-isoeffective doses as a function of the total absorbed dose computed with the fixed RBE model (dashed line), and the MLQ model with and without synergism (solid black and gray lines), respectively, and brain tumor parameters shown in Tables I and II.

isoeffective dose for the same absorbed dose. Thus, in the abovementioned example, synergism increases in about 7% the isoeffective dose for 15 Gy of absorbed dose.

Clinical Cutaneous Melanoma

Seven patients with cutaneous nodular melanoma of the extremities were treated using the mixed thermal-epithermal neutron beam of the RA-6 reactor (Centro Atómico Bariloche, Argentina) (*12, 40*). As part of the Phase I/II BNCT clinical trial, 10 irradiations were performed that comprised different anatomical areas such as thigh, calf, heel and foot sole.

A statistical analysis of the clinical results was previously reported in González *et al*. (*41*), involving the outcome of 104 identified melanoma nodules. In that work, the objective response (OR) of the tumors was considered as a positive response. Local responses were graded according to WHO criteria. Tumor volumes were computed either on post-treatment CT scans or by clinical inspection, external marking and photographic documentation. A minimum follow-up of 3 months was considered for assessing responses.

In this work, we re-evaluate the clinical dosimetry of the cutaneous melanoma treatments by applying the formalism and procedures presented in Mathematical Approach: and The Parameters of the Model sections. The radiobiological parameters α_R, α_B, α_n, β_R, β_B and β_n of Eq. (18) for this pathology were computed from an *in vitro* cell survival experiment using the human melanoma metastatic cell line Mel-J (*42*).[4] For the fitting, the same considerations as explained in the previous example were followed. A repair time of 1 h was also assumed (Appendix I). In Table III, the obtained radiobiological parameters of Eq. (18) are presented.

[4] Additional data were provided by Rossini AE (private communication).

TABLE III
Obtained Radiobiological Parameters for the *In Vitro* Mel-J Cell Survival Experiment

	α (Gy^{-1})	β (Gy^{-2})
Reference ^{60}Co γ photons	0.0482	0.0333
Beam γ photons	0.0482	0.0333
Neutrons	0.5775	0.0464
Boron (BPA)	0.8156	0.1021

Responses of the 104 subcutaneous nodular lesions were analyzed with regard to the RBE-weighted and isoeffective minimum doses, and the tumor size. In this work, only complete responses (CR) were considered as positive responses (i.e., 49 out of 104 of analyzed lesions showed CR).

To compare the BNCT melanoma clinical outcome with the tumor control rate achieved with standard radiotherapy, we have derived a suitable dose-response clinical reference for single dose treatments. For this, we have used the clinical data from 239 recurrent or metastatic malignant melanomas presented by Bentzen *et al*. (*13*), and proposed a tumor control probability model for any fractionated regime (TCP_{MLQ}) that, for high single doses, does not overestimate the control effect. Details on the clinical reference construction are presented in Appendix II.

Figure 4 shows the distribution of tumor diameters and minimum doses of the lesions together with their response, assuming for dose calculations the same tumor-to-blood ^{10}B concentration ratio used in the treatments (i.e., a T/B ratio of 3.5), and

(a) Eq. (7) and the fixed RBE factors used in the melanoma clinical trial [1 for X rays/beam γ photons, 3 for neutrons, with 3.8 for boron (BPA)], and
(b) the general expression (16) with the radiobiological parameters α and β listed in Table III.

In addition, Fig. 4 shows the 50%, 80% and 95% iso-tumor control probability curves predicted by the tumor control probability model TCP_{MLQ} introduced in Appendix II.

A simple analysis of the data shown in Fig. 4 reveals that the range and values of the minimum photon-isoeffective doses are drastically reduced compared to those obtained with the fixed RBE model. Additionally, the single-fraction isoeffective curves that are the clinical reference data for standard radiotherapy show that the fixed RBE model is not adequate to compute photon-isoeffective doses. Note that in the region at the right of the 95% tumor control isocurve almost all lesions should present complete response. While this is clearly not the case for the fixed RBE approach, the MLQ formalism distributes the lesions more adequately in

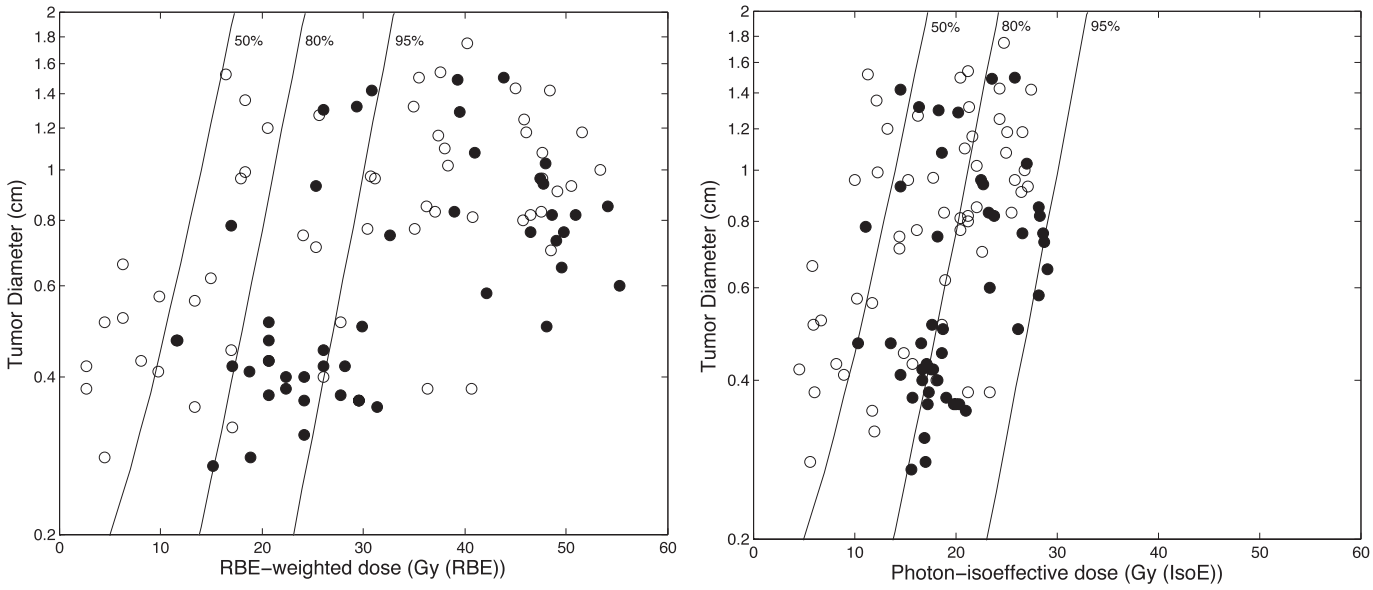

FIG. 4. Scatter plots showing the distribution of tumor diameters and minimum doses of the lesions with their response for fixed RBE-weighted (left) and photon isoeffective dose (right) models. Filled circles indicate complete response, and open circles indicate any other clinical outcome. Continuous lines represent the iso-tumor control probability curves computed with the TCP_{MLQ} for 50%, 80% and 95% of tumor control.

the size-dose space. Therefore, the fixed RBE approach is not suitable to understand the observed BNCT clinical outcome in terms of the photon radiotherapy results.

DISCUSSION

The formalism presented in this work was conceived with the idea of providing a suitable framework for calculating photon-isoeffective doses in BNCT. We started from stressing the fact that multiplying each dose component by a fixed RBE factor (as is customarily carried out in BNCT) leads to an ''isoeffective dose'' that is almost always incorrect. Then, a more realistic approach was developed that essentially exploits all the experimental information available from survival experiments. The inclusion of first-order repair by means of the modified LQ model and synergistic interactions did not complicate unnecessarily the photon-isoeffective dose calculations. Moreover, if variations of the Lea-Catcheside factor for the reference radiation data can be neglected, the photon-isoeffective dose calculation is reduced to solving a simple quadratic equation.

The introduced formalism to compute photon-isoeffective doses considers the interaction between sublethal lesions produced by different radiations, i.e., synergism. We based our formalism on the linear-quadratic expression containing a mixed, or synergistic, term because this expression naturally follows from the Dual Radiation Action theory. In addition, this theory permitted the inclusion of the generalized Lea-Catcheside time factor G in the synergistic contribution. Nevertheless, other radiobiological models that would allow first-order lesion repair and synergism could be used for our approach without invalidating the presented results.

In the Brain Tumors section we have determined the RBE factors with and without considering synergism for GS9L and a surviving fraction of 0.01 (Table II). Note that for both approaches the sets of RBEs are very similar. Conversely, the resulting α coefficients for the neutron component are very different (0.49 Gy^{-1} vs. 0.84 Gy^{-1}) as a consequence of forcing the quadratic term (and synergism) to be disregarded. Therefore, while the fixed RBE method for both sets of fixed RBEs would result in very similar RBE-weighted doses for any absorbed dose, the MLQ model will predict different isoeffective doses, especially in the high-dose region, which is of major importance in BNCT (as shown in Fig. 3).

We have analyzed the clinical BNCT melanoma outcomes in light of the presented formalism. For computing photon-isoeffective doses, the same tumor-to-blood ^{10}B concentration ratio used for the clinical dosimetry of 3.5 was assumed. However, experimental data presented by our group in the context of the Argentine clinical trial (*43*), among data from other authors (*44*), would suggest a lower mean boron uptake for the particular case of nodular melanomas (NM) (the type of melanoma that has been treated thus far in Argentina). For example, a mean T/B experimental ratio of 2.5 $\pm$ 0.6 ($\pm$1 SD) was reported by the CNEA-Roffo BNCT group in ref. (*43*).

As mentioned in the Clinical Cutaneous Melanoma section, the fixed RBE-weighted doses computed for the melanoma clinical trial are grossly overestimated when compared to the dose-response standard radiotherapy

clinical results. One may wonder if this overestimation effect could be explained only in terms of a high T/B ratio assumed for dose calculations. To assess this, we have computed the expected number of nodules with positive response for the fixed RBE and MLQ models under the assumption that each lesion has a probability of being controlled given by the TCP_{MLQ}. To evaluate whether the difference between the observed and expected numbers of positive responses can be due to the randomness of the process, the P value was computed for each model. Results for both approaches of computing doses show that P values for a 3.5 T/B ratio were almost zero. However, when T/B ratios similar to those determined experimentally are considered for calculations (i.e., ratios as low as 2 or smaller), the fixed RBE model is always rejected ($P \approx$ for all T/B ratios) while the predicted numbers of positive responses with the MLQ model have very good chances to occur ($P > 0.1$).

CONCLUSIONS

A suitable framework for calculating photon-isoeffective doses in boron neutron capture therapy was introduced with the aim to relate the effects observed with such a radiation technique to the outcome after standard photon therapy. The approach presented essentially exploits all the experimental information available from survival experiments, and includes some natural radiation phenomena, i.e., first-order repair of sublethal lesions and synergistic interactions between different radiations that, although usually neglected, should be considered in the BNCT dosimetry scenario. In addition, it is sufficiently simple to be included in any treatment planning system devoted to BNCT.

The assessment of the clinical outcome of the Argentine cutaneous melanoma treatments was accomplished using a dose-response clinical reference specifically derived in this work for single-fraction dose treatments. Results showed that the fixed RBE approach is not suitable to explain the observed clinical results in terms of the photon radiotherapy data, even if only half the ^{10}B concentration in the tumors were assumed. For the same group of BNCT patients, the MLQ approach derives isoeffective doses that are much more consistent to those considered therapeutic with single-fraction radiation therapies. It would be interesting, however, if additional clinical dose-response data from other series of treated patients (including different BNCT targets) were assessed following the proposed methodology. Apart from the evidence resulting from the analyzed clinical protocol, the extremely high single-fraction fixed RBE-based doses should certainly cast doubts on the simplified classical procedure to compute isoeffective doses in BNCT.

Finally, an extension of the proposed formalism is currently under development to deal with normal tissue responses and to compute photon-isoeffective doses for early and late effects.

APPENDIX I

The Factor G_{ij}

Considered in general, $G_{ij}(\theta)$ accounts for the repair of pairs of sublesions produced during the time θ, each one produced by radiations i and j.

If production of one of the sublesions does not affect the production of the other one, it can be shown that $G_{ij}(\theta)$ can be expressed as a sum of independent G factors, i.e., $G_{ij}(\theta) = a_i G_i(\theta) + a_j G_j(\theta)$, each one weighted by the relative proportion between components a_i and a_j, with $a_i + a_j = 1$.

Assuming that the repair kinetics is well described by a bi-exponential decline with fast and slow characteristic repair times t_{0_f} and t_{0_s} independent of LET (*45*) (or equivalently, independent of the component of the BNCT mixed field):

$$G_k(\theta, t_{0_f}, t_{0_s}) = a_{k_f} G(\theta, t_{0_f}) + a_{k_s} G(\theta, t_{0_s}),$$

where a_{k_f} and a_{k_s} are the relative contributions of the sublesions repaired by the fast and slow kinetics for radiation component k (with $a_{k_f} + a_{k_s} = 1$). $G(\theta,t_0)$ is the generalized Lea-Catcheside time factor for simultaneous build up and repair of radiation damage,

$$G(\theta, t_0) = 2\left(\frac{2t_0}{\theta} - 2\left(\frac{2t_0}{\theta}\right)^2 (1 - e^{-\theta/t_0})\right), \qquad \text{A1}$$

considering a constant dose rate irradiation.

After some algebra,

$$G_{ij}(\theta) = G(\theta, t_{0_s}) - (a_i a_{i_f} + a_j a_{j_f})\big(G(\theta, t_{0_s}) - G\big(\theta, t_{0_f}\big)\big).$$

Now, considering irradiation times involved in typical cell survival experiments carried out in BNCT (i.e., θ between 10–30 min) and repair times t_{0_f} and t_{0_s} of about 30 min and 14 h (*45*),

$$G_{ij}(\theta) \cong G(\theta, t_0 = 1h), \ \forall i, j$$

which means that selecting a convenient single value for t_0 equal to 1 h, the 16 functions G_{ij} can be well approximated by a single G function. For example, for a 15 min irradiation of a mixture of low- and high-LET radiations with relative proportions of 0.2 and 0.8, and relative proportions of sublesions repaired by fast kinetics of 0.53 and 0.2 (*45*), respectively, $G_{ij}(\theta = 15 \text{ min}) = 0.94$ while $G(\theta = 15 \text{ min}, t_0 = 1 \text{ h}) = 0.92$ the relative difference being less than 3%.

APPENDIX II

Constructing an Appropriate Dose-Response Clinical Reference for Single-Dose Melanoma Treatments

We have used the clinical data obtained from a series of 121 patients having 239 recurrent or metastatic malignant melanomas as presented by Bentzen *et al*. (*13*) to construct ''the best'' dose-response clinical reference for single-dose melanoma treatments.

Dose-response clinical data with correction for tumor size were reported in ref. (*13*) together with a suitable four-parameter TCP_{LQ} model for explaining the outcomes as follows:

$$TCP_{LQ}(\phi, D, d) = \exp(-c_1 \phi^{c_2} \exp(-D(\alpha + \beta d))). \qquad \text{A2}$$

In this model, ϕ represents the average tumor diameter with c_1 and c_2 parameters that modulate the effect of tumor volume on local control probability, and with $S_{LQ}(D,d) = \exp(-D(\alpha + \beta d))$ the simplest LQ survival expression that accounts for fractionated regimens with total dose D and dose per fraction d.

BNCT is a single radiation fraction therapy that delivers large radiation doses per treatment, such as in the case of stereotactic radiosurgery or stereotactic radiotherapy. Although the tumor control model given by Eq. (A2) can be applied for single-dose treatments, the behavior of the

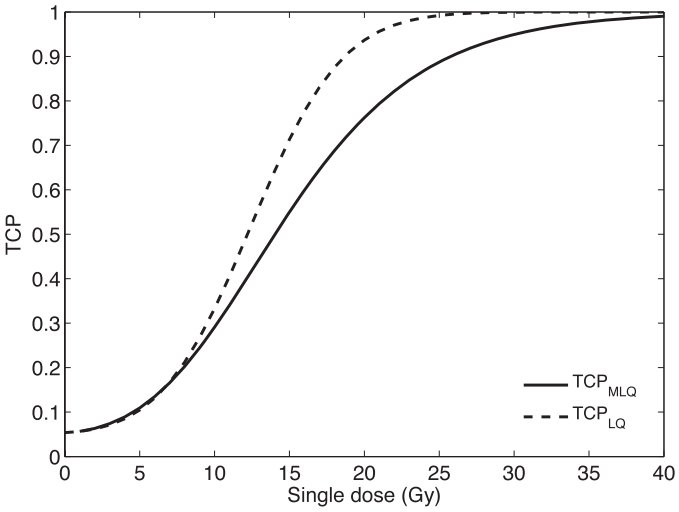

FIG. 5. Comparison between tumor control probabilities models, TCP_{LQ} and TCP_{MLQ}, for a 1 cm tumor diameter and single-fraction radiation therapy. Parameters of the models were derived from the clinical data of recurrent or metastatic malignant melanomas, as presented by Bentzen *et al*. (*10*).

simplest LQ model for the cell survival has been questioned for high-dose levels. Taking into account the BNCT dosimetry scenario, we have proposed a modified version of the TCP_{LQ} model that explicitly includes the first-order lesion repair, replacing S_{LQ} in Eq. (A2) by the S_{MLQ} expression for a fractionated regime:

$$S_{MLQ}(D,d) = \exp(-D(\alpha + G(\theta)\beta d)). \tag{A3}$$

If one assumes that the dose per fraction is delivered at a constant dose rate $\dot{d}$ for time θ, and $G(\theta)$ given by Eq. (A1), expression (A3) can be written

$$S_{MLQ}(D,d) = \exp(-D(w_1 - w_2(1 - e^{-w_3 d})/d))), \tag{A4}$$

with $w_1 = \alpha + 2\beta t_0\dot{d}$, $w_2 = 2\beta(t_0\dot{d})^2$, and $w_3 = 1/t_0\dot{d}$, and t_0 the characteristic repair time. Note that the slope of the log-S_{MLQ} curve tends to a constant value at high doses as observed in survival experiments (*46*), whereas the LQ model predicts a constantly decreasing slope. Moreover, Eq. (A3) is functionally equivalent to one of the earliest survival models, named the Hug-Kellerer cell survival equation (*47*), when the latter is extended to a fractionated regime (see Appendix III).

The resulting tumor control model TCP_{MLQ} is the following five-parameter equation:

$$TCP_{MLQ}(\phi,D,d) = \exp\big(-c_1{'}\phi^{c_2{'}}\exp\big(-D\big(w_1 + w_2\big(1 - e^{-w_3 d}\big)/d\big)\big)\big). \tag{A5}$$

Taking $d = D/n$ (where n is the number of fractions) and considering the validity of the S_{LQ} model in the low and mid-range of doses, we should have

$$i.\quad \lim_{D\to 0} TCP_{LQ} = \lim_{D\to 0} TCP_{MLQ}$$

$$ii.\quad \lim_{D\to 0} \frac{d(TCP_{LQ})}{dD} = \lim_{D\to 0} \frac{d(TCP_{MLQ})}{dD},$$

for all n (i.e., for any multifraction regime). Conditions *i*. and *ii*. lead to the following relations

$$\begin{aligned} &i.\quad c_1\phi^{c_2} = c_1{'}\phi^{c_2{'}},\\ &ii.\quad \alpha = w_1 - w_2 w_3. \end{aligned} \tag{A6}$$

Bentzen *et al*. (*13*) presented the four-parameter estimates of Eq. (A2).

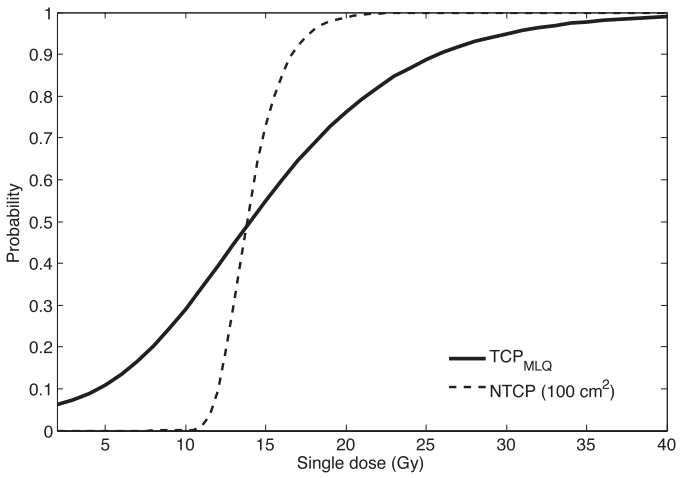

FIG. 6. Comparison between TCP_{MLQ} and the NTCP curve for a reference skin area of 100 cm^2 and moist desquamation reported in ref. (*41*).

Their parameter values were $c_1 = 2.92$, $c_2 = 72$, $\alpha = 0.0053$ Gy^{-1}, and $\beta = 0.0092$ Gy^{-2} . Then, using relations (A6), Eq. (A4) is finally reduced to

$$TCP_{MLQ}(\phi,D,d) = \exp\big(-c_1\phi^{c_2}\exp\big(-D\big(\alpha + w_2 w_3 + w_2\big(1 - e^{-w_3 d}\big)/d\big)\big)\big), \tag{A7}$$

with w_2 and w_3 as the only two adjustable parameters.

We have used the dose-response clinical data for the 5 and 9 Gy/fx patient groups [extracted from Fig. 5b and c in ref. (*13*)] to obtain these parameters by means of a least-square minimization procedure. The final estimates are $w_2 = 2.01$ and $w_3 = 0.107$ Gy^{-1}. Figure 5 presents the comparison between TCP_{LQ} and TCP_{MLQ} for a 1 cm tumor diameter and single-fraction radiation therapy, considering the parameters of the obtained models.

This figure shows that the TCP_{MLQ} derives higher single-fraction doses compared to the TCP_{LQ} for the same control probability, with the difference becoming noticeable for doses above 7 Gy. This effect was also observed by Ekstrand (*48*) who analyzed the Hug-Kellerer equation as the universal cell survival curve (S_{HK}) to determine single-fraction doses that are equivalent to the dose in a conventional multi-fraction radiation therapy.

A review of a recent work that applies high-dose single-fraction treatments indicates that 90% control doses of melanoma metastases ranges between 17–25 Gy (*49*). Since the proposed TCP_{MLQ} model is in concordance with these values and takes into account a survival model that better fits the experimental results in the high-dose region, we take this tumor control model as a more appropriate dose-response clinical reference for single-dose melanoma treatments.

In cases of cutaneous melanoma, skin is considered the critical normal structure or organ at risk. Thus, it is the organ that limits the dose delivered. In Fig. 6, we compare the TCP_{MLQ} shown in Fig. 5 and the Normal Tissue Complication Probability (NTCP) curve for a reference skin area of 100 cm^2 and dry desquamation, as derived in (*41*).

APPENDIX III

Derivation of the Hug-Kellerer Survival Model for a Multifraction Regime of Dose Delivery

Hug and Kellerer (*47*) derived a survival model of the form

$$S_{HK}(D) = \exp(-k_1 D + k_2(1 - e^{-k_3 D})), \tag{A8}$$

with the condition that at $D = 0$, $\ln(S_{HK}) = 0$ and k_i, $i = 1,\ldots,3$ adjustable parameters.

Let us assume that the biological effect E_1 for one dose fraction of size d is

$$E_1 = k_1 d - k_2(1 - e^{-k_3 d}).$$

Following the assumptions stated by Douglas and Fowler (*50*) to derive the effect for a multifraction regime using the LQ model, we have shown that the cumulative effect after n equal fractions of size d is $E_n = nE_1$. The survival curve for fractionated doses of fraction size d in the semi-log representation is supported by a straight line. Defining the slope k' of the supporting line such that after a dose d the effect $E1 = k'd$, then:

$$k' = k_1 - k_2(1 - e^{-k_3 d})/d. \quad \text{A9}$$

For a series of n fractions of size d, the total effect is

$$E_n = nk'd = nd(k_1 - k_2(1 - e^{-k_3 d})/d) = D(k_1 - k_2(1 - e^{-k_3 d})/d). \quad \text{A10}$$

Therefore, the overall survival for a fractionated regime is then

$$S_{HK}(D, d) = \exp\left(-D\left(k_1 + \frac{k_2(1 - e^{-k_3 d})}{d}\right)\right).$$

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