Advances in BORON NEUTRON CAPTURE THERAPY

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INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 2023

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Printed by the IAEA in Austria
June 2023

IAEA Library Cataloguing in Publication Data

Names: International Atomic Energy Agency.
Title: Advances in boron neutron capture therapy / International Atomic Energy Agency.
Description: Vienna : International Atomic Energy Agency, 2023. | Includes bibliographical references.
Identifiers: IAEAL 23-01601 | ISBN 978–92–0–132723–9 (paperback : alk. paper) | ISBN 978–92–0–132623–2 (pdf)
Subjects: LCSH: | Boron-neutron capture therapy. | Cancer—Treatment. | Radiotherapy.
Classification: UDC 661.65:615.849 | CRCP/BOR/002

FOREWORD

Boron neutron capture therapy is a combination cancer therapy utilizing an external beam of neutrons of appropriate energies and a 10B-containing pharmaceutical that preferentially concentrates in tumour tissues of the patient. The nuclear reaction between the neutron and the boron nucleus generates an alpha particle and a recoiling ^{7}Li nucleus that create a high degree of localized damage to the tumour cell. This concept, while simple and first proposed in 1936 by G. Locher, has proven challenging to implement and involves truly multidisciplinary teams. One difficulty in the past was that there were few neutron sources around the world of sufficient intensity and of the required energies for boron neutron capture therapy. The only neutron sources suitable were research reactors, which were distributed at universities and government laboratories around the world. Research reactors are not clinical environments, and, while many clinical trials were conducted and several centres reported encouraging results, the number of patients treated was small and the comparison of results from different centres was not simple. In 2001, the IAEA published Current Status of Neutron Capture Therapy (IAEA-TECDOC-1223), which summarized the state of the field based around reactor sources.

In the past two decades, the number of research reactors involved in boron neutron capture therapy has precipitously declined. However, during the same period, compact accelerator based neutron sources have been developed utilizing a variety of different accelerator technologies. Accelerators have the advantages that they can be installed directly in hospitals and clinics, providing a more suitable environment for treating patients, and that they can be registered as medical devices. In Japan, in 2020 the use of a cyclotron based neutron source in combination with a boron pharmaceutical and treatment planning device was approved for the treatment of unresectable, locally advanced, and recurrent carcinoma of the head and neck, funded through the national health insurance system.

These developments have led to renewed interest in boron neutron capture therapy around the world, to significant commercial investment, and to the realization that it was time for the IAEA to issue another report reflecting the many advances in the field. This report is the output of two virtual technical meetings on the subject, one in July 2020 attended by 106 participants from 20 Member States and the second in March 2022 attended by 111 participants from 18 Member States.

The IAEA acknowledges the valuable contributions and support of the numerous international experts who contributed to the drafting and review of this publication, in particular, W. Sauerwein (Germany) for his assistance in organizing the first consultancy and technical meetings and K. Igawa (Japan) for her assistance in coordinating and networking throughout this project. The IAEA officers responsible for this publication were I. Swainson, D. Ridikas, and A. Jalilian of the Division of Physical and Chemical Sciences and O. Belyakov of the Division of Human Health.

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10 METHODS AND MODELS OF DOSE CALCULATION

Boron neutron capture therapy is characterized by the interaction of a mixed radiation field with biological tissues. Thermal neutrons are captured by ^{10}B, producing an α particle and a Li ion (Fig. 15), and by other elements in tissue, among which the most relevant is ^{14}N, producing a proton (Table 7). These charged particles have moderate-to-high ionization density values and short ranges in tissue (Table 20). Epithermal neutrons thermalize in tissue mainly through elastic scattering from hydrogen (moderation), each losing on average half of its energy per collision and producing a recoil proton that deposits dose. Finally, neutrons are captured by ^{1}H in a reaction that produces low-LET radiation: a 2.224 MeV γ ray. Another source of low-LET radiation is the γ rays present in the beam or produced in neutron interactions with surrounding materials: this structural component is unavoidable but kept as low as possible during design of the beam and collimator system (see Section 4). Dosimetry is thus characterized by the calculation of the absorbed dose due to the charged particles heavier than electrons (depositing all their energy locally) and the electrons set in motion by the sparsely ionizing photons. With sophisticated transport calculation techniques, the different contributions are tracked separately.

TABLE 20. PROPERTIES OF CHARGED PARTICLES RELEVANT TO DOSE AND DOSE DISTRIBUTION PRODUCED BY NEUTRON CAPTURE REACTIONS [569–570]

	$^{10}B(n,\alpha)^{7}Li$		$^{14}N(n,p)^{14}C$
	α	^{7}Li	p
LET* (keV/μm)	164	151	44
Range in tissue (μm)	9	5	11

* Averaged over track intersection segments within a cell

Biological effects are the result of the action of ionizing radiation in living systems. These effects are directly related to absorbed dose. Therefore, a deep understanding of the spatial scale and geometry of the problem and of the methods to correctly calculate dose is essential to evaluate and optimize the clinical use of BNCT. Absorbed doses can be calculated using different strategies according to the physical situation, for example, assuming charged particle or electronic equilibrium (see Section 10.1.1.4), which makes calculation more straightforward. In preclinical models such as cell cultures or small animals, or in the case of calculation of dose to skin for patients, the equilibrium hypothesis may not be correct. It is thus necessary to apply more detailed simulations. Section 10.2 deals with this issue: the need to set up the correct absorbed dose calculation in different scenarios. Two approaches have been described: macroscopic (Section 10.2.1) and microscopic (Section 10.2.2), separating the issue of dose calculation to different spatial scales and starting from different perspectives: the whole sample/tissue/patient or the single cell.

Each of the BNCT radiation components has different biological effects: high and low LET components produce different ionization densities. The high-LET radiation (Table 20), densely ionizing, directly damages the DNA. Low-LET radiation, sparsely ionizing, mainly causes indirect damage by forming free radicals. The fact that there is not a unique relationship between absorbed dose and induced biological effects, prompts the need for translation of BNCT doses into a reference radiation dose capable of predicting clinical effects. To this end, the clinical experience with photon therapy is used as a reference. Radiobiological experiments with cell cultures or animals irradiated with BNCT, with neutrons only, and with photons, provide the fundamental information for models which aim to translate the BNCT absorbed dose into the dose of the reference radiation producing the same effect. With a BNCT dose expressed in photon equivalent units, i.e., with a photon isoeffective dose, medical doctors can

prescribe doses and predict the outcome of the therapy according to the clinical experience gained with photon radiotherapy. Different strategies conceived to translate BNCT dose into photon equivalent units are described in Section 10.3.4, highlighting the range of validity of the traditional and modern models and the equivalent dose unit.

To deliver a safe and effective BNCT treatment, it is necessary to calculate absorbed dose in the most exact and precise way and to know how to relate this physical quantity to its effects in tumour and in normal tissues. The key ingredients are correct dose calculation, representative radiobiological data, and reliable models to translate mixed-field absorbed dose into photon-equivalent units. Advice presented in Sections 10.2–10.3 is thus particularly important: incorrect assumptions in dose calculation and incorrect models may propagate significant errors in the determination of isoeffective dose in patients, leading to a bias in evaluating the relationship between clinical outcome and calculated dose.

10.1 GENERAL CONCEPTS

The following subsections outline some of the fundamental concepts and inputs that are required for dose calculation.

10.1.1 KERMA and absorbed dose

10.1.1.1 KERMA

KERMA is an acronym for Kinetic Energy Released per unit MAss, defined as the sum of the initial kinetic energies of all the charged particles liberated by uncharged ionizing radiation (photons and neutrons) in a volume of matter, divided by its mass (Gy) [571].

10.1.1.2 Absorbed dose

'Absorbed dose' refers to the energy imparted by ionizing radiation per unit mass of irradiated material measured by the SI unit gray (Gy) [571].

10.1.1.3 Equilibrium states of radiation

General definitions and solutions for absorbed dose require complete knowledge of the radiation fields involved at all points. This requirement, however, can be relaxed by assuming the existence of equilibrium conditions for the radiation fields. Under these hypotheses, detailed knowledge of spatial, directional or energy dependence can be omitted, depending on the type of equilibrium that is assumed. An equilibrium state is defined as one in which the balance between the radiant energy of the incoming and outgoing particles in a given volume is zero.

10.1.1.4 Charged particle equilibrium

Given the importance of this case in dosimetry, a partial equilibrium condition is defined, known as charged particle equilibrium (CPE). This means that the balance of the radiant energy of the incoming and outgoing charged particles, in an infinitesimal volume, is zero [571]. CPE is of particular importance when a material medium is irradiated by an external beam of uncharged particles (photons, neutrons).

10.1.1.5 KERMA and dose in boron neutron capture therapy

The knowledge of the mean energy imparted to matter within a certain volume, i.e., the absorbed dose, is critical for all radiobiological calculations that seek to understand the relationship to the observed effect. Simplifications like those described above need to be carefully considered and reported regarding their adoption, especially in BNCT. In BNCT, absorbed dose components are typically referred to by common names; e.g., boron dose, thermal neutron dose, fast neutron dose, and photon dose (see Table 7 and later discussion in Sections 10.3.3.1). Structural or induced photons deserve special attention since the KERMA approximation is not applicable at air–solid interfaces in the first millimetres (the electron build-up layer). On the other hand, Bremsstrahlung photons, generated from electron interactions, deposit their energy elsewhere. However, this contribution is unimportant for light ions and low energy electrons in low Z materials (i.e., living tissue), and it is usually already considered in the mass absorption coefficients. As mentioned above, in the case of interfaces such as skin, assessments based on KERMA are not reliable and a detailed dose calculation with full particle transport needs to be considered. Section 10.2 explores these considerations more deeply for typical situation where BNCT absorbed dose needs to be calculated.

Other factors that require consideration for the calculation of the absorbed dose are the accuracy of the cross-section data used in Monte Carlo simulations, and the spatial scale of interest. These issues are discussed briefly in the next section.

10.1.2 Nuclear and atomic data

Reliable data libraries to be used in the Monte Carlo transport are necessary to estimate the components of the mixed field responsible of dose deposition in tissues. For neutron transport, the quantity required for estimating the role of each element is the isotopic macroscopic cross section, defined as:

$$\Sigma_i = n_i \sigma_i = \frac{\varrho N_A x_i}{A_i} \sigma_i \tag{16}$$

where ϱ is the material density, N_A is Avogadro's number, x_i the mass proportion of the isotope, A_i its atomic mass, and σ_i the total interaction cross section. This gives the probability per unit length that a neutron of energy E interacts with a nucleus of the isotope i. These values are dependent on the neutron energy. For tissues in particular, macroscopic cross sections depend on the material composition. Table 21 gives the probability of interaction for a representative tissue for BNCT (adult brain with the composition defined by the ICRU Report 46 [572]). It shows that the probability is highest for ^{1}H, followed by ^{16}O, with much lower probabilities ^{12}C, ^{14}N, and negligibly low values for the minor elements and isotopes (illustrated in Fig. 60). The following interactions may take place with some of the nuclei in tissue:

- Elastic scattering (including the moderating effect of light nuclei);
- Inelastic scattering (if the neutron has enough energy to excite the target nucleus);
- Neutron capture.

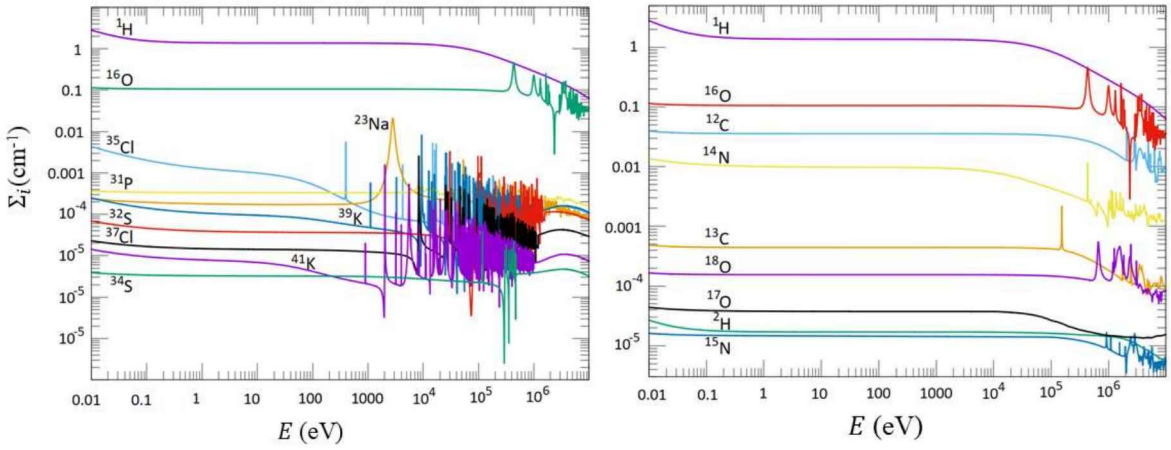

FIG. 60. Macroscopic cross sections for the components of brain tissue as a function of neutron energy. Data are taken from cross sections of the database ENDF/B-VIII.0[22] (courtesy of I. Porras, University of Granada).

TABLE 21. ELEMENTAL AND ISOTOPIC COMPOSITION OF ADULT BRAIN TISSUE (DENSITY 1.04 g/cm^3)

	A_i (g/mol)	Element mass fraction	Isotopic fraction	x_i	$\frac{x_i}{A_i}$ (mol/g)	$\frac{\varrho N_A x_i}{A_i}$ (at/(b·cm))
^{1}H	1.008	0.107	0.99985	1.070×10^{-1}	1.062×10^{-1}	6.648×10^{-2}
^{2}H	2.014	0.107	0.00015	1.605×10^{-5}	7.969×10^{-6}	4.991×10^{-6}
^{12}C	12.000	0.145	0.98900	1.434×10^{-1}	1.195×10^{-2}	7.484×10^{-3}
^{13}C	13.003	0.145	0.01100	1.595×10^{-3}	1.227×10^{-4}	7.682×10^{-5}
^{14}N	14.003	0.022	0.99634	2.192×10^{-2}	1.565×10^{-3}	9.803×10^{-4}
^{15}N	15.000	0.022	0.00366	8.052×10^{-5}	5.368×10^{-6}	3.362×10^{-6}
^{16}O	15.995	0.712	0.99762	7.103×10^{-1}	4.441×10^{-2}	2.781×10^{-2}
^{17}O	16.999	0.712	0.00038	2.706×10^{-4}	1.592×10^{-5}	9.968×10^{-6}
^{18}O	17.999	0.712	0.00200	1.424×10^{-3}	7.911×10^{-5}	4.955×10^{-5}
^{23}Na	22.990	0.002	1.00000	2.000×10^{-3}	8.700×10^{-5}	5.448×10^{-5}
^{31}P	30.974	0.004	1.00000	4.000×10^{-3}	1.291×10^{-4}	8.088×10^{-5}
^{32}S	31.972	0.002	0.95020	1.900×10^{-3}	5.944×10^{-5}	3.723×10^{-5}
^{33}S	32.971	0.002	0.00750	1.500×10^{-5}	4.549×10^{-7}	2.849×10^{-7}
^{34}S	33.968	0.002	0.04210	8.420×10^{-5}	2.479×10^{-6}	1.552×10^{-6}
^{36}S	35.967	0.002	0.00020	4.000×10^{-7}	1.112×10^{-8}	6.965×10^{-9}
^{35}Cl	34.969	0.003	0.75770	2.273×10^{-3}	6.500×10^{-5}	4.071×10^{-5}
^{37}Cl	36.966	0.003	0.24230	7.269×10^{-4}	1.966×10^{-5}	1.232×10^{-5}
^{39}K	38.964	0.003	0.93260	2.798×10^{-3}	7.181×10^{-5}	4.497×10^{-5}
^{40}K	39.964	0.003	0.00012	3.600×10^{-7}	9.008×10^{-9}	5.642×10^{-9}
^{41}K	40.962	0.003	0.06230	1.869×10^{-4}	4.563×10^{-6}	2.858×10^{-6}

The probability of each is given by the ratio between the cross section of the process and the total interaction cross section (the sum of all). With ^{1}H, only elastic scattering and (n,γ) neutron capture reactions are possible. In the latter case, a 2.224 MeV γ ray is produced. The interaction of neutrons in tissue are well described by Monte Carlo codes. All evaluated data bases show a perfect agreement in case of hydrogen: ENDF, since the version ENDF/B-V.2 (1994) to the most recent ENDF/B-VIII.0 (2018)[23] [573], JENDL data, from JENDL-3.2 (1994)[24] to JENDL-4.0 (2012) [574] and JEFF data, from 3.0 to 3.3 (2017)[25]. The agreement between all the evaluations and experimental data is also good. The capture process involving epithermal

[22] ENDF: https://www-nds.iaea.org/exfor/endf.htm
[23] ENDF/B-VIII.0: https://www.nndc.bnl.gov/endf/b8.0/index.html
[24] JENDL-3.2: https://inis.iaea.org/collection/NCLCollectionStore/_Public/26/038/26038454.pdf
[25] JEFF-3.3: https://www.oecd-nea.org/dbdata/jeff/jeff33/

neutrons is about four orders of magnitude less probable than elastic scattering; therefore, neutrons lose energy primarily by elastic collisions with hydrogen. When thermalized, they will still produce collisions until they are captured (by H, N or other minor elements as Cl) or escape from the body.

With respect to oxygen, the agreement is very good between different data bases (and the experimental values, except for energies above the first resonance). The dominating process is elastic scattering, and capture processes are much less important than for hydrogen. However, as can be seen in Fig. 61 the (n,α) process may play some role if neutrons have energy greater than 2.35 MeV. As the cross section is lower than 1 barn, this capture will not produce a significant perturbation of the neutron flux, but it may contribute to the dose. Some discrepancies are found between different data sets. In cases where the neutron spectrum has a high energy tail, the contribution of this process to the dose ought to be at least estimated.

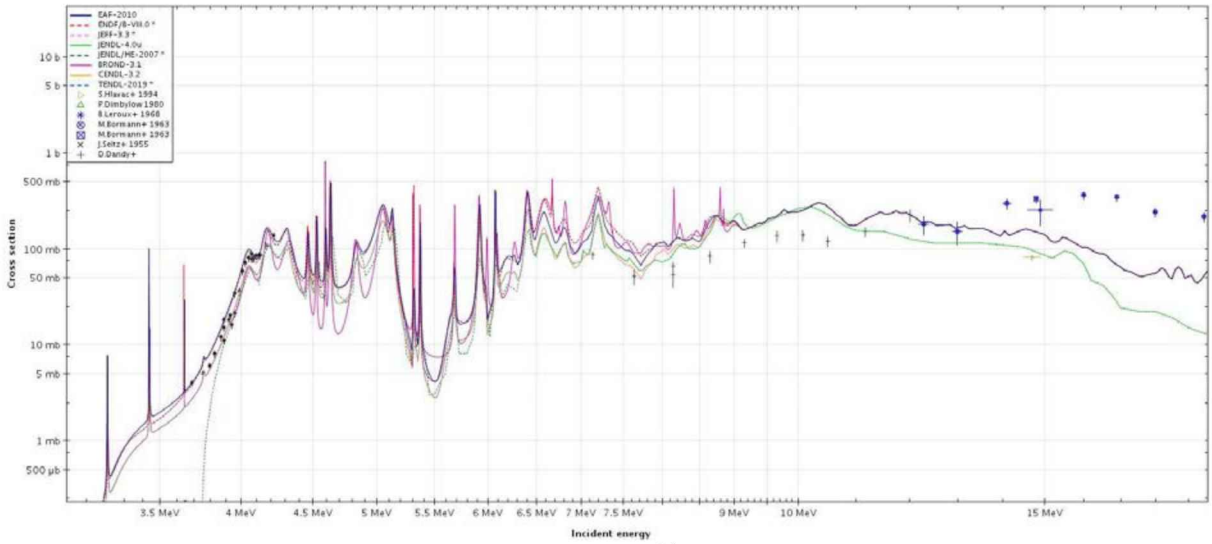

FIG. 61. Variation between cross section datasets for the $^{16}O(n,\alpha)$ reaction. Data prepared from the JANIS database[26] (courtesy of I. Porras, University of Granada).

During the thermalization process, as the neutron energy falls the capture process (for which the cross sections usually present a $1/v$ behaviour) becomes increasingly important. The most likely capture process is radiative capture for most of the elements in organic tissues (except for ^{14}N and ^{10}B). The probability per unit length of a neutron producing secondary photons when interacting with nucleus i is given by:

$$\Sigma_{i,\gamma} = n_i \, \sigma_{i,\gamma} = \frac{\varrho N_A x_i}{A_i} \sigma_{i,\gamma} \qquad (17)$$

where $\sigma_{i,\gamma}$ is the (n,γ) cross section. The energy transferred to secondary photons per unit length can be evaluated from the product $\Sigma_{i,\gamma} Q$, where Q is the reaction Q-value (Section 2.1.2). These are evaluated for thermal neutrons (for which capture reactions are most likely) in Table 22 for the most relevant elements.

Although neutron capture by ^{1}H is the most important contributor to secondary photons, the role of ^{35}Cl ought to be considered. The impact of the $^{35}Cl(n,\gamma)$ reaction has been shown to contribute to the dose delivered in normal brain at levels up to 12% of the total normal tissue dose (when ^{10}B is absent) [394]. Data on this cross section present some uncertainties, as there

[26] JANIS: https://www.oecd-nea.org/jcms/pl_39910/janis

are discrepancies between experimental data and evaluations and the $1/v$ behaviour is not confirmed by experimental data. For this reason, a measurement of this reaction was proposed at the neutron time of flight (n_TOF) facility at CERN, and the results are currently under analysis [575].

TABLE 22. QUANTITIES TO CALCULATE THE MACROSCOPIC CROSS SECTION OF RADIATIVE CAPTURE FOR THE PRINCIPAL ELEMENTS IN TISSUES

i	$\frac{\varrho N_A x_i}{A_i}$ (at/(b·cm))	$\sigma_{i,\gamma}$(0.025 eV) (b)	$\Sigma_{i,\gamma}$(0.025 eV) (cm^{-1})	Q (MeV)	$\Sigma_{i,\gamma}Q$ (MeV/cm)	Percentage
^{1}H	6.64825×10^{-2}	0.3326000	2.21121×10^{-2}	2.224	4.9177×10^{-2}	73.844
^{12}C	7.48440×10^{-3}	0.0038600	2.88900×10^{-5}	4.946	1.4289×10^{-4}	0.214
^{14}N	9.8035×10^{-4}	0.0749913	7.35180×10^{-5}	10.833	7.9642×10^{-4}	1.196
^{16}O	2.78123×10^{-2}	0.0001700	4.72810×10^{-6}	4.143	1.9589×10^{-5}	0.029
^{23}Na	5.44841×10^{-5}	0.5280000	2.87680×10^{-5}	6.960	2.0022×10^{-4}	0.300
^{31}P	8.08798×10^{-5}	0.1693610	1.36980×10^{-5}	7.935	1.0869×10^{-4}	0.163
^{32}S	3.72261×10^{-5}	0.5282150	1.96630×10^{-5}	8.641	1.6991×10^{-4}	0.255
^{35}Cl	4.07109×10^{-5}	43.6122000	1.77549×10^{-3}	8.580	1.5234×10^{-2}	22.875
^{39}K	4.49708×10^{-5}	2.1274200	9.56720×10^{-5}	7.800	7.4624×10^{-4}	1.120

The (n,γ) reaction with ^{14}N lacks experimental data in the EXFOR database[27] (only three points which do not match the evaluations except one at thermal energy). Although this process accounts just for 1.2% of the total energy released by photons, a confirmation of the $1/v$ behaviour would be desirable by a dedicated measurement.

Different evaluated data sets are in fair agreement for the ^{14}N(n,p) reaction, except near the region of resonances, where JENDL-4.0 presents some differences with respect to ENDF/B-VIII and JEFF-3.3. However, in this region this reaction has less importance with respect to the total KERMA than in the thermal region. The great importance of this reaction for low-energy neutrons and the mentioned discrepancies between the experimental data and evaluations (Fig. 62) motivated a new measurement at the n_TOF facility[28] at CERN, Switzerland, which is currently under analysis [576]. The reduction of this uncertainty will improve the accuracy of the neutron dose determination in normal tissues.

In the same experiment, the cross section of ^{35}Cl(n,p) was also measured, which may be relevant at certain energies because of its strong resonances. The first, at 398 keV, makes this process dominate the brain KERMA factor, although its effect in a continuous epithermal beam is expected to be small as the resonance is very narrow. Nevertheless, it is interesting to measure these resonances as there is some discrepancy between evaluations and experimental data.

Finally, the boron neutron capture reaction (Fig. 15) is the main one responsible for dose deposition in BNCT, especially in tumour when ^{10}B is preferentially concentrated within cancer cells. This is a well-known reaction for which all cross section datasets coincide, in good agreement with experimental data. It is considered a standard for neutron cross section measurements.

[27] EXFOR: https://www-nds.iaea.org/exfor/
[28] https://home.cern/science/experiments/n_tof

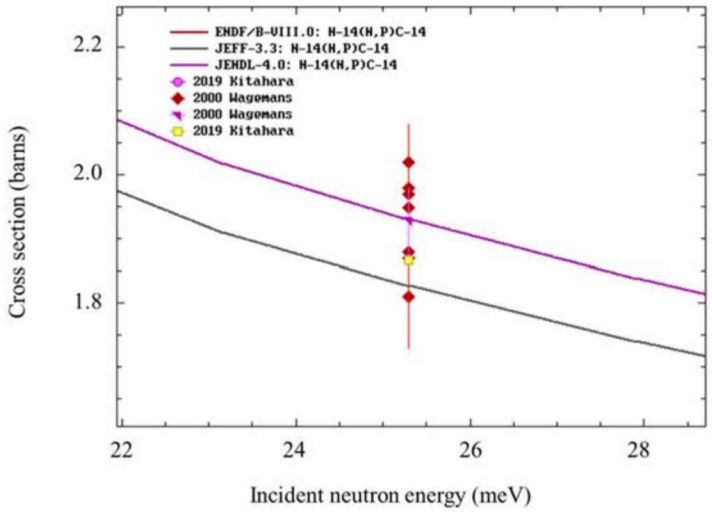

FIG. 62. Cross section data for the $^{14}N(n,p)$ reaction near thermal neutron energies showing the variation among three databases and four experimental measurements (courtesy of I. Porras, University of Granada).

Even if discrepancies are found in processes whose contribution to the total absorbed dose is low, the use of different nuclear data may result in different calculated absorbed doses, especially in the fast energy range. For this reason, it is good practice to take this aspect into consideration, when precise dose calculation is needed. These considerations show that the choice of the nuclear data may play a role in the result of dosimetry and the evaluation of the data table to be used is a very important issue. The same holds for the choice of the Monte Carlo code, because the numerical treatment (tables, interpolations, cut-offs, score calculation) and the physical models implemented can lead to differences between results of the same simulated system. For this reason, it is meaningful to benchmark different codes and to gain deeper insights into the differences between the model and the physical reality according to the simulation tool selected.

10.1.3 Macroscopic and microscopic scales

The calculation of the boron dose, D_B, calls for additional considerations regarding the ranges of the emitted α and ^{7}Li particles because they are comparable to the cell size (Table 20). This fact, together with the nature of the boron compounds and their cellular localization, requires distinction to be made between spatial scales of interest.

It has been shown that a large variation of boron microdistribution in tumour and normal cells is possible, either extracellular, intracellular, uniform, attached to the cell membrane, located in the cell cytoplasm, etc. and all these situations can coexist in different tissues (and change in time) during irradiation. Therefore, KERMA factors as a surrogate quantity for dose are not always applicable since a uniform distribution assumption is needed at a particular length-scale. If the scale of interest is orders of magnitude greater than the cell size (e.g., clinical treatment volume, organs at risk, etc., see Section 12) and CPE conditions are fulfilled in a given volume of interest, then an average boron concentration suffices for the calculation and KERMA factors can be used. If, however, the scale of interest is comparable to the particle ranges (e.g., monolayer of cells in culture or tumour cells scattered within normal tissue) then a detailed dose calculation (and eventually a microdosimetric approach, see Section 10.2.2), might be necessary.

The same can be said regarding nitrogen (or thermal neutron) dose, D_N. Although not as relevant as boron dose, D_B, nitrogen may be non-uniformly distributed in multiple situations

(e.g., cell cultures, tumour cells interspersed in normal tissue with higher nitrogen content than normal tissues, etc.). In such situations involve the same considerations regarding the scale of interest.

10.2 METHODS FOR CALCULATING ABSORBED DOSES

The following sections discuss the methods for calculating doses over different length scales. In particular, the dose calculation is intended to be simulated with Monte Carlo transport codes, for which one of the assumptions is that the particle density in the system is sufficiently low to neglect interactions between them. In some cases, dose calculation could be performed using other tools such as analytical codes, which are not considered here.

10.2.1 Macroscopic calculation

10.2.1.1 Dose calculation in preclinical models

Radiobiological models are used to study BNCT effects and to compare them with those of conventional photon therapy. The dose–effect relationship in these models is used to convert absorbed dose into photon-equivalent units, as explained below in Section 10.3. In any such strategy, the robustness of the translation of BNCT dose into suitable units for predicting the clinical outcome depends on the validity of the dose–effect curves that are generated.

The preclinical models typically used are monolayer cell cultures (mainly tumour cells) and small animals (rats, mice). In Section 9, the types of models and the biological assays are described in detail. Here, the focus is on dose calculation to construct the dose–effect curves.

One typical radiobiological experiment involves the assessment of cell survival as a function of dose, employing monolayer cell cultures with thickness of around 10 μm. Typically, these are tumour cells: survival is taken as an indicator of the capacity of BNCT to kill a tumour, with the assumption that tumour control directly depends on the number of inactivated cells. In these experiments, cells are cultured as adherent in flasks to a certain point, treated with boron, and then irradiated in a thermal neutron 'beam' (or field). Dose–survival curves are built for photon, neutron-only, and neutron + boron irradiations. In BNCT, separate dose components are considered because they have different spatial distributions and different biological consequences. Absorbed dose needs to be calculated with Monte Carlo transport codes, and the components that contribute, as summarized in Table 7, are:

- High-LET charged particles generated by neutron capture by boron (when present): D_B;
- Intermediate LET charged particles produced by neutron capture by nitrogen and by neutron scattering on hydrogen: D_N and D_H;
- Low-LET photons coming from the irradiation beam and environment as well as from neutron capture by hydrogen: D_γ.

As explained above, the products of the neutron interactions have different LETs and ranges, and equilibrium may or may not be fulfilled in any specific case.

If equilibrium holds, dose is equal to KERMA. In this case, calculation is more straightforward, because KERMA is obtained by neutron/photon fluence multiplied by fluence-to-KERMA conversion factors which are specified in the input file for Monte Carlo simulation. In this situation, the first piece of advice is to choose suitable fluence-to-KERMA conversion factors tables. Reference [577] highlights the importance of including tables comprising factors for

low energy neutrons. In fact, if the lower limit of the KERMA-energy table is too high, fluence of lower energy will be converted into KERMA using the lowest available factor. This can cause incorrect estimation of the thermal component of the dose, which is very important in the case of BNCT, because the interactions of neutrons with nitrogen and boron have larger cross sections at lower energies. In Ref. [577], conversion tables derived from ICRU Report 63 [578], which extended those from ICRU Report 46 [572] to lower energies, are used and the difference in dose calculations are shown.

Another way of calculating absorbed dose in case of equilibrium is to calculate the reaction rate of the event of interest (for example, neutron capture by nitrogen) and multiply it by the Q value of the reaction, with the assumption that all the energy of the produced proton and of the recoil nucleus is deposited locally. In both cases, only the primary radiation is transported, and the simulation can reach statistical convergence in a short time.

The accuracy of the equilibrium assumption has been tested for short ranged, high LET, charged particles in monolayer cell cultures and found to be inaccurate. In fact, for a cell layer of the order of 10 μm, KERMA overestimates dose by about 10% for the boron component and by about 40% for nitrogen [579]. Thus, the calculation needs to include transport of all the secondary particles. This involves more sophisticated computational strategies. In fact, generating and transporting the secondary particles generated from the primary neutron source (i.e., simulating all the reactions occurring in the volume of interest), would be highly inefficient, and statistical convergence may be too difficult to obtain. Moreover, as described above, cross sections of charged particle production need to be well validated. Hence, simulation might be divided into two steps: (i) characterizing the primary neutron/γ field around the volume of interest, and (ii) using this field to generate charged particles. For high-LET components, one strategy is to sample α particles, ^{7}Li nuclei, and protons in the monolayer of cells, transport them and calculate their dose contributions. If nitrogen and boron are also present elsewhere (for example in the culture medium), reaction products need to be generated there too. To be precise, ^{14}C also needs to be sampled and transported, but, given its very short range, that part of the Q value transported by the recoiling carbon nucleus can be assumed to be deposited locally. The total dose deposited then needs to be normalized by the reaction rate of each previously calculated interaction.

For the low-LET component due to photons, electron transport is always necessary, unless the experiment is specially designed to avoid this requirement. Electrons are generated in cells but also in the surrounding materials, depending on the photon spectrum present in the facility. To define the portion of the geometry which contributes to electron dose in cells, it is necessary to establish the furthest range of the generated electrons. As electron transport is quite expensive in terms of computational time, a useful strategy is to produce a track-by-track neutron/photon source at a sufficient distance from the cells to consider all the electrons that can reach the volume of interest. The track-by-track approach reproduces the local primary field allowing a shorter calculation time, because it limits the need for fully detailed dose calculations to a reduced portion of the geometry.

Dose due to α and Li ions depends critically on the boron concentration present in cells during irradiation. In any simulation it is best to specify a representative boron concentration in the material describing the cells, as its presence may influence the neutron transport. However, D_B ought to be calculated by normalizing the results using the actual concentration taken up by cells at the moment of irradiation (i.e., measured in cells cultivated in the same way and on the same day as those used for the survival assessment). This is particularly important when cells are irradiated without boron in the culture medium. In fact, the dose–survival curve will change

if D_B is not evaluated with a representative ^{10}B-concentration, as in most cases total BNCT dose is dominated by the boron component.

Some types of cells are cultivated in suspension and irradiated in vials instead of in flasks. In this case, during irradiation they form a pellet in the bottom of the holder, constituting a thicker volume than a monolayer adherent cell layer (some tens of μm versus about 10 μm). The geometry of the pellet depends on the quantity of cells present in the vial and in each case the possibility to use a KERMA approach for dose needs to be verified. Electronic equilibrium depends on the quantity of culture medium surrounding the pellet, but a detailed transport of electrons is probably necessary.

Other in-vitro models may allow the calculation of KERMA instead of dose. For example, in tissue samples cultivated in vitro, typically with larger thicknesses, the high-LET charged component could be absorbed entirely within the volume of interest. The same holds for spheroids or other 3D-cell constructs. It is thus important to verify the validity of the equilibrium hypothesis in order to choose the most adequate and efficient computational strategy on a case-by-case basis.

For small animal models, the same best practice holds true: to verify whether the hypothesis of equilibrium holds in each specific experiment. If dose needs to be calculated inside entire internal organs, high-LET charged particle equilibrium exists, because the linear dimensions of the organs are several orders of magnitude longer than the particle range. However, sometimes dose needs to be calculated in thin parts of the animal, i.e., small superficial nodules, thin layers of skin, or exposed tissues. In this case, part of the energy of secondary particles may escape the volume of interest, requiring detailed transport calculations. For γ dose, transient electronic equilibrium may hold in the inner organs, but skin, superficial tumours, or structures close to the interface of different materials may be critical and require detailed simulation.

Charged particles are normally transported using a condensed history approach in Monte Carlo simulations [580]. When the volume of interest is very small, e.g., in cells or thin exposed tissues, it is important to set the value of the energy step into which the condensed history is divided such that a sufficient number of steps is calculated within the cells or tissues.

As explained in more detail below, transport of thermal neutrons in matter can be affected by the molecular binding of atoms and by their motion. When dose components due to low energy neutrons need to be computed, it is important to use cross sections considering these effects (often described as 'thermal treatment'). In calculations related to radiobiological models, this effect is especially relevant because they are irradiated in thermal neutron fields (or with epithermal neutron beams with an interposed moderator). It is therefore important to use the specific cross sections, as described in Ref. [577].

To summarize, it is always necessary to verify the condition of equilibrium in the radiobiological experiment:

- For monolayer adherent cell cultures, detailed transport of all the secondary particles is necessary to avoid overestimation;
- For suspensions, tissues cultivated in-vitro, 3D cell constructs and spheroids, the validity of assuming the CPE condition needs to be verified. Electronic equilibrium does not exist in typical irradiation set-ups;

- For small animals, CPE is likely to be satisfied, as well as transient electronic equilibrium in the inner organs. However, for superficial small nodules and thin layers of tissues exposed to neutrons, small volumes close to the interface between different materials may be critical for KERMA/dose calculation;
- Boron concentration needs to be known as precisely as possible, considering the biological variability that causes different boron uptake in different experiments even when the administration protocol is the same. While for animal models this is more difficult, for cells, boron measurement ought to be performed in cultures prepared on the same day and in the same way as those irradiated for survival experiments;
- For low energy neutrons, use cross sections that consider the specific molecular binding and motion of hydrogen;
- Specific computational strategies are needed to ensure efficient and statistically reliable simulation, for correct cross section selection (i.e., thermal treatment for low-energy neutrons), and to ensure correct transport of charged particles by condensed history.

As noted above, the same radiobiological models exposed to neutrons are also exposed to a reference photon dose for comparison. It is important to verify that this part of dose evaluation is also correct by verifying that the nominal dose imparted by the irradiation system corresponds to the true absorbed dose. Sometimes, in fact, equilibrium may hold in the calibration set-up, while it may be lacking in the cells/animal irradiation configuration due to geometrical constraints. In this case, a simulation is necessary to compute a normalization factor between the nominal and the true absorbed dose.

10.2.1.2 Dose calculation in patients

This section focuses on the simulation of absorbed dose in in-patient models; most of the suggestions for in-patient dose calculations are the same as those described above for radiobiological models.

For in-patient dosimetry, a model for Monte Carlo transport calculations is obtained from the medical images of the patient. Ideally, the most precise model is obtained by converting the minimal geometrical unit of the medical image into a voxel whose material is inferred from the same study. Dose would thus be calculated in these small volumes, and Monte Carlo methods could be used to perform detailed simulation of dose absorbed in each voxel. However, since equilibrium is surely satisfied in most of the patient volume, calculation has always been performed to obtain KERMA, using superimposed meshes for scoring neutron/photon fluence and coupling them to fluence-to-KERMA conversion tables [577].

This approach has some limitations, for example in skin, where secondary charged particles may escape the tissue and deposit their energy elsewhere, without being replaced by others coming from external volumes. Moreover, it may not hold in small voxels at the interface of materials with very different composition/density such as soft/lung tissues. Skin is an important organ in BNCT, both for superficial and deep-seated tumours, because it is sometimes the organ that limits irradiation time. Especially when using BPA as the boron carrier, skin takes up a higher boron concentration than other normal tissues do. Thus, the tolerance dose may be reached in skin before other organs. For this reason, a possible solution is to dedicate part of the calculation to a detailed dose deposition simulation in those regions of the patient geometry where equilibrium cannot be assumed [581]. This is relevant when the region is the one limiting the irradiation time or is a critical organ at risk (see Section 12.5).

As explained in Ref. [6], for thermal neutron transport in tissues, it is better to use cross sections that consider thermal treatment. This simulates the interaction of low-energy neutrons with the target nucleus considering both its motion and its chemical binding. In the case of biological tissues, this is especially relevant for hydrogen. For BNCT, the effect of the molecular binding for low energy neutrons is often considered by using the cross section for water molecules at 300 K. However, more accurate results can be obtained using cross sections that consider the binding and dynamics of hydrogen in specific molecules within each irradiated tissue [582–583].

In patients, even more importantly than in animal models, the presence of boron in tissues needs to be modelled in the simulation. The change in low energy neutron fluence due to interaction with ^{10}B (self-shielding) affects the calculation of the boron, nitrogen, and hydrogen dose components. Thus, it is better to include a representative ^{10}B-concentration in the description of materials (see Section 11.1.1 concerning thermal neutron flux depression due to boron). More refined results will be possible in the future when the true boron distribution can be determined (see Sections 8 and 9.3) and included in the patient model for the Treatment Planning Systems (TPS).

As for the case of radiobiological models, there follows a list of good practice for absorbed dose in human voxelized patient models:

- Be aware that KERMA may overestimate the dose in skin or in small regions close to interfaces between different materials/densities when these regions constitute a limiting tissue for irradiation (Section 10.2.1.1);
- For accurate neutron transport, describe the materials adding the expected boron concentration (within 20–30%) in irradiated tissues;
- Use thermal treatment to consider molecular binding and the motion of target atoms (hydrogen);
- Use proper fluence-to-KERMA conversion factors, accounting for low-energy neutrons (Section 10.2.1.1);
- Especially when the neutron spectrum has a fast component, consider minor reactions due to capture by Cl and O (Section 10.1.2);
- For accurate dose delivery, calculate boron dose using information on measured boron concentration in blood during the treatment to ensure that the boron dose component is known as precisely as possible.

10.2.1.3 Further considerations

The possibility of obtaining statistically robust results in very small volumes usually requires the use of non-analogue Monte Carlo techniques. This refers to statistical bias that is artificially introduced into the physical probability density functions that describe the interaction of particles, with the goal of improving effectiveness, i.e., to obtain a result with low variance in shorter calculation times, without affecting the correctness of the score. These techniques are embedded in the codes, and statistical convergence is affected in this case by complex effects, not only by the number of particles transported. A user has to pay attention and check the convergence of the results, in particular, to check if the variance associated with the result is a reliable indicator of sufficient statistics. Some codes, such as MCNP, provide several tests to check that the score calculated is statistically reliable.

Another consideration is the necessity to use adequately validated models. Monte Carlo calculations are only reliable if they can reproduce experimental results. In the case of mixed-field dosimetry, validation is particularly difficult because the measurement of absorbed dose in biological systems is challenging with respect to the set-up and for the detectors to be employed. However, it is possible to validate models in relevant parts of the calculations, for example, in their ability to adequately calculate the neutron flux and the photon dose present in the irradiation position. Thus, it is possible to prepare a model of the irradiation facility and to calculate flux/dose for simple situations. It is also possible to employ detectors (such as activation wires or foils or other small systems such as self-powered neutron detectors) applied to cell flasks or to the skin of small animals to evaluate the reproducibility of the measurements by the computational model. Such detectors can be also applied to the skin of patients during irradiation as a monitor of fluence/dose. The experimental results can be used to compute normalization factors to adjust the Monte Carlo results.

10.2.2 Microdosimetric calculations

Due to the short ranges of protons, α particles, and ^{7}Li ions produced by neutron reactions, the absorbed doses are heterogeneously distributed on the microscopic scale in BNCT radiation fields. This heterogeneity influences the biological effectiveness of this therapy, and many dosimetric studies have been devoted to its evaluation. Those studies are designated as 'microdosimetry' [29] and usually distinguished from conventional dosimetry because the stochastic nature of the energy depositions needs to be considered. Thus, the absorbed doses in microscopic sites are generally expressed by their frequency and dose probability density functions, $f(z)$ and $d(z)$, respectively, where z denotes the specific energy defined in ICRU Report 36 [584]. It has the unit of J/kg (or Gy) as for absorbed dose, but it is a stochastic quantity. The principles and application of microdosimetry to BNCT are summarized in Ref. [585].

Assuming that the scale of interest is comparable to the cell size (i.e., the microscopic scale), it is important to verify whether a microdosimetric approach is needed to better estimate the actual dose imparted to cells [584]. Here, it is necessary to consider: (a) the ionization density of a given BNCT dose component and (b) the charged particle production rate of that dose component per unit volume, examined at microscopic (i.e., μm) scales. For electrons set in motion by photons (sparsely ionizing radiation), the number of events needed to deposit 1 Gy of absorbed dose in a cell is sufficiently large (more than 1000 per Gy) to preclude the need of an approach that considers the stochastic aspects at the cellular level. For ^{10}B neutron capture reactions (high ionization density), however, the mean number of reactions needed to produce 1 Gy is of the order of 3 per cell, considering a spherical cell of about 10 μm in diameter [569]. Considering nitrogen neutron capture reactions (intermediate ionization density), although less significant than boron reactions, the mean number of protons and ^{14}C recoils that contribute to 1 Gy of absorbed dose in a cell is about 14, again considering a cell diameter of about 10 μm. Since Poisson statistics govern the behaviour of random particle traversals [586], these mean numbers are equal to the variance of the number of hits. Thus, cell-to-cell variability is very important, including the possibility that certain cells receive very few events (or none) even at therapeutic doses.

In BNCT radiation fields, both intra- and intercellular heterogeneities in ^{10}B-distribution significantly influence the specific energy in a cell nucleus, z_n, which can be regarded as a

[29] Microdosimetry is the branch of radiation biophysics that studies the spatial, temporal and spectral stochastic aspects of energy deposition by radiation in microscopic structures.

better index for expressing the biological effectiveness in comparison to the equilibrium absorbed dose or KERMA. The intracellular heterogeneity changes the mean value, $\bar{z}_n$, which becomes larger when ^{10}B atoms are accumulated closer to the cell nucleus.

10.2.2.1 Analytical calculations

Analytical approaches usually require assumptions regarding the description of the intersection (and energy deposited) between the particle track and the site, the latter typically described as a simple geometric body. Usual shapes include spheres and spheroids to simulate cells, cylinders for blood vessels, slabs for layered tissues, or experimental radiobiological set-ups, etc. Hypotheses regarding rectilinear paths and continuous slowing-down approximations are usually adequate to accurately calculate the average dose deposited under non-equilibrium conditions. In terms of boron localization, uniform, bi-valued and surface source distributions can be included in the models, including regular lattices to compute crossfire effects [570, 587–588].

One important advantage of analytical descriptions (vs. Monte Carlo calculations) is the possibility of obtaining continuous functions that describe the dependence of dose on site size, shape, and microdistribution in a simple manner. Although restricted to simplified descriptions, analytical approaches can provide a complete portrayal of the full state space of a multivariable problem. Deposited energy spectra, dependent on-site geometry and boron localization, can be straightforwardly obtained, including time-dependent calculations (particularly important for considering the kinetics of a boron compound during irradiation).

Mixed analytical and numerical approaches can be used to add some degree of complexity, especially regarding the actual shape and size of tumour and normal cells, by utilizing the concepts of stereology and integral geometry [589]. Stereology deals with obtaining higher-dimensional information from the analysis of lower-dimensional random sections of the sample in question. Thus, in terms of chord-length distributions (CLD), the actual population-averaged geometry of the sensitive site can be considered. Moreover, if stereological analysis is performed on a histological sample that contains a heterogeneous cell population, the CLD will be sensitive to the composition of that sample. It is important to consider the appropriate randomness to correctly describe the full process [590]. Briefly, the concept of randomness in radiation biophysics lies in the realm of geometric probabilities (the field of mathematics that studies the application of probabilities to random geometric sets) and allows determination of the distribution of outcomes of the intersection between two geometric objects under a given random process that rules their intersection. This random process, in radiation biophysics, is composed of a ‘site’ (e.g., the cell) and a ‘probe’ (the track), where the outcome (e.g., track length, energy deposition, DNA breaks, etc.) will be influenced by the ‘sampling process’ (the irradiation), which will depend, among other things, on the track source distribution. If particle tracks are uniformly and isotropically produced, then μ-randomness is the appropriate assumption to perform the analytical calculation. However, internal sources or surface distributed sources are described by different kinds of randomness (‘I-randomness’ and ‘S-randomness’) and these need to be used if the origins of the reactions are inside the volume or located on its boundaries. CLDs under different types of randomness are very different in shape, mean chord-length value, and variance, and therefore, when coupled with energy deposition along the track, lead to very different average microscopic doses [591].

10.2.2.2 Monte Carlo calculations

Monte Carlo simulation is also a powerful tool to determine the doses on microscopic length-scales, though it generally requires longer computational times compared with analytical calculations. Historically, two types of Monte Carlo codes have been developed for radiation transport: one type simulates atomic interaction event-by-event, while the other employs the continuous slowing down approximation or condensed history method with reduced computation times. The former is called a 'track-structure code' and the latter a 'general purpose particle transport simulation code'.

Track-structure codes can determine the doses even over nanometre scales, and thus, have the potential to reveal the complex nature of DNA damage induced by BNCT. However, no track-structure code that is applicable to the BNCT radiation fields is available so far because of the lack of evaluated cross section data for atomic interactions induced by α particles and ^{7}Li ions. General purpose particle transport simulation codes are widely used for cellular scale dosimetry in addition to the macroscopic dose calculations described in Section 10.2.1.2. They can also be used for confirming the accuracy of analytical calculations, which ought to agree with the corresponding Monte Carlo simulations of a representative set of points in the state space of the problem. Such comparison provides a good starting-point from which to pursue more complex descriptions.

10.2.2.3 Microscopic dose correction factors

KERMA factors for calculating boron absorbed dose depend on a single value of the boron concentration at a given point in tissue and assume that the average energy per reaction is deposited at that point. Therefore, in situations where incomplete energy balance between particle hits exists, like cells exposed to different or non-uniform boron concentrations, the actual average absorbed dose in a cell depends on a space-dependent boron concentration function, or in other words, on a scalar field of boron reactions. Superposition of sources is usually a suitable method for decomposing the reaction field into approximately constant and region-delimited boron distribution primary fields.

The simplest case of a bi-valued boron distribution leads to the definitions of intra and extra-site distributions. Any bi-valued source distribution can be expressed as the superposition of a uniform and an intra-site distribution, either positive or negative [585]. In this case, it can be demonstrated that a factor that depends on the reaction-rate ratio and site size and shape can be employed to 'correct' the boron KERMA (calculated assuming a uniform boron distribution).

It is, therefore, possible to obtain the actual average boron dose imparted to cells, and also other microdosimetric quantities depending on boron localization, through use of bi-valued microdistributions. These correction factors, referred to as 'Microscopic Dose Correction Factors' can be used to understand the dependence of the effectiveness of BNCT on the boron microdistribution, size and shape of the cell and, in general, to correct every parameter that accompanies the boron dose term in any expression, like in the case of a boron compound's CBE factor or the radiobiological parameters of photon isoeffective dose–effect relationships [585].

Empirical observations [244] suggest a relationship between the slope of BNCT survival curves and sensitive site characteristics, obtained by stereological analysis of histological sections of different tumours, expressed as the nucleocytoplasmic cell ratio and cell size. These empirical observations corroborate the fact that the biological effectiveness of the boron reaction is not

only related to the radiation sensitivity of a given tumour cell line but also on the microdistribution of sources (Section 9.4). The latter arises from the pharmacokinetics of two different boron compounds which are known to have diverse mechanisms for uptake and localization. These observations are in line with the aforementioned approach, establishing the need to apply geometry and source dependent form factors to the KERMA, in order to calculate the correct dose in cells [566].

10.2.2.4 Summary

The following points are important considerations:

- The specific localization of boron atoms in tumour and normal cells. If the distribution is not uniform, it is not possible to use KERMA as a surrogate quantity for calculating the average dose deposited in the cells, since the problem is no longer 'scale-independent';
- In the case of non-uniform distributions of boron or nitrogen reactions, methods for estimating the actual average dose imparted to the cells are needed. These methods need to consider the lack of CPE conditions due to the incomplete balance of energy transferred in and out of a sensitive microscopic site;
- In the case of boron and nitrogen reactions, the small number of events needed to impart therapeutic doses has to be considered, since they determine the variance of the specific energy, and thus the biological effect. Thus, a microdosimetric approach is required.

10.3 TRANSLATING BNCT DOSES INTO A REFERENCE RADIATION DOSE

The secondary charged particles that contribute to the total absorbed dose have very different LETs. These particles produce ionization patterns in living cells that may result in different cellular injury for the same absorbed dose. Since the same total absorbed dose delivered with different relative contributions of the main components may lead to a different outcome, a method is required for translating BNCT doses into a reference radiation dose capable of quantifying clinical effects.

The reference radiation dose needs to also enable the specialist to:

- Apply the clinical experience gained with the reference therapy to optimize BNCT;
- Compare protocols and results from different institutions applying BNCT;
- Have a simple and practical language to prescribe doses in BNCT;
- Facilitate combined radiation treatments.

10.3.1 Reference radiation

Photon beam therapy has long been considered the reference radiation therapy modality. A large body of experience has been built up worldwide over about 70 years with MV photons. Most clinical radiotherapy uses photon beams in the range 4–18 MV. Less than 1% of the patients worldwide are treated with protons or other hadrons, although the number is increasing with the number of new facilities [592]. These reasons justify remaining with photon beam therapy as the reference radiation treatment modality of choice, and the benefit of any new or unconventional techniques such as BNCT ought to be evaluated in relation to photon radiotherapy.

Dose delivery schemes with photon radiotherapy and BNCT are generally different. While BNCT administers the full dose in one or two applications, traditional photon treatments

require dose splitting in multiple fractions of 1.5 to 3 Gy administered daily over a period of 3–7 weeks.

To avoid making unnecessary conversions between the selected photon reference protocol and BNCT, the first choice for comparison would be that the treatment conditions are equal. In this regard, clinical data for single fraction photon dose schemes are preferable. Second choice, if single fraction radiotherapy data are not available, is hypofractionated radiation therapy, since large doses are delivered in a few fractions. The conversion of hypofractionated radiation doses to single doses can be performed using the linear–quadratic model (see Section 10.3.3.2). In that case, the absorbed dose in tumour per fraction, the so-called fraction size, as well as the α/β ratio of the reference therapy needs to be explicitly mentioned [593]. However, since there is evidence that the resulting single doses may underestimate the effects of hypofractionated radiation, special attention needs to be paid to the results of conversion.

10.3.2 Relative and compound biological effectiveness

Biological effects are the result of the action of ionizing radiation in living systems. These effects are directly related to absorbed dose. However, since they also depend on other factors, such as dose delivery scheme, dose rate, radiation quality, biological system and end points, there is no unique relationship between absorbed dose and induced biological effects.

At equal absorbed doses, radiations of different quality produce different levels of biological and clinical effects. The differences in effectiveness are related to differences in energy deposition along the particle tracks and through subcellular structures [594]. The concept of Relative Biological Effectiveness (RBE) was introduced to quantify differences in biological effectiveness of different radiation qualities. The RBE is a ratio between two absorbed doses with two radiation qualities, one of which is the 'reference radiation', that both produce the same effect in a given biological system under identical conditions [594]. It is a clear, well-defined radiobiological concept and possesses two notable characteristics:

- It is unnecessary to provide a numerical expression for quantifying the effect, i.e., qualitative descriptions on an arbitrary scale can be used to determine the ratio of doses that produce the effect (e.g., lens opacity, skin erythema, or motor skill performance);
- Once the intermediate and complex mechanisms that arise from radiation-quality dependent lesions have ended, the observed effect is independent of the nature of those different mechanisms. Such complexities just produce equal radiation-quality independent modifications, with differences only in the kinetics of lesion formation [586].

An RBE value has an associated experimental uncertainty as it is the result of an experiment. An RBE value depends on the biological system studied as well as the type and level of effect. Therefore, the dose and experimental conditions in which a given RBE value was determined needs to be specified [595]. The RBE of a given radiation quality varies markedly with dose, biological system, and effect. Thus, it cannot be considered as a single number.

In BNCT, the Compound Biological Effectiveness (CBE) is employed to emphasize the observed dependence of the relative biological effectiveness of the α and ^{7}Li particles altogether, i.e., the 'boron reaction' effectiveness, with the spatial location of the carrier compound. Compound biological effectiveness factors are measured experimentally, in vivo or in vitro, for different boron compounds, specific tissues or cell types, and for diverse biological end points [378, 435, 596]. Usually, KERMA has been used to compute the ratio between the reference and the boron dose that results in the same effect. Important differences

in CBE factors are usually found depending on the compound used. These differences can be explained by decomposing the CBE factor into the product of three quantities:

- A 'form factor', which depends on the compound microdistribution and target geometry;
- The ratio of survival slopes, which accounts for any differences in intrinsic radiosensitivity between the ballistic efficiency of α and ^{7}Li particles for the particular compound microdistribution and a uniform microdistribution;
- A reference boron RBE obtained under CPE conditions or, equivalently, under a uniform production of boron neutron capture reactions.

Compound biological effectiveness factors have already been considered in practical treatment planning of BNCT. For example, the CBE values of BPA for cells in culture are greater than the corresponding values for BSH, owing to cell permeability of BPA (see Section 7.4). In contrast, the intercellular heterogeneity changes its probability density, $f(z_n)$ (see Section 10.2.2); the variance of $f(z_n)$ becomes larger in cases where ^{10}B tends to be accumulated in certain cells, and a microdosimetric approach is needed. In addition, uptake of ^{10}B-compounds is dependent on the cell cycle, and both BSH and BPA are taken up at higher rates at the G_2/M than at the G_0/G_1 phase [597]. A larger variance of $f(z_n)$ results in lower biological effectiveness particularly at higher doses because of the overkill effect [389].

10.3.3 The standard model based on single biological effectiveness values

The term 'photon-equivalent dose' was largely used in the clinical application of BNCT to indicate the dose of a reference photon radiation that is estimated to produce the same biological effect as the combination of the different absorbed doses administered with this therapy. A variety of units to indicate the administered dose in photon equivalent units have been used by the BNCT community such as Gy(W), Gy-RBE, Gy-Eq and Gy_w.

In radiation therapy, the term 'isoeffective dose' or D_{IsoE} is introduced to imply a comparison with a dose delivered under reference conditions [594]. The term 'photon isoeffective dose' ought to be used to describe a photon dose that would produce the same effects on a given biological system as the doses delivered under BNCT treatment conditions.

There is an obvious risk of confusion as the unit Gy is used for two quantities (absorbed dose and isoeffective dose, D_{IsoE}). This potential confusion could be harmful (and potentially lethal) for the patient [594]. Following the International System of Units (SI) convention, the number of grays has to be given along with the specific name of the quantity. No additional modifier (subscript, asterisk, etc.) is allowed in the name of the unit to specify the quantity that is involved [598]. Historical forms to indicate photon-equivalent units can be still found throughout this publication as they have been traditionally employed. However, considering the difficulty related to the fact that both absorbed dose and isoeffective dose have the same unit (Gy), the ICRU and the IAEA, together with particle therapy communities, agreed to introduce the unit 'Gy (IsoE)' for the isoeffective dose, D_{IsoE}. In this way, the risk of confusion in clinical practice between the quantities that could be harmful for patients, is avoided or at least reduced. The space between 'Gy' and '(IsoE)' is necessary to comply with the requirements of the International System of Units [598].

10.3.3.1 Description of the standard model

The standard model for calculating the photon dose that would produce the same effects on a given biological system as the dose delivered under BNCT treatment conditions is given by a weighted sum of the primary absorbed dose components:

$$D_{\mathrm{IsoE}} = w_1 D_1 + w_2 D_2 + w_3 D_3 + w_4 D_4 \tag{18}$$

where the components $D_1 = D_{\mathrm{B}}$, $D_2 = D_{\mathrm{N}}$, $D_3 = D_{\mathrm{H}}$ and $D_4 = D_{\gamma}$, as defined in Table 7.

The standard model converts each term of the total absorbed dose to a photon isoeffective dose term, multiplying the absorbed doses by fixed weighting factors, w_i. The w_i values used in expression (18) are the RBE and CBE of the different radiation qualities determined from radiobiological experiments (Section 9.2) for a given biological system, endpoint, and level of effect.

The biological system and associated effect most considered in BNCT for the determination of these weighting factors are in vitro cell cultures and fraction of surviving cells. Other systems and effects such as radiation damage to normal tissue and tumour control on in vivo models have been less considered.

10.3.3.2 Validity and limitations of the model

Both RBE and CBE depend upon the biological system and the type and level of effect. Therefore, the unrestricted use of single RBE and CBE factors in expression (18) determined for a given level of effect in a particular system will generally lead to inaccurate photon isoeffective dose estimates.

Figure 63 shows the limitations of the standard model. The fraction of surviving cells S for the photon reference radiation 'R' and radiation 'A' shown in Fig. 63a can be described, using the linear–quadratic model, by

$$S_{\mathrm{R}} = \exp[-(\alpha_{\mathrm{R}} D + \beta_{\mathrm{R}} D^2)], \quad S_{\mathrm{A}} = \exp[-(\alpha_{\mathrm{A}} D)] \tag{19}$$

with α_{R} and α_{A} are the linear coefficients of both radiations, and β_{R} the quadratic coefficient of the photon reference radiation, R.

The RBE for 1% survival level is 3 (Fig. 63a). Therefore, according to the standard model, the photon reference dose D_{IsoE} that produces the same survival as the dose D delivered with radiation 'A' is

$$D_{\mathrm{IsoE}} = 3D \tag{20}$$

However, to produce the same survival fraction as the dose D, the D_{IsoE} needs to satisfy

$$\exp[-(\alpha_{\mathrm{R}} D_{\mathrm{IsoE}} + \beta_{\mathrm{R}} D_{\mathrm{IsoE}}{}^2)] = \exp[-(\alpha_{\mathrm{A}} D)] \tag{21}$$

Thus, the correct expression for D_{IsoE} is

$$D_{\mathrm{IsoE}} = \frac{-\alpha_{\mathrm{R}} + \sqrt{\alpha_{\mathrm{R}}^2 + 4\beta_{\mathrm{R}} \alpha_{\mathrm{A}} D}}{2\beta_{\mathrm{R}}} \tag{22}$$

Figure 63(b) compares D_{IsoE} given by Eqs (20) and (22). For absorbed doses lower than $D_x = 4$ Gy, the standard model depicted by the straight line underestimates the correct D_{IsoE} value. Conversely, for absorbed doses above $D_x = 4$ Gy the standard model overestimates D_{IsoE}. Note that, while the low dose region is associated with absorbed doses typically delivered to normal tissues, the high dose region is associated with values administered to the tumours. This fact requires special attention because the general behaviour of the standard model is not conservative; the resulting D_{IsoE} values could be potentially harmful (or insufficient) for the patients.

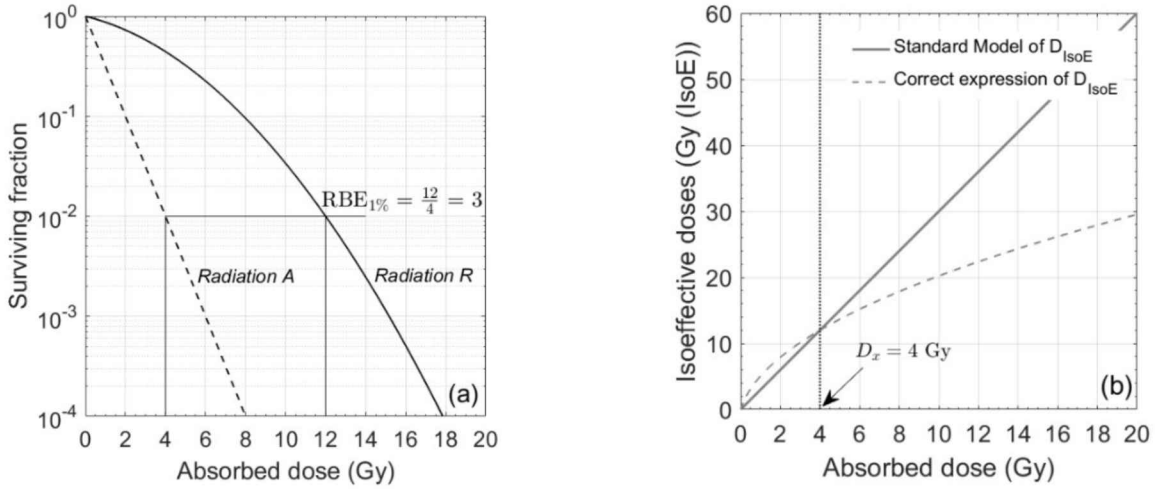

FIG. 63 (a) Fraction of surviving cells for a photon reference radiation R and an example radiation A. (b) Comparison of the standard model (Eq. (20)) and the correct expression of D_{IsoE}, (Eq. (22)) as a function of the total absorbed dose. D_x = 4 Gy represents the absorbed dose where the standard model and correct expressed for D_{IsoE} cross (courtesy of S. González, CNEA).

The range in which the standard model gives a reasonable approximation is very narrow:

(a) In the neighbourhood of D_x;
(b) In the dose interval from 0 Gy to a few grays, when the initial slope of Eq. (22) is similar to the slope of the standard model. In this case, both curves are similar up to a certain low dose value.

The only condition under which the standard model and Eq. (22) match is through neglection of the quadratic term in the survival model for the reference photon radiation (Eq. (19)). This approach is discouraged, however, since an important fraction of cell death due to the accumulation of sublethal damage (SLD) is typical of low LET radiation and hence the quadratic term is crucial.

10.3.4 Models for calculating photon isoeffective doses

The following sections describe the models developed in the last decade to determine photon isoeffective doses in BNCT. These models are based on widely known and well-accepted theories, and progressively incorporate degrees of sophistication according to the dose–response relationship and the phenomena considered. Specific models with parameters derived from in vitro and in vivo radiobiological data prepared for prospective use in the clinic under medical judgment are listed at the end of this section.

10.3.4.1 Definition and general considerations

Following recommendations introduced in Ref. [594], a publication co-sponsored by IAEA and ICRU, the term 'photon isoeffective dose' with the unit 'Gy (IsoE)' needs to be adopted to describe the photon dose that would produce the same effects on a given biological system as the doses delivered under BNCT treatment conditions. Where the Gy (IsoE) unit is used, some explanation needs to also be provided for the applied photon isoeffective dose model (either constant RBE model or more complex dose models).

The concept of photon isoeffective dose requires mathematical expressions which quantify the effect of interest under both photon and BNCT treatment conditions. For example, consider that a radiation specialist wants to determine the D_{IsoE} that, delivered in a single fraction scheme, would produce the same tumour control as the combination of the main absorbed doses in BNCT. Then, she/he will need to have models that describe the 'tumour control' effect after single-fraction photon radiotherapy and BNCT.

Both macroscopic and microscopic approaches were developed for estimating photon isoeffective dose. The macroscopic approach here assumes that calculations are independent of the spatial scale. In contrast, the microscopic approach is based on absorbed doses on cellular and sub-cellular scales. Information on the boron microdistribution (see the techniques in Sections 8 and discussion in Sections 9.3–9.4, and 9.6.1) is indispensable in the latter approach.

Phenomena that deserve special attention when describing the biological effects, particularly in the case of BNCT are:

(a) Synergism between different radiations;
(b) Sublethal damage repair.

10.3.4.2 Photon isoeffective doses and biological endpoints

The photon isoeffective dose model is intimately linked to the biological effect of interest and, consequently, to the dose–response relationship.

Models based on dose–response curves for cell survival

Such models can be based on formalisms over two different length scales, macroscopic and microscopic:

Macroscopic formalism

The simplest model is based on dose–response curves for cell survival and neglects sublethal lesion repair (for both photon and BNCT treatment conditions) and synergism between radiations (in the case of BNCT). It is derived by replacing radiation 'A' in Section 10.3.3.2 by the radiations D_1, D_2, D_3 and D_4 delivered in BNCT (Eq. (18)). Then, if the fraction of surviving cells for BNCT is

$$S_{\mathrm{BNCT}} = \exp[-(\alpha_1 D_1 + \alpha_2 D_2 + \alpha_3 D_3 + \alpha_4 D_4 + \beta_4 D_4{}^2)], \tag{23}$$

with α_i, β_i (i = 1,…,4) the coefficients of the model, the correct expression for D_{IsoE} is

$$D_{\mathrm{IsoE}} = \frac{-\alpha_R + \sqrt{\alpha_R^2 + 4\beta_R(\alpha_1 D_1 + \alpha_2 D_2 + \alpha_3 D_3 + \alpha_4 D_4 + \beta_4 D_4{}^2)}}{2\beta_R} \tag{24}$$

Equation (23) shows that only the γ dose component of the BNCT field is allowed a quadratic term, thus permitting accumulation and combination of sublethal damage for the low LET component exclusively.

When combining high-LET radiations with low-LET radiations simultaneously, synergistic effects may appear [599]. This means that sublethal lesions produced by one radiation (e.g., by the α particles of the BNCT reaction) can interact with the sublethal lesions produced by any other radiation (e.g., by the 583 keV protons from neutron capture by nitrogen) to form lethal damage. The yield of sublethal lesions per unit dose for each radiation component *i* is accounted for by $\sqrt{\beta_i}$. Then, the term $\beta_4 D_4^2$ in S_{BNCT} (Eq. 23) is replaced by

$$\beta_1 D_1^2+\beta_2 D_2^2+\beta_3 D_3^2+\beta_4 D_4^2+2\sum_{i<j}\sqrt{\beta_i\beta_j}D_i D_j \tag{25}$$

and the same needs to be done in expression (24) for D_{IsoE}.

Typical treatment times in BNCT vary between 30 to 90 minutes, values that are greater than or at least comparable to the typical repair half-times of sublethal damage for the fast repair component (in the range of 5–30 min). The reduction in the probability of SLD interaction when repair mechanisms are present is accounted for by the generalized Lea–Catcheside time factors, *G,* that modify the quadratic terms of Eq. (25). Analytical expressions for these factors for simultaneous delivery of high and low-LET radiations are provided in Refs [392, 600].

In the case of normal tissues exposed during a BNCT treatment, more than 50% of the total absorbed dose may be due to the low-LET component. Hence, for these tissues it may be of particular importance to consider these reduction factors in the calculation of D_{IsoE}.

Microscopic formalism

In contrast to the macroscopic approach, the difference between the survival probability of each cell, S_{C}, and survival fraction of a certain cell group, S_{G}, needs to be considered in the microscopic approach [28], as expressed below:

$$S_{\mathrm{G}}(D) = \int_0^{\infty} S_{\mathrm{C}}(z_{\mathrm{C}}) f_{\mathrm{C}}(z_{\mathrm{C}}, D)\,\mathrm{d}z_{\mathrm{C}} \tag{26}$$

where D is the absorbed dose in the cell group and $f_{\mathrm{C}}(z_{\mathrm{C}}, D)$ is the probability density of the specific energy in each cell or cell nucleus, z_{C}, for mean absorbed dose D. Note that the specific energy is the stochastic quantity introduced to express the heterogeneity of the absorbed doses in microscopic sites.

For conventional radiotherapy such as XRT, the variance of $f_{\mathrm{C}}(z_{\mathrm{C}}, D)$ is negligibly small, i.e., the approximation of $f_{\mathrm{C}}(z_{\mathrm{C}}, D) = \delta(z_{\mathrm{C}}, D)$ is well established, where δ is the Dirac delta function. In that case, $S_{\mathrm{G}}(D) = S_{\mathrm{C}}(D)$. In contrast, $f_{\mathrm{C}}(z_{\mathrm{C}}, D)$ needs to be carefully evaluated in the case of BNCT because of the large dose heterogeneity as described in Section 10.2.2 Information on the intercellular boron distribution is indispensable in the evaluation. The intracellular boron distribution (Sections 7, 9.3–9.4, and 9.6.1) is also important in solving Eq. (26) because it significantly influences the survival probability of each cell, $S_{\mathrm{C}}(z_{\mathrm{C}})$, by changing the microscopic dose correction factor.

Once $f_{\mathrm{C}}(z_{\mathrm{C}}, D)$ and $S_{\mathrm{C}}(z_{\mathrm{C}})$ are evaluated, $S_{\mathrm{C}}(D)$ can be easily determined by solving Eq. (26) numerically. Then, the photon-isoeffective dose, D_{IsoE}, can be obtained from

$$D_{IsoE} = \frac{-\alpha_R + \sqrt{\alpha_R^2 + 4\beta_R \ln[S_G(D)]}}{2\beta_R} \quad (27)$$

If the fractionated size, X, is adopted as the reference treatment, Eq. (27) can be replaced with

$$D_{IsoE} = \frac{-\ln[S_G(D)]}{\alpha_R + \beta_R X} \quad (28)$$

An advantage of the microscopic model over the macroscopic one is that it can roughly predict the biological effectiveness of newly developed boron compounds if information on their intra- and intercellular heterogeneity is available.

Models based on dose–response curves for tumour control and normal tissue toxicity

In addition to models of cancer in vitro, there are several in vivo models that have been extensively used in BNCT, as they better describe the interactions between tissues and organs, as well as the biological pathways involved, which includes the vascular system and its pivotal role in tumour growth.

These models can be used to obtain the response of dose-limiting normal tissue as well as the dose–response data for local tumour control. As physiological complexity is taken into account, with some restrictions, these results can be extrapolated to clinical scenarios. In addition, since these responses are closely linked to those evaluated in the clinic, their use in determining the isoeffective dose is strongly suggested.

The determination of the photon isoeffective dose in BNCT with Eq. (29) requires suitable mathematical expressions to describe the probability of effect E for both the reference photon radiation R and for BNCT.

$$E_R(D_{IsoE}) = E_{BNCT}(D_1, D_2, D_3, D_4) \quad (29)$$

A general Tumour Control Probability (TCP) model can be written as

$$TCP = \exp[-(c_1 v^{c_2} S)] \quad (30)$$

where v represents the tumour volume (in cm^3), c_1 and c_2 the parameters that modulate its effect on local control probability and S the fraction of surviving cells.

When S for the reference radiation and BNCT are expressed by the simple linear–quadratic models of Eqs. (19) and (23) the value of D_{IsoE} that solves

$$TCP_R(D_{IsoE}) = TCP_{BNCT}(D_1, D_2, D_3, D_4) \quad (31)$$

coincides with Eq. (24) (whenever, for both radiation treatments, the target tumour cell population for the same probability of local tumour control is equal). Moreover, this result holds for models in which the TCP is simply a function of the fraction of surviving cells.

The general expression for the photon isoeffective dose $D_{IsoE,}$ when both synergism and repair mechanisms are considered in Eq. (30), is

$$D_{\mathrm{IsoE}}=\frac{-\alpha_{\mathrm{R}}+\sqrt{\alpha_{\mathrm{R}}^2+4\beta_{\mathrm{R}}\left(\ln\left(\frac{c_1^*}{c_1}v^{c_2^*-c_2}\right)+\sum_{i=1}^{4}\left(\alpha_i D_i+G_i\beta_i D_i^2\right)+2\sum_{i<j}G_{ij}\sqrt{\beta_i\beta_j}D_iD_j\right)}}{2\beta_{\mathrm{R}}} \tag{32}$$

with c_1, c_2 and c_1^*, c_2^* being the parameters of the volume for the reference and BNCT, respectively, and G the time factors for a simultaneous mixed irradiation reported in Refs [392, 600]. If the target cells are the same for both radiation treatments, $c_1 = c_1^*$ and $c_2 = c_2^*$, and the logarithmic tumour volume term disappears.

The most widely used Normal Tissue Complication Probability (NTCP) model in clinical radiobiology is the Lyman model [601]. The model for a single-fraction photon reference dose D is given by

$$\mathrm{NTCP_R}=\frac{1}{\sqrt{2\pi}}\int_{-\infty}^{s'}\exp\left(-\frac{t^2}{2}\right)\mathrm{d}t \tag{33}$$

where

$$s'=\frac{D-\mathrm{TD_{50}}}{m\cdot\mathrm{TD_{50}}} \tag{34}$$

and where m is the NTCP vs. dose curve slope and $\mathrm{TD_{50}}$, the tolerance dose for a complication probability of 0.5 (median toxic dose).

An NTCP model for BNCT based on Lyman's model is proposed in Ref. [385], obtained by replacing D in expression (34) by D_{IsoE} given in Eq. (24) (or for the more general case, in Eq. (32) but without the logarithmic term). Thus, the value of D_{IsoE} that solves

$$\mathrm{NTCP_R}(D_{\mathrm{IsoE}}) = \mathrm{NTCP_{BNCT}}(D_1, D_2, D_3, D_4) \tag{35}$$

coincides with Eqs (24) or (32) (without the logarithm).

10.3.5 Determination of radiobiological parameters

10.3.5.1 Coefficients from dose–response curves for cell survival.

Several groups have made cell survival measurements under various conditions to try to evaluate fixed RBE factors for different cell lines. They generally consist of determining the dose response to the:

- Photon reference radiation;
- BNCT beam only (n + γ);
- BNCT beam in the presence of the boron carrier [1].

In Section 10.2.1, details on how to determine the absorbed dose in preclinical experiments are provided. Here, a methodology is suggested to obtain a suitable set of parameters from typical cell survival experiments carried out in BNCT.

The simplest model of D_{IsoE} given by Eq. (24) involves a total of seven radiobiological parameters, i.e., the

- Two coefficients α_R, β_R of the photon reference radiation, R;
- Four linear coefficients α_i of the contributions in BNCT;
- One quadratic coefficient β_4 for the γ component of BNCT.

Based on the argument that similar biological responses are obtained when a system is exposed to radiations with comparable lineal energy spectra, the number of free model parameters can be reduced as follows:

- For photons, $\alpha_4 = \alpha_R$ and $\beta_4 = \beta_R$. The lineal energy spectra of the reference photons (e.g., from ^{60}Co, ~1 MeV) and photons in the beam (mostly ~2 MeV) are almost the same;
- For neutrons, $\alpha_2 = \alpha_3$. Fast neutrons in BNCT beams generally have $E \lesssim 1$ MeV, where elastic recoils with ^{1}H nuclei dominate the charged particle slowing down spectrum (feeding through to the value of α_3), with energies comparable to those of protons produced from thermal neutron capture by nitrogen (feeding through to the value of α_2).

Equation (19) is first used to fit the photon data to obtain the coefficients α_R and β_R. Considering the estimated coefficients and previous considerations, the survival model from Eq. (23) is used to determine the remaining free parameters, α_1 and α_2.

The fitting procedure can be carried out sequentially or simultaneously. In the sequential approach, the alpha coefficient of the neutron component ($\alpha_2 = \alpha_3$) is determined first from the fitting of the data for BNCT beam only. Then, the obtained result is used to calculate the alpha coefficient of the boron component, α_1, by fitting the (BNCT + boron compound) dose–response data. The dose–response data from irradiation with a BNCT beam in the presence of the boron compound contains information on the action of the products that result from all neutron interactions, in particular, from neutron interactions with nitrogen and hydrogen present in tissues. In the simultaneous approach, a fitting procedure involving a minimization of both BNCT beam only and (BNCT + boron compound) cell survival data can be carried out to fully exploit all the experimental information.

The general procedure and considerations to determine the parameters of the photon isoeffective dose model when synergism and SLD repair are considered are the same. However, the following points need to be considered:

- The number of free model parameters increases due to the inclusion of the quadratic coefficients for the high LET components. In this case, simultaneous minimization can be quite challenging;
- Time reduction factors, *G*, depend on the SLD repair kinetic model and the characteristic repair times of the cell line under study. A bi-exponential modelling characteristic slow and fast repair times that are independent of LET (i.e., of the component of the BNCT field) can be assumed for the calculation of *G* factors. In this case, fast and slow repair times for the specific cell line and the proportions of the SLD repaired by the two kinetics for both low and high LET radiations need to be known.

10.3.5.2 Coefficients from dose–response curves for tumour control and normal tissue toxicity

Models based on dose–response curves for tumour control can give, as previously shown, formulae for the isoeffective dose which coincide with those coming from survival curves. However, the probabilistic nature of these models means that determination of the radiobiological parameters requires a different approach. The main difference is that, instead of dose–survival curves, the input information is dose–tumour control data:

- 1, if the tumour was controlled (i.e., showed complete response);
- 0, otherwise.

There are two approaches for parameter determination:

(a) The first is based in maximum likelihood estimation and consists of finding the values of the parameters that maximize the likelihood function. This function involves the TCP model, tumour doses, volumes, and responses. From the dose and volume of each tumour, the probability that the tumour is controlled (or not) is computed as a function of the parameters. Then, the likelihood function is the product of the probabilities of all observed responses. Like models based on survival curves, one can make different simplifications or reductions in the number of parameters. Also, the maximization can be carried out for all parameters simultaneously or sequentially, with the simultaneous optimization being rather challenging;
(b) The second is to perform curve fitting, just as described in the case of dose–survival curves but considering the TCP model: the functions are given by Eq. (30) with the corresponding expression of S for the reference radiation 'R' and for BNCT, and the data to be fitted consists of dose and volume of each tumour and 0 or 1 according to the tumour response. In this way, the method searches for parameters that give TCPs close to 1 for tumours which were controlled and close to 0 for those which were not. Again, reduction of the number of parameters and sequential/simultaneous optimization can be performed.

Approaches for parameter determination when the input is dose–normal tissue radiotoxicity data are the same as those for tumour control. In this case, responses are:

- 1, if the normal tissue reaches or exceeds the radiotoxic effect considered clinically relevant;
- 0, otherwise.

The determination of model coefficients involves NTCP models, normal tissue doses, responses, and eventually irradiated volumes or areas.

10.3.6 Range of validity and advice

The macroscopic approach for derivation of the photon isoeffective doses in BNCT is based on well-known grounds and can be easily applied to any tissue and effect so long as dose–response data and numerical expressions for quantifying the effect of interest are available for both the photon reference radiation, 'R', and BNCT.

The models can be easily entered into any mathematical analysis tool or treatment planning system and, as they are fed with the absorbed doses calculated during treatment planning, their application in the clinic is straightforward. The models presented in Section 10.3.4 can be used

to compute photon isoeffective doses for both uniform and non-uniform absorbed dose distribution scenarios. In the non-uniform dose case, a photon isoeffective dose is obtained for each point of the volume of interest. An equivalent uniform dose for this volume (or its corresponding TCP/NTCP) can be determined following different strategies (see, e.g., Refs [602–603]).

Parameters of the photon isoeffective dose model based on dose–response data for cell survival have been derived already for different cell lines. The models for D_{IsoE} calculation that are ready for use in the clinic are for gliosarcoma [385, 393], metastatic melanoma [385], osteosarcoma [604], and SCC [605].

In addition, parameters derived from dose–response data for tumour control and normal tissue radiotoxicity were also reported for some tumours and tissues. In particular, the models that are ready to use in the clinic are for SCC tumours [385], and for the two dose-limiting normal tissues: mucosal membrane (endpoint: mucositis G3 or higher [385]) and normal brain (endpoint: incidence of myelopathy [393]).

A link to a photon isoeffective dose calculator is provided for those who wish to explore some existing models before developing their own tools.[30]

As for RBE, photon isoeffective dose models depend upon the biological system and the type of effect. The available models cover most of the main targets and dose-limiting normal tissues involved in BNCT. However, models for other important normal tissues, such as skin, are still needed. The applicability of any of the existing models to calculate photon isoeffective doses in these cases needs to be left to medical professional judgment.

The introduction of the concept of microdosimetry in the treatment planning of BNCT is desirable for more precise estimation of its biological effectiveness. From the viewpoint of microdosimetry, development of ^{10}B-compounds that are accumulated closer to cell nucleus and homogeneously distributed in all tumour cells is the key issue because cell-nucleus specific energies with higher mean values and lower variances could result in higher therapeutic effect. In principle, the biological effectiveness of ^{10}B-compounds can be estimated from their intra- and intercellular heterogeneity and knowing the size of the target cells and its nucleus. Therefore, measurements of ^{10}B-distributions in cellular and subcellular scales are strongly needed. This requires further improvement of high-resolution imaging devices such as α cameras and track-etch detectors (see Sections 8.2.2–8.2.3).

[30] Photon isoeffective dose calculator, https://bnct.com.ar/calculator.html