Applied Radiation and Isotopes 163 (2020) 109205

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: http://www.elsevier.com/locate/apradiso

Radiobiology data of melanoma cells after low-energy neutron irradiation and boron compound administration

María Pedrosa-Rivera [a,b,*], M. José Ruiz-Magaña [c], Patricia Álvarez [c], Ignacio Porras [b], Javier Praena [b], Manuel P. Sabariego [b], Ulli Köster [a], Michael Haertlein [a], V. Trevor Forsyth [a,d], Torsten Soldner [a], José C. Ramírez [e], Clara Jover [e], Daniel Jimena [e], Juan L. Osorio [e], Ian Postuma [f], Carmen Ruiz-Ruiz [c]

[a] Institut Laue-Langevin, 71 Avenue des Martyrs, 38042, Grenoble, Cedex 9, France
[b] Departamento de Física Atómica, Molecular y Nuclear, Facultad de Ciencias, Universidad de Granada, 18071, Granada, Spain
[c] Departamento de Bioquímica y Biología Molecular III e Inmunología, Facultad de Medicina, Universidad de Granada, 18071, Granada, Spain
[d] Faculty of Natural Sciences, Keele University, Staffordshire, ST5 5BG, UK
[e] Servicio de Radiofísica y Protección Radiológica, Hospital Universitario Virgen de las Nieves, Avda Fuerzas Armadas 2, 18014, Granada, Spain
[f] Istituto Nazionale di Fisica Nucleare (INFN), Sezione di Pavia, via A. Bassi 6, 27100, Pavia, Italy

A B S T R A C T

The cold neutron beam at the PF1b line at the Institut Laue-Langevin (ILL), without fast neutrons and a low contribution of gamma rays, is a very suitable facility to measure cell damage following low-energy neutron irradiation. The biological damage associated with the thermal and the boron doses can be obtained in order to evaluate the relative biological effectiveness (RBE) for Boron Neutron Capture Therapy.

Three different experiments were carried out on the A375 melanoma cell line: the first one in a hospital LINAC, to obtain the reference radiation data, and the other two at the ILL, in which the damage to cells with and without boron compounds added was measured.

1. Introduction

Boron neutron capture therapy (BNCT) is a unique form of external radiotherapy that is selective at the cellular level and has already produced promising results in various clinical trials worldwide. One of the main problems for the development of BNCT is that the dosimetry and treatment planning has not reached the accuracy of other more conventional radiotherapies (Wennervirta et al., 2019). Hence, a better estimation of the biological damage produced by the dose delivered in BNCT is essential.

There are four main dose components during BNCT neutron irradiation (Goorley et al., 2002): D_t, thermal neutron dose mostly due to the reaction $^{14}N(n,p)^{14}C$; D_f, fast neutron dose arising mainly from neutron collisions with hydrogen; D_γ, from gamma rays either coming together with the neutron beam or emitted after a neutron capture; and D_B, the boron dose, arising from neutron capture by boron compounds accumulated in the cells. The total biological dose, D_w, is normally written in a form that contains weighting factors (or relative biological effectiveness, RBE) for each component of the dose and is compared to a reference photon dose, D_0. These weighting factors are defined as $w_i = D_0 / D_i$ for a particular endpoint. The biological dose (also called weighted dose or effective dose) is then expressed as

$$D_W = w_f D_f + w_t D_t + w_\gamma D_\gamma + w_B D_B = D_0. \quad (1)$$

No cell repair or synergy effects are taken into account in this biological dose estimation. More sophisticated radiobiological formalisms take into account the linear-quadratic response of cells to radiation (González and Cruz, 2012; Pedrosa-Rivera et al., 2020a). However, all models require good experimental data for a correct estimation of the biological dose. Given that the biological effect depends on the types of cells under study and on the end-point, it is important to obtain data for a range of different conditions.

Some of the weighting factors currently used were obtained from glioblastoma rat models irradiated at the Brookhaven Medical Research Reactor using a neutron beam where more than 30% of the dose was from gamma rays and more than 45% from fast neutrons (Coderre et al., 1993). The data extracted from those experiments have been used in BNCT for years for different tumor types. Dedicated radiobiological data for other tissues using "clean" neutron beams may help to better adapt the dose for each treatment. Moreover, the difficulty of isolating the

* Corresponding author. Institut Laue-Langevin, 71 Avenue des Martyrs, 38042, Grenoble, Cedex 9, France.
E-mail address: mpedrosa@ugr.es (M. Pedrosa-Rivera).

https://doi.org/10.1016/j.apradiso.2020.109205
Received 1 October 2019; Received in revised form 11 December 2019; Accepted 21 April 2020
Available online 26 April 2020

effect of thermal neutrons led to the use of equal neutron weighting factors for thermal and epithermal dose components; this assumption has not yet been justified on the basis of experimental data (Hopewell et al., 2011). For this reason, irradiation studies in well-characterized low energy neutron beams are essential in establishing each weighting factor.

For thermal and slower neutrons almost all capture cross-sections are inversely proportional to the neutron velocity (Mughabghab, 1997). Moreover, the energies of the incident neutrons are negligible compared to the Q value of the capture reaction. Consequently, the physical dose and biological effect are proportional to the number of captures, irrespective of the exact thermal or subthermal neutron spectrum. Thus, "clean" cold neutron beams are perfect surrogates for the study of thermal neutron radiobiology.

The beam line PF1b at the ILL high-flux reactor provides a high flux cold neutron beam where biological experiments can be performed (Abele et al., 2006). The absence of fast neutrons and contaminating gamma rays, and an optimized experimental arrangement, means that experiments to evaluate the weighting factors w_t and w_B can be carried out (Pedrosa-Rivera et al., 2020b).

Three different experiments were carried out in order to obtain the w_t and w_B for the A375 melanoma cell line. The first was performed with a photon beam from a hospital linear accelerator (LINAC) and served as the reference dose. The other two, which were aimed at identifying the effect of low energy neutrons without and with the addition of BPA, were performed on PF1b at ILL. The end-point of clonogenic ability was studied after the irradiations. Different reference dose data were used to check the influence on the variability of the different RBE.

2. Materials and methods

2.1. Cell culture

A375 cells were kindly provided by Dr. Lucie Sancey (Institute for Advanced Biosciences, Grenoble) and cultivated in RPMI medium (HyClone, Logan, USA) completed with 10% fetal bovine serum (FBS; Gibco, California, USA), 1 μM L-glutamine (Gibco) and 100 IU/ml penicillin and 100 IU/ml streptomycin (Sigma-Aldrich, St. Louis, USA) at 37 °C in a humidified CO_2, 95% air incubator.

2.2. Irradiations at the medical LINAC

The photon irradiations were carried out at an Elekta Versa HD™ 6 MV medical LINAC at the university hospital "Virgen de las Nieves" in Granada. Cells were seeded in common T25 cell culture flasks (Sigma-Aldrich, St Louis, MO, USA). The accelerator has a source surface distance (DFS) of 100 cm. To guarantee electronic equilibrium, the flasks, filled with culture media, were placed inside a PMMA (polymethylmethacrylate) cask full of distilled water and situated above 14 cm of solid water, similar to previous gamma irradiation experiments (Mackonis et al., 2007; Butterworth et al., 2010) (see Fig. 1). A computed tomography scan of the set-up was processed through the treatment-planning program (Pinnacle, Philips) for dose calculation and in order to design the field size where the cells are homogeneously irradiated. Cells were irradiated with 0,5, 2, 4 and 6 Gy at a dose rate of 1 Gy/min.

2.3. Irradiations at ILL

The PF1b line is situated 80 m away from a liquid deuterium cold source in ILL's high flux reactor. A ballistic supermirror bent-guide conducts the cold neutron beam to the experimental area. Fast neutrons and gamma rays from the reactor are not transported by such a guide. A 2.5 m long collimation system made of a series of lead-backed boron carbide and lithium fluoride collimators was used to constrain the beam to a pencil-like shape of 2 cm diameter. After the collimation, the thermal equivalent capture flux was determined by gold foil activation as $1.05{\cdot}10^{9}$cm^{-2}s^{-1} in September 2018 and $2.85{\cdot}10^{9}$ cm^{-2}s^{-1} in June 2019, depending on the reactor power and the upstream collimator sizes.

Cells were attached inside quartz cuvettes of 2 mm width (in beam direction) filled with culture media. Two cuvettes, arranged one behind the other, were irradiated at the same time. The neutron scattering in water results in a reduction of the capture flux, and thus the neutron dose, by about a factor two from the first to the second sample. Thus, per simultaneous irradiation of such a sample stack, two data points differing by a factor two in neutron dose were obtained. The sample irradiation position was surrounded by the first layer of ^{6}LiF shielding to avoid secondary gamma-ray emission from scattered neutrons. The beam, set-up and related simulations have been described in previous work (Pedrosa-Rivera et al., 2020b).

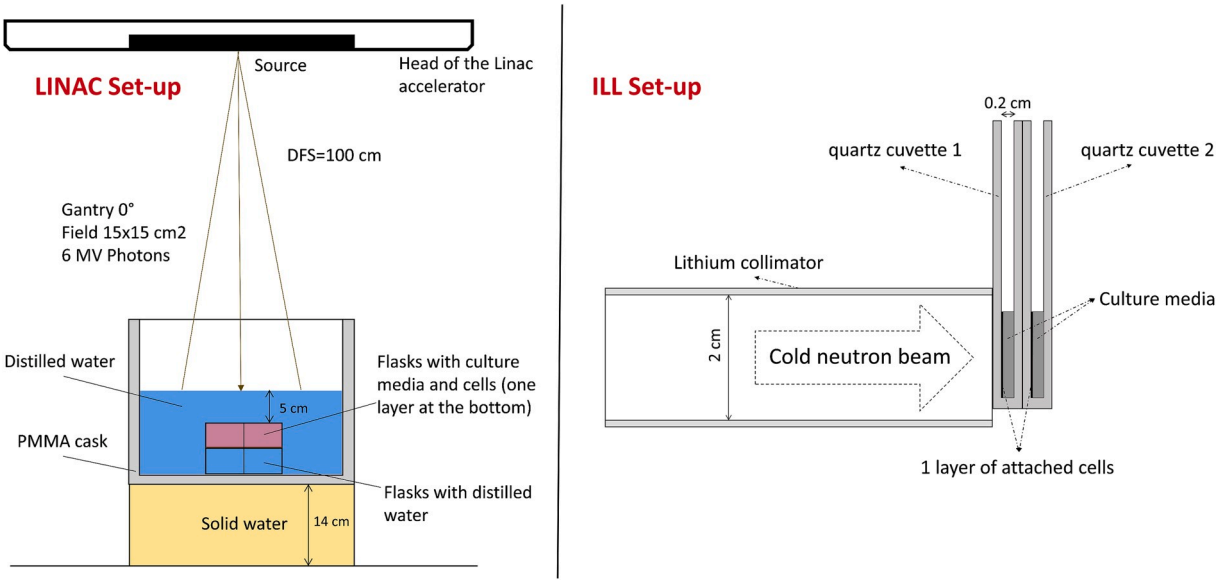

Fig. 1. Experimental arrangements used for the sample irradiation at the two different facilities. For the medical LINAC, cells are attached inside T25 flasks that are submerged in distilled water. For the irradiation at ILL, cells are attached inside 2 mm quartz cuvettes.

Irradiation times for samples without boron compound were from 15 min to 75 min while the boron-containing samples were irradiated between 1 and 3 min.

An L2 (level 2 safety) biological lab installed near PF1b enabled efficient cell management and high throughput of experiments.

2.4. Boron compound measurements

BPA (Boronophenylalanine) 95% enriched in ^{10}B was added to the culture media 5 h prior to irradiation in a 80 ppm concentration. The medium was changed to a boron-free medium 5 min before the irradiations to avoid any involvement of the captures in the media on the cell effect.

Boron uptake measurements were carried out by neutron autoradiography (Postuma et al., 2016). This was performed in the thermal column of the TRIGA MARK II nuclear research reactor at LENA laboratories of the University of Pavia. Cells were dried on the top of a mylar foil that was then positioned on a CR39 track detector. Upon neutron capture by boron in the cell sample, the recoiling alphas entered the CR39 and induced structural damage along their tracks. These latent tracks were then revealed by etching in a PEW40 solution (KOH + C_2H_5OH + H_2O). Tracks were then recorded with a Leica MZ16A microscope in transmission light through a CCD camera. Images were analyzed using track counting software which returns the track density. This value can then be related to the boron concentration in the cell sample by using the appropriate calibration curve.

2.5. Survival assay

After irradiation in the medical LINAC and at ILL, cells were detached, counted and prepared for clonogenic assay. Colonies were counted after 7 days, and the survival was expressed according to the plating efficiency calculated.

2.6. Determination of RBE

The survival curves obtained after irradiations can be described by the linear quadratic model (Fowler, 1989):

$$S = \prod_i S_i = \prod_i e^{-\alpha_i D_i - \beta_i D_i^2}, \quad (2)$$

where the index i refers to the different dose components: gamma, thermal and boron (there is no epithermal dose component in any of the present irradiations). In the irradiation at the medical LINAC, the effect is only due to gamma rays therefore survival can be described with α_γ and β_γ parameters. At ILL, for cells without boron compound, the dose is mostly delivered by cold neutrons and by secondary capture gamma rays from the sample holder (see Table 1), so parameters α_γ, β_γ, α_n, β_n will be needed to trace the curve. The effect due only to the neutrons can be extracted using equation (2). Finally, for BPA-containing samples, the survival effect will be described by the product of S_γ, S_n and S_B, where S_B corresponds to neutrons captured in boron, which makes it compound dependent. S_B is then derived by comparison with the survival curves of boron free cell assays .

Once α_n, β_n (and α_B, β_B) are estimated, the RBE can be calculated by the ratio between a reference irradiation dose with photons and the dose corresponding to just neutrons (or to captures in boron respectively), for a specific survival.

Table 1
Dose components from ILL irradiations of melanoma cells (composition in (Maughan et al., 1997)) extracted from MCNPX simulations for the experiment in June 2019, with a thermal equivalent neutron flux of $2.85{\cdot}10^9$ $cm^{-2}s^{-1}$. The statistical error from the Monte Carlo simulations is less than 1% and the error for the kerma factors used to estimate the dose (Goorley et al., 2002) is less than 5%. The neutron flux remains constant over weeks.

Sample	Thermal neutron dose rate (Gy/h)	Gamma dose rate (Gy/h)	Fast neutron dose rate (Gy/h)	Boron dose rate (Gy/h) per ppm ^{10}B
Cells in quartz 1	5.68	1.25	$<10^{-6}$	1.34
Cells in quartz 2	2.65	0.94	$<10^{-6}$	0.63

3. Results

3.1. Dosimetry

Doses at the PF1b neutron beam at ILL were determined by Monte Carlo simulations with MCNPX program, as reported in detail in (Pedrosa-Rivera et al., 2020b). Table 1 shows the dose rates of each dose component in the described configuration.

3.2. A375 survival

Cell survival after the three different irradiations is shown in Fig. 2 plotted against the total absorbed dose. Boron uptake measurements indicate 33±4 ppm of ^{10}B inside the cells. The total absorbed dose is estimated using the kerma factor per ppm assuming that the boron is uniformly distributed inside the cells. Obviously, the effect of boron capture is significantly higher than that of the other irradiation types. The fitting parameters of the curves, α_i and β_i, are shown in Table 2

3.3. Weighting factors (RBE factors) from different reference doses

Photons dose is taken as the reference radiation (D_0). However, a disparity is found in the data regarding cell survival under different photon irradiations. By analyzing different results of A375 cell irradiation from nine different experiments (with dose rates of 0.2–6 Gy/min) three from ^{137}Cs irradiators (Munshi et al., 2005; Munshi et al., 2006; Gómez-Millán et al., 2012), three from X-rays tubes of around 200 kVp (Schick et al., 2015; Buontempo et al., 2018; Min et al., 2005) and two from 6 MV LINACs (Li et al., 2015), including our experiment, we can observe considerable differences in the final survival (shown in Fig. 3). Low dose rate irradiations lead to higher survival and high dose rate irradiations result in lower survival with a more quadratic tendency presumably as a result of the lower possibility of cell repair.

This diversity of results would lead to a significant variation of the deduced RBE values, which are obtained from the comparison of the neutron data at ILL. At a survival of 1%, depending on the reference dose used, thermal neutron RBE values fluctuate from 1.1 to 3.5 (at other survivals the variation is even stronger, from 2.1 to 7.4 at Survival of 50%). For the CBE (Compound biological effectiveness), at 1% survival the RBE varies from 3.0 to 5.2. Even if only one data set was considered, large uncertainties are found for each calculated RBE (more than 50% in some cases), caused by the errors on the fitting of the reference data.

The observed variability is evidence of the importance of setting a reference dose data irradiation type (energy and dose rate). As the main objective of reference irradiation used for RBE calculations is to provide a good estimation of the biological effect, the more data at the same conditions can be found for the reference irradiation, the better. It is also important that the irradiation has enough data to provide a good fit in order to obtain a final RBE assessment.

These results indicate the need to improve the medical LINAC A375 photon irradiations data (or at other photon sources and at different dose rates). In combination with the neutron irradiation data at ILL, this will allow better estimation of the thermal and boron RBE values associated with the BNCT dosimetric estimations.

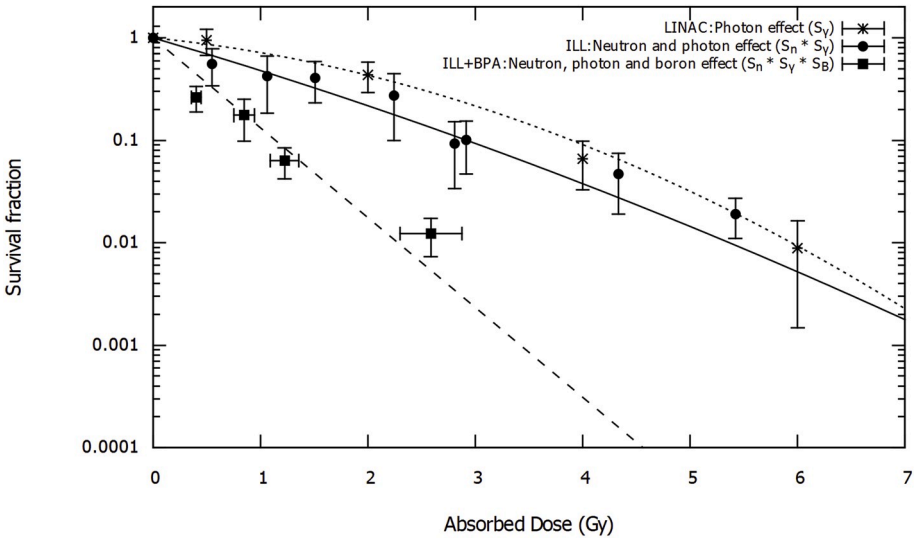

Fig. 2. Clonogenic survival of A375 cells as a function of the dose for the different irradiations performed at the medical LINAC in Granada and at the cold neutron source at ILL in Grenoble (data for cells without boron from (Porras et al., 2018)).

Table 2
Alpha and beta parameters (± standard error) resulted from fitting, with equation (2), the survival results of each irradiation. The data for D_t and D_B dose components were extracted from the survival data of the ILL irradiations using $S_t = S_{ILL}/S_\gamma$ and $S_B = S_{ILL+BPA}/(S_\gamma S_t)$.

Radiation	α_i (Gy^{-1})	β_i(Gy^{-2})
LINAC, X-rays (D_γ)	0.24±0.05	0.09±0.01
ILL	0.70±0.21	0.03±0.08
ILL, only cold neutrons (D_t)	0.84±0.05	–
ILL + BPA	2.02±0.74	0.00±0.37
ILL + BPA, only boron capture (D_B)	2.24±0.25	–

4. Conclusion

A BNCT beam has mixed irradiation fields. The analysis of the individual dose components and their biological effect is important to estimate the total damage. This damage will depend not only on the irradiation type, but also on the tissue and end-point. At the cold neutron line PF1b at ILL, the response of cell cultures to only thermal neutrons as well as to the boron capture reaction can be measured.

When translating these results to clinical applications, in addition, radiobiological data from photon irradiations are required, more precisely even twice for two distinct steps: first, photons are present at a different level as unwanted contamination of any type of neutron beam used for BNCT or radiobiological research for BNCT respectively. The "pure" neutron effect has to be extracted by subtracting the effect of the residual photon contribution. Obviously, with a "purer" neutron beam, the photon contribution and hence the uncertainty resulting from this deduction is correspondingly reduced and that is the particular strength of our new measurements at PF1b. Still, for estimating the RBE of the dose components in BNCT, we do require reliable data for photon irradiations which represent the reference irradiation and thus the numerator in the RBE calculation. We have found that the dispersion of values from previous photon measurements would lead to high uncertainties in the derived neutron or boron RBE values. It is therefore necessary to perform an accurate estimation of the survival under photon irradiation

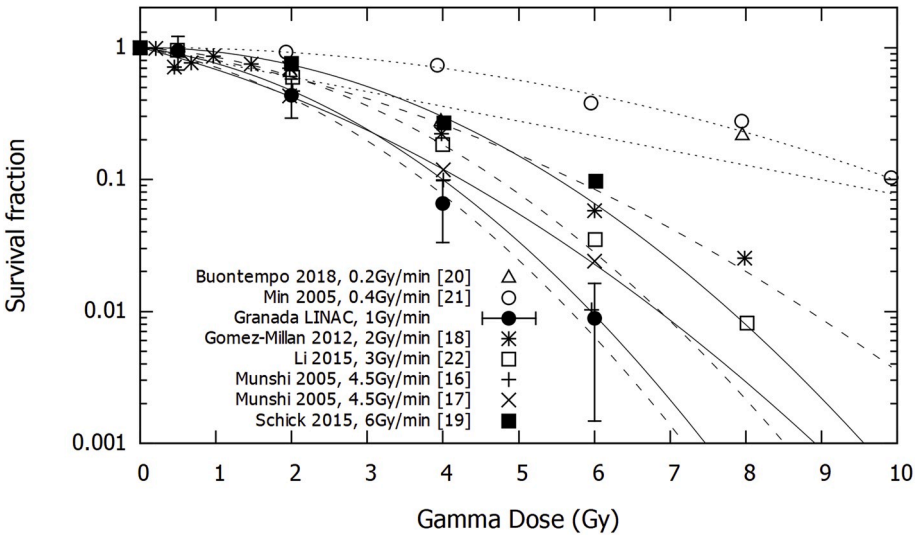

Fig. 3. Clonogenic survival of A375 cells as a function of the dose for 9 different photon irradiations (Munshi et al., 2005; Munshi et al., 2006; Gómez-Millán et al., 2012; Schick et al., 2015; Buontempo et al., 2018; Min et al., 2005; Li et al., 2015). Dotted lines for fitting low dose rate data (0.2-0.4 Gy/min), dashed lines for fitting medium dose rate data (1–3 Gy/min) and solid lines for fitting high dose rate data (4–6 Gy/min).

prior to deriving a reliable value for the neutron or boron RBE.

An experimental configuration has been described here for the reference irradiation of cell cultures using a very precise photon dose from a medical LINAC used for conventional photon therapy system - which amongst other things is useful in providing a comparison with a standard radiation field for which there is a lot of clinical experience. For this reason, we plan to perform further irradiations for different cell lines at the hospital LINAC in Granada. Ultimately two data sets will be required, a low dose rate set (order of Gy/h) for subtracting the effect of the residual photon contribution and a high dose rate set (order of Gy/min, representative for clinical radiation therapy) to calculate the RBE and CBE values.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

We acknowledge financial support for this work from the Fundación Científica de la Asociación Española Contra el Cáncer (AECC) under grant PS16163811PORR, Junta de Andalucía (Andalusian Regional Government), under contract P11-FQM-8229, Spanish MINECO and FEDER funds under contract FIS2015-69941-C2-1-P, and the founders of the University of Granada Chair Neutrons for Medicine: Spanish Fundación ACS, Capitán Antonio, la Kuadrilla de Iznalloz and Sonriendo se puede ganar. M.P. acknowledges a grant under the program Becas de Iniciación a la Investigación from the Universidad de Granada (Plan Propio de Investigación). VTF acknowledges support from EPSRC that resulted in the creation of Deuteration Laboratory with ILL's Life Sciences Group. The open access fee was covered by FILL2030, a European Union project within the European Commission's Horizon 2020 Research and Innovation programme under grant agreement N°731096.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apradiso.2020.109205.

References

Abele, H., Dubbers, D., Häse, H., Klein, M., Knöpfler, A., Kreuz, M., et al., 2006. Characterization of a ballistic supermirror neutron guide. Nucl. Instrum. Methods A 562, 407.

Buontempo, F., Orsini, E., Zironi, I., Isolan, L., Cappellini, A., Rapino, S., et al., 2018. Enhancing radiosensitivity of melanoma cells through very high dose rate pulses released by a plasma focus device. PloS One 13, e0199312.

Butterworth, K.T., McGarry, C.K., O'Sullivan, J.M., Hounsell, A.R., Prise, K.M., 2010. A study of the biological effects of modulated 6 MV radiation fields. Phys. Med. Biol. 55, 1607.

Coderre, J.A., Makar, M.S., Micca, P.L., Nawrocky, M.M., Liu, H.B., Joel, D.D., et al., 1993. Derivations of relative biological effectiveness for the high-LET radiations produced during boron neutron capture irradiations of the 9L rat gliosarcoma in vitro and in vivo. Int. J Radiat. Oncol. 27, 1121.

Fowler, J.F., 1989. The linear-quadratic formula and progress in fractionated radiotherapy. Br. J. Radiol. 62, 679.

Gómez-Millán, J., Katz, I.S.S., de Araujo Farias, V., Linares-Fernández, J.L., López-Peñalver, J., Ortiz-Ferrón, G., et al., 2012. The importance of bystander effects in radiation therapy in melanoma skin-cancer cells and umbilical-cord stromal stem cells. Radiat. Oncol. 102, 450.

González, S.J., Cruz, G.A., 2012. The photon-iso-effective dose in boron neutron capture therapy. Radiat. Res. 178, 609.

Goorley, J.T., Kiger III, W.S., Zamenhof, R.G., 2002. Reference dosimetry calculations for neutron capture therapy with comparison of analytical and voxel models. Med. Phys. 29, 145.

Hopewell, J.W., Morris, G., Schwint, A., Coderre, J.A., 2011. The radiobiological principles of boron neutron capture therapy: a critical review. Appl. Radiat. Isot. 69, 1756.

Li, P., Shi, Y.W., Li, B.X., Xu, W.C., Shi, Z.L., Zhou, C., Fu, S., 2015. Photo-thermal effect enhances the efficiency of radiotherapy using Arg-Gly-Asp peptides-conjugated gold nanorods that target αvβ3 in melanoma cancer cells. J. Nanobiotechnol. 13, 52.

Mackonis, E.C., Suchowerska, N., Zhang, M., Ebert, M., McKenzie, D.R., Jackson, M., 2007. Cellular response to modulated radiation fields. Phys. Med. Biol. 52, 5469.

Maughan, R.L., Chuba, P.J., Porter, A.T., Ben-Josef, E., Lucas, D.R., 1997. The elemental composition of tumors: kerma data for neutrons. Med. Phys. 24, 1241.

Min, F.L., Zhang, H., Li, W.J., Gao, Q.X., Zhou, G.M., 2005. Effect of exogenous wild-type p53 on melanoma cell death pathways induced by irradiation at different linear energy transfer. Vitro Cell. Dev-An. 41, 284.

Mughabghab, S.F., 1997. Atlas of Neutron Resonances: Resonance Parameters and Thermal Cross Sections Z= 1-100. Elsevier.

Munshi, A., Kurland, J.F., Nishikawa, T., Tanaka, T., Hobbs, M.L., Tucker, S.L., et al., 2005. Histone deacetylase inhibitors radiosensitize human melanoma cells by suppressing DNA repair activity. Clin. Canc. Res. 11, 4912.

Munshi, A., Tanaka, T., Hobbs, M.L., Tucker, S.L., Richon, V.M., Meyn, R.E., 2006. Vorinostat, a histone deacetylase inhibitor, enhances the response of human tumor cells to ionizing radiation through prolongation of γ-H2AX foci. Mol. Canc. Therapeut. 5, 1967.

Pedrosa-Rivera, M., Praena, J., Porras, I., Ruiz-Magaña, M.J., Ruiz-Ruiz, C., 2020a. A simple approximation for the evaluation of the photon isoeffective dose in Boron Neutron Capture Therapy based on dose-independent weighting factors. Appl. Radiat. Isotopes 157, 109018.

Pedrosa-Rivera, M., Ruiz-Magaña, M.J., Porras, I., Praena, J., Torres-Sánchez, P., Sabariego, M.P., et al., 2020b. Neutron radiobiology studies with a pure cold neutron beam. Nucl. Instrum. Methods B 462, 24.

Porras, I., Arias de Saavedra, F., Busser, B., Chaperot, L., Forsyth, T., Köster, U., et al., 2018. Experiment 3-07-376: Radiobiology in Vitro Measurements for Boron Neutron Capture Therapy. Institut Laue-Langevin. https://doi.org/10.5291/ILL-DATA.3-07-376.

Postuma, I., Bortolussi, S., Protti, N., Ballarini, F., Bruschi, P., Ciani, L., et al., 2016. An improved neutron autoradiography set-up for ^{10}B concentration measurements in biological samples. Rep. Pract. Oncol. Radiat. 21, 123.

Schick, U., Kyula, J., Barker, H., Patel, R., Zaidi, S., Gregory, C., et al., 2015. Trametinib radiosensitises RAS-and BRAF-mutated melanoma by perturbing cell cycle and inducing senescence. Radiat. Oncol. 117, 364.

Wennervirta, J.M., Koivunoro, H., Gonzalez, S., Provenzano, L., Kankaanranta, L., Vaalavirta, L.A., Joensuu, H.T., 2019. A retrospective study of predictors for radiation induced severe oral mucositis in BPA-mediated BNCT of head and neck cancer patients. Int. J. Radiat. Oncol. 105, E407.